PRESENT AND FUTURE OF EMDR IN CLINICAL PSYCHOLOGY AND PSYCHOTHERAPY

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PRESENT AND FUTURE OF EMDR IN CLINICAL PSYCHOLOGY AND PSYCHOTHERAPY

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Eye Movement Desensitization Reprocessing (EMDR) therapy is an evidence-based psychotherapy which has been recognized by the World Health Organization (WHO) as a first-choice treatment for Posttraumatic Stress Disorder (PTSD). Beyond PTSD, there has been increasing research into its mechanism of action and in the efficacy of EMDR in other psychiatric and somatic disorders with comorbid psychological trauma. The motivation of this research topic was to offer new and innovative research on EMDR across the globe to an increasing number of clinicians and researchers with an interest in this trauma-focused intervention.

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EDITORIAL
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Editorial: Present and Future of EMDR in Clinical Psychology and Psychotherapy

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Keywords: EMDR therapy, EMDR research, eye movement desensitization and reprocessing, psychological trauma, mechanism of action, PTSD

Editorial on the Research Topic

Present and Future of EMDR in Clinical Psychology and Psychotherapy

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Eye Movement Desensitization Reprocessing (EMDR) therapy is an evidence-based psychotherapy which has been recognized by the World Health Organization (WHO) as a first-choice treatment for Posttraumatic Stress Disorder (PTSD; WHO, 2013). The new International Society for Traumatic Stress Studies (ISTSS) guidelines (Berliner et al., 2019) rated EMDR as strongly recommended in the treatment of PTSD in children, adolescents and adults. These recommendations were based on high quality systematic reviews developed through Cochrane database, the National Institute for Health and Care Excellence (NICE) guidelines, and the aforementioned WHO recommendation, as well as on the results of randomized controlled trials. In the last decade, there has been increasing research into the efficacy of EMDR in other psychiatric and somatic disorders with comorbid psychological trauma (Valiente-Gómez et al.). EMDR is based on the Adaptive Information Processing (AIP) model, which posits that much of psychopathology is due to the maladaptive encoding of and/or incomplete processing of traumatic or disturbing adverse life experiences (Hase et al.). Two recent articles have gone a step further and are highly relevant to the field. One, published in Nature by Baek et al. (2019), reveals EMDR's mechanism of action and neuroanatomical pathway using an animal model. The authors found that bilateral stimulation, as compared to controlled conditions, led to a clear and persistent decrease in fear behavior. Furthermore, the authors observed that bilateral stimulation increased neuronal activity in the superior colliculus and the mediodorsal thalamus, thus dampening the excitability of neurons in the basolateral nucleus of the amygdala. The other article is a review in Neuron about the encoding of aversive memory by Maddox et al. (2019). The authors also discuss EMDR in detail as an effective psychotherapy for re-writing the engrams of traumatic memories, which represent the basis for the persistency of traumatic memories, following an encoding of the threat experience in the neural circuits.

These publications are in line with 22 articles which were included in a Research Topic "Present and Future of EMDR in Clinical Psychology and Psychotherapy." The main motivation for this Research Topic was an increasing interest from scientists who focus their research on EMDR and from clinicians who use EMDR in clinical practice in different private and public psychiatric or psychotherapeutic settings. Currently, more than 25,000 psychologists and psychiatrists across 31 European countries are trained in EMDR and are members of the EMDR Europe Association (personal correspondence Isabel Fernandez). With currently almost 180,000 views since its publication in 2017, and being positioned within the top 50 of the current Research Topic, we believe that this reflects the increasing clinical and research interest in the corresponding fields of psychology and psychiatry. Articles published in this Research Topic include EMDR therapy in new psychiatric and somatic comorbidities with psychological trauma, such as depression (Hase et al.; Ostacoli et al.), substance use disorder (Carletto et al.), panic disorder (Horst et al.), and glioblastoma (Szpringer et al.). These articles highlight the contribution of EMDR therapy to the treatment of these disorders and its positive effect on trauma-associated and/or psychiatric symptoms by addressing traumatic and stressful experiences underlying the life history of these clients. A systematic review also addressed, as stated before, the evidence of EMDR beyond PTSD in further psychiatric disorders (Valiente-Gómez et al.). Furthermore, one article investigated the effect of EMDR on psychological trauma in clinical sub-threshold states like low self-esteem (Griffioen et al.). The Research Topic also includes one meta-analysis of EMDR in children and adolescents with PTSD (Moreno-Alcázar et al.), which represents an extremely important field as trauma-orientated therapies should be applied from an early age, and another systematic review about the evidence of EMDR in adult PTSD (Wilson et al.). As the most recent American Psychological Association (APA) recommendations on psychological and pharmacological treatments for PTSD in adults (2019) caused controversy due to its "conditional" recommendation of EMDR for the treatment of PTSD, a comment and rectification of available literature was also added to this Research Topic (Dominguez and Lee). Due to this comment, the APA published recently an updated version of the clinical practice guideline with the view that future systematic reviews and meta-analysis will probably change the level of recommendation for EMDR, and also narrative exposure therapy, from conditional to strong.

New data were provided from five EMDR group protocols for dementia caregivers (Passoni et al.), in mass disasters (Maslovaric et al.; Trentini et al.), for Syrian refugees (Yurtsever et al.) and in complex PTSD and dissociation (Gonzalez-Vazquez et al.). Due to often limited resources for individual psychotherapy, these data of EMDR group interventions are of vital importance in offering trauma-focused psychotherapy to a broader audience. Further articles review or investigate its underlying AIP model (Hase et al.) and its mechanism of action (Boukezzi et al.; Landin-Romero et al.; Matthijssen et al.; Pagani et al.; Pagani et al.; Santarnecchi et al.). Of note, the first author of one systematic review about the mechanism of action of EMDR therapy (Landin-Romero et al.) was awarded the Frontiers Young Researchers Award in 2018.

In summary, due to increasing scientific and clinical interest in EMDR within the psychological and psychiatric fields worldwide, a successful Research Topic "Present and Future of EMDR in Clinical Psychology and Psychotherapy" has been published. We included 22 articles covering a variety of innovative clinical and neurobiological aspects of EMDR. Further to this Research Topic, additional groundbreaking articles for the EMDR field have been published in 2019, such as the Baek et al. (2019) study revealing the mechanism of action of EMDR in animals. This underlines the growing interest in EMDR. However, further robust randomized controlled trials of EMDR applications in in well-researched and as yet unstudied psychopathological disorders are necessary, as well as methodology-based scientific research about the specific mechanisms of action underlying EMDR clinical efficacy in humans.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. All authors had the idea of this clinical topic and served as editors for all included articles.

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PERSPECTIVE
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The AIP Model of EMDR Therapy and Pathogenic Memories

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Eye Movement Desensitization and Reprocessing (EMDR) therapy has been widely recognized as an efficacious treatment for post-traumatic stress disorder (PTSD). In the last years more insight has been gained regarding the efficacy of EMDR therapy in a broad field of mental disorders beyond PTSD. The cornerstone of EMDR therapy is its unique model of pathogenesis and change: the adaptive information processing (AIP) model. The AIP model developed by F. Shapiro has found support and differentiation in recent studies on the importance of memories in the pathogenesis of a range of mental disorders beside PTSD. However, theoretical publications or research on the application of the AIP model are still rare. The increasing acceptance of ideas that relate the origin of many mental disorders to the formation and consolidation of implicit dysfunctional memory lead to formation of the theory of pathogenic memories. Within the theory of pathogenic memories these implicit dysfunctional memories are considered to form basis of a variety of mental disorders. The theory of pathogenic memories seems compatible to the AIP model of EMDR therapy, which offers strategies to effectively access and transmute these memories leading to amelioration or resolution of symptoms. Merging the AIP model with the theory of pathogenic memories may initiate research. In consequence, patients suffering from such memory-based disorders may be earlier diagnosed and treated more effectively.

Keywords: EMDR therapy, mental disorders, pathogenic memory, psychotherapy, PTSD, psychosomatic medicine

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INTRODUCTION

Eye Movement Desensitization and Reprocessing (EMDR) therapy was introduced in 1987 as a treatment for post-traumatic stress disorder (PTSD). EMDR therapy is not only an evidence-based treatment of PTSD (Bisson and Andrew, 2007; Watts et al., 2013; World Health Organization [WHO], 2013; Schulz et al., 2015), but is also a potentially effective treatment for various other mental disorders as affective disorders (Landin-Romero et al., 2013; Hofmann et al., 2014; Novo et al., 2014; Hase et al., 2015), chronic pain (Schneider et al., 2005; Wilensky, 2006; de Roos et al., 2010; Gerhardt et al., 2016), addiction (Hase et al., 2008; Abel and O'Brien, 2010), or obsessive compulsive disorders (Marsden et al., 2017). Functional imaging studies enable us to understand the working mechanisms of EMDR therapy to a great extent (Pagani et al., 2012; Lee and Cuijpers, 2013).

F. Shapiro developed a model of pathogenesis and change based on her experiences in EMDR therapy treatment sessions. This model is unique to EMDR therapy and is called adaptive information processing (AIP) model, abbreviated AIP model (Shapiro, 2001a). Since then the development and practice of EMDR therapy has been guided by the AIP model.

One of the key tenets of the AIP model predicts that dysfunctionally stored and not fully processed memories are the cause of a number of mental disorders, including, e.g., PTSD, affective disorders, chronic pain, addiction, and various other disorders. However, the exact nature of memory and its mechanism in detail is far more difficult to determine than the fact that after a certain event, a certain psychopathology appears, which can be effectively addressed by EMDR therapy.

THE AIP MODEL OF EMDR THERAPY

From her experiences in EMDR treatment sessions, Shapiro developed a unique theoretical model for the pathogenesis and change relating to EMDR therapy (Shapiro, 2001a,b). Since then, EMDR therapy has been guided by the AIP model (Shapiro, 2007; Shapiro and Laliotis, 2011). The AIP model focuses on the patient's resources. Within the AIP model, one assumes that the human brain can usually process stressful information to complete integration. Only if this innate information processing system is impaired, the memory will be stored in a raw, unprocessed, and maladaptive form. A particularly distressing incident may then become stored in state-specific form. This implies also the inability to connect with other memory networks that hold adaptive information. Shapiro hypothesizes that when a memory is encoded in such excitatory, state-specific form, the original perceptions can be triggered by a variety of internal and external stimuli. In the view of the AIP model dysfunctionally stored memories form the basis for future maladaptive responses, because perceptions of current situations are automatically linked with associated memory networks of these unprocessed, dysfunctionally stored memories. For instance childhood experiences also may be encoded with survival mechanisms and include feelings of danger that are inappropriate for adults. However, these past events retain their power because they have not been appropriately assimilated over time into adaptive networks (Solomon and Shapiro, 2008). One of the key tenets of the AIP model is that these dysfunctionally stored and not fully processed memories form the basis of psychopathology. Activation of these memories, even years after the event, can lead to a spectrum of symptoms including intrusions that can range from an overwhelming experience, mostly called flashback, to barely noticeable intrusions. These memories lack the feeling of remembering, as described by Barry as memories without "memory awareness" (Barry et al., 2006). This contributes to the lively, actual experience, and sometimes makes it difficult to connect symptoms to the memories behind them.

The overwhelming experience and high amount of traumatic stress in a traumatic experience according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association [APA], 2013) can be assumed to explain the disruption in information processing. But there can be many more causes imaginable as clinical experiences show (Hase and Balmaceda, 2015). Intense feelings of helplessness beside traumatic events or misinterpretations of an event as being extremely dangerous could also have these consequences. Other intense emotions based in previous experiences could lead to disruption in information processing. With children and adolescents the attachment to a caregiver or a sense of meaning seems to be a prerequisite for the processing of a stressful life experience. Accordingly the absence of an attachment figure could lead to impairment in information processing and thus to the development of PTSD even in the absence of a criterion A event (Verlinden et al., 2013). Of course abusive behavior of an attachment figure or neglect would likely lead to such consquences. Exhaustion and physical conditions in somatic disorders could explain the disruption in information processing as well as the influence of drugs in drug rape or during medical procedures. Of course this short list of possible causes is not comprehensive. It needs more rigorous research to determine the prerequisites beyond type A trauma.

In accordance with the AIP model these dysfunctionally stored memories become the focus of EMDR protocols and procedures in order to activate the information processing system thus transmuting these memories by so-called "reprocessing." The subsequent integration into adaptive memory networks leads to a resolution of symptoms and enables learning (Solomon and Shapiro, 2008).

PATHOGENIC MEMORIES

Although the scientific discourse tends to associate memories that create intrusions with criterion A events and the definition of PTSD, non-criterion A events have been shown to create even more intrusions than criterion A events (Gold et al., 2005). Additionally, data from a survey of 832 adult subjects indicated that stressful life events can generate at least as many PTSD symptoms as traumatic events (Kendler et al., 2003). McFarlane (2010) showed that stressful life experiences can lead to intrusions without a fully developed PTSD. McFarlane (2010) also demonstrated that these intrusions relate to many mental disorders and poor health in general. Following these findings intrusions seem to be a common memory-based symptom, which is not necessarily linked with a PTSD diagnosis or criterion A event. Nevertheless, intrusions indicate a memory-based pathology beyond PTSD that can be linked with other mental disorders. This is consistent with a publication of Heinz et al. (2016) discussing basic learning mechanisms as representations of a basic dimension of mental disorders. They advocate for a research focus on such basic dimensions rather than pursuing a narrow focus on single disorders.

Centonze et al. (2005) described the importance of pathogenic memories from a theoretical perspective. There approach is based on the increasing acceptance of theories that relate the origin of many psychiatric symptoms to the formation and consolidation of implicit dysfunctional memory (Centonze

et al., 2005). Since their publication other prominent authors have engaged in this discussion. Alberini and LeDoux (2013) summarize research on memory reconsolidation and dwell on the therapeutic perspective. In their opinion further research on memory reconsilidation could help to ameliorate maladaptive memories and potentiate adaptive behaviors in psychopathology (Alberini and LeDoux, 2013). Sillivan et al. (2015) explore the possibilities of latest research on epigenetic modification. They advocate for a recognition of the contribution of epigenetic mechanisms to how pathological memories associated with addiction and PTSD are stored, expressed, and subsequently modified, possibly leading to novel therapeutic targets (Sillivan et al., 2015).

Summarizing current neurobiological research, Centonze et al. (2005) state: "Experimental research examining the neural bases of non-declarative memory (such as habit formation, classical conditioning, and fear conditioning) has offered intriguing insight into how functional and dysfunctional implicit learning affects the brain." They give evidence on the importance of long-term modification of synaptic transmission in particular as the most plausible mechanisms underlying memory trace encoding compulsions, addiction, anxiety, and phobias. Compulsions and other stereotypies are viewed as pathological habits (nearly automated implicit motor abilities) encoded as aberrant synaptic plasticity in the corticobasal ganglia loop. Centonze et al. (2005) refer to addictive drugs abusing the molecular mechanisms of reward-based associative learning by inducing long-term changes in synaptic effectiveness in those brain areas serving basic biological needs, such as feeding and sexual interaction. Finally, anxiety, panic disorder, and phobias are viewed as uncontrolled and repetitive defensive reactions secondary to abnormal fear conditioning – a form of implicit associative learning, encoded as long-term potentiation (LTP) in the lateral amygdala. In consequence, Centonze et al. (2005) propose that an effective psychotherapy must be directed to erase maladaptive pathogenic memories and research should focus on the development of techniques to remove pathogenic memories. Although they mentioned neither the AIP model, nor EMDR therapy, the concept of pathogenic memories could probably open another view on recent developments in EMDR research.

It seems to be of interest to explore the overlap of the theory of pathogenic memory and the AIP model, regarding practical implications for EMDR therapy in reprocessing maladaptive implicit memories, especially as the cited authors are advocating for the developments of therapeutic tools to modify pathogenic memories. As Centonze et al. (2005) coined the term "pathogenic memory" but did not give a precise definition, one should start here.

DEFINITION AND PERSPECTIVE

A clinical core feature of a pathogenic memories would be experiencing intrusions while the memory is activated, e.g., by sensory cues. A second feature of such memories may include vegetative arousal or other biological activity. Vegetative arousal may be felt by the patient when the memory is activated. EMDR therapists use this arousal to measure the "subjective level of disturbance" (also called SUD = subjective units of disturbance) in EMDR therapy. Craving and pain can be also understood as intrusions and assessed in similar ways (subjective level of urge, subjective level of pain). Studies show that if the memory is reprocessed in EMDR therapy, the vegetative arousal linked to the memory subsides and the SUD scores indicate change or, e.g., pain is reduced.

In addition the definition of trauma could loose some significance. The future question would not be about how traumatic an event is, but rather on the pathology developing after the event. This could lead to better understanding of the processing of certain "non-traumatic," but nevertheless pathogenic memories within EMDR therapy. Considering the experiences of EMDR clinicians worldwide, the number of patients suffering from pathogenic memories may be much greater than that of patients suffering from PTSD alone.

Patients who may benefit from this conceptual expansion of memory pathology and subsequent reprocessing with EMDR could be suffering from a variety of mental disorders as laid out in the section "Introduction." We will now focus on addiction, pain, and affective disorders as there seems to be more background by research or evidence by controlled studies.

(A) Patients with addiction disorders. A specific "addiction memory" was already postulated by Wolffgramm in 1995 from his studies of animal models (Wolffgramm and Heyne, 1995; Heyne et al., 1999). Wolffgramm and Heyne (1995) postulated that addiction memory contributes to craving and the chronic course of addiction. Interestingly, the removal of the addiction memory by altering the brain's ability to learn led to a complete remission of the disorder, at least in Wolffgramm's animal model (Wolffgramm, 2004). Patients will most likely experience intrusions of an activated addiction memory as craving for the specific drug of abuse. In clinical studies, the reprocessing of these pathogenic craving memories within EMDR therapy improved the clinical course of patients with addiction memories (Hase et al., 2008; Abel and O'Brien, 2010).

(B) Patients with pain disorders. Phantom limb pain can be understood as the somatosensory intrusion of a pathogenic "pain memory." One can assume that this memory is mainly based on the painful experiences before the limb was lost. Recent research showed that the prevalence of phantom limb pain after amputation of a limb or parts of it can be minimized by blocking nervous transmission for a prolonged period of time post-amputation, probably preventing the formation of pain memory (Borghi et al., 2010, 2014).

Reprocessing of pain memory should lead to symptom reduction. In three case series with a total of 30 phantom limb pain patients which were treated with EMDR therapy, 50% lost their pain completely (Schneider et al., 2005; Wilensky, 2006; de Roos et al., 2010). Additionally, Gerhardt et al. (2016) reported in a pilot study that patients with stressful memories and chronic back pain benefitted significantly from EMDR therapy, with 50% of patients losing their back pain completely.

(C) Patients with affective disorders. The importance of implicit memory in the pathogenesis of depression was already described by Barry et al. (2006). Recent studies link certain

types of depression to stressful life events (Kendler et al., 2003). Until now, this was mainly considered a risk factor or a contributing factor for depression, but the concept of pathogenic memories offers another point of view. Since treatment options for recurrent depressive disorder patients and those with chronic depression are limited, further research investigating the role of depressive episode-triggering memories as well as EMDR therapy for the treatment of depressive disorders shows promise to improve the treatment of depression (Hofmann et al., 2014; Hase et al., 2015) and bipolar affective disorder (Landin-Romero et al., 2013; Novo et al., 2014).

Summarizing on the AIP Model and Pathogenic Memories

The concept of pathogenic memories as the basis of mental and psychosomatic disorders can be easily integrated in the AIP model. The term "pathogenic memory" describes accurately the dysfunctionally stored memory as described by Shapiro in the AIP model. This opens up a new understanding of pathogenesis and therapeutic change in mental disorders far beyond PTSD. PTSD may be the prototypical disorder based in disruption of memory processing, but not the only one. These ideas could explain the development and progress of depression, the formation of pain memory leading to phantom limb pain, the role of addiction memory in addictive disorders, the deviational offender phantasies based on memories of abuse, the revenge phantasies of soldiers stemming from the battlefield memories and many more. On the other hand, EMDR therapy provides us not only with techniques to detect pathogenic memories but also with elaborated treatment plans (protocols), procedures, and techniques for a variety of mental disorders and has convincing evidence in the treatment of PTSD. This is a great advantage to Centonze's appeal to remove pathogenic memories but lacking the tools to achieve this goal. Many studies on memory reprocessing in EMDR therapy with different disorders gave evidence on this AIP informed approach. It seems possible to target pathogenic memories and reprocess them, thus leading to transmutation, contributing to mental and physical equilibrium, and leading to long-lasting change.

DISCUSSION

There is a growing body of research showing that memories can contribute to pathology in many mental disorders. Research proposes to extend the range of disorders that are linked with pathogenic memories beyond PTSD and other trauma-based disorders. This is in line with the EMDR literature, where the AIP model of EMDR has predicted that PTSD is not the only memory-based disorder and has linked many other disorders to "dysfunctionally stored memories."

One of the drawbacks of the AIP model is that it is difficult to determine what "dysfunctionally stored" means on a neurobiological level, which limits the scope of the AIP model. However, one could replace this term with the term "pathogenic" to define memories as causing symptoms without precisely needing to know their neurobiological details. In this way, more patients could benefit from a memory-related diagnosis and an adequate treatment. Meanwhile, research on memory pathology and its neurobiological underpinnings, as well as research on the clinical application of this knowledge could be supported by clear-cut research questions. This research direction also offers the possibility to move toward a diagnostic group of (mainly) "memory-based disorders" that are not exclusively focused on trauma-related events. This may lead to a broader application of well-researched EMDR protocols and procedures offering more help to patients who experience limited success undergoing psychotherapy as usual.

AUTHOR CONTRIBUTIONS

MH and AH laid the theme out and wrote the manuscript; UB contributed to the manuscript; and LO and PL assisted in the literature search.

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Auditory and Visual Memories in PTSD Patients Targeted with Eye Movements and Counting: The Effect of Modality-Specific Loading of Working Memory

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Introduction: Eye movement desensitization and reprocessing (EMDR) therapy is an evidence-based treatment for post-traumatic stress disorder (PTSD). A key element of this therapy is simultaneously recalling an emotionally disturbing memory and performing a dual task that loads working memory. Memories targeted with this therapy are mainly visual, though there is some evidence that auditory memories can also be targeted.

Objective: The present study tested whether auditory memories can be targeted with EMDR in PTSD patients. A second objective was to test whether taxing the patient (performing a dual task while recalling a memory) in a modality specific way (auditory demanding for auditory memories and visually demanding for visual memories) was more effective in reducing the emotionality experienced than taxing in cross-modality.

Methods: Thirty-six patients diagnosed with PTSD were asked to recall two disturbing memories, one mainly visual, the other one mainly auditory. They rated the emotionality of the memories before being exposed to any condition. Both memories were then recalled under three alternating conditions [visual taxation, auditory taxation, and a control condition (CC), which comprised staring a non-moving dot] – counterbalanced in order – and patients rerated emotionality after each condition.

Results: All three conditions were equally effective in reducing the emotionality of the auditory memory. Auditory loading was more effective in reducing the emotionality in the visual intrusion than the CC, but did not differ from the visual load.

Conclusion: Auditory and visual aversive memories were less emotional after working memory taxation (WMT). This has some clinical implications for EMDR therapy, where mainly visual intrusions are targeted. In this study, there was no benefit of modality specificity. Further fundamental research should be conducted to specify the best protocol for WMT.

Keywords: EMDR, working memory taxation, visual intrusions, auditory intrusions, modality specificity, eye movements

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a debilitating disorder which is categorized as a trauma- and stressor-related disorder in DSM 5. It can be developed after being exposed to a traumatic event. The disorder is characterized by suffering from repeatedly re-experiencing the traumatic event (in flashbacks or nightmares), avoidance of trauma-related stimuli, negative alterations in mood and cognition, and alterations in arousal and reactivity (American Psychiatric Association, 2015). Several psychological treatments are effective in treating PTSD. One of those treatments is eye movement desensitization and reprocessing (EMDR) therapy. A core feature of EMDR therapy is that a disturbing memory is held in mind by a patient while simultaneously making horizontal eye movements (EMs). These movements are typically induced by following a moving dot that is displayed on a light bar or the therapist's fingers, moving a hand continuously back and forth in front of the patient's eyes. Clinical trials and meta-analyses have demonstrated the effectiveness of EMDR in treating PTSD (for meta-analyses, see, e.g., Bradley et al., 2005; Seidler and Wagner, 2006; Bisson et al., 2007; Chen et al., 2014; Cusack et al., 2016).

Evidence that EMDR is an effective treatment for PTSD does not imply knowing what the underlying working mechanism is. One explanatory hypothesis for how EMDR works, which is gaining accumulating evidence, is based on the working memory (WM) model (Baddeley and Hitch, 1974). The hypothesis states that recalling memories requires WM resources, which are limited. If a dual task, which also uses WM capacity, is performed during recall, fewer resources will be available for recall. As a consequence, the recalled memory will be less emotional and less vivid and will be reconsolidated as less emotional and less vivid in long-term memory (Van den Hout et al., 2010). EMs are considered a dual task. Consistent with the hypotheses from WM theory, memories have been found to not only become less disturbing and less vivid after execution of an EM task but also after a range of other tasks that load WM (e.g., counting, watching an array of small squares that constantly and randomly change between black and white, mindful breathing) (e.g., Andrade et al., 1997; Kavanagh et al., 2001; Kemps and Tiggemann, 2007; Gunter and Bodner, 2008; Van den Hout et al., 2010, 2011a; Engelhard et al., 2011).

In therapy, EMDR focuses on the intrusive memories of traumatic events – one of the hallmark symptoms of PTSD. Ehlers et al. (2002) asked patients with PTSD to describe the content of their typical intrusive memory and concluded that visual intrusions were more common (70–97%) than bodily sensations (28–66%), sounds (38–51%), smell (48–51%), actions (22–65%), or thoughts (26–60%). Hackmann et al. (2004) interviewed 22 patients with chronic PTSD about the content of their intrusive memories and found the majority included visual and/or bodily sensations. Auditory content was experienced in about half of the intrusions. Taste and smell sensations were least common. Hence, it is clear that intrusive memories can appear in different sensory modalities. EMDR aims at reducing PTSD symptoms by reducing emotional intensity of *visual* images. However, the question remains if intrusions in other sensory modalities can be successfully targeted with EMDR?

The WM model (Baddeley and Hitch, 1974) comprises the central executive (CE) and two so-called "slave" systems; the visuospatial sketchpad (VSSP) and the phonological loop (PL). The CE carries out higher order cognitive functions (i.e., problem solving and planning), whereas the VSSP is concerned with processing and storing visual and spatial information and the PL with processing and storing auditory information (Andrade et al., 1997). The VSSP is thus involved in visual imagery and the PL in auditory imagery (Kristjánsdóttir and Lee, 2011). Earlier studies show some inconsistencies in whether the CE is merely responsible for the reduction in vividness and emotionality of memories or if this is a consequence of loading the slave systems, the latter implying a benefit of modality-specific demanding tasks (Andrade and Baddeley, 1993 in Andrade et al., 1997; Baddeley and Andrade, 2000; Gunter and Bodner, 2008; Kristjánsdóttir and Lee, 2011). In a series of experiments Andrade and Baddeley (1993 in Andrade et al., 1997) showed that counting made auditory images less vivid, whereas tapping tasks made visual images less vivid. They asked participants to imagine how things looked or sounded. They did so while performing either a task taxing the PL (counting) or the VSSP (tapping a pattern). After imagining how things looked or sounded they were asked to rate the vividness of their image on a scale from 0 (no image) to 10 (as clear as normal). Tasks matched in modality appeared to have a larger effect on vividness ratings than tasks not matched in modality. Andrade et al. (1997) conducted another series of experiments where they asked participants to imagine neutral or negative stimuli (consisting of earlier presented neutral or negative photographs) and to perform different dual tasks (counting, a simple tapping task, a complex tapping task, and EM) and a control task (monitoring a non-moving letter on a screen). They consistently found concurrent tasks had a larger effect on vividness. The results were less clear and less consistent for emotionality. In the last of their series of experiments they used personal memories and found that concurrent visuospatial tasks reduced the emotionality ratings, but the effect was much smaller for the vividness ratings. They concluded that the locus of the effect was the VSSP (Andrade et al., 1997). However, the authors did not test the effect of a concurrent phonological load on auditory personal memories. Baddeley and Andrade (2000) conducted seven experiments, exposing participants to novel stimuli, being either visual or auditory (e.g., shapes or musical notes) while conducting a visual, auditory, or control dual task. They found an interaction between modality of images and the dual task on vividness ratings. For familiar or meaningful scenes or sounds this modality-specific effect was still present, but smaller. Baddeley and Andrade (2000) therefore concluded that the slave systems are involved in reducing vividness, and that the CE also plays a role here.

A limitation of the studies described above is that there were no baseline measurements. Participants rated their images after the working memory taxation (WMT), leaving it unclear if there was any difference before conducting the task. Kemps and Tiggemann (2007) conducted two studies to investigate the effect

of concurrent visual and auditory interference on emotional images, one of them contained a baseline measurement. They instructed 68 undergraduates to recall a specific visual or auditory image of happy and distressing memories, while they were exposed to either EM, articulatory suppression (counting aloud), or a control condition (CC). There was a large general effect of WM loading, but superimposed on that general effect, the authors reported a modality-specific effect: vividness and emotionality ratings were reduced to a greater extent when the modality of taxation was matched to the modality of the image.

Gunter and Bodner (2008), however, found no effect of modality specificity in reducing the distress of negative memories. They asked participants to hold distressing memories in mind while performing an auditory shadowing task or a demanding visuospatial task or EM. They found equal benefits for EM and the auditory task, but a demanding visuospatial task was more beneficial. Furthermore, Kristjánsdóttir and Lee (2011) asked participants to recall an unpleasant autobiographical memory while performing each of three dual-attention tasks (EM, listening to counting, or a CC). They found that EM led to a greater decrease in vividness than listening to counting. They also found that EM and listening to counting were equally effective in reducing emotionality. Both effects were present irrespective of the modality of the memory. This was taken to support the crucial role of the CE relative to the VSSP or the PL. However, it is unclear how cognitively demanding the tasks were, leaving it unclear if effects could really be attributed to CE or if the VSSP and PL still play a role.

The studies reported by Gunter and Bodner (2008) and by Kristjánsdóttir and Lee (2011) were carried out to clarify how EMDR yields it positive effects. A crucial limitation of their studies is that non-clinical samples were used and, therefore, it is unclear whether the findings can be generalized to PTSD patients. The issue is an empirical one. Given its clinical importance it requires settling, although there may be no reason in advance to believe that a clinical sample would react differently than a non-clinical sample to WMT on disturbing memories. A second, perhaps more important limitation is that none of the studies cited above actually measured the *degree* of WMT of the dual tasks being used. This can lead to the conclusion – if not finding a modality specific effect – that the effect can be attributed to the CE, while it could actually be a consequence of a task being more demanding than another task. Also, no modality specificity can be inferred if the analysis only includes visual memories, hence a dual visuospatial task could just require more effort than a dual auditory task. A model in which both the CE and the slave systems are responsible for the effect on emotionality and vividness in emotional disturbing images is also possible. This would therefore lead to an absence of the modality specificity effect found in some of the previous studies.

In summary, some of the above studies indicate that auditory memories can be made less emotional and vivid by dual tasks in non-clinical samples. Furthermore, there are some studies indicating there is a greater reduction of vividness and emotionality ratings if the dual task is matched to the modality of the memory. The aim of this study is to test whether auditory intrusions can be targeted with EMDR in PTSD patients. A second objective is to test whether modality-specific loading [auditory (visual) loading of auditory (visual) intrusions] is more effective in reducing the emotionality experienced than taxing in cross modality.

MATERIALS AND METHODS

Patients

Thirty-eight patients with PTSD were recruited to the study. Diagnosis of PTSD was made by a trained clinician (clinical psychologist/psychiatrist) and based on DSM IV-TR criteria (American Psychiatric Association, 2000). Two patients were excluded on starting participation. One was too scared to participate and expressed that she thought she was unsuitable for the experiment. The other patient was unable to select memories which could be targeted. Data from 36 patients (32 females and 4 males) with a mean age of 39.19 ($SD = 11.19$) were collected. Apart from the PTSD, 77.8% had at least one other Axis I diagnosis and 33.3% had at least one Axis II diagnosis. They all received treatment in several Dutch mental health institutions. Eighteen patients received treatment at an Academic Anxiety Center, nine at a Medical Center, and nine at different Faculty Assertive Community Treatment Centers. Apart from being diagnosed with PTSD, inclusion criteria were that the patient had to have an estimated IQ higher than 80, be at least 18 years of age and have sufficient mastery of the Dutch language. Exclusion criteria were an acute suicide risk and severe visual or hearing impairments. IQ, mastery of the Dutch language, and suicide risk were estimated by the therapist referring the patient for the study. No data were obtained about the type of trauma, length or quantity of the trauma, or years since index trauma. Therefore, no exclusions were made based on one of these trauma-related factors. Although data from 36 patients were collected, for the auditory memory, data from only 30 patients ($M = 38.93$, $SD = 12.09$) were included into the analysis and for the visual memory this was the case for 31 patients ($M = 39.58$, $SD = 12.09$). (See design for further explanation on this.) For specific patient characteristics see **Table 1**.

Procedure

Study procedures were approved by the medical ethics institutional review board of the University Medical Center, Utrecht, Netherlands. Therapists from the participating mental health institutions were asked to check their caseload, select all patients meeting the criteria, and approach them for participation. Patients were given an information letter and were able to consider participating for at least a few days. Upon giving oral consent to their therapist they were referred to the researchers. The researchers are unaware whether and how many patients refused participation. All patients received treatment as usual while participating in the study.

After giving written informed consent, patients were briefed in short about the study. They were instructed to recall two emotionally disturbing memories that were still giving emotional distress, one mainly auditory and one mainly visual.

TABLE 1 | Patient characteristics.

	Auditory memory ($N = 30$)	Visual memory ($N = 31$)
Gender		
Female	26 (86.7%)	27 (87.1%)
Male	4 (13.3%)	4 (12.9%)
Axis I disorder		
PTSD	7 (23.3%)	7 (22.6%)
PTSD + mood disorder	9 (30%)	7 (22.6%)
PTSD + anxiety disorder	5 (16.7%)	7 (22.6%)
PTSD + other disorders	6 (20%)	7 (22.6%)
PTSD + addiction + other	2 (6.7%)	2 (6.5%)
PTSD + addiction	1 (3.3%)	1 (3.2%)
Comorbid Axis II disorder		
No diagnosis	19 (63.3%)	23 (74.2%)
≥Axis II diagnosis	11 (36.7%)	8 (25.8%)
Education level		
Primary school	2 (6.7%)	2 (6.5%)
Secondary school	11 (36.6%)	12 (38.7%)
Lower vocational education	1 (3.3%)	1 (3.2%)
Secondary vocational education	10 (33.3%)	9 (29%)
Higher professional education	6 (20%)	7 (22.6%)
Psychopharmacological drugs		
No use of medication	6 (20%)	7 (22.6%)
Antidepressants (AD)	7 (23.3%)	6 (19.4%)
Benzodiazepines (BD)	1 (3.3%)	3 (9.7%)
Antipsychotics (AP)	1 (3.3%)	1 (3.2%)
AD and/or BD and/or AP	5 (16.5%)	5 (16%)
Other (single or combination)	10 (33.3%)	9 (28.8%)

While recalling the visual (auditory) memory, the subjects were instructed to either consequently make EM (visual taxation, VT), to count down (auditory taxation, AT) or to stare at a non-moving dot (CC). After selection, the extent to which the memories were auditory or visual was rated on one 100 mm Visual Analog Scale (VAS), ranging from completely auditory to completely visual. For selection, a threshold of 50% auditory (visual) was applied. After this, other sensory modalities (gustatory, kinesthetic, and olfactory) were checked whether they were not more dominant than the auditory (visual) modality in the selected memory, by asking participants to divide a 100 mm VAS to the extent in which all sensory modalities were present in the memory. The order of the type of memory (visual vs. auditory) and the conditions (VT, AT, and CC) were counterbalanced. Once instructed, the patients were asked to recall the emotionally disturbing [visual (auditory)] memory and to rate the disturbance on a scale from 0 to 10 [the subjective units of disturbance (SUD) score; see below]. The memories were then recalled approximately 30 min each, while being exposed to each condition (VT, AT, and CC) twice for 5 min. To mimic EMDR procedures, after every 1 min during a 5-min period the condition was interrupted to check what was going through the patient's mind. Answers were not discussed by their content but were followed by the instruction "concentrate on that" after which the next 1-min period of the condition was continued.

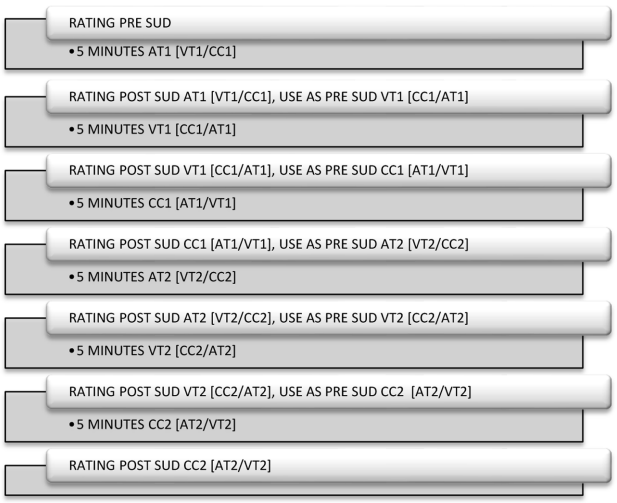

FIGURE 1 | Timeline showing the presentation for all conditions.

During each condition, participants were seated in front of a light bar. During the CC, the bar displayed a non-moving dot in the center of the bar. During the VT, a moving dot was displayed. During the AT, the bar displayed nothing. The speed used for the moving dot in the VT condition and the type of counting task was based on previous research from Van den Hout et al. (2010, 2011a) and Engelhard et al. (2011). In these studies individuals carried out a reaction time (RT) task. An increase in response time was observed when an additional task was added. The delay in response time as a result of EMs with 1 cycle (left–right–left) per second (RT of 115 ms) versus the response delay as a result of a countdown from 1000 (RT of 97 ms) was approximately equal (Engelhard et al., 2011; van den Hout et al., 2011b). Therefore, these two tasks were considered suitable to induce similar WM load.

Design

The study had a two (time; pre- and post-) by three (conditions: VT, AT, and CC) repeated measures within-subject design. For a detailed timeline see **Figure 1**.

This design was used both for the auditory as well as the visual memory. The dependent variable was the SUD score, which indicated the level of distress or emotional disturbance experienced by the patient in terms of the recalled emotional target image. SUD scores were verbally expressed by the patient and SUD scores are routinely used in EMDR. Data were analyzed with SPSS version 23. To obtain sufficient statistical power (power 0.8, with an α-level of 0.05 and an expected medium effect size, $f = 0.25$), 36 patients were needed.

Although the intention was to present all conditions (VT, AT, and CC) twice, 6 out of 36 patients reached SUD 0 – meaning experiencing no emotional disturbance when recalling the auditory memory – before the presentation of all conditions was completed. Before completing all conditions twice, 21 patients reached SUD 0. Clinically, this was an encouraging

observation demonstrating that this procedure was efficient in reducing SUD scores. As there was insufficient data for the second presentation, the respective SUD was excluded, meaning only data pertaining to the first exposure was analyzed. Hence, the final sample comprised 30 patients.

The same pattern of rapidly decreasing SUD was observed for the visual memory. Five out of 36 patients did not complete all conditions at least once, and in total only 14 patients were presented with all conditions twice. One person stopped halfway during the experiment because he was tired, but still was included into the analyses, because he went through all conditions once. Thirty-one patients were included in the analyses and their first exposure to the three conditions.

Materials

Subjective Units of Disturbance (SUD)

Subjective units of disturbance scores ranged from 0 (no emotional disturbance) to 10 (the worst emotional disturbance possible). Patients were asked to verbally rate their SUD scores concerning the emotional target image before and after each condition (VT, AT, and CC).

EMDR Protocol

Patients were tested individually by the researchers (authors 1 and 2; both EMDR therapists) using steps 1, 2 and 3 (introduction, assessment, and desensitization) from the standard Dutch EMDR protocol (De Jongh and Ten Broeke, 2012). A slightly altered version was used for the auditory memory. In this altered version, all words referring to "visual" sensory modality were altered into words referring to the auditory modality.

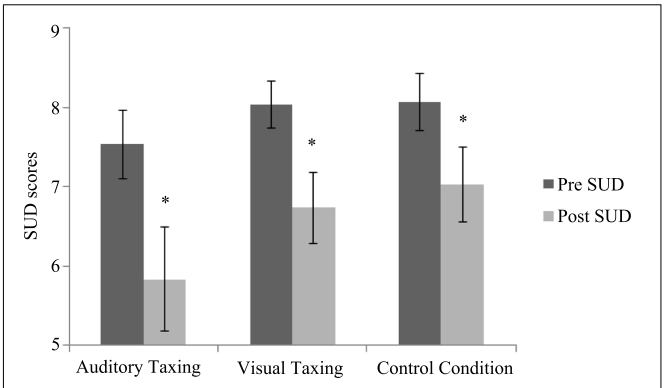

FIGURE 2 | Pre- and post-SUD scores of the auditory memory are shown per condition. Error bars depict ±1 SEM (*$p < 0.05$).

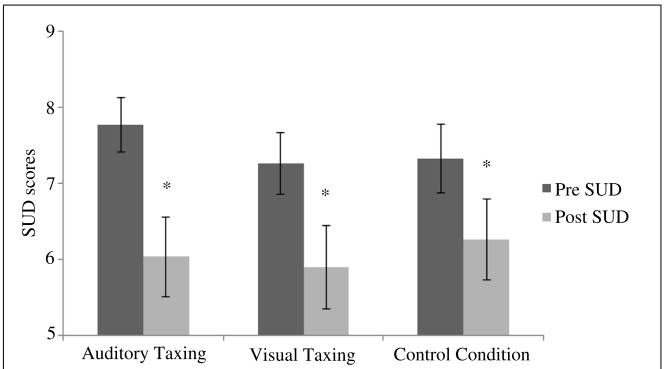

FIGURE 3 | Pre- and post-SUD scores of the visual memory are shown per condition. Error bars depict ±1 SEM (*$p < 0.05$).

RESULTS

Baseline

The average SUD pre-score was 8.97 (standard deviation, $SD = 0.96$) for the auditory memory ($N = 30$) and 8.87 ($SD = 1.06$) for the visual memory ($N = 31$). The difference was not significant [$t(35) = 0.19$, $p = 0.85$].

Auditory Memory

A two (time: pre- and post-) by three (conditions: VT, AT, and CC) repeated measures ANOVA was conducted. A main effect for time [$F(1,29) = 42.00$, $p < 0.01$] was found, but there was no main effect for condition [$F(2,58) = 2.02$, $p = 0.14$] and no time × condition interaction [$F(2,58) = 1.70$, $p = 0.19$] was found. The pre- and post-SUD scores of the VT, AT, and CC are depicted in **Figure 2**, showing that regardless of the condition, the SUD dropped from pre- to post.

Visual Memory

A two (time: pre- and post-) by three (conditions: VT, AT, and CC) repeated measures ANOVA was conducted. The pre- and post-SUD scores of the VT, AT, and CC are graphically depicted in **Figure 3**, showing that, regardless of the condition, the SUD dropped from pre- to post. This was reflected in a main effect for time [$F(1,30) = 47.06$, $p < 0.01$]. There was no main effect for condition [$F(2,60) = 0.25$, $p = 0.78$]. However, a time × condition interaction [$F(2,60) = 3.31$, $p = 0.04$] was found. *Post hoc* analyses with no correction for multiple comparisons revealed AT outperformed the CC ($p = 0.02$) but none of the interactions differed significantly after Bonferroni correction was applied ($p > 0.055$).

DISCUSSION

The first aim of the present study was to test whether auditory intrusions could be successfully targeted with EMDR in PTSD patients. The second aim was to assess whether modality-specific loading of WM was more effective than providing non-modality-specific loads in reducing emotionality experienced in auditory and visual intrusions. This was assessed by asking PTSD patients to recall an auditory and visual emotional memory while engaging in modality-specific WMT (EMs or counting) or a CC. Although earlier studies showed the effect of WMT on non-autobiographical auditory material (e.g., Andrade et al., 1997; Baddeley and Andrade, 2000) and on autobiographical memories with (some) auditory content (Kemps and Tiggemann, 2007; Kristjánsdóttir and Lee, 2011) in non-clinical samples, to the best

of our knowledge this is the first study to examine this in patients. Earlier studies did not control for the degree of interference of the tasks on the WM. The current study did try to match the degree of loading in the relevant condition (EMs and counting) in an attempt to improve the comparison. The results of the study are clear and indicate that emotionality can be reduced in both visual and auditory disturbing memories in PTSD patients. Furthermore, no difference was found between AT, VT, or the CC. This indicates no modality-specific effect and no support for the efficacy of WMT.

A possible explanation for finding an effect in the CC is that the CC may also be demanding. Although Lee and Cuijpers (2013) showed an additive effect of EMs in EMDR treatment and laboratory studies [significantly moderate (Cohen's $d = 0.41$) and significantly large ($d = 0.74$)], this was not found in a recent study by Sack et al. (2016). They found EMs had no advantage over fixation on a non-moving hand. Our hypothesis is that fixation on a non-moving stimulus still requires cognitive resources. This was also strengthened by the observation by the researchers that some patients in the CC were intensely focused on the non-moving dot. However, future research should address whether staring at a non-moving dot also requires effort or if there is another explanation for the absence of difference in effect between the AT and VT versus the CC. A possible explanation for not finding a modality-specific effect is that – although the tasks were specifically chosen to be equally demanding – the tasks may actually not have been exactly matched and possibly the auditory dual task was more taxing than the visual task. On the other hand, some patients had difficulty pursuing the moving dot and were therefore unable to follow it at times. This could potentially have led to missing out on WMT. It is also possible that the auditory and visual tasks are not equally loading the PL or the VSSP, respectively, but that the AT has a more cognitive component to it than the VT, hence using more of the CE capacity. Furthermore, there can be individual differences in PL and VSSP functioning, which were not taken into account. Furthermore, the CC may have a more cognitive component than the VT or a more visual component than the AT. Future research should therefore address these points and could pre-test individuals with a RT test to optimize the comparability of the tasks.

A limitation of the study is the sample size. The power calculation showed 36 patients needed be included, whereas only 30 and 31, respectively, were included for analyses of the auditory and visual memory. The other patients had already reached SUD 0 (meaning experiencing no emotional distress) exposure to all conditions. This being a very welcome observation on the one hand, creates a power-problem on the other hand.

Working with visually disturbing memories in EMDR therapy does elicit positive effects on PTSD symptoms, so it is expected that this effect is generalizable to memories in other sensory modalities. Although future research is needed to examine whether EMDR or staring at a non-moving dot (the CC) for emotionally disturbing auditory memories has an effect on PTSD symptoms, positive clinical effects may be anticipated. The current study only consisted of one experimental "session" and no symptoms of PTSD were measured. Measuring the severity of PTSD symptoms and offering multiple sessions to patients are recommended for future research.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "Medical Ethical Committee of the University Medical Center, Utrecht" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the "Medical Ethical Committee of the University Medical Center, Utrecht."

AUTHOR CONTRIBUTIONS

SM, LV, and MvdH designed the research. SM and LV collected the data. SM, LV, and IH analyzed the data. SM, MvdH, IH, and LV wrote the paper and approved the final manuscript.

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Eye Movement Desensitization and Reprocessing and Slow Wave Sleep: A Putative Mechanism of Action

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Eye Movement Desensitization and Reprocessing (EMDR) is considered highly efficacious for the treatment of Post-traumatic Stress Disorder and has proved to be a valid treatment approach with a wide range of applications. However, EMDR's mechanisms of action is not yet fully understood. This is an active area of clinical and neurophysiological research, and several different hypotheses have been proposed. This paper discusses a conjecture which focuses on the similarity between the delta waves recorded by electroencephalography during Slow Wave Sleep (SWS) and those registered upon typical EMDR bilateral stimulation (eye movements or alternate tapping) during recurrent distressing memories of an emotionally traumatic event. SWS appears to have a key role in memory consolidation and in the reorganization of distant functional networks, as well as Eye Movements seem to reduce traumatic episodic memory and favor the reconsolidation of new associated information. The SWS hypothesis may put forward an explanation of how EMDR works, and is discussed also in light of other theories and neurobiological findings.

Keywords: EMDR, mechanism of action, eye movements, sleep, slow wave sleep, REM, orienting response, working memory

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INTRODUCTION

Eye Movement Desensitization and Reprocessing (EMDR) is a well-established psychological treatment for Post-traumatic Stress Disorder (PTSD) (Bradley et al., 2005; Chen et al., 2014). Furthermore, it has shown its efficacy in reducing anxiety levels in PTSD patients (Högberg et al., 2007, 2008; Bisson et al., 2013; Capezzani et al., 2013; McGuire et al., 2014; Faretta et al., 2016) and trauma-associated and psychiatric symptoms in various comorbid psychiatric diseases (Novo et al., 2014; Hase et al., 2015; Van Den Berg et al., 2015).

The neurobiological correlates of PTSD have been increasingly investigated by neuroimaging studies showing changes in cerebral blood flow (Bonne et al., 2003; Pagani et al., 2005; Lindauer et al., 2008; Nardo et al., 2011, 2015; for review see Bremner, 2007), metabolism (Pissiota et al., 2002; Osuch et al., 2008; Kim et al., 2012; Zhu et al., 2016), neuronal volume and density (Lindauer et al., 2004; Looi et al., 2009; Nardo et al., 2010, 2013; O'Doherty et al., 2015, 2017) and more recently in brain electric signal (Lee et al., 2014; Lobo et al., 2015), concordant with an involvement of the limbic system in the hyperarousal responsible for clinical symptoms. When reliving the traumatic events, the reduced control

of the prefrontal cortex over hyperreactive amygdala and hippocampus is thought to be the core functional mechanisms of PTSD (Shin et al., 2006; Etkin and Wager, 2007).

Several neuroimaging investigations have demonstrated the effect of EMDR on cortical and sub-cortical regions involved in PTSD, depicting a clear association between disappearance of symptoms and the normalization of brain changes (Lansing et al., 2005; Pagani et al., 2007, 2012, 2015; Nardo et al., 2010; Landin-Romero et al., 2013; Trentini et al., 2015; Laugharne et al., 2016; for review see Pagani et al., 2013). Whole session monitoring of cortical activations by EEG made EMDR the first psychotherapy in which neurobiological correlates have been depicted in real time (Pagani et al., 2011, 2012).

A strong demand for the need of knowing how EMDR works has followed and here we shortly describe some of the hypotheses.

The original theory of Adaptive Information Processing (AIP) proposed by Shapiro (2001) stated that humans have an innate information processing system that stores new experiences into existing memory networks in an adaptive state. Pathology arises when new information is inadequately processed and then stored in a maladaptive mode. When memories are adequately processed, symptoms can be eliminated and memories integrated.

The orienting and relaxation response (OR) hypothesis offers a theoretical framework which may support the explanation that bilateral stimulation produces relaxation. The OR is a natural attentional reflex that can occur with any novel environmental stimulus increasing readiness to respond to danger (Wilson et al., 1996; Barrowcliff et al., 2003, 2004). The initial freeze response is accompanied by changes in autonomic responses. In the absence of danger, it is rapidly replaced with a feeling of relaxation holding the potential to desensitize the traumatic memory, suppressing its associated disturbance. Eye movements (EMs) trigger an OR that can (i) facilitate access to the traumatic memory without avoidance and (ii) cause subsequent rapid extinction after the determination of no immediate threat (Armstrong and Vaughan, 1996).

The working memory account postulates that a central executive system is responsible for the integration of information stored in different slave subsystems, i.e., the visuospatial sketchpad processing visual and spatial information (Baddeley and Hitch, 1974; Hornsveld et al., 2010, 2011; van den Hout et al., 2010, 2011, 2012, 2013). The dual task (i.e., the EMs and the visual imagery) draws on the limited-capacity of the slave subsystems and on the central executive working memory resources. EMs, competing with and disrupting working memory resources, change the somatic perceptions, reduce vividness and decrease the emotionality of traumatic imagery.

The thalamic binding model (Bergmann, 2008) posits that bilateral stimulation facilitates the activation of the ventrolateral and central lateral thalamic nuclei *via* lateral cerebellum, facilitating the integration of somatosensory, memory, cognitive, emotional, and synchronized hemispheric functions that are disrupted in PTSD.

These studies assigned an important role to EMs, which seem to be not only the underpinning mechanism of EMDR complementing traumatic memory extinction, but also the factor accounting for a faster response to treatment compared to other psychotherapies (Nijdam et al., 2012).

It was recently highlighted (Pagani et al., 2012) that during successful EMDR therapy the cortical firing shifted from limbic structures toward regions with cognitive valence. In these studies, the occurrence of bilateral EMs was immediately accompanied by a synchronization of all cortical activity at a frequency in the delta range (**Figure 1**).

Despite these evidence, the role of EMs or, in general, bilateral stimulation in producing the neurobiological effects of EMDR is still unclear.

Based on this neurobiological evidence it is tempting to hypothesize a role of rapid eye movement (REM) and slow wave sleep (SWS) in the mechanism of action of EMDR. This follows the REM hypothesis for the mechanism of action of EMDR proposed by Stickgold (2002), according to which alternate bilateral stimulations typical of EMDR shift the brain into a memory processing mode similar to that of REM sleep.

Sleep has a bracing function, facilitates emotional processes and it is important for synaptic plasticity, emotional processing and memory formation. Long-lasting sleep disturbances are hallmark symptoms of PTSD that could interfere with a correct memory processing (Roszell et al., 1991; Leskin et al., 2002; Harvey et al., 2003) also causing functional and structural changes (Nardo et al., 2015).

PHYSIOLOGICAL BASIS OF SWS AND MEMORY CONSOLIDATION

To properly introduce our reasoning of a further role of SWS, it is essential to quote concepts and physiological bases well detailed in the works by Born et al. (2006) and Harper et al. (2009).

Memory recordings occurring during the waking state are temporarily stored in short-term memory and transferred to the neocortex during sleep. The combined episodic and emotional memory is replayed in the memory-editing matrix of the hippocampal-amygdalar complex as well as in neocortex during the first stage of SWS. In this process, memory is reinforced and extinguished by potentiation and depotentiation, respectively, of synapses of neurons recruited to form the memory chain. The excitatory glutamatergic pre-synaptic neurons release an amount of glutamate proportional to the strength of the signal. This in turn binds to the transmembrane α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (AMPA), mediating the fast-synaptic transmission in central nervous system (CNS) networks, as the memory trace system. The opening of AMPA allows positively charged sodium into the post-synaptic neuron causing its depolarization. Stronger and repeated signals, as occurs during memory formation, cause more AMPA receptors to be transferred onto the surface of the post-synaptic neuron resulting in a larger sodium influx and in the opening of N-Methyl-D-aspartate (NMDA) glutamate receptors. This in turn favors the influx of positively charged calcium further strengthening the signal transmission. Synapses of the memory track are then potentiated, generating new proteins and gene expression resulting in the growth of new

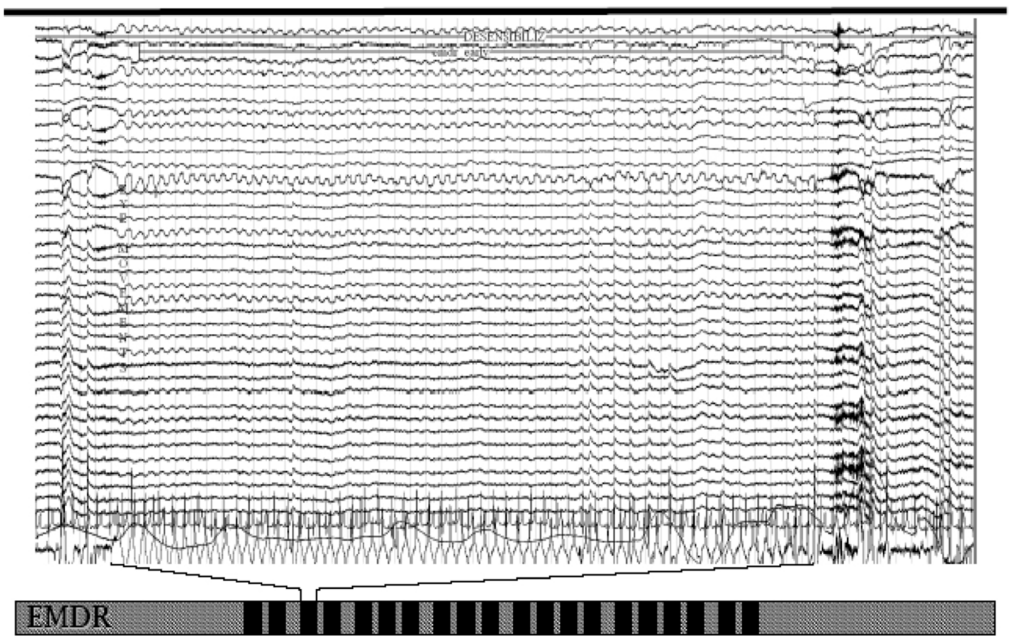

FIGURE 1 | EEG tracing upon eye movements during an eye movement desensitization and reprocessing (EMDR) session. Note the slow wave sleep (SWS)-like frequency from the beginning to the end of bilateral stimulation.

dendritic spines and new synaptic connections. The subsequent genetic expression and formation of permanent long-term memory occur mainly during REM sleep. In case of over-potentiation, low-frequency stimulation has a normalizing role depotentiating AMPA receptors, subsequently removed from the post-synaptic membrane, resulting in memory degradation. Following depotentiation, the receptors can no longer open and subsequently a substantial amount of them is removed from the post-synaptic membrane. The over-potentiated synapse is no longer able to convey the strong signals and henceforward is weakened. Potentiation and depotentiation (synaptic plasticity, adding or subtracting AMPA receptors) are carried out on synapses in the hippocampal-amygdalar complex and changes in their balance within the neural mechanisms of memory should be the molecular target for effective therapy.

Physiological normal sleep presents cyclic alternated pattern of REM and non-REM (SWS). EEG recordings show synchronous delta wave activity (0.5–4 cycles/s, i.e., 0.5–4 Hz) during SWS, and synchronous theta waves (4–8 Hertz) during REM sleep. SWS provides an optimal milieu for transferring edited memories from the hippocampus to the neocortex, as well as stimulating the integration of these into neocortical neuronal networks.

When new information is filtered by the sensorimotor cortex and simultaneously transferred to hippocampal networks, only the strong and repeated signals induce specific replication when the memory is replayed during SWS in the following night(s). During such phase, the cortical networks in which encoding originally took place produce slow oscillations (<1 Hz) that reactivate the hippocampal memory. This memory replay originates an input directed toward the same cortical synapses in synchronicity with high frequency activity originating in the thalamus. The combined action of these two signals, as described above, potentiates the synapses supporting the consolidation of long-term memory. In this phase, it is the combination and the alternation of slow and rapid waves that favors the transfer from hippocampus back to neocortex of the fresh memory encoded during the waking state. During REM sleep, also due to the absence of slow waves, there is a decrease of such activity suggesting a more intense memory consolidation at neocortical level. In this phase, new associations of emotional events mediated by limbic structures take place.

To summarize, during wakefulness autobiographical, emotional and potentially traumatic events are conveyed and represented into the sensorimotor cortex. From such perceptual representation system information are transferred to subcortical limbic structures as hippocampus (episodic) and amygdala (associated affect) where an initial formation and potentiation of memory occurs. During SWS global synaptic weakening along with slow consolidation of information take place. Relevant memory circuits are reactivated and long-term potentiation is induced. During REM sleep, a further potentiation of the reactivated connections in neocortical memory network occurs.

The recording of the episodic aspect of memory in the hippocampus results in a normal potentiation of hippocampal synapses. Traumatic events may cause over-potentiation of amygdalar synapses and all post-synaptic AMPA binding sites will be occupied by glutamate. In such circumstances, the transfer to neocortex mainly through anterior cingulate cortex cannot occur since memories need the same synchronized

signal intensity at emotional and cognitive level for the correct processing. Fragmented non-processed episodic and traumatic memories are trapped in hippocampus or amygdala without the contextual integration needed to encode them in long-term memory in association neocortex and persist sometimes for life.

THE LINK BETWEEN SWS AND BILATERAL STIMULATION IN EMDR

Bilateral stimulation typical of EMDR causes immediate slowing of the depolarization rate of neurons from the dominant waking state frequency of around 7 Hz to about 1.5 Hz (Harper et al., 2009; Pagani et al., 2011, 2012). The change of neuronal firing to low-frequency waves is a change from conditions favorable for synaptic potentiation to ones favorable for depotentiation.

In animals, low-frequency stimulation (5 Hertz) has shown to cause a depotentiation of amygdalar AMPA receptors involved in the retention of traumatic memory (Mao, 2006) and 900 stimuli at 1–5 Hz depotentiated synapses mediating memory (Kopp et al., 2006). This is about the number and the frequency of EMs during a typical EMDR session in which holding the attention on a traumatic memory targets the relevant synapses where it was originally encoded. It is worth noting that SWS occurs 3–5 times during night while bilateral stimulation is performed 25–30 times upon each EMDR session. This might account for the very fast processing of bad memories experienced by clients in a single or in a few EMDR sessions.

During EMDR sessions therapists performs bilateral stimulation at about 1–2 cycles/s (1–2 Hz) eliciting slow waves similar to the ones recorded during SWS. This suggests that memories aroused during therapy are continuously reactivated, replayed and encoded into existing memory networks.

A memory trace is weakened when held in attention and in such condition it is easily depotentiated. During an EMDR session the focus of the attention is on the fragmented traumatic memory and its synaptic traces in the amygdalar-hippocampal complex. EMDR decreases affective aspects of traumatic memories in the amygdala and leaves intact the associated cognitive aspects in the hippocampus. The affective and cognitive aspects of the memory are then merged in anterior cingulate cortex and sent to higher brain centers, where an encoding process within the association areas provide a clear distinction between the past and the present. The pathological memory trace is no longer confined by its over-potentiation to the limbic memory areas.

According to this model, desensitization indicated by the *D* in EMDR results from Depotentiation of fear memory synapses (Harper et al., 2009).

These speculations are supported by some recent neurophysiological findings. Harper et al. (2009) reported that, upon EMs, EEG tracing recorded in the delta range (1.5 Hertz) resembled the ones registered during SWS by Rétey et al. (2005). Such delta waves also paced β-waves (frequency of 13.5 Hertz), speaking in favor, during bilateral stimulation, of a general resonance in brain electric activity consonant with EMs. Recently, Pagani et al. (2011, 2012) in two separate investigations reported that the eye-movement component of EMDR induced an EEG pattern similar to the one described by Harper et al. (2009). This seems to confirm that the neurophysiological effect of bilateral stimulation by means of EMs or smooth pursuit (1–2 Hz) produces delta waves activity as during SWS (0.5–3 Hz).

It can be further speculated that the consolidation of emotional memory in neocortex during an EMDR session, often resulting in a sudden symptoms disappearance, is associated with periods in which slow (1.5 Hz) and fast (4–12 Hz, theta-alpha, typical waking state) waves are elicited by the alternation of bilateral stimulation and installation of positive cognition. This would mimic the previously described condition occurring during sleep in which memories are transferred from subcortical structures and encoded into neocortex.

If confirmed by future studies, the molecular and neurobiological mechanisms underlying our model could merge the effects explained by the OR theory, by the working memory account and by the hypothesis of Stickgold (2008).

In fact, we posit that bilateral stimulation mimics the low-frequency stimulation typical of SWS, inducing a depotentiation of the AMPA receptors of amygdalar synapses, which in turn lead to a weakening of the traumatic memory. This reduction of the over-potentiation of amygdalar synapses makes traumatic memory more accessible, and facilitates the connection between emotional memory and episodic memory, thus promoting a shift of memory to associative and neocortical areas. This is also consonant with the findings of Pagani et al. (2012) that showed in EMDR a shift of the traumatic memories from an implicit subcortical status to cortical regions that integrate them into existing semantic memory. Moreover, the depotentiation caused by low-frequency stimulation (i.e., EMDR bilateral stimulation) results in memory degradation and weakening, thus exerting the effect of reducing the vividness and emotionality of the traumatic memory, finally promoting a detachment from the past traumatic event.

These effects are the same described in clinical setting by the OR and the working memory models.

In assonance with OR hypothesis, delta waves elicited by bilateral stimulation facilitate the access to the dysfunctionally stored traumatic memory during wake consciousness. Thanks also to the absence of danger characterized by the therapeutic context, favoring relaxation, the extinction of traumatic memory and its reprocessing by associative and cortical areas could take place. The relaxation associated with the fading of the emotional memory is likely due to the reduction of the over-potentiation of amygdalar synapses occurring in real time during EMDR therapy.

Our speculation is also in agreement with the working memory account, since the effects of SWS-like neurophysiological conditions reproduced by EMDR bilateral stimulation, reducing in real time the over-potentiation of the amygdala and the relative hyperarousal, impact during therapy on vividness and on emotionality of traumatic memories, contributing to the sense of distancing from the original event described by patients.

Both models are based on the weakening of a memory when recalled and held in attention, but with different underlying explanations. In the working memory account, the imagery deflation effect is explained by the dual tasking (i.e., the competition between recall of the memory and the bilateral stimulation task) that affect the limited-capacity of the working memory. In our SWS model, memory degradation is determined by the depotentiation of AMPA receptors by EMDR bilateral stimulations miming SWS low-frequency stimulations occurring during sleep.

Lastly, our hypothesis follows the footsteps drawn by Stickgold (2002, 2008), deepening the role of SWS-like state induced by EMDR bilateral stimulation which promotes the transfer of episodic memory to semantic memory, that will be then consolidated during REM-like states.

Hippocampal-amygdala complex memories are transferred to neocortex, replayed, and consolidated into semantic associative memory networks. Information is then integrated to create meaning and learning from the event. The transfer might occur during slow-wave-sleep (1–3 Hz) and definitive memory consolidation during REM sleep (about 4–6 Hz). The traumatic episodic memory is weakened and then removed from hippocampus.

CONCLUSION

In conclusion, this perspective article proposes that bilateral stimulation during EMDR might reproduce the neurophysiological conditions favorable for memory integration in associative neocortex, weakening the perception of the traumatic memory, reducing its vividness and inducing a sense of relaxation and safety.

Quoting Stickgold (2002): "*We are not claiming that we have solid evidence for all of the links and interpretations in the train of logic presented here.[. . .] Our goal is to demonstrate that there is a reasonable explanation of how EMDR works, which is consonant with modern neurobiology and cognitive neuroscience[. . .].*"

Our aim is also to encourage further research in investigating the mechanisms of action of already proven effective psychotherapies such as EMDR, with experimental studies that might combine theoretical assumptions, molecular biology, neurophysiology, neuropsychology, brain imaging and clinical evidences in patients' cohorts.

AUTHOR CONTRIBUTIONS

MP was responsible for the conception of the work, that was integrated and critically revised by SC, BA, and RL-R. All authors have approved the final manuscript.

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Conflict of Interest Statement: All authors have been invited as speakers in national and international EMDR conferences.

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SYSTEMATIC REVIEW
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How Does Eye Movement Desensitization and Reprocessing Therapy Work? A Systematic Review on Suggested Mechanisms of Action

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Background: Eye movement desensitization and reprocessing [EMDR] is an innovative, evidence-based and effective psychotherapy for post-traumatic stress disorder [PTSD]. As with other psychotherapies, the effectiveness of EMDR contrasts with a limited knowledge of its underlying mechanism of action. In its relatively short life as a therapeutic option, EMDR has not been without controversy, in particular regarding the role of the bilateral stimulation as an active component of the therapy. The high prevalence of EMDR in clinical practice and the dramatic increase in EMDR research in recent years, with more than 26 randomized controlled trials published to date, highlight the need for a better understanding of its mechanism of action.

Methods: We conducted a thorough systematic search of studies published until January 2018, using PubMed, ScienceDirect, Web of Knowledge and Scopus databases that examined the mechanism of action of EMDR or provided conclusions within the framework of current theoretical models of EMDR functioning.

Results: Eighty-seven studies were selected for review and classified into three overarching models; (i) psychological models (ii) psychophysiological models and (iii) neurobiological models. The evidence available from each study was analyzed and discussed. Results demonstrated a reasonable empirical support for the working memory hypothesis and for the physiological changes associated with successful EMDR therapy. Recently, more sophisticated structural and functional neuroimaging studies using high resolution structural and temporal techniques are starting to provide preliminary evidence into the neuronal correlates before, during and after EMDR therapy.

Discussion: Despite the increasing number of studies that published in recent years, the research into the mechanisms underlying EMDR therapy is still in its infancy. Studies in well-defined clinical and non-clinical populations, larger sample sizes and tighter methodological control are further needed in order to establish firm conclusions.

Keywords: eye movement desensitization and reprocessing, mechanism of action, eye movements, bilateral stimulation, systematic review

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INTRODUCTION

While the methodology that guides the Eye Movement Desensitization and Reprocessing [EMDR] intervention has been clinically validated, its mechanism of action remains elusive. Since the early 90's, different speculative theories, models and hypotheses have been proposed (with ever growing sophistication) to explain the neurobiological underpinnings of EMDR. Furthermore, the growing popularity of EMDR as evidenced by the increasing number of studies available in research databases, suggests that a systematic review is timely. Finally, the implementation of EMDR in clinical practice before unraveling its mechanism of action has motivated stark criticism by some authors (Herbert et al., 2000).

The current manuscript have two main aims. The first aim is to provide an overview of the development of EMDR over the last 25 years, including the procedural aspects of EMDR and current controversies about its efficacy. The second aim is to conduct a systematic review of the theoretical hypotheses and available empirical evidence regarding the mechanism of action of EMDR.

The Development of Eye Movement Desensitization and the First Study

The year 2014 marked the 25th anniversary of the introduction of EMDR, a relatively novel psychotherapy now well-established and recognized internationally as an empirically supported treatment for trauma. The American psychologist Francine Shapiro first developed EMDR upon her chance observation while walking through a park that certain saccadic eye movements [EMs] reduced the intensity of disturbing thoughts. She then noticed that bringing the EMs under voluntary control while thinking about a distressing memory reduced the anxiety associated to it. Shapiro then conducted a randomized controlled trial in which she administered one session of eye movement desensitization [EMD] to 22 patients suffering from traumatic memories (Shapiro, 1989a,b). The results of this study indicated that EMD successfully desensitized traumatic memories and decreased anxiety levels in traumatized subjects when compared to a control group that received a procedure similar to flooding. This effect was followed by a significant improvement in the negative cognitions associated with the traumatic memories, characterized by an increase in the appraised validity of a positive self-belief. These results were further maintained after 1 and 3 months of follow-up.

From EMD to EMDR: The Standard EMDR Therapy Protocol

Shapiro's initial studies supported the hypothesis that EMs facilitated the desensitization of trauma memories (Shapiro, 1989a). In subsequent years, EMD grew into EMDR in recognition of its hypothesized memory reprocessing effects, and evolved toward a structured eight-phase approach using standardized procedures to address the past, present, and future aspects of a traumatic memory (Shapiro, 2001). The traumatic memory is composed of a set of multi-sensory images, negative cognitions, negative emotions, and related unpleasant physical sensations. The EMDR therapy standard protocol includes the following preparation steps: history and treatment plan [Phase I], preparation phase with an introduction to the EMDR protocol and development of coping strategies [Phase II], and an assessment phase with visualization of an image of the traumatic incident, identification of beliefs and emotions associated with the disturbing event, rating of disturbance recalling the traumatic incident, and rating the validity of preferred cognitions of the client (Phase III). The desensitization and reprocessing takes place within Phase IV and represents the core component of the intervention: the client focuses on a dual attention stimulus - generally eye movements- while holding in mind the image, thoughts and/or sensations associated with the disturbing memory. Bilateral tactile taps or auditory tones are used instead of eye movements for clients who have difficulty in visual tracking. Following each brief set of bilateral stimulation (BLS), the client is asked to identify the associative information that was elicited. Following standardized procedures, this new material usually becomes the focus of the next set. BLS is also used during Phase V, which aims to incorporate and strengthen a positive cognition to replace the negative cognition associated with the trauma, as well as in Phase VI which entails the body scan to reprocess any remaining bodily sensations. In Phase VII the client is guided through relaxation techniques designed to re-establish emotional stability if distress has been experienced, and for use between sessions. Finally, the phase of re-evaluation [Phase VIII] involves identifying outcomes from the prior session. At this point, the therapist will decide whether it is best to continue working on previous targets or continue with newer ones. The length of an individual treatment session is typically 50–90 min, and single memories are typically processed within one-to-three sessions. Based on feedback from clinicians and patients alike, the completion of the EMDR standardized protocol is a cognitively demanding task and requires attention, self-consciousness, autobiographical semantic memory, and metacognition to successfully identify the potential dysfunctional processes underlying the traumatic memory.

Evidence for the Efficacy of EMDR in PTSD and in Other Comorbid Mental Disorders

In spite of initial controversies, the efficacy of EMDR treatment for PTSD is now well documented (e.g., Shepherd et al., 2000; Davidson and Parker, 2001; Bradley et al., 2005; Novo Navarro et al., 2016). Since the original observation of Shapiro, over 300 studies have examined the clinical application of EMDR and several meta-analyses have shown higher or similar efficacy in PTSD compared to pharmacological or other psychological interventions (Born et al., 2006; Bisson et al., 2007, 2013; Chen et al., 2014). EMDR is now recognized by the National Institute for Health and Clinical Excellence (Born et al., 2005) and the World Health Organization (Born et al., 2013) as a treatment of choice for post-traumatic stress disorder. The accumulating evidence on how trauma and life events–adverse or not–can become causal factors in the etiology of different psychological disorders (Lytle et al., 2002; Christman et al., 2003; Lohr et al., 2003; Taylor et al., 2003; Van Loey and Van

Son, 2003) is motivating clinicians and practitioners to offer EMDR as a comprehensive therapy for different conditions, regardless of whether there is evidence of diagnosis of PTSD, or comorbid traumatic memories. As such, evidence for a variety of EMDR therapy applications has recently been reported in randomized controlled trials of bipolar disorder (Novo et al., 2014; Moreno-Alcázar et al., 2015), psychosis (van den Berg et al., 2015a,b), unipolar depression (Hase et al., 2015), dental phobia (Doering et al., 2013), obsessive compulsive disorder (Nazari et al., 2011), panic disorder (Faretta, 2012), alcohol dependency (Perez-Dandieu and Tapia, 2014), and pain management (Tesarz et al., 2014).

The Adaptive Information Processing Model

The Adaptive Information Processing (AIP) model is the theory that guides the EMDR treatment procedures and offers an explanation for the basis of pathology (Shapiro, 1994, 2001, 2007). This model postulates that humans have an innate information processing system that assimilates new experiences and stores them into existing memory networks in an adaptive state. These networks link the thoughts, images, emotions, and sensations associated with experiences. According to the AIP model, pathology arises when new information is inadequately processed and then stored in a maladaptive mode in the memory networks, along with associated distorted thoughts, sensations and emotions. Thus, external stimulation similar to the adverse experience can trigger sensations and images from the traumatic event so that the person re-experiences feelings or bodily sensations. If these memories remain unprocessed, they become the basis of the symptoms of PTSD. Conversely, AIP theory hypothesizes that when the memories are adequately processed, symptoms can be eliminated and integrated. Shapiro proposed that EMDR can assist in processing the traumatic memories, and that different forms of bilateral stimulation such as the EMs, would facilitate this processing (Shapiro, 2001; Shapiro and Maxfield, 2002).

Controversies Surrounding EMDR Therapy

Since its inception, EMDR has generated a considerable debate, particularly regarding the role of the EMs as an active ingredient of treatment. Similarly, there is ongoing controversy on whether the underlying mechanisms in EMDR differ substantially from those operating in trauma-focused cognitive-behavioral therapy [tfCBT] and standard exposure.

The use of a dual attention tasks is perhaps one of the most distinctive elements of EMDR. As described above, this involves the client focusing on the worst image of a traumatic memory while concurrently engaging in an external task, typically following the therapist's fingers using rhythmic, bilateral, saccadic EMs. The EMs were originally described as the "crucial component" of EMDR (Shapiro, 1989a,b). Some studies are suggestive of a unique contribution of the EMs to successful treatment (Andrade et al., 1997; Kavanagh et al., 2001; van den Hout et al., 2001; Lee and Drummond, 2008), while others have not find clear differences in the outcome comparing EMDR with and without EMs (Cahill et al., 1999; Davidson and Parker, 2001). Head-to-head comparison between the results of these early studies is not possible as they differ considerably in terms of design, samples and outcome measures. Therefore, some authors argue that the claims of no significant effect of the EMs on treatment outcome are unwarranted (Jeffries and Davis, 2013). In recent years, studies have found accumulating evidence on the contribution of BLS (and in particular the EMs) to treatment gains, including a meta-analysis of 26 randomized controlled trials that found a significant contribution of the EMs in processing emotional memories (Lee and Cuijpers, 2013). Research has also found that other forms of BLS, such as bilateral tactile taps or auditory tones, are also effective methods of reducing vividness in trauma (van den Hout et al., 2011b; de Jongh et al., 2013). This evidence led Shapiro to conclude that dual attention may be the mechanism responsible for the treatment gains rather than any effect unique to the EMs (Shapiro and Laliotis, 2015).

A second contentious issue in EMDR revolved around the potential overlap with other psychotherapies, in particular with tfCBT. While tfCBT consists of exposure techniques combined with cognitive interventions, EMDR is an eclectic form of psychotherapy that incorporates structured procedures and protocols. Although many of the EMDR procedures appear to overlap with tfCBT, the UK National Institute of Health and Clinical Excellence [NICE] has stated that these two approaches are different since specific training programs are required [NICE, 2005, p. 55]. Like tfCBT, EMDR aims to reduce subjective distress and strengthen adaptive cognitions related to the traumatic event. Unlike tfCBT, EMDR does not involve (i) detailed descriptions of the event, (ii) direct challenging of beliefs, (iii) extended exposure, or (iv) homework. Rogers and Silvers have described in detail the differences between how exposure (a key component of tfCBT) and EMDR protocols are employed (Rogers and Silver, 2002). Evidence has grown in recent years that EMDR therapy produces diverse and compelling treatment effects, including a reconsolidation of memory structures through mechanisms that differ from those of traditional exposure therapy (Lee et al., 2006; Ecker et al., 2012). Ultimately, the debate on the overlap between EMDR and tfCBT is flawed, at least in terms of their underlying mechanisms of action, given the limited knowledge of the impact of different psychotherapies on neurobiological changes associated with PTSD and other anxiety disorders.

Objectives and Importance of the Current Review

Previous systematic reviews and meta-analyses of EMDR have been limited to specific elements and hypotheses or were non-systematic in nature (Gunter and Bodner, 2009; McGuire et al., 2014). Some examples of this are reviews focusing on the effect of the EMs on the therapy (Jeffries and Davis, 2013; Lee and Cuijpers, 2013), and on the physiological (Elofsson et al., 2008) and the neurobiological correlate of EMDR (Bergmann, 2008; Pagani et al., 2013). In the current work, we have conducted a comprehensive review of the literature that examined different

hypothesis for the mechanism of action of EMDR using the PRISMA guidelines for transparent reporting of reviews and meta-analyses. PRISMA is an evidence-based minimum of 27 items grounded on evidence that establishes the minimum criteria for reporting systematic reviews. Although it focuses on reporting reviews of randomized controlled trials, it can also be used as a basis for reporting systematic reviews of other types of research (Moher et al., 2009).

METHODS

Studes examinig the mechanism of action of EMDR were identified using PubMed, ScienceDirect, Web of Knowledge and Scopus databases. The systematic literature search included studes published from 01/01/1989 until 31/12/2017 based on the PRISMA guidelines (**Supplementary Data Sheet**). The search terms were selected from the thesaurus of the National Library of Medicine (Medical Subject Heading Terms, MeSH) and the American Psychological Association (Psychological Index Terms) and included the terms "eye movement desensitization and reprocessing," "EMDR," "mechanism," "action," "effects," and "correlates." The final search equation was defined using the Boolean conectors "AND" and "OR" following the formulation: ("eye movement desensitization and reprocessing" OR "EMDR") AND ("mechanism" OR "action" OR "effects" OR "correlates"). The automatic search was later completed with a manual search using reference lists of included papers and web-based searches in an EMDR-centered library (https://emdria.omeka.net/). Titles, abstract, methods and results of the articles identified were screened for pertinent information. Reference lists of eligible articles and relevant review articles were also screened for potential publications for inclusion. The search did not include any subheadings ot tags (i.e., search fields "All fields"). Due to the significant heterogeneity of the studies, a formal quantitative synthesis (i.e., meta-analysis) was not possible. Instead, a systematic review was conducted, using the PRISMA guidelines as referenced above.

Inclusion Criteria and Exclusion Criteria

The final selection of research articles was conducted using the following criteria: (i) original articles published in peer-reviewed journals, (ii) in adult populations that (iii) examined the mechanism of action of EMDR and/or (iv) any form of BLS (EM, tactile, sound) within the EMDR protocol or (v) provided conclusions regarding the potential mechanism of action of EMDR. Selected theoretical, speculative papers were also included if they were first to provide an mechanistic hypothesis for EMDR to guide future empirical research. The criteria for exclusion were: (i) articles that did not contain original research (i.e., reviews and meta-analyses, guidelines and/or protocols), (ii) clinical trials and/or focus on treatment gains or efficacy and (iii) empirical studies with quasi-experimental designs (single case and/or no control group). The studies were selected by RL-R and AM-A. Discrepancies were resolved by MP and BLA (**Supplementary Table 1**).

RESULTS

Figure 1 shows a flow-chart for the selection of eligible studies. The search strategy initially identified 841 studies thorugh database searching and 20 additional studies through manual searches in other sources (i.e., Shapiro Libray). After removing duplicates ($n = 394$), RL-R, and AM-A screened titles and abstracts and excluded studies that were considered non-pertinent ($n = 74$). If inclusion criteria were met, the full text article was retrieved and screened in full for the analysis.

A total of 87 studies written in English met the inclusion criteria and were selected for review. The studies were classified into broad categories according to three overarching models/hypothesis for the mechanism of action underlying EMDR: (i) psychological models (ii) psychophysiological models and (iii) neurobiological models. A summary of the main characteristics of each study, including participants, methods, sample size, control conditions, study design, outcomes and conclusions can be gathered from **Tables 1–3**.

DISCUSSION

Psychological Models

Classic Conditioning: Orienting and Relaxation Responses

Dyck was the first author to provide an account of the underlying mechanism of EMDR, largely in terms of classic conditioning theory (Dyck, 1993). He argued that re-experiencing the trauma in the context of the desensitization session would operate as an extinction trial of the traumatic experience. Unfortunately, Dyck did not back up this hypothesis with empirical data. Other psychological models have attempted to explain the treatment gains of EMDR through similar learning and adaptive mechanisms, such as the orienting response (OR). Pavlov first described the orienting (or investigatory) response in 1927. The OR is a natural attentional reflex that can occur with any novel environmental stimulus and produces a specific set of changes that increase readiness to respond to danger. The OR toward any stimulus that constitute a potential threat manifests itself as an initial freeze response accompanied by changes in autonomic responses that include increased blood flow, heart rate, and skin conductance. In the absence of danger, this initial response is rapidly replaced with a feeling of relaxation. According to some authors, this relaxation response holds the potential to desensitize the traumatic memory, suppressing its associated disturbance. Armstrong and Vaughan used this idea to propose an extinction model whereby the EMs trigger an orienting response that (i) facilitates access to the traumatic memory without avoidance and (ii) causes subsequent rapid extinction after the determination of no immediate threat (Armstrong and Vaughan, 1996).

Similarly, MacCulloch and Feldman (1996) and Wilson et al. (1996) proposed a combination of Pavlovian and Darwinian theories whereby the dual attention task provoked by the EMs serves to trigger an OR. This OR pairs an adaptive explorative response with clinically induced unpleasant memories to remove their negative effect. These authors have suggested a similar role to other forms of BLS (i.e., tactile or auditory) in eliciting

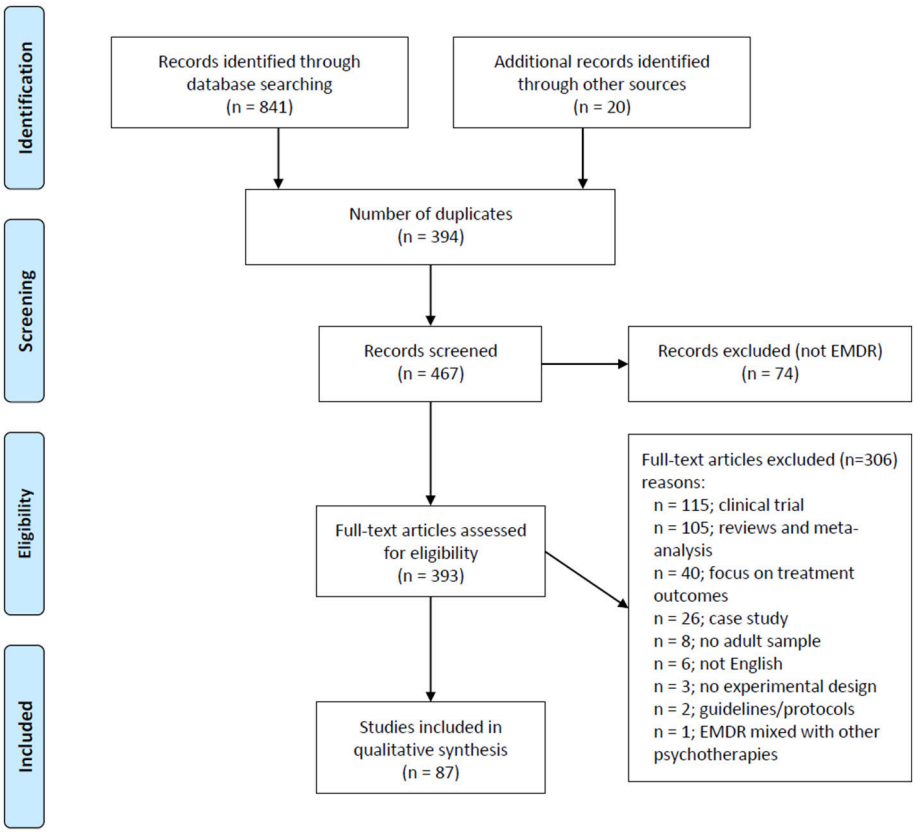

FIGURE 1 | Flow chart for the selection of eligible studies.

the OR. This initial analysis has been followed by several psychophysiological studies that have leaned support to the central role of the OR as the underlying mechanism of EMDR, using EMs only (Kuiken et al., 2002; Barrowcliff et al., 2003, 2004) and the full EMDR protocol (Aubert-Khalfa et al., 2008; Sack et al., 2008; Schubert et al., 2008; Frustaci et al., 2010), mostly in healthy individuals but also in clinical populations (Schubert et al., 2016). The results of these studies are summarized in the corresponding section for psychophysiological models.

The Working Memory Account

In 1974, Baddeley and Hitch introduced the multicomponent model of working memory (Baddeley and Hitch, 1974). This theory proposes a "central executive" system responsible for the integration and coordination of information stored in different slave subsystems. One of these subsystems is the phonological loop, which stores verbal and auditory information. Another is the visuospatial sketchpad, which stores visuospatial information. According to the working memory model, during EMDR sessions, memories are held in the visuospatial sketchpad. The working memory hypothesis suggests that the dual task (i.e., the EMs and the visual imagery) draw on the limited-capacity of the visuospatial sketchpad and central executive working memory resources. The competition in resources will impair imagery, and as such, the disturbing images would become less emotional and vivid. The working memory account also argues that the degradation of a traumatic image held in working memory provides patients with a healthy sense of distance from a traumatic event.

Sharpley et al. were the first to introduce the idea that the effect of EMDR is mediated by the distancing from the traumatic memory and the reduction of imagery vividness (Sharpley et al., 1996b). Years later, researchers would demonstrate that this effect is mediated by the EMs disrupting working memory resources, thereby reducing vividness and decreasing the emotionality of traumatic imagery (Andrade et al., 1997; Kavanagh et al., 2001). Follow up studies also found a significant role of EMs in the emotional detachment from traumatic memories (Baddeley and Andrade, 2000; van den Hout et al., 2013). In support of taxing working memory resources, analog research proved that implementing other demanding tasks during recall also reduced vividness and emotionality of negative memories (Engelhard et al., 2010b; de Jongh et al., 2013). Research on the working memory hypothesis has consistently demonstrated that performance is degraded when participants engage in two simultaneous tasks that require the same working memory resources, suggesting that the EMs in EMDR impairs the ability to hold a visual image in conscious awareness, resulting in the

TABLE 1 | Psychological models ($n = 32$).

Author, year	Type of study	Sample (*n*)	EM/Full protocol	Control condition	Main findings	Conclusions
THE ORIENTING AND RELAXATION RESPONSE						
Dyck, 1993	Speculative theory	NA	NA	NA	NA	Classic conditioning theory as a framework for the effects of EM in traumatic memories.
Armstrong and Vaughan, 1996	Speculative theory	NA	NA	NA	NA	The EM trigger an OR that facilitates attention to the trauma memory without avoidance.
MacCulloch and Feldman, 1996	Speculative theory	NA	NA	NA	NA	Combination of Pavlovian and Darwinian theory to explain the effectiveness of EMDR. Positive elements of the OR are paired unpleasant memories to remove their negative effect.
Wilson et al., 1996	Empirical study	HC ($n = 18$)	Full protocol	Full protocol with no EM Tapping	EMDR group showed desensitization. Autonomic changes during EMDR compatible with a relaxation response.	The EMDR therapeutic effect is provoked by pairing distress with an unlearned relaxation response.
Kuiken et al., 2010	Empirical study	HC ($n = 101$)	EM	No EM	Rapid bilateral EM activate the orienting response and, by doing so, facilitate attention to and comprehension of figurative, especially metaphoric, expressions.	Rapid EM in the EMDR protocol prompt novel shifts in memory (e.g., diminution of threat), belief (e.g., recognizing unintentional responsibility), and emotion (e.g., changing fear to anger).
THE WORKING MEMORY ACCOUNT						
Sharpley et al., 1996b	Empirical study	HC = 24	EMDR	Rapid Induction Relaxation	EMDR reduced the vividness more significantly vs. control conditions.	EMDR reduces the vividness of a memory-based image.
Andrade et al., 1997	Empirical study	Exp 1:HC = 46 Exp 2: HC = 18 Exp 3: HC = 30 Exp 4: HC = 24	EM	Fixed eyes Tapping No dual task	EMs reduced vividness and emotiveness of trauma vs. control conditions.	EMDR effects are mediated by the visuospatial sketchpad of working memory.
Kavanagh et al., 2001	Empirical study	HC = 18	EM	Visual noise Exposure alone	EMs reduced vividness and emotiveness of trauma vs. control conditions.	A visuospatial task (e.g. EMs) offer a temporary response aid for imaginal exposure without affecting desensitization.
van den Hout et al., 2001	Empirical study	HC = 60	EM	Finger tapping No dual task	EMs reduced vividness of positive and negative recollections.	The effect of EMs is mediated by VSSP taxation.
Gunter and Bodner, 2008	Empirical study	Exp 1: HC = 36 Exp 2: HC = 36 Exp 3: HC = 72	EM	Stationary eyes Horizontal EMs Auditory shadowing Drawing	Vertical and horizontal EMs reduce vividness and increase arousal.	The central executive of the WM is taxed when a person performs a distractor task while attempting to hold a memory in mind.
Maxfield et al., 2008	Empirical study	Exp 1: HC =24 Exp 2: HC =36	EM	No EM Slow EM Fast EM	Fast EMs produce significant decrease of emotional intensity.	The decrease of emotional intensity is mediated by competition for WM resources
Lilley et al., 2009	Empirical study	HC = 18	EM	Counting No concurrent task	EMs reduces vividness and emotionality.	Concurrent tasks matched to the modality of trauma images lessening emotional responses to recollections of trauma.

(Continued)

TABLE 1 | Continued

Author, year	Type of study	Sample (*n*)	EM/Full protocol	Control condition	Main findings	Conclusions
van den Hout et al., 2011b	Empirical study	HC = 15	EM	Bilateral "beeps"	EMs slow down reaction times to auditive cues.	The effect of beeps on taxing negative memories are inferior to those of EMs.
Kristjánsdóttir and Lee, 2011	Empirical study	HC = 36	EM	Counting	Vividness and emotionality significantly decreased after EMs and counting, with EMs producing the greatest effect irrespective memory modality.	Results are consistent with the taxation of the central executive of WM.
van den Hout et al., 2012	Empirical study	PTSD = 12	EM	Beeps Recall only	EMs are better than tones in reducing vividness. Tones are better than recall only.	Results support for WM model. Tones may outperform EMs in cases where trauma memories are vague.
Smeets et al., 2012	Empirical study	HC = 61	EM	Eyes stationary	EMs outperformed eyes stationary condition in reducing vividness first and then emotionality.	Emotionality is reduced only after vividness has dropped.
van den Hout et al., 2013	Empirical study	HC = 32	EM	Eyes stationary	In the EM group, self-rated vividness of the recalled+EM picture decreased, relative to the non-recalled picture. In the no-EM group there was no difference between the recalled versus non-recalled picture.	Reduction of memory vividness due to recall+EM is also evident from non-self-report data.
Novo Novo Navarro et al., 2013	Empirical study	HC = 50	EM	Eye rest condition	No significant differences between EM and fixed eye condition in recall.	EM did not improve auditory and visual consolidation of memory, undermining this WM taxing as a mechanism of action of EMDR
de Jongh et al., 2013	Empirical study	PTSD = 32 Other mental disorder = 32	EM	Tones Eye rest condition	Effects of EMs >tones > recall only.	EM effects of taxing WM on disturbing memories do no differ between PTSD and other metal disorders.
Leer et al., 2014	Empirical study	HC = 73	Recall with EM	Recall only	Recall with EM decrease vividness vs. recall only.	Recall with EM causes 24-h changes in memory vividness/emotionality.
van den Hout et al., 2014	Empirical study	HC = 40	Recall with EM	Recall only	Negative memories are rated as less vivid after "recall + EM" but not after "recall only". This was not found for neutral memories.	Emotional memories are more taxing than neutral memories.
Leer et al., 2017	Empirical study	HC (*n* = 26)	EM	Recall with no EM	EM slow down reaction time in a stimulus discrimination task.	EM during recall attenuates memory performance and renders stimulus attributes less accessible
van Veen et al., 2016	Empirical study	HC (*n* = 108)	EM	Recall with no EM	EM showed a larger decrease in self-reported vividness and emotionality than control conditions.	Recall of an aversive memory loads working memory but drops in vividness and emotionality do not immediately reduce the cognitive load of recalling the memory
van Schie et al., 2016	Empirical study	HC (*n* = 66)	EM	recall + slow EM, and recall + fast EM	Speed differences of EM do not affect recall. Cognitively demanding dual task increases the intervention's effectiveness.	Adjusting EM speed is not helpful to reduce emotionality of aversive memories.

(Continued)

TABLE 1 | Continued

Author, year	Type of study	Sample (*n*)	EM/Full protocol	Control condition	Main findings	Conclusions
van Veen et al., 2015	Empirical study	HC (*n* = 106)	EM	recall + fast EM, recall + slow EM, or recall only	recall + fast EM led to less emotional, less vivid and more difficult to retrieve images than recall + slow EM and recall only.	Results support the WM theory: the more taxing a dual-task is, the more a memory image degrades
Engelhard et al., 2010a	Empirical study	HC = 28	EM	Exposure	EMs reduce vividness of past and future feared events.	Taxing of WM provokes degradation of visual imagery about feared future events.
Engelhard et al., 2010b	Empirical study	HC = 60	EM	Tetris game	EMs and Tetris draw on WM, vs. a no dual-task. Compared to recall only, EM and Tetris both decreased emotionality.	Both EMs and Tetris tax WM.
Engelhard et al., 2011	Empirical study	HC = 37	EM	Stationary eyes recall	Recall + EMs reduces vividness and emotionality vs. recall only.	EMs affect intrusive images about the future.
Onderdonk and van den Hout, 2016	Empirical study	HC (n = 17)	EM	Visual task analogous to EM	Study 1 found that RT was slowest in the EM condition. Study 2 found decreases in memory vividness and emotionality after EM. The visual analogous task was similar to the control condition.	Performing EM taxes more WM resources and has greater impact on both memory vividness and emotionality than analogous visual tasks. This demonstrates that the effects observed in EMDR treatment are the result of more than occupying WM systems with visual stimuli alone.
Boukezzi et al., 2017b	Empirical study	HC (n = 18)	BLS coupled with positive/negative conditioning	positive/negative conditioning without BLS	Fear extinction were facilitated by BLS and associated with reduced skin conductance.	The BLS effect during fear extinction may rely on taxation of working memory, reducing vividness and emotionality, or may provoke memory reconsolidation.
Littel et al., 2017b	Empirical study	HC (*n* =74)	EM	Recall with no EM	In the absence of arousal, neutral memory vividness did not decrease after recall + EM relative to recall only.	Results of the current study indicate that arousal is a prerequisite for the effectiveness of dual task interventions.
Patel and McDowall, 2017	Empirical study	HC (*n* =31)	EM	Recall with no EM	Fast eye movements lowered vividness but not emotionality self-ratings ratings.	Extension to the working memory explanation. The eye movements lower the number of intrusive thoughts of negative memories during suppression.

EM, eye movements; EMDR, eye movement desensitization and reprocessing; HC, healthy controls; NA, not applicable; OR, orienting response; PTSD, posttraumatic stress disorder; VSSP, visuospatial sketchpad WM, working memory; BLS, bilateral stimulation.

TABLE 2 | Psychophysiological models ($n = 18$).

Author, year	Type of study	Sample (n)	EM/Full protocol	Control condition	Main findings	Conclusions
Kuiken et al., 2002	Empirical study	HC ($n = 25$)	EM	Visual fixation (noEM)	EM facilitates attentional and semantic flexibility.	EM induced attentional and semantic flexibility facilitates OR and transformations in the clients traumatic memory.
Barrowcliff et al., 2003	Empirical study	HC ($n = 18$)	EM	Visual fixation (noEM) High-low frequency tones Attentional task	Lower levels of electrodermal arousal were identified in EM compared to noEM.	EM facilitate a process of psycho-physiological de-arousal
Barrowcliff et al., 2004	Empirical study	HC ($n = 80$)	EM	Stationary eyes (noEM)	EM resulted in decreased psychophysiological response and reductions on vividness and emotionality in positive and negative memories.	EM facilitate a process of psycho-physiological de-arousal
Aubert-Khalfa et al., 2008	Empirical study	HC = 6	EMDR	Pre-post treatment Within-group	Post-treatment reductions of clinical scores and psychophysiological response.	Successful EMDR treatment reduces psychophysiological arousal associated with trauma
Elofsson et al., 2008	Empirical study	PTSD ($n = 13$)	EMDR	NA	Psycho-physiological changes compatible with de-arousal during EMDR.	EM during EMDR activate cholinergic and inhibit sympathetic systems, similarly to the changes observed during REM sleep
Schubert et al., 2008	Empirical study	PTSD ($n = 10$)	EMDR	NA	EMDR provokes (i) an increase of psychophysiological response at stimulation onsets and (ii) stress related arousal during ongoing stimulation. Across the entire EDMR significant decreases of psycho-physiological activity was observed.	EMDR is associated with autonomic de-arousal over time
Sack et al., 2008	Empirical study	PTSD ($n = 10$)	EMDR	NA	Treatment with EMDR was followed by a significant reduction of subjective disturbance; trauma related symptoms and reduced psycho-physiological reactivity.	The successful processing of trauma mediated by repetitive ORs causes an habituation of the psycho-physiological response.
Frustaci et al., 2010	Empirical study	HC (sub-syndromal PTSD) = 4	EMDR	Pre-post treatment Within group	EMDR decreased symptoms and increased parasympathetic tone.	Results support physiological de-arousal reductions driven by EMDR also in sub-syndromal PTSD.
Kapoula et al., 2010	Empirical study	HC ($n = 7$)	EMDR	NA	EMDR decrease the number of saccade intrusions and increase the smooth components of the ocular pursuit.	EMDR reduces distress mediated by cholinergic effects known to improve ocular pursuit.
Hornsveld et al., 2010	Empirical study	HC ($n = 60$)	EM	recall + noEM; recall + music	Greater decline in emotionality and concentration after EM compared to recall-only and recall-with-music.	EM reduce vividness resulting in detachment from the trauma.
El Khoury-Malhame et al., 2011	Empirical study	HC ($n = 19$)	EMDR	Emotional Stroop Target detection task	EMDR contributes to removal of PTSD symptoms vs. control conditions. After successful EMDR therapy patients respond similarly to controls in attentional tasks.	Removal of PTSD symptoms with EMDR eliminates attentional bias towards aversive cues.

(Continued)

TABLE 2 | Continued

Author, year	Type of study	Sample (n)	EM/Full protocol	Control condition	Main findings	Conclusions
Stickgold, 2002, 2008	Speculative theory	NA	NA	NA	NA	EMDR induces a neurobiological state similar to that of the REM sleep that contributes to integrate traumatic memories into general semantic networks.
Sharpley et al., 1996a	Empirical study	HC ($n = 20$)	EM	Rolling eyes upwards	EM were not associated with increased relaxation as measured by heart rate and alpha activity.	EMDR effects does not rest upon alpha-induction or cause overall relaxation.
Schubert et al., 2011	Empirical study	HC ($n = 64$)	EMDR	EMDR with no-EM	EMDR with EM was associated with greater reduction of distress. EMDR led to greater dearousal on physiological variables.	The dual-attention tasks in EMDR create orienting responses and short-term dearousal which may aid in the processing and integration of trauma memories. The relaxation response associated with EMs in EMDR may serve to moderate arousal throughout treatment sessions.
Raboni et al., 2014	Empirical study	PTSD ($n = 13$) HC ($n = 11$)	EMDR	Pre-post treatment Within group Between group	EMDR decrease symptoms of depression and anxiety in PTSD.	Reduced sympathetic activation may explain the improvements observed after EMDR.
Farina et al., 2015	Empirical study	PTSD ($n = 6$)	EMDR	Pre-post design	EMDR was associated with alpha power increases in the left inferior temporal gyrus and HRV. Finally, the values of lagged coherence were negatively associated with subjective units of disturbance and positively associated with parasympathetic activity.	Results suggest that EMDR leads to an integration of dissociated aspects of traumatic memories and, consequently, a decrease of hyperarousal symptoms
Schubert et al., 2016	Empirical study	PTSD ($n = 20$)	EMDR	Pre-post treatment Within group	EMDR treatment was followed by significant reductions in PTSD, depression, and anxiety symptoms. Decreases in heart rate, respiration rate, and skin conductance indicated physiological dearousal within treatment sessions.	Support for the orienting response-relaxation and physiological dearousal during and after successful EMDR treatment
Pagani and Carletto, 2017	Speculative theory	NA	NA	NA	NA	Slow-wave sleep, like EM in EMDR has a key role in memory consolidation and in the reorganization of distant functional networks, as well as lead to a weakening of traumatic episodic memory and a reconsolidation of new associated information.

EM, eye movements; EMDR, eye movement desensitization and reprocessing; HC, healthy controls; NA, not applicable; OR, orienting response; PTSD, posttraumatic stress disorder; REM, rapid eye movement.

TABLE 3 | Neurobiological models ($n = 37$).

Author, year	Type of study	Sample (*n*)	EM/Full protocol	Control condition	Findings/Outcome	Implications for the mechanism of action
CHANGES IN INTERHEMISPHERIC CONNECTIVITY						
Christman et al., 2003	Empirical study	HC ($n = 280$)	Saccadic and smooth pursuit EM	Horizontal vs. vertical EM vs. no EM	Saccadic EM enhanced episodic memory retrieval.	EM enhance interhemispheric interaction facilitating retrieval of episodic memories.
Christman et al., 2006	Empirical study	HC ($n = 86$)	Saccadic and smooth pursuit EM	Horizontal vs. vertical EM vs. no EM	Saccadic EM led to recall of earlier childhood events.	EM enhance interhemispheric interaction facilitating retrieval of episodic memories.
Rasolkhani-Kalhorn and Harper, 2006	Speculative theory	NA	NA	NA	NA	Depotentiation may be the biological basis of EMDR. Induction of low frequency stimulation by EM can lead to modification of fear memory traces.
Parker and Dagnall, 2007	Empirical study	HC ($n = 102$)	EM	Horizontal vs. vertical EM vs. no EM	Saccadic eye movements increased true recognition of words and decreased false recognition.	EM may increase interhemispheric interaction leading to increased contextual information associated with previously learnt items.
Parker et al., 2008	Empirical study	HC ($n = 96$)	EM	Horizontal vs. vertical EM vs. no EM	EM increased associative recognition and recollection.	EM (dual processing task) improve performance of associative learning tasks. This mechanisms may be explained by increased interhemispheric interaction.
Parker et al., 2009	Empirical study	HC ($n = 72$)	EM	Horizontal vs. vertical EM vs. no EM	Horizontal EM increase true memories and recollection EM also decreased the magnitude of the misinformation effect.	Horizontal EM enhance the monitoring and dual processing of source memories.
Brunyé et al., 2009	Empirical study	HC ($n = 72$)	EM	Horizontal vs. vertical EM vs. no EM	Horizontal EM increased recognition in verbal and non-verbal memory tests.	The effects of horizontal EM in EMDR may induce increased interhemispheric brain activity.
Nieuwenhuis et al., 2013	Empirical study	HC ($n = 50$)	EM	Horizontal EM no EM (on-screen fixation) simultaneous tactile stimulation simultaneous auditory stimulation	Horizontal EM and tactile stimulation enhance memory retrieval.	EM-driven bilateral stimulation of the brain increase functional connectivity between the two hemispheres, leading to enhanced memory retrieval.
Keller et al., 2016	Empirical study	HC ($n = 30$)	EM	Stationary eyes	EM were not associated with enhanced interhemispheric coherence but with were associated with intrahemispheric coherence in the right frontal and temporal areas.	A cortical coherence extension for the interhemispheric coherence hypothesis is suggested.
Yaggie et al., 2016	Empirical study	HC ($n = 46$)	EM	Stationary eyes Between/within-groups experimental design	No differences in vividness and emotional valence between all conditions. No significant increases in interhemispheric coherence measured by EEG. Increases in intrahemispheric coherence associated to EM.	Support for a two-stage cortical coherence model, integrating findings from other hypothesis and models.

(Continued)

TABLE 3 | Continued

Author, year	Type of study	Sample (*n*)	EM/Full protocol	Control condition	Findings/Outcome	Implications for the mechanism of action
STRUCTURAL AND FUNCTIONAL BRAIN CHANGES ASSOCIATED WITH EMDR THERAPY						
O'Driscoll et al., 1998	PET	HC = 10	EM	Saccadic vs. smooth pursuit movements	Saccadic movements are associated with increased metabolism of the frontal cortex.	Differential activation between smooth pursuit and saccadic eye movements.
Levin et al., 1999	SPECT	PTSD = 6	EMDR	Pre-post treatment Within group	Post EMDR hyper activation of ACC and left PFC.	Successful EMDR treatment in PTSD may enhance the ability to differentiate real from imagined threat.
Lamprecht et al., 2004	EEG, ERP	PTSD = 10	EMDR	Pre-post treatment Within group	Post EMDR reduced OR to novel stimuli and arousal level.	Clinical improvement of trauma in PTSD patients may be related to changes in information processing.
Lansing et al., 2005	SPECT	PTSD = 6	EMDR	Pre-post treatment Within group	Changes in perfusion post EDMR treatment. Decrease perfusion in the left and right occipital, left parietal, and right precentral lobes Increased perfusion in the left inferior frontal gyrus.	Significant functional differences in brain activity from pre- to post-EMDR imaging consistent with psychotherapy effects on depression and anxiety disorders.
Oh and Choi, 2007	SPECT	PTSD = 2	EMDR	Pre-post treatment Within group	Increased perfusion in PFC and decreased perfusion in temporal association cortex.	EMDR treatment reverse the functional imbalance between the limbic area and the prefrontal cortex.
Letizia et al., 2007	MRI	PTSD = 1	EMDR	Pre-post treatment Single case	Increased hippocampal volume.	Psychotherapy may induce alterations in gene expression and structural changes in the brain.
Pagani et al., 2007	SPECT	PTSD = 15 HC = 22	EDMR	Pre-post treatment Within group Between group	Reduction toward normalization in EMDR respondents in pre-limbic cortices and increases in the PFC.	The imaging findings are consistent with previously described imaging changes of psychotherapy on anxiety disorders.
Propper et al., 2007	EEG	HC = 22	EM	Horizontal vs. vertical EM vs. noEM	EM led to decreased interhemispheric coherence.	EM may induce changes but not necessarily decreases in interhemispheric interaction.
Harper et al., 2009	EEG	PTSD = 6	EMDR	Within group analysis	Symptoms of PTSD were reduced after EMDR. EEG activity was compatible to de-potentiation memory synapses.	Treatment gains in EMDR may result from de-potentiation of fear in memory synapses.
Ohtani et al., 2009	NIRS	PTSD = 13	EMDR	Pre-, during, post-treatment Within group	Decreased activity in PFC during recall with EM.	Reduced activity in the PFC may be part of the biological basis for the efficacy of EMDR in PTSD.
Grbesa et al., 2010	EEG	PTSD = 1	EMDR	Pre-, during and post- treatment Within subject	Low level electrocortical amplitude was observed during EMDR. Increased EEG amplitude was observed after successful treatment.	Successful EMDR treatment correlates with sudden increases of electrocortcial amplitude activity.
Nardo et al., 2010	MRI	PTSD = 21 HC = 22	EMDR	Between group	Lower GM density was found in the left posterior cingulate, parahippocampal, limbic and paralimbic cortices in non-responders to EMDR therapy.	GM lower density in limbic and paralimbic cortices is associated with PTSD diagnosis, trauma load, and EMDR treatment outcome, suggesting that PTSD is characterized by memory and dissociative disturbances.
Bossini et al., 2011	MRI	PTSD = 10	EMDR	Pre-post treatment Within group	Increased hippocampal volume post EMDR.	EMDR may induce alterations in gene expression and structural changes in the brain.

(Continued)

TABLE 3 | Continued

Author, year	Type of study	Sample (*n*)	EM/Full Protocol	Control Condition	Findings/Outcome	Implications for the mechanism of action
Pagani et al., 2012	EEG	PTSD = 10 HC = 10	EMDR	Pre-, during and post treatment Within and between group	Activations shifted from frontal to temporal regions over the course of the treatment.	Traumatic events are processed at cognitive level following successful EMDR therapy.
Samara et al., 2011	EEG	HC (*n* = 14)	EM	noEM	Interhemispheric phase and amplitude coherence in EEG were not affected by EM. There were no associations between changes in EM-related interhemispheric connectivity and memory performance.	These findings do not support the interhemispheric interaction hypothesis.
Landin-Romero et al., 2013	fMRI	Subsyndromal traumatized bipolar patient (*n* =1) HC = 30	EMDR	Pre-post treatment Between and within group	Post-treatment normalization of patterns of activation and deactivation.	EMDR may modulate large scale networks in the brain
Herkt et al., 2014	fMRI	HC = 20	Alternating BLS	Non alternating BLS No stimulation	Specific increase in activation of the right amygdala for the bilateral alternating auditory stimulation. Decrease activation of the dorsolateral prefrontal cortex associated to alternating BLS.	Support for increase in limbic processing along with decreased frontal activation as the neurobiological correlate of the therapeutic reintegration of information.
Boukezzi et al., 2017a	MRI	PTSD (*n* = 18)	EMDR	Supportive therapy	EMDR was associated with grey matter increases in the prefrontal cortex.	EMDR-driven symptom removal is associated with enhancement of brain structures involved in emotional regulation.
Littel et al., 2017a	Empirical study	HC (*n* = 56)	EM	Eyes stationary	No effects of EM on memory emotionality when associated with blockage of noradrenaline.	Noradrenaline is crucial for EMDR effectiveness.
Bossini et al., 2017	MRI	PTSD (*n* = 19) HC (*n* = 19)	EMDR	Pre-post design	EMDR was associated with increased grey matter volume in thalamus and parahippocampal regions.	EMDR mechanism of action work at the level of the thalamus, an area implicated in PTSD.
Thomaes et al., 2016	fMRI	PTSD (*n* = 8)	EM	Recall with no EM	Recall with EM is associated with reduced activation in amygdala and reduced prefrontal connectivity.	EM reduce activity and connectivity in emotional processing related areas.
Laugharne et al., 2016	MRI	PTSD (*n* = 20)	EMDR	Prolonged exposure	Left amygdala mean volume increased following EMDR treatment but not exposure.	Results suggest different underlying processes for the efficacy of EMDR and prolonged exposure.
Jung et al., 2016	MRI	PTSD (*n* = 17) HC (*n* = 11)	EMDR	Pre-post design	Successful treatment showed significant effects on global and local network properties.	Subthreshold manifestation of PTSD may be due to a disruption in the optimal balance in the functional brain networks and that this disruption can be ameliorated by psychotherapy.
Pagani et al., 2015	Empirical study	noPTSD trauma (*n* = 40) HC (*n* = 20)	EMDR	Pre-post design	Orbitofrontal activity shifted to posterior associative regions post-treatment. Participants with chronic exposure to trauma showed similar cortical firing at both stages.	During EMDR memory retention of the traumatic event moves from regions with implicit emotional valence to association areas in which the experience is integrated and consolidated.

(Continued)

TABLE 3 | Continued

Author, year	Type of study	Sample (*n*)	EM/Full Protocol	Control Condition	Findings/Outcome	Implications for the mechanism of action
Rimini et al., 2016	Empirical study	HC ($n = 21$)	EMDR	Pre-post design	EM during EMDR were associated with increased prefrontal oxygenation during recall of aversive memories.	EM were correlated with a reduced oxy-Hb concentration, which may be linked to a reduced working activity of PFC.
Amano and Toichi, 2016b	Empirical study	HC ($n = 15$)	EMDR	Pre-post design	EM was associated with a significant increase in oxy-Hb in the right superior temporal sulcus and a decrease in the wide bilateral areas of the PFC.	EM may help the recall of pleasant memories. The reduction in the PFC suggests that EM induce relaxation.
Amano and Toichi, 2016a	Empirical study	PTSD ($n = 7$)	EMDR	Pre-post design	EMDR was associated with a significant reduction in the right temporal cortex, and a trend toward a reduction in the left orbitofrontal cortex.	Successful EMDR treatment involves brain regions related to memory representation and emotion.

ACC, anterior cingulate cortex; EEG, electroencephalogram; EM, eye movements; EMDR, eye movement desensitization and reprocessing; ERP, event related potentials; fMRI, functional magnetic resonance imaging; HC, healthy controls; GM, gray matter; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; NA, not applicable; OR, orienting response; PTSD, posttraumatic stress disorder; PET, positron emission tomography; PFC, prefrontal cortex; SPECT, single photon emission computer tomography; BLS, bilateral stimulation.

degradation of its vividness (Andrade et al., 1997; Kavanagh et al., 2001; van den Hout et al., 2001; Gunter and Bodner, 2008; Maxfield et al., 2008). Further research have refined these results, with the finding that the EMs are superior to other forms of BLS, such as auditive "beeps" and relaxing music, in decreasing the vividness and emotionality of disturbing memories in healthy participants (Hornsveld et al., 2010, 2011; van den Hout et al., 2010, 2011a, 2012).

Other authors have proposed a different mechanism to taxing working memory in decreasing vividness and emotionality whereby the EMs would change the somatic perceptions accompanying retrieval toward relaxation, resulting in decreased affect and therefore decreased vividness of the imagery (van den Hout et al., 2001, 2013; Lilley et al., 2009). This explanation has many similarities to the reciprocal inhibition techniques (i.e., systematic desensitization) first described by Wolpe. Here, a state incompatible with the anxiety (i.e., relaxation) is evoked at the same time as the anxiety-provoking stimuli, ultimately leading to its desensitization (Wolpe, 1954).

Psychophysiological Models

Physiological Changes Associated With the Orienting Response

In her revision of the EMDR principles and procedures, Shapiro suggested that the EMs and the dual attentional task led to specific psychophysiological changes that may underlie treatment efficacy. A set of studies has strived to determine whether the EMs indeed produce physiological effects and to identify the nature of these changes.

Wilson et al. were first to report within-subject psychophysiological changes in participants receiving a single session of EMDR (Wilson et al., 1996). They observed that heart rate and galvanic skin response decreased over a set of EMs and that the fingertip skin temperature was significantly higher at the end of the treatment session than at the start. In addition to these effects, the EMs were accompanied by changes in respiratory patterns, consistent with a relaxation response. These physiological changes are compatible with a de-arousal response following EMDR treatment. Elofsson et al. recorded and compared several psychophysiological measurements during EMs vs. phases without EMs. They found that pulse rate went down during EMs and up again afterward, an effect that became more and more pronounced as the session proceeded. Finger temperature increased immediately after the onset of EMs and continued to increase steadily before dropping immediately when the EMs ceased. On the other hand, skin conductance and heart rate were lowered during stimulation. All these changes are compatible with an increased parasympathetic contribution to autonomic activity (Elofsson et al., 2008). Barrowcliff et al. found that skin conductance was reduced during the horizontal EMs in healthy individuals (Barrowcliff et al., 2003). Sack et al. exposed 10 patients with PTSD to standard EMDR treatment and examined effects within and between stimulation sets on different respiration and heart measurements (Sack et al., 2008). The onset of each stimulation period was instead associated with a sharp increase in parasympathetic tone. This was followed by increased respiration rate and decreased heart rate during

ongoing stimulation, indicating stress-related arousal. The trend across entire sessions was one of physiological de-arousal.

REM Sleep

In her initial description of the EMD theory, Shapiro suggested that the rhythmic, multi-saccadic EMs in EMDR may work as a brain-inhibitory mechanism to reduce anxiety when associated with the traumatic memory, in the same way the material surfacing during dreaming is desensitized by rapid eye movement (REM). This apparent analogy between REM sleep and EMDR was further developed by Stickgold, who proposed the REM hypothesis for the mechanism of action of EMDR. According to this hypothesis, the EMs in EMDR would induce a similar brain state to that occurring during REM sleep. Years of sleep research that has demonstrated that REM sleep serves a number of adaptive functions, including memory consolidation via the integration of emotionally charged autobiographical memories into general semantic networks (Born et al., 2006; Stickgold and Wehrwein, 2009). Similarly, EMDR would promote the reorganization of the traumatic memories, reducing the strength of the traumatic episodic memories that are mediated by the hippocampus and the associated negative emotion processed by the amygdala (Stickgold, 2002, 2008).

This hypothesis has received some indirect support from psychophysiological research. Elofsson et al. have argued that the physiological profile of EMDR fits well with the REM account (Elofsson et al., 2008; Sondergaard and Elofsson, 2008). Indirect evidence of REM-like mechanisms mediating the therapeutic effect of EMDR has been provided in a study by Raboni et al. where improved sleep and partial recovery of depressive and anxiety symptoms was observed in 13 PTSD patients after successive treatment with EMDR (Raboni et al., 2014). The authors speculated that the improvements observed after treatment where mediated by an EMDR-driven reduction of the sympathetic activation and suggested that EMDR played a role in restoring normal sleep patterns and lowering the probability of developing PTSD after a traumatic event. Nonetheless, it should be noted that there is lack of studies addressing the REM hypothesis directly. Indeed, the smooth eye pursuit that occurs during BLS in EMDR therapy is actually very different from the saccadic movements elicited during REM sleep. Instead, recent speculative theories associate the EM in EMDR to EM during slow-wave sleep, in terms of both the smooth pursuit and frequency (Pagani and Carletto, 2017; Pagani et al., 2017). Slow-wave sleep has a key role in memory consolidation and in the reorganization of distant functional networks, and leads to weakening of traumatic memories and a reconsolidation of new information. Similarly, other authors suggest that depotentiation, induced by low frequency stimulation (i.e., smooth EM pursuit), may be the biological basis of EMDR removing fear memory traces. These theories, however, remain to be tested empirically.

Neurobiological Models

The advent of non-invasive neuroimaging techniques such as the electroencephalogram (EEG), single-positron emission computed tomography (SPECT), near-infrared spectroscopy (NIRS) and structural and functional magnetic resonance imaging (sMRI, fMRI) have enabled the *in-vivo* examination of structural and functional brain changes. Neuroimaging techniques have been used with relative success in an attempt to shed light on the neurobiological correlates of diverse psychotherapies (Linden, 2006; Abbass et al., 2014; Weingarten and Strauman, 2015). Early data from different functional and anatomical studies in PTSD have supported neurobiological models that can be used to examine changes after intervention with EMDR and other psychotherapies (Lindauer et al., 2005; Bryant et al., 2008). These findings have provided a solid foundation to direct research efforts, in order to unravel the brain correlates underlying the efficacy of EMDR.

Changes in Interhemispheric Connectivity

A set of studies in non-clinical populations have tried to explain the treatment gains of EMDR based on changing interactions between the left and right brain hemispheres. Specifically, some researchers have speculated that the EMs in EMDR facilitate associative memory processing and episodic memory retrieval through increased interhemispheric communication via the corpus callosum. This hypothesis is partially based on a previous functional imaging study that has shown that saccadic eye movements generated more frontal cortical activity than do smooth pursuit eye movements (O'Driscoll et al., 1998). The effect of different conditions of EMs (i.e., saccadic vs. smooth ocular pursuit; horizontal vs. vertical EMs) on episodic memory and interhemispheric activity has been examined in a set of studies using EEG. These studies showed that saccadic horizontal EMs enhanced memory retrieval while significantly decreasing false memories. This effect was further mediated by changes in interhemispheric interaction driven by the EMs (Christman et al., 2003, 2006; Propper et al., 2007; Brunyé et al., 2009; Nieuwenhuis et al., 2013). Other studies have found that saccadic EMs facilitate processing of associative memories, lending partial support to this hypothesis (Parker and Dagnall, 2007; Parker et al., 2008, 2009). In recent years, an extension of the interhemispheric connectivity hypothesis have been suggested, including a two-stage cortical coherence model whereby *intra*-hemispheric changes in the right hemisphere may occur along with interhemispheric changes (Keller et al., 2016; Yaggie et al., 2016).

Neural Integration and Thalamic Binding Model

Empirical studies of the past decade have shown the thalamus to be centrally involved in the integration of perceptual, somatosensory, memorial, and cognitive processes; a process alternatively referred to as thalamo-cortical temporal binding or neural global mapping (Llinás and Ribary, 2001; Llinas et al., 2002). The thalamo-cortical binding model serves as a theory for the integration of sensory information and it is supported by neuroimaging studies that consistently find decreases in thalamic activity in PTSD (Lanius et al., 2001, 2003). This model has been proposed to explain the effects of the EMs on the neural networks. Bergmann has suggested that the BLS facilitates the subsequent activation of the ventrolateral and central lateral thalamic nuclei via activation of the lateral cerebellum (Bergmann, 2008). Accordingly, the activation of this circuitry is hypothesized to

facilitate the integration of somatosensory, memory, cognitive, emotional, and synchronized hemispheric functions that are disrupted in PTSD. It is important to note that this is just a speculative theory, as this model has not been empirically tested yet. Bergmann has proposed a range of neurobiological research designs capable of testing the role the EMs (or alternate forms of BLS) on thalamic function, interhemispheric coherence and temporal binding (Bergmann, 2012).

On a similar scope, Corrigan has proposed that auditory, visual, and tactile BLS would facilitate the simulation of thalamo-cingulate tracts (Corrigan, 2002). This stimulation would lead to the deactivation of the ventral—affective—anterior cingulate gyrus, which in turn would enable the reciprocal inhibition of the dorsal (cognitive) anterior cingulate gyrus. This cascade of brain functional changes would ultimately result in increased cognitive control over overreacting affective processing systems and to the reduction of the emotional distress. This hypothesis has the support of several years of neuroimaging research has shown that these neuronal mechanisms are altered in PTSD (Pitman et al., 2012). A number of recent functional neuroimaging studies have reported activity changes in these neuronal networks after EMDR treatment, providing further support for this hypothesis (Levin et al., 1999; Lansing et al., 2005; Landin-Romero et al., 2013) [for more details on these studies see section below].

Structural and Functional Brain Changes Associated With EMDR Therapy

In recent years, a new wave of increasingly sophisticated neuroimaging studies has been carried out to uncover the neurobiological underpinnings of EMDR. These studies seem better suited to answer persistent questions surrounding the mechanism of action of EMDR while addressing some of the limitations of early research. In particular, studies examining neuroimaging and behavioral changes "on-line," before, during and after therapy, hold promise to unravel the neurobiological signatures of EMDR.

A small set of brain imaging studies has investigated the structural brain correlates of EMDR therapy, with a focus on memory (e.g., Letizia et al., 2007) and emotion processing structures. Nardo et al. performed a magnetic resonance imaging [MRI] study in 21 PTSD patients compared with 22 healthy controls (Nardo et al., 2010). They found decreased gray matter density in several limbic and paralytic regions in patients who did not respond to EMDR compared to EMDR responders. Lower gray matter density in the posterior, parahippocampal and insular cortices was correlated with PTSD diagnosis, trauma load and poor therapy outcome, suggesting that reduced neuronal integrity in these regions may drive the lack of response to therapy. Bossini et al. examined structural changes in 10 patients with PTSD who had the hippocampi manually delineated using high-resolution MRI scans (Bossini et al., 2011). After 8 weeks of EMDR treatment, patients no longer met PTSD criteria and showed significant bilateral increases of hippocampal volume, which led the authors to speculate with the possibility of volumetric effects induced by psychotherapy. However, this interpretation should be taken with caution, as these structural changes might have been derived by neurogenesis or increased water/electrolyte content.

In the first functional imaging study, Levin and cols. examined changes in metabolism with single-proton emission computer tomography [SPECT] and a symptom provocation paradigm before and after three sessions of EMDR in one patient with PTSD (Levin et al., 1999). The results showed increased activity post-EMDR treatment in the anterior cingulate gyrus and the left frontal lobe. The authors concluded that activation of these areas facilitates the distinction between real threats and traumatic memories that are no longer relevant to current experience. Lansing et al. also investigated brain activation using SPECT during the recall of a traumatic event in 6 traumatized police officers before and after EMDR therapy (Lansing et al., 2005). They found significant metabolic decreases in occipital, left parietal and posterior frontal lobes and metabolic increases in the left inferior frontal gyrus after successful removal of the PTSD symptoms. These findings confirmed the impact of successful EMDR therapy in increasing prefrontal control over hyperactive limbic subsystems and provided preliminary support to neural integration models. Pagani et al. confirmed these results in a further SPECT study of 15 patients and 22 non-symptomatic controls who had suffered the same trauma (Pagani et al., 2007). A subgroup of responders to EMDR showed a significant metabolic normalization after therapy in posterior cortical regions and in the hippocampus and an increase of blood perfusion in the lateral prefrontal cortex. Oh et al. have conducted the most recent SPECT EMDR study to date in two patients suffering from psychological traffic trauma compared to 10 healthy controls. They found increased metabolism in bilateral dorsolateral prefrontal cortex and decreased metabolism in the temporal association cortex following successful EMDR therapy (Oh and Choi, 2007).

Brain functional changes concurrent to EMDR therapy have also been examined with other neuroimaging techniques different to SPECT. Ohtani et al. performed the first near-infrared spectroscopy (NIRS) study to monitor brain hemodynamic changes related EMDR treatment during memory recall. In this study, recall with EMs was associated with significant decreases in blood flow in the lateral prefrontal cortex compared to recall without EMs. Further, the concentration of oxygenated hemoglobin was correlated with clinical improvement post treatment (Ohtani et al., 2009). The authors suggested that the effectiveness of EMDR might be associated with the reduction of lateral prefrontal cortex over activation during trauma-related recall. In another pioneering fMRI study, Landin-Romero et al. examined changes in brain activity in a sub-syndromal and traumatized bipolar patient following successful EMDR therapy. The results showed that symptom recovery post-treatment was followed by a functional normalization of brain activity compared to 30 matched healthy controls (Landin-Romero et al., 2013). This normalization was particularly marked in the default mode network, a subset of brain regions that that activate during self-directed mentation and that de-activates during performance of a wide range of cognitive test. It is now widely accepted that the default mode network is dysfunctional in several severe mental disorders, including PTSD (Buckner et al., 2008). The authors

speculated with large scale network modulation, specifically in the default mode network, as a potential neurobiological correlate of successful EMDR therapy.

Electroencephalogram (EEG) studies have also examined brain changes after EMDR therapy in PTSD (Lamprecht et al., 2004; Harper et al., 2009; Grbesa et al., 2010; Pagani et al., 2012). In the study by Lamprecht et al. successful treatment was accompanied with reductions of the P3a component upon auditory stimulation (Lamprecht et al., 2004). In EEG research, the P3a component has been related to the engagement of attention and the processing of novel information. This finding led the authors to conclude that the observed clinical improvement was driven by changes in information processing, presumably associated to a reduced OR to novel stimuli and reduced arousal level. EEG was also used by Pagani et al. to examine on-line neurophysiological changes in PTSD patients and healthy controls during EMDR therapy (Pagani et al., 2012). When participants were focusing on the traumatic experience and during bilateral stimulation, the EEG signals relative to 20-30 s periods of bilateral stimulation were analyzed to obtain the neurobiological responses to EMDR therapy in real-time across the whole session. Results showed different neural signatures between patients and controls. Patients showed greater activity in the orbitofrontal cortex and parahippocampal gyrus while controls showed greater activation in large areas of the frontal, temporal, and parietal lobes, especially in the right hemisphere. During the first EMDR session, while still symptomatic, patients showed significantly higher activity in orbitofrontal, prefrontal and anterior cingulate cortices. Conversely, when symptoms disappeared, upon bilateral stimulation, and trauma recall, patients showed a shift in cortical activity toward associative left temporo-occipital regions. These changes were correlated to neuropsychological scores, suggesting that traumatic events are processed at the cognitive level following successful EMDR therapy.

CONCLUSIONS

The aims of the current manuscript are twofold: first, to provide an historical overview of the introduction and development of EMDR over the last 25 years and second, to conduct a systematic review of the mechanisms of action underlying treatment gains in EMDR therapy. Eighty-seven EMDR research studies met the inclusion criteria and were organized into 3 greater categories according to different hypotheses underlying treatment gains in EMDR; psychological, psychophysiological and neurobiological. Thirty-two papers were classified as psychological models. Of these, 27 examined the working memory hypothesis, nowadays considered one of the leading explanations for the changes associated to successful EMDR therapy. Eighteen studies examined physiological effects using different measurements of autonomic function. Finally, 37 studies were classified within the neurobiological models.

Psychological models offer a theoretical framework in which an OR elicited by BLS lead to relaxation and decreased affect associated to traumatic imagery. This hypothesis has received direct experimental support from psychophysiological studies (Wilson et al., 1996; Barrowcliff et al., 2003) suggesting that distraction is not the mechanism behind these effects. The leading psychological explanation for the EMDR treatments effects is arguably the working memory model. Research on the working memory account has demonstrated reductions in vividness of disturbing memories in healthy subjects (van den Hout et al., 2011b, 2012, 2014; van Veen et al., 2015, 2016; Onderdonk and van den Hout, 2016; van Schie et al., 2016; Leer et al., 2017). However, the psychological models, and in particular the working memory account, have also received criticism. First, most studies are performed in non-clinical populations and therefore cannot address which additional mechanisms contribute to treatment effects in PTSD. Results are often not supported by concurrent neurobiological evidence and only offer partial explanations. Research on the working memory hypothesis has also relied on conditions that do not fully match those used in the standard EMDR protocol. At least two different studies have found no significant effects on memory following EMs in healthy participants (Novo Navarro et al., 2013; van Schie et al., 2015). Further, the working memory hypothesis fails to explain some well-documented effects of EMDR. These include the state of relaxation most patients experience after a few sets of bilateral stimulation (Wilson et al., 1996; Schubert et al., 2008), the spontaneous generation of positive insight, the reports of increased recognition of accurate information, attentional flexibility (El Khoury-Malhame et al., 2011) and improved retrieval of episodic memory (Shapiro and Laliotis, 2015). Finally, most early psychological models ascribe to the EMs, and later to other forms of BLS, the underlying mechanism of action of EMDR, ignoring the potential additive effects of other components of the therapy. Here, it should be noted that dual attention does not require BLS and/or EM, as this effect can also be achieved by the addition of any other "distraction task (e.g., focusing in a point in space). Further, recent studies have also found that emotional arousal (Littel et al., 2017b) and noradrenergic transmission (Littel et al., 2017a) are prerequisites for the effectiveness of dual task interventions (i.e., EMDR or others). To conclude, from the psychological model perspective, the EMs complement traumatic memory extinction by neurobiological mechanisms that are yet to be uncovered, and that these models cannot address.

Physiological studies have found that the EMs are associated with a de-arousal response driven by increased parasympathetic relative to sympathetic changes. This might happen jointly with other physiological indicators, such as an improvement in the smooth ocular pursuit during the EMs (Kapoula et al., 2010). Another hypothesis proposed that EMDR induce a physiological state similar to REM sleep but failed to explain the effects of different types of BLS (i.e., audible tones, tactile stimulation) in the reorganization of traumatic memories. Some authors consider the OR a leading candidate for such mechanism and research models to test this hypothesis have been proposed (Stickgold, 2002, 2008). However, these hypotheses are yet to be tested directly and more research is needed to determine to what extent the

physiological effects driven by EMs are associated with treatment outcome.

A series of early EEG studies found that the EMs led to changes in interhemispheric interaction, facilitating in turn retrieval of episodic memories. These effects are consistent with the theoretical framework of EMDR–the AIP model- and with patient reports of increased autobiographical memory retrieval during therapy. However, some findings have cast doubt on this hypothesis. Studies have found that vertical EMs decrease memory emotionality as effectively as horizontal movements, ruling out the vertical EM as main drivers of interhemispheric changes (Gunter and Bodner, 2008). Another EEG study did not find EEG changes following EMs and improved memory retrieval, undermining any effects of increased interhemispheric communication in treatment response (Samara et al., 2011). Therefore, evidence to date seems to conclude that enhanced interhemispheric communication is not driving the changes to traumatic recollections induced by EMs, which highlights the need for more EEG research and/or other neuroimaging techniques.

Bergmann authored an influential explanation of the EMDR clinical effects integrating findings from psychological theories and neuroscience research (Bergmann, 2008). In this theory the OR "resets" the thalamus, which in turn enhances cortical temporal binding of consciousness leading to both memory retrieval and integration in semantic networks. Similarly, Corrigan has proposed that EMDR facilitates the stimulation of thalamo-cingulate tracts which would inhibit the affective subdivision of the anterior cingulate cortex, facilitating an increase in affective filtering and a concomitant decrease in affective amplification (Corrigan, 2002). Recently, neuroimaging studies have drawn from these neurobiological models and from neuroimaging findings in clinical populations to provide a significant leap in the understanding of the neurobiological correlates of EMDR. Some of these studies have examined brain functional changes associated to EMDR "online," that is, before, during and after the application of the standard EMDR protocol, both in patients and in healthy populations. Results have described a restoration of the cortical control over the hyper aroused subcortical limbic structures (Pagani et al., 2015; Amano and Toichi, 2016b; Laugharne et al., 2016; Rimini et al., 2016; Thomaes et al., 2016; Bossini et al., 2017). However, these brain functional changes are not specific of EMDR, and similar neuronal effects can be observed in other forms of anxiety-focused psychotherapy. Moreover, the physiological foundations of these changes are currently unknown, and therefore, these neuroimaging studies cannot explain what specific mechanisms produce treatment effects in EMDR. With few exceptions, the majority of neuroimaging studies reviewed here have significant methodological limitations, including a small sample size, lack of control conditions and inconsistent conceptualization of the parameters measured. Consequently, neuroimaging research findings should be considered promising but preliminary and conclusions concerning the EMDR neurobiological correlates speculative.

Importantly, approximately half of the studies (42/87) included in this systematic review have investigated the mechanisms underlying BLS, and more specifically the EMs, compared to different control conditions. The other half (45/87) were conducted using a more holistic approach, examining mechanisms associated to the full 8-phase EMDR protocol. The specific contribution of the EMs to EMDR therapy has been a contentious issue for several years and nowadays its exact role is still under investigation (Matzke et al., 2015). The interest surrounding the EMs is partially motivated by Shapiro herself who once described it as a crucial component of EMDR therapeutic effects. This statement has been revised posteriorly, due to the evidence suggesting a similar role for other forms of BLS. The BLS and specifically the EMs, seem to be not only the distinctive characteristic of EMDR, but also the factor accounting for the faster response in EMDR therapy compared to other psychotherapies (Nijdam et al., 2012). Research has also found the EMs provide faster effects that any other forms of BLS and a recent meta-analysis of 26 randomized controlled trials reported a moderate but significant additive effect size of the EMs to treatment gains (Lee and Cuijpers, 2013). However, whether similar effects can be achieved in EMDR therapy using other dual attention tasks (i.e., not BLS) remain to be fully established.

To conclude, this review argues that the current understanding of the mechanisms of action underlying EMDR is similar to the parable of the Blind Men and the Elephant[1] in that there is no agreed definition of what the candidate mechanisms are (i.e., EMs, BLS, dual attention, etc.) and how these mechanisms can be measured or demonstrated. EMDR is a complex therapy with a number of underlying processes simultaneously at play. Moreover, multiple mechanisms may work to produce treatment gains in EMDR; hence, an integrative model may be necessary in order to capture its myriad effects. An example of this is the recently proposed integrative model for the neural mechanism of EMDR (Coubard, 2016), which integrates theories of EMDR, neurophysiological findings on EM, and functional brain imaging of PTSD to study attentional and/or emotional disorders, such as anxiety disorders. Other integrative proposals (e.g., Sack et al., 2008; Schubert et al., 2008) suggest that dual-attention tasks ORs and short-term dearousal enable the processing of trauma memories. Through the reciprocal inhibition (i.e., pairing a relaxation response with distressing memories), the negative appraisals weaken the avoidance trauma decreases. Here, the EM (or maybe any other dual-attention task) may reduce distress to enable processing of trauma information. Although the reviewed models, often overlapping with each other, suggest directions for future research, there is a need of advocating for conceptual clarity and consistency. Future investigations should use objective measures established

[1]In the parable of the Blind Men and the Elephant, a group of six blind men touch only one part of an elephant in order to learn what it is like. Based on their individual experience they suggest that the elephant is like a wall, spear, snake, tree, fan or rope. They then compare their experience and learn that they are in complete disagreement.

by previous research and evaluate several mechanisms in the context of the full EMDR protocol, before, during, and after treatment. The neurobiological foundations of temporal binding, limbic regulation, frontal lobe activation, and reciprocal anterior cingulate cortex suppression, are sufficiently interrelated to preclude mutual exclusion and should be investigated in well-designed studies, using reliable, multidimensional neurobiological indexes. Future findings will undoubtedly shed increasing light on the interrelationship of different mechanism in the successful treatment outcomes of EMDR.

AUTHOR CONTRIBUTIONS

All authors contributed to design of the review. RL-R and AM-A conducted literature searches and RL-R wrote the first draft of the manuscript, with supervision from BLA (primary supervisor) and MP. All authors contributed to interpretation of the literature and revisions to the manuscript and all have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2018.01395/full#supplementary-material

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Conflict of Interest Statement: RL-R, AM-A, MP, and BLA have been invited as speakers in national and international EMDR conferences.

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Metabolic and Electrophysiological Changes Associated to Clinical Improvement in Two Severely Traumatized Subjects Treated With EMDR—A Pilot Study

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Neuroimaging represents a powerful tool to investigate the neurobiological correlates of Eye Movements Desensitization and Reprocessing (EMDR). The impact of EMDR on cortical and sub-cortical brain regions has been proven by several investigations demonstrating a clear association between symptoms disappearance and changes in cortical structure and functionality. The aim of this study was to assess by electroencephalography (EEG) and for the first time by positron emission tomography (PET) the changes occurring after EMDR therapy in two cases of psychological trauma following brain concussion and comatose state due to traffic accident. A 28 and a 29 years old men underwent extensive neuropsychological examination, which investigated: (i) categorical and phonological verbal fluency; (ii) episodic verbal memory; (iii) executive functions; (iv) visuospatial abilities; (v) attention and working memory as well as clinical assessment by means of psychopathological tests (CAPS, IES, BDI, SCL90R, and DES). They were then treated by eight sessions of EMDR. During the first session EEG monitoring was continuously performed and ^{18}F-FDG PET scans, depicting brain metabolism, were acquired at rest within a week (T0). After the last session, in which the two clients were considered to be symptoms-free, neuropsychological, clinical, and PET assessment were repeated (T1). PET data were semi-quantitatively compared to a group of 18 normal controls, as for EEG the preferential cortical activations were disclosed by thresholding the individual z-score to a $p < 0.05$. There was a significant improvement in clinical condition for both clients associated with a significant decrease in CAPS scores. IES and BDI were found to be pathological at T0 and improved at T1 in only one subject. Visuo-constructive abilities and abstract reasoning improved after EMDR in both subjects. As for EEG, the most striking changes occurred in fronto-temporal-parietal

cortex in subject 1 while subject 2 showed only minor changes. PET showed more pronounced metabolism in orbito-frontal and prefrontal cortex at T1 as compared to T0 in both subjects. In conclusion both clients had a clear clinical improvement in PTSD symptoms associated with metabolic and electrophysiological changes in limbic and associative cortex, respectively, highlighting the value of EMDR also in such extreme pathological conditions.

Keywords: EMDR, PET imaging, EEG, neuropsychological tests, psychological tests

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a clinical condition that may affect victims of major psychological trauma and is one of the major contributors of mental suffering (Breslau et al., 1991; Kessler, 2000; Breslau, 2001; Darves-Bornoz et al., 2008). The traumatic event is re-experienced in flashbacks with involuntary vivid replays, concomitant autonomic reactions, and negative feelings. Leading to avoidance of reminders, irritability, and social and emotional withdrawal (American Psychiatric Association, 1994). The recurring negative trauma memory acts as new trauma experience sensitizing the brain networks engaged in fear response and resulting into the emotional bodily reactions of autonomic arousal.

In the last decades neuroimaging has represented a powerful tool to investigate the neurobiological correlates of PTSD. Consistent findings of modifications in cerebral blood flow (Single Photon Emission Computer Tomography, SPECT) (Zubieta et al., 1999; Bonne et al., 2003; Pagani et al., 2005a, 2007; Lindauer et al., 2008; Nardo et al., 2015), in metabolism (Positron Emission Tomography, PET) (Pissiota et al., 2002; Osuch et al., 2008; Molina et al., 2010; Kim et al., 2012; Zhu et al., 2016), in neuronal volume and density (Magnetic Resonance Imaging, MRI) (Lindauer et al., 2004; Looi et al., 2009; Nardo et al., 2010, 2013; O'doherty et al., 2015; Wrocklage et al., 2017), and more recently in brain electric signal (Electroencephalography, EEG) (Lee et al., 2014; Lobo et al., 2015) have been reported.

Although to date the number of studies is still quite limited, a clear implication of the limbic system, involved in processing both positive and negative emotions, in the symptomatic hyperarousal has been advocated. Upon recollection of traumatic events, the reduced medial prefrontal cortex and anterior cingulate control over hyperreactive amygdala and hippocampus initiates a pathological process thought to be the core functional mechanisms implicated in PTSD (Shin et al., 2006). However, other structures have been shown to be involved in PTSD such as thalamus (Lanius et al., 2004), insula (Chen et al., 2006; Herringa et al., 2012), Broca's area (Cottraux et al., 2015), caudate (Looi et al., 2009) as well as posterior cingulate cortex (Yamasue et al., 2003; Rogers et al., 2009).

Physical traumas might cause severe psychopathological and neuropsychological disturbances possibly resulting in PTSD symptoms and leading to metabolic and morphological changes in the brain.

Eye Movements Desensitization and Reprocessing (EMDR) is an information processing therapy for anxiety disorders focusing on trauma elaboration (Shapiro, 1989). EMDR uses upon stressful recollections alternating bilateral tactile or auditory stimulation as well as brief eye movements sets of ∼30 s. Such dual task is a distinctive character distinguishing EMDR from other trauma exposure therapies. EMDR is based on the adaptive information processing model (AIP model) (Shapiro, 2001), according to which a high level of disturbance caused by traumatic experiences results in a failure of the information processing system to properly elaborate and contextualize into the semantic memory network the autobiographical event. Through EMDR the dysfunctional stored experiences will be transformed into adaptive ones, consolidating them into the natural neural processes of memory (Shapiro, 2012). Recently EMDR has been included in the most relevant international trauma treatment guidelines (United Kingdom Department of Health, 2001; Dutch National Steering Committee Guidelines Mental Health Care, 2003; INSERM, 2004; Ursano et al., 2004) and considered as evidence-based practice for the treatment of PTSD [The Substance Abuse and Mental Health Services Administration (SAMHSA), 2011], anxiety and depression symptoms (United Kingdom Department of Health, 2001).

The clinical impact of EMDR has been proven by several investigations (Högberg et al., 2007, 2008; Bisson et al., 2013; Capezzani et al., 2013; McGuire et al., 2014; Faretta et al., 2016) also demonstrating a clear association between symptoms disappearance and changes in cortical structure and functionality (Lamprecht et al., 2004; Lansing et al., 2005; Bremner, 2007; Choi et al., 2007; Pagani et al., 2007, 2012, 2013, 2015; Ohtani et al., 2009; Trentini et al., 2015; Laugharne et al., 2016).

The aim of this study was to assess by extensive neuropsychological and psychopathological test as well as by EEG and, for the first time, PET the changes occurring after EMDR therapy in two cases of psychological trauma following brain concussion due to traffic accident.

METHODS

Subjects

Two subjects that underwent severe traffic accident, following which they were hospitalized for about 3 months in Intensive Care in a comatose state, were recruited for the study.

Subject 1 (AR)

Twenty-nine years old man with severe head trauma caused by a motorbike accident in 2010. MRI showed several white-matter hyperintensities in fronto-parietal cortex and corpus

callosum, the latter appearing thinner than usual, as well as a large post-traumatic encephalomalacia in mesio-occipital cortex. At neurological examination, a deficit of the right visual field and postural tremor of the upper limbs were found. The neuropsychological profile was characterized by impulsivity, poor inhibitory control, and impairment of working memory as well as of verbal, semantic, and visuospatial long-term memory.

Subject 2 (ED)

Twenty-eight years old man with severe head trauma caused by a car accident in 2009. MRI showed large hyperintense areas in cortical and subcortical right temporo-occipital and mesial frontal lobe, bilaterally. The findings were attributed to stabilized traumatic-based tissue suffering. Hypointensities of the same causal nature were described in centrum semiovale and corona radiata. Neurological examination showed a reduction of visual field, left hemiparesis with light spasticity of the upper limb and light left hemi-cerebellar syndrome with subjective instability. The neuropsychological profile highlighted deficits in reading, in visuospatial and executive functions as well as in long-term memory.

Controls

Eighteen participants (mean age 33 years [SD 5.86, range 22–40]; females 10/18) who were referred to the same PET center as the patients for a suspected diagnosis of cancer in whom no oncologic disease was uncovered by ^{18}F-FDG-PET and who had a normal neurologic assessment served as controls. Exclusion criteria were presence of major systemic illness, major vision disturbances, psychiatric illnesses, paraneoplastic encephalitis, and diseases affecting brain functioning and metabolism.

EMDR

The eight phases of EMDR standard protocol were carefully followed to comply with fidelity to treatment procedure and the sessions followed the standard procedures. In brief, the eight phases of the therapeutic protocol were as follows: (1). Client History: history-taking, client evaluation, identification of traumatic memories, treatment planning; (2). Preparation: stabilization and access to positive affects; (3). Assessment: guidance to accessing the perceptual, cognitive, affective, and somatic components of the disturbing memory, as well as to identifying a preferred self–referential positive cognition. Rating of feelings using the Validity of Cognition (VOC) scale, and of level of emotional disturbance by the Subjective Units of Disturbance (SUD); (4). Desensitization: focusing on the traumatic memory for about 30 s while the therapist engages in bilateral stimulation. After each set, the client reports any elicited material, which is then processed until the SUD score decreases to zero; (5). Installation: focusing on the positive cognition while recalling the memory and engaging in new sets of bilateral stimulation, until the VOC score is 7; (6). Body Scan: processing of any residual physical disturbance associated with the memories until the body is clear and free of any disturbance; (7). Closure: Completion of an EMDR session and between sessions is ensured; (8). Reevaluation: at the beginning of subsequent sessions checking whether results were kept unchanged or needed further reprocessing.

Study Design

EMDR therapy and EEGs were carried out in the private therapy room of a trained psychologist (PLP). The room was quiet and airy and therapeutic alliance was easily established. During the first session (T0), the therapist assessed the presence the psychological trauma and neuropsychological as well as neurocognitive test were administered. The two subjects were, separately, asked to record a digital file with the autobiographical narrative of their traumatic experience. After some days, they were asked to come for the second session to start EMDR therapy. EEG recording was continuously performed while the patients were:

- at rest with eyes open and closed;
- listening to the script with eyes closed;
- during a second period with eyes closed;
- during EMDR therapy;
- during a final period of rest.

The same protocol was repeated during the last EMDR session (T1), after the patient completely processed the trauma and reported no disturbance with SUD = 0, VOC = 7 and clear Body Scan.

PET scans were performed at the Department of Nuclear Medicine of the University of Rome "Tor Vergata" within a week after the first and after the last EMDR sessions.

The study was approved by the Ethical Committee of the Institute of Cognitive Sciences and Technologies and the subjects signed an informed consent and agreed to participate to the study.

Clinical Assessment

Neurocognitive Evaluation

The two subjects underwent extensive neurocognitive testing, investigating: (i) categorical and phonological verbal fluency; (ii) executive functions; (iii) visuospatial abilities; (iv) attention and working memory (**Table 1**).

Psychopathological Evaluation

MINI-Plus, according to the DSM-IV criteria, assesses the presence of a wide range of psychiatric disorders including PTSD diagnosis.

CAPS measures frequency and intensity of PTSD symptoms rated for the last-week period. Seventeen items describe the classical PTSD cluster symptoms: re-experiencing, avoidance and numbing, and hyperarousal as well as symptoms associated with PTSD features. The CAPS total score ranging from 0 to 136 classifies PTSD as: 0–19: asymptomatic/few symptoms; 20–39: mild PTSD/subthreshold; 40–59: moderate PTSD/threshold; 60–79: severe PTSD symptoms; and ≥ 80: extreme PTSD symptoms.

Self-Administered Questionnaires

IES regards the response to stressful events during the past week tackling specifically areas of intrusion and avoidance. Total scores

TABLE 1 | Neuropsychological tests.

TEST	Subject 1 (AR)		Subject 2 (ED)	
	T0	T1	T0	T1
MMSE	15	17	20	19
Clock drawing test	**5**	**1***	6	5
TMT A	62	58	244	293
TMT B	312	260	420	NC
TMT B-A	250	202	176	
REY imm	18	24	27	28
REY delayed	0	0	0	0
Fig REY imm	**31**	**35***	0	5
Fig REY delayed	0	2	0	0
Digit span	5	5	**5**	**6***
Digit span inverse	2	2	4	4
Phonemic fluency	24	25	31	25
Semantic fluency	27	29	41	24
Ideomotor apraxia	20	20	18	18
Attentive matrices	35	33	15	14
Babcock story recall	3	3,3	4	4
Babcock delayed	3	3	4	5
Frontal assessment battery	9	11	15	13
Raven progressive matrices	**29**	**33***	**33**	**35***

In bold the tests whose scores improved after being transformed into the Equivalent Scores.*

range from 0 to 75. Scores above 26 are considered to be clinically significant.

BDI measures symptoms of depression related to cognition and affection as well as to somatic changes bothering clients in the previous week (0 = not at all to 3 = severe). Total scores range from 0 to 63, with scores above 18 indicating moderate to severe depressive symptoms.

SCL-90 R reports symptoms of psychological problems in the last 7 days allowing to assess their frequency. Clients rate the items using a 5-point scale (1 = no problem to 5 = very serious). It has 3 global indexes measuring the extent or depth of individual's psychiatric disturbance; the total number of questions rated above 1 point and the intensity of symptoms.

EEG

EEG Procedure

The detailed EEG methodology and statistics has been described elsewhere (Pagani et al., 2011). In brief, 37-channel EEG was recorded using a pre-cabled electrode cap. Data were exported to EDF using NPX Lab 2010 (www.brainterface.com). In EMDR recordings only the epochs corresponding to the periods of bilateral stimulation were selected and exported creating files lasting several minutes. Data were analyzed in the EEGLAB environment (http://www.sccn.ucsd.edu/eeglab/index.html; Delorme and Makeig, 2004), digitally band-pass filtered between 1 and 45 Hz and re-referenced to average reference. Artifactual non-cerebral source activities were identified and rejected using a semiautomatic procedure based on Independent Component Analysis (Porcaro et al., 2009). To compute intracerebral electrical sources, we used exact low- resolution brain electromagnetic tomography (eLORETA) software (http://www.uzh.ch/keyinst/loreta.htm). Computations were made using the Montreal Neurological Institute (MNI; Montreal, Quebec, Canada) MNI152 template (Mazziotta et al., 2001), with the three-dimensional solution space restricted to cortical gray matter and hippocampi, as determined by probabilistic Talairach atlas (Lancaster et al., 2000). Intracerebral volume (eLORETA inverse solution space) was partitioned in 6,239 cubic voxels of 5 mm in which electric activity is represented for each voxel. Anatomical labels as Brodmann areas (BAs) are also reported using MNI space, with correction to Talairach space (Brett et al., 2002). Images corresponded to the estimated neuronal generators of brain activity within each band (Frei et al., 2001). The ranges of frequency bands were: delta (δ), 1.5–4 Hz; theta (θ) 4–8 Hz; alpha (α) 8–12 Hz; beta 1 (β1) 12–20 Hz; beta 2 (β2) 20–30 Hz; gamma (γ) 30–45 Hz.

Because all eLORETA inverse spatial solution voxels have a certain current density and for exploratory nature of the actual case analyses, we accepted only cluster of voxels whose Z-score was>1.5 (i.e., only the values >1.5 times the standard deviation of the standardized data in the LORETA spatial solution) and we accepted only clusters of voxels >27 voxels (an intracerebral volume cube with an edge of 15 mm).

PET

Image Acquisition and Preliminary Analysis

The two subjects fasted for at least 5 h before the i.v. of ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) infusion. Serum glucose level was a minimum of 95 mg/ml, in both of them. They were administered i.v. infusions of 210 MBq of ^{18}F-FDG, were hydrated with 500 ml of NaCl 0.9% and rested 20 min in a dark silent room before undergoing PET examination.

The Discovery VCT PET/CT system (GE Medical Systems, Tennessee, USA) was used to assess FDG brain distribution in all subjects by means of a 3D-mode standard technique in a 256 × 256 matrix. Reconstruction was performed using the 3-dimensional reconstruction method of ordered-subset expectation maximization (OSEM) with 20 subsets and four iterations. The system combines a high-speed ultra 16-detector-row (912 detectors per row), a CT unit and a PET scanner with 10,080 bismuth germanate crystals in 24 rings (axial full width at half-maximum 1-cm radius, 5.2 mm in 3D mode, 157 mm axial field of view). A low-amperage CT scan of the head for attenuation correction (40 mA; 120 Kv) was performed before PET image acquisition.

Statistical Analyses

We carried out preprocessing and statistical analyses bySPM8-normalizing the images to a customized ^{18}F-FDG template. The spatially normalized PET images (voxel size 2 mm) were smoothed with an 8-mm isotropic Gaussian filter. Brain PET analyses were performed, separately for each subject, before and after EMDR therapy. Individual data were compared on a voxel-by-voxel basis to those from the normal controls using a "two-sample t-test" design of SPM8 adjusted for single patient routine (Lange et al., 2016) and implemented in Matlab R2010a

(MathWorks, Natick, Massachusetts, USA). The height threshold was set at a very conservative level of $p < 0.0001$ (Family Wise Correction of $p < 0.001$ at cluster level) and age and sex were used as covariate, to regress out their impact on the results. Based on the spatial resolution of the PET camera and to further improve the statistical power of the analyses only cluster larger than 92 voxels ($4.5 \times 4.5 \times 4.5$ voxels $= 9 \times 9 \times 9$ mm^3) were considered as significant. We identified the BAs matching the SPM output to the Talairach coordinates using the subroutine implemented by Matthew Brett (http://brainmap.org/index.html).

The choice of assessing brain metabolism in the two subjects by comparing metabolism pre- and post-EMDR to a reference group was driven by the lack of statistical reliability in comparing directly the PET datasets as acquired during the first and the second session, due to the excess of noise in the single within-subject analyses.

RESULTS

Subject 1(AR)

At cognitive level, AR showed post-EMDR as compared to pre-EMDR a dramatic improvement in visuo-constructive abilities and verbal memory (Clock Drawing Test and Rey immediate recall, respectively) as well as for abstract reasoning (Raven's Progressive Matrices, executive function), see **Table 1.**

The most striking improvement post-EMDR was in PTSD symptomatology as revealed by CAPS scores (see **Table 2**). Significant improvement was also found for IES, BDI, and DES scores.

After EMDR AR showed a substantial decrease of the re-experience (intrusive thoughts and flashback) and avoidance (meeting the people associated with the motorcycle accident) symptoms. The main improvement was in the pre-EMDR hyperarousal with a great reduction of the startle response, a regularization of the sleep-wake rhythm and a reduction of the internal tension, the latter very high before therapy.

EEG during script listening consistently showed for all bands a statistically significant disappearance during the last EMDR session as compared to the first one of the preferential cortical activation in left occipitoparietal-temporal cortex as well as in bilateral posterior cingulate/precuneus. Analogously a significant preferential activation at T1 was recorded in right prefrontal cortex and temporal pole, extending as for the gamma band to the right temporo-occipital cortex (**Figure 1**, script listening).

Upon bilateral stimulation and reliving of the index trauma the preferential activation in bilateral posterior cingulate/precuneus found at T0 disappeared at T1. However, at high frequencies, frontotemporal activation was found at both sessions and a large left prefrontal-temporal-occipital appeared at T1 (**Figure 1**, bilateral stimulation).

TABLE 2 | Psychopathological tests.

	Subject 1 (AR)					Subject 2 (ED)				
	CAPS RE-EXP	**CAPS AVOI**	**CAPS AROU**	**CAPS ASSOC**	**CAPS TOT**	**CAPS RE-EXP**	**CAPS AVOI**	**CAPS AROU**	**CAPS ASSOC**	**CAPS TOT**
T0	8	22	24	6	**60**	0	30	14	10	**54**
T1	2	14	6	6	**28***	0	21	2	2	**25***
	IES INTR	**IES AVOI**	**IES TOT**			**IES INTR**	**IES AVOI**	**IES TOT**		
T0	23	20	**43**			0	0	0		
T1	4	7	**11***			3	0	3		
	BDI COG	**BDI SOM**	**BDI TOT**			**BDI COG**	**BDI SOM**	**BDI TOT**		
T0	7	3	10			1	3	4		
T1	3	2	5			1	4	5		
	SCL90R GSI	**SCL90R PSDI**	**SCL90R PST**			**SCL90R GSI**	**SCL90R PSDI**	**SCL90R PST**		
T0	1.4	2.0	63			2.2	2.7	72		
T1	1.3	1.9	61			1.7	2.4	65		
	DES					**DES**				
T0	**56**					16				
T1	**27***					28				

CAPS, Clinician-Administered PTSD Scale; CAPS–RE-EXP, CAPS re-experiencing symptoms; CAPS–AVOI, CAPS avoidant-numbing symptoms; CAPS–AROU, CAPS hyper-arousal symptoms; CAPS–ASSOC, CAPS associated features; CAPS–TOT, CAPS total score; IES, Impact of Event Scale; IES–INT, IES intrusion symptoms; IES–AVO, IES avoidance symptoms; IES–TOT, IES total score. BDI, Beck Depression Inventory. BDI–COG, BDI cognitive symptoms; BDI–SOM, BDI somatic symptoms; BDI–TOT, BDI total score. SCL-90-R, Symptom CheckList-90-Revised; SCL-90-R–GSI, SCL-90-R Global Severity Index; SCL-90-R–PSDI, SCL-90-R Positive Symptom Distress Index; SCL-90-R–PST, SCL-90-R Positive Symptom Total. In bold the remarkable decreases of tests scores.*

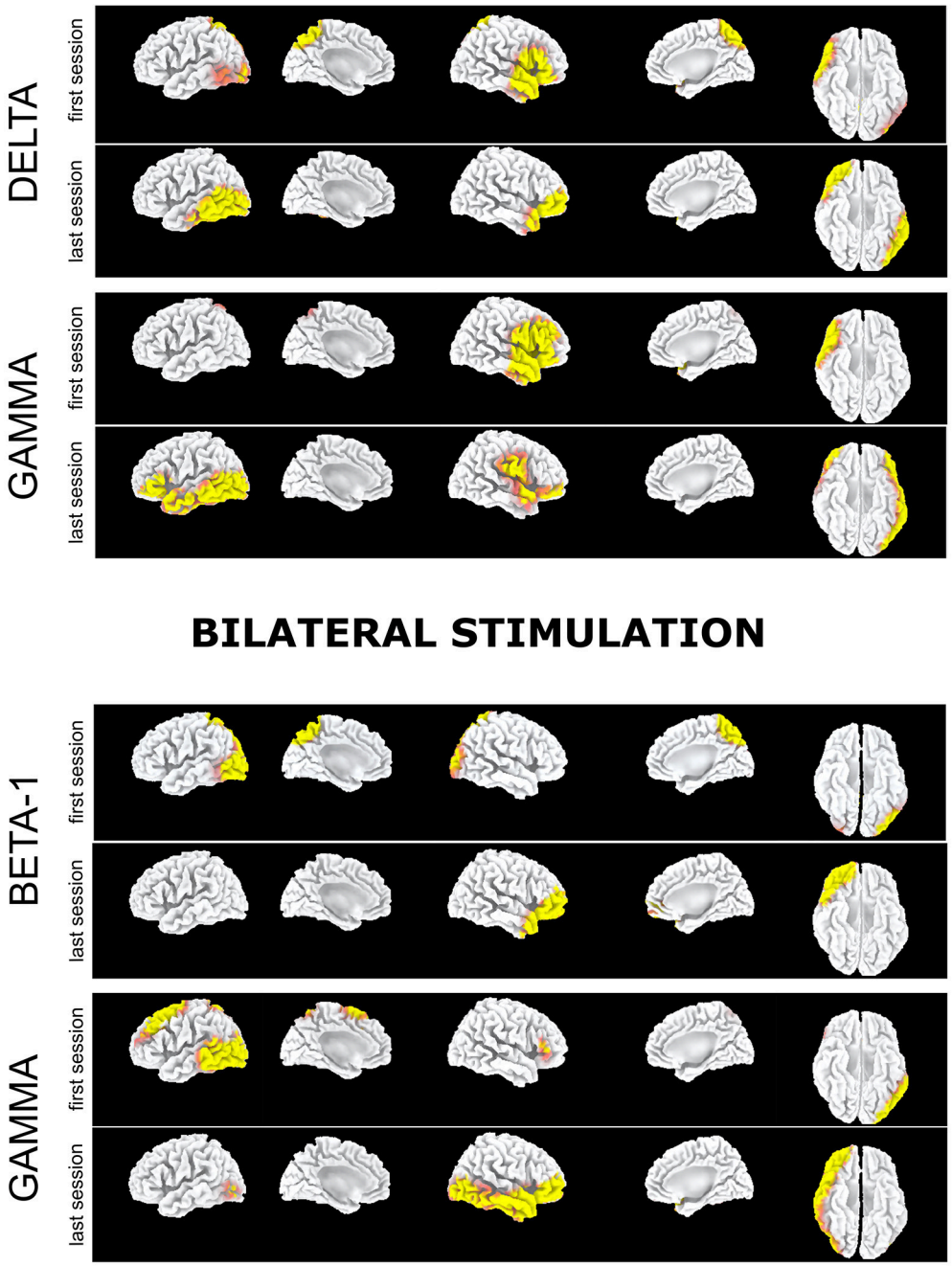

FIGURE 1 | Subject 1 (AR): Delta band: Preferential activation during script listening upon the first (above) and the last (below) EMDR sessions. Gamma band: Preferential activation during script listening upon the first (above) and the last (below) EMDR sessions. Beta1 band: Preferential activation during bilateral stimulation upon the first (above) and the last (below) EMDR sessions. Gamma band: Preferential activation during bilateral stimulation upon the first (above) and the last (below) EMDR sessions.

FDG-PET showed at T0, as compared to the control group, significant hypometabolism in left visual association cortex and right precuneus, posterior cingulate cortex and thalamus that was unchanged after therapy. On the other hand, a significant hypermetabolic area in bilateral prefrontal and anterior cingulate cortex appeared post-EMDR and the large hypermetabolic clusters found pre-EMDR in motor, temporo-parietal, and orbitofrontal cortices

decreased in size and significance level after therapy (**Table 3**, **Figure 3A**).

Subject 2 (ED)

Post-EMDR there was an improvement in short term memory (Digit Span), semantic memory (Babcock imm) and abstract reasoning (Raven's Progressive Matrices, **Table 1**). Also, CAPS score decreased significantly underscoring the remarkable reduction of symptoms. On the other hand, the scores of the self-administered questionnaires were already within the normal values pre-EMDR and did not change (**Table 2**).

The memories of the accident were few and nonspecific both pre- and post-EMDR. After therapy ED showed an improvement in forward looking and a great reduction of the anhedonia. A reduction in avoidance (meeting people he knew before the neurological impairment occurred), irritability and neurovegetative symptoms was also observed.

At the last EMDR session, EEG during script listening showed a reduction at low frequencies (**Figure 2**, script listening, delta band) or at high frequencies (**Figure 2**, script listening, beta-2 band) of the preferential cortical activation found during the first session in bilateral prefrontal cortex and temporal pole.

Such preferential activations were not recorded during bilateral stimulation in which at T1 as compared to T0 an increased cortical activation was found in left parieto-occipital cortex in theta band (**Figure 2**, bilateral stimulation). Notably in this subject during bilateral stimulation an activation in right associative visual cortex was systematically found during both sessions and a faint activation in left prefrontal cortex appeared at T1 in theta and beta-2 bands (**Figure 2**, bilateral stimulation) .

FDG-PET highlighted the disappearance during the last session of the hypometabolism found at T0, beside several temporal and anterior and posterior cingulate areas (**Table 4**), in parahippocampal and fusiform gyrus. In agreement with the EEG findings, at T1 a relatively higher metabolism was found in right precuneus, parietal, and posterior cingulate cortex as compared to T0 as well as a relative hypermetabolism in left putamen and orbitofrontal cortex (**Table 5**, **Figure 3B**). The hypermetabolism found at T0 in right orbitofrontal and temporal cortex did not substantially changed.

DISCUSSION

The aim of the present study was two-fold: (i) evaluate the efficacy of EMDR in treating the post-traumatic psychological sequelae

TABLE 3 | Cerebral regions showing in Subject 1 (AR) a significantly higher metabolism at PET as compared to a group of 18 control subjects.

AR POST EMDR vs. CTRL		**Hypermetabolic areas**					
Cluster size	**Cluster level**	**Peak**	**Talairach coordinates**			**Cerebral regions**	**Brodmann areas**
equivk	**p(FWE-corr)**	**Equivalent Z-score**	**x**	**Y**	**z**		
698	0.0000	6.15	40	−30	−15	R Fusiform Gyrus	20
		5.45	65	−43	−5	R Middle Temporal Gyrus	21
288	0.0001	5.58	46	−28	29	R Inferior Parietal Lobule	40
244	0.0003	5.54	63	−36	18	R Superior Temporal Gyrus	22
311	0.0001	5.40	−18	−31	49	L Paracentral Lobule	5
		4.99	−22	−21	45	L Precentral Gyrus	4
398	0.0000	5.09	26	16	3	R Lentiform Nucleus	Putamen
		4.73	22	15	−16	R Inferior Frontal Gyrus	47
562	0.0000	4.90	24	41	2	**R Anterior Cingulate**	**32**
		4.89	40	58	−6	**R Middle Frontal Gyrus**	**10**
181	0.0014	4.57	−18	54	−6	**L Superior Frontal Gyrus**	**10**
AR PRE EMDR vs. CTRL							
1,344	0.0000	6.11	42.0	−32.0	−17.0	R Fusiform Gyrus	20
		5.79	65.0	−49.0	−1.0	R Middle Temporal Gyrus	21
		5.70	63.0	−36.0	18.0	R Superior Temporal Gyrus	22
652	0.0000	5.62	44.0	−28.0	29.0	R Postcentral Gyrus	2
		4.54	63.0	−31.0	35.0	R Inferior Parietal Lobule	40
		5.22	−18.0	−31.0	49.0	L Paracentral Lobule	5
397	0.0000	5.08	−22.0	−21.0	45.0	L Precentral Gyrus	4
		5.13	24.0	15.0	−16.0	R Inferior Frontal Gyrus	47
458	0.0000	5.07	26.0	16.0	3.0	R Lentiform Nucleus	Putamen
		4.93	24.0	43.0	2.0	R Superior Frontal Gyrus	22
373	0.0000	4.60	28.0	48.0	−9.0	R Middle Frontal Gyrus	11

In bold the regions showing a significant change between the two conditions.

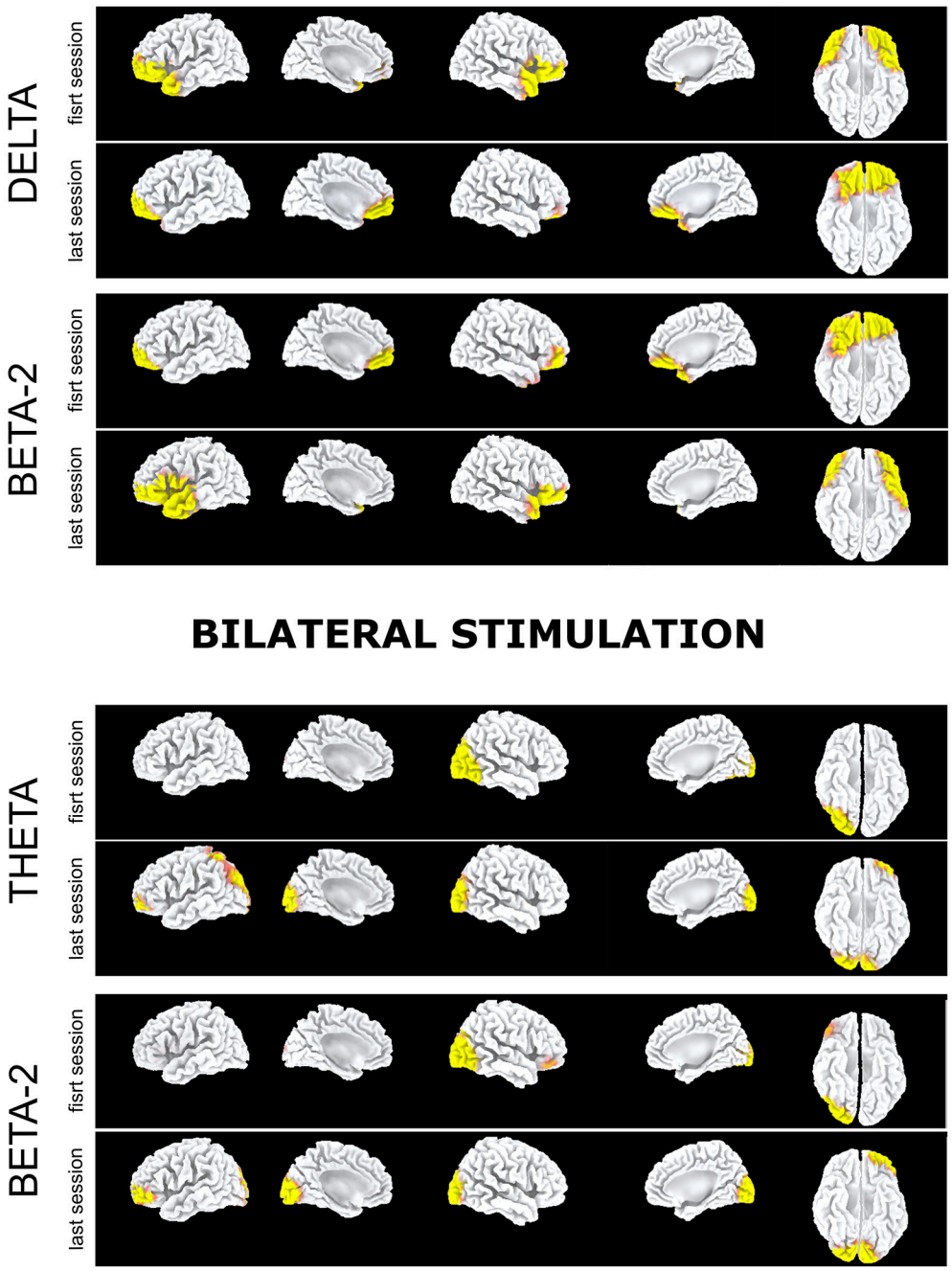

FIGURE 2 | Subject 2 (ED): Delta band. Preferential activation during script listening upon the first (above) and the last (below) EMDR sessions; Beta2 band. Preferential activation during script listening upon the first (above) and the last (below) EMDR sessions; Theta band. Preferential activation during bilateral stimulation upon the first (above) and the last (below) EMDR sessions; Beta2 band. Preferential activation during bilateral stimulation upon the first (above) and the last (below) EMDR sessions.

of life-threatening traffic accidents followed by a comatose state; (ii) perform a complete neurobiological evaluation of the therapy outcome adding the metabolic status to the assessment of the cortical electrical activity.

The general neurocognitive status was not substantially modified by EMDR therapy with poor performances in the most of neurocognitive test both before and after therapy. However, in both subjects there was an improvement in the

TABLE 4 | Cerebral regions showing in Subject 2 (ED) a significantly lower metabolism as compared to a group of 18 control subjects.

CTRL vs. ED POST EMDR		**Hypometabolic areas**					
Cluster size	**Cluster level**	**Peak**	**Talairach coordinates**			**Cerebral regions**	**Brodmann areas**
equivk	**p(FWE-corr)**	**Equivalent Z-score**	**x**	**y**	**z**		
4,174	0.0000	6.26	61	−40	−15	Right Inferior Temporal Gyrus	20
		5.78	12	−29	0	Right Thalamus	*
364	0.0000	5.06	−4	−30	29	Left Posterior Cingulate	23
		4.81	6	−28	29	Right Posterior Cingulate	23
2,596	0.0000	4.91	4	19	36	Right Anterior Cingulate	32
		4.80	−2	43	13	Left Anterior Cingulate	32
CTRL vs. ED PRE EMDR							
4,270	0.0000	6.27	61	−44	−15	Right Middle Temporal Gyrus	20
		5.74	12	−29	0	Right Thalamus	*
400	0.0000	4.98	−4	−30	29	Left Posterior Cingulate	23
		4.75	6	−26	31	Right Posterior Cingulate	23
1,919	0.0000	4.96	2	25	28	Right Anterior Cingulate	32
		4.71	−2	45	14	**Left Medial Frontal Gyrus**	**9**
		4.94	−22	−15	−28	**Left Parahippocampal Gyrus**	**35**
122	0.0076	4.90	0	−61	20	Left Precuneus	23
133	0.0054	3.94	8	−56	14	Right Posterior Cingulate	23
122	0.0076	4.08	−22	−51	−9	**Left Fusiform Gyrus**	**37**

In bold the regions showing a significant change between the two conditions.

TABLE 5 | Cerebral regions showing in Subject 2 (ED) a significantly higher metabolism at PET as compared to a group of 18 control subjects.

ED POST EMDR vs. CTRL		**Hypermetabolic areas**					
Cluster size	**Cluster level**	**Peak**	**Talairach coordinates**			**Cerebral regions**	**Brodmann areas**
equivk	**p(FWE-corr)**	**Equivalent Z-score**	**x**	**y**	**z**		
786	0.0000	5.44	22	42	−9	Right Middle Frontal Gyrus	11
		5.13	22	15	−16	Right Inferior Frontal Gyrus	47
		4.86	26	16	1	Right Lentiform Nucleus	Putamen
515	0.0000	5.22	40	0	−34	Right Inferior Temporal Gyrus	20
		4.67	53	1	−24	Right Middle Temporal Gyrus	21
		4.58	44	12	−29	Right Superior Temporal Gyrus	38
230	0.0004	5.11	−46	−13	19	**Left Postcentral Gyrus**	**43**
285	0.0001	4.77	18	−29	49	**Right Paracentral Lobule**	**5**
		4.61	18	−44	57	**Right Precuneus**	**7**
		4.35	22	−23	45	**Right Posterior Cingulate**	**31**
234	0.0003	4.64	−22	15	−4	**Left Lentiform Nucleus**	**Putamen**
		4.37	−22	13	−16	**Left Inferior Frontal Gyrus**	**47**
ED PRE EMDR vs. CTRL							
759	0.0000	5.27	24	42	−7	Right Middle Frontal Gyrus	11
		5.16	18	31	−8	Right Sub-Gyral	47
		5.14	26	16	3	Right Lentiform Nucleus	Putamen
322	0.0000	4.90	40	0	−30	Right Middle Temporal Gyrus	21
		6.44	44	10	−29	Right Superior Temporal Gyrus	38

In bold the regions showing a significant change between the two conditions.

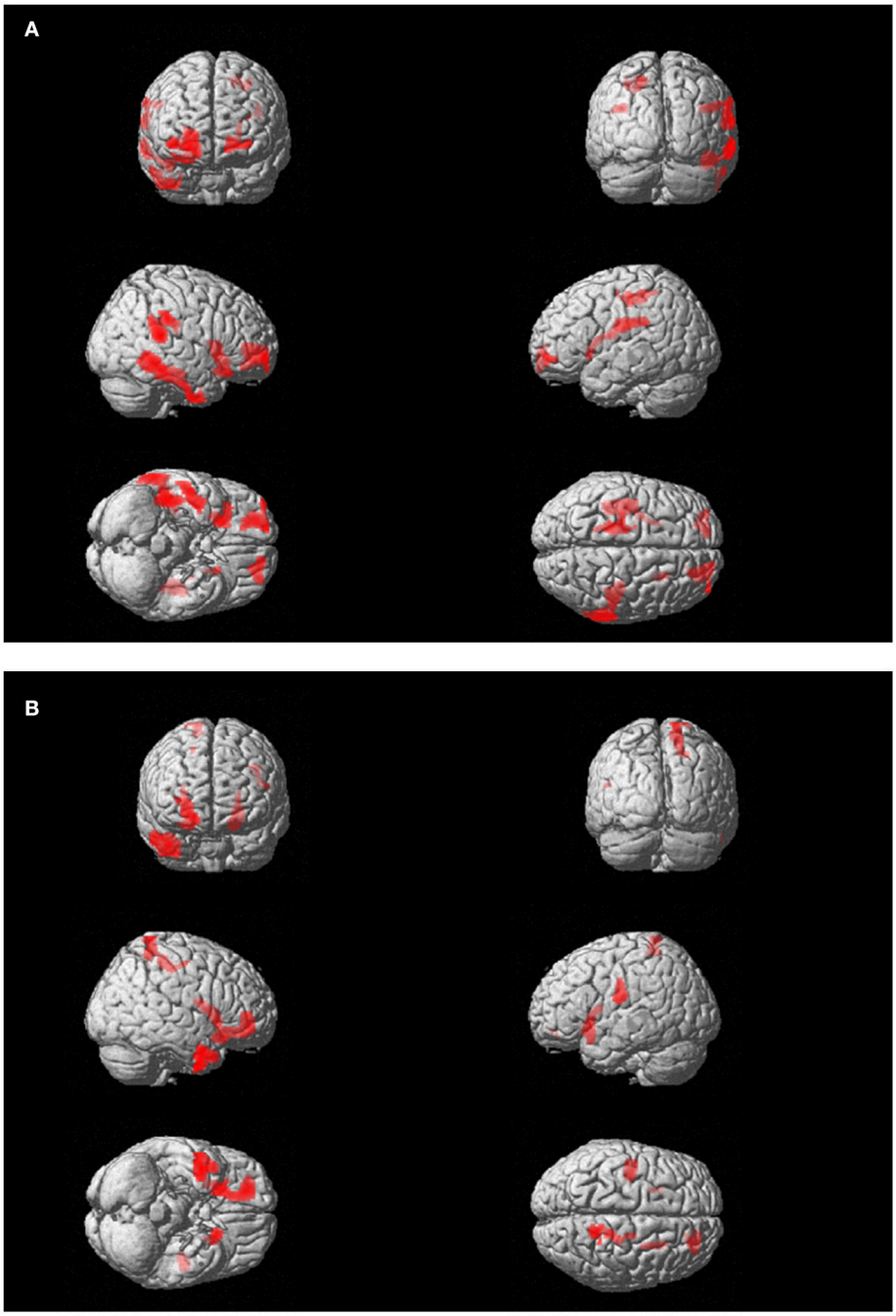

FIGURE 3 | (A) Subject 1 (AR): PET findings in AR post-EMDR compared with 18 control subjects. Statistically significant different hypermetabolic regions p(FWE-corr) are highlighted on a glass-brain template. Top left frontal view; top right posterior view, middle right-side view; middle right: left-side view; bottom left: view from below; bottom right: view from above. **(B)** Subject 2 (ED): PET findings in ED post-EMDR compared with 18 control subjects. Statistically significant different hypermetabolic regions p(FWE-corr) are highlighted on a glass-brain template. Top left frontal view; top right posterior view, middle right-side view; middle right: left-side view; bottom left: view from below; bottom right: view from above.

scores of tests reflecting abstract reasoning and verbal memory and AR had a significant progress toward the normative values in visuospatial abilities (**Table 1**). The improvement in these constructs was possibly associated at T1 to a better attention and verbal understanding as well as to a reduction in depressive mood that might have influenced the results of the tests pre-EMDR.

EMDR was very effective in reducing PTSD symptoms in both subjects. CAPS scores decreased significantly in all

subscales (relieving, avoidance, arousal, and association) and the two subjects showed clinical improvement with symptoms reduction (**Table 2**). In both subjects, there was a decrease in avoiding either people associated to the accident (AR) or known before the neurological impairment occurred (ED). Furthermore, all symptoms reported pre-EMDR as intrusive thoughts, hyperarousal, sleep disturbances, irritability, and vegetative symptoms were greatly reduced.

Furthermore, for AR the significant decrease of the scores of IES, BDI, and DES scales spoke in favor of a post-EMDR drop of post-traumatic, depressive, and dissociative symptoms. The appropriateness of self-administered questionnaires to depict neurobiological changes occurring before and after therapy has been demonstrated by two recent investigations in which the neuropsychological scores highly correlated with the activation induced by trauma exposure in the same regions in which functional changes between the two conditions were found (Nardo et al., 2011; Trentini et al., 2015).

Post-Traumatic stress disorder results in well-known alterations affecting cortical and subcortical regions. Several studies converge in ascribing to the hyperactivation of the limbic structures and to an insufficient cortical control upon reliving of negative emotion the neurobiological core of PTSD (Shin et al., 2006). Decreased top-down cognitive control of the prefrontal and the anterior cingulate cortices results during stressful conditions in an abnormal response of amygdala, hippocampus, and insula causing PTSD symptoms to appear. On the other hand, inconsistent results have described (reduction or no changes) in hippocampal volume and a few investigations have reported gray matter volume or density reduction in other structures (Nardo et al., 2010, 2013; O'doherty et al., 2015, 2017; Wrocklage et al., 2017).

EMDR has been recognized as elective treatment in reducing PTSD symptoms (Lehman et al., 2004; Bisson et al., 2013; Tol et al., 2013) and it has also been proven to be useful in other pathological conditions as depression (Acarturk et al., 2018); bipolar disorder (Moreno-Alcazar et al., 2017), chronic pain (Tesarz et al., 2014), and substance use disorder (Schafer et al., 2017). To the best of our knowledge this is the first study investigating EMDR efficacy also in case of severe physical trauma followed by brain anatomical and functional changes. Furthermore, in both the investigated cases clinical evidence of psychopathological and cognitive symptoms was still actual after more than 8 years from the event, suggesting the presence of a chronic PTSD associated with deteriorated brain conditions. Both subjects suffered of extensive neuronal damage. White matter as well as gray matter structural changes were found in cortical and subcortical regions with large post-traumatic encephalomalacia in occipital cortex, possibly consequence of the severe brain concussion. Furthermore, both subjects showed neurological deficits with impairment in motor, visuospatial, and various cognitive functions.

In our study, the neurobiological effect of EMDR went beyond the normalization of the dysfunctional cortico-limbic response as demonstrated by recent studies (Pagani et al., 2012, 2015; Trentini et al., 2015) and could overcome the impact that organic damage had on subjects' psychopathology.

For the first time, PET was performed to test the metabolic changes following EMDR therapy. Previous studies revealed following Cognitive Behavioral Therapy decreased FDG-PET resting state glucose metabolism in frontal regions and increased metabolism in anterior cingulate gyrus and related regions (Goldapple et al., 2004) as well as increased metabolism in anterior cingulate gyrus and related regions (Kennedy et al., 2007). Accordingly, SPECT investigations assessing cerebral blood flow (CBF), normally coupled with metabolism and performed before and after psychotherapy, showed frontal CBF changes associated with symptoms disappearance (Lansing et al., 2005; Pagani et al., 2007; Peres et al., 2007; Lindauer et al., 2008). Functional neuroimaging methodologies have been refined in the last decades with improvements in whole brain (Friston et al., 1991) and regional (Thurfjell et al., 2000) analyses. Both SPECT (Bonne et al., 2003; Pagani et al., 2005b, 2007; Lindauer et al., 2008; Nardo et al., 2015) and PET (Bremner et al., 1999, 2003; Shin et al., 1999, 2004; Gilboa et al., 2004) investigations have been performed to disclose in PTSD the regional activations upon the reliving of the traumatic event submitting to the experimental subjects sensory stimuli (visual or auditory), often with a strong autobiographical connotation. Such studies have been conclusive in disclosing the neurobiological model of PTSD above described.

Due to the dynamics of the accidents and of the subsequent brain damage we found in the two subjects at T0 in both EEG and PET examinations different electrical cortical and metabolic patterns which changed significantly after EMDR therapy.

It has to be underscored that in the present study EEG was recorded during active emotional stimulations (script listening or during phase four of EMDR therapy) while PET examinations were performed in the so-called resting state, when a participant is asked to lie quietly in the scanner without performing any specific task. In this condition signal increases and decreases are due to spontaneous or "intrinsic" neuronal fluctuations upon radiopharmaceutical administration and the following 10–20 min in which the concentration in the brain reaches a steady-state. Metabolic resting-state data depict the pattern characteristic of normal psychology and psychological disorders as well as psychological functions associated with the self. In the case of traumatized individuals, the rumination and the mental wandering within the scanner gantry may result, beyond the neurodegenerative status, in hypo-or hyperactivations characterizing their psychopathological status and hence being unique for each subject. In our two subjects, PET was able to capture such condition of distress and represent its metabolic pattern. As expected from the MRI findings, AR showed a severe hypometabolism in left visual association cortex in the occipito-parietal lobes that did not show any change post-EMDR. As compared to the control subjects, large areas of hypermetabolism that were found in temporoparietal cortex at T0 diminishing significantly at T1 (**Table 3**). However, in accordance with the EEG findings during both script listening and bilateral stimulation a new hypermetabolic cluster appeared in prefrontal and anterior cingulate cortex, speaking in favor of a possible better top-down control on the subcortical hyperarousal (**Figures 1**, **3A**). A similar concordance of findings was present in ED in which EEG upon bilateral stimulation showed at T1 an

activation of the right prefrontal cortex similar to the one found post-EMDR by PET. As discussed above the two methodologies as applied in the present study are different in nature. EEG captured the preferential cortical electrical activation during specific tasks while PET was performed in a (theoretical) resting state, depicting a more static metabolic status. However, it can be speculated that following successful EMDR therapy state (EEG) and trait (PET) conditions may converge into similar patterns. In this respect, the increased relative activation of prefrontal cortex at T1 in both subjects and disclosed by both methodologies may reflect as the successful attempt of cortical structures to reduce the subcortical hyperarousal, hypothesis supported by the great improvement in clinical status.

On the other hand, beside the changes toward a more preeminent activity in prefrontal cortex, both methodologies showed changes in other regions. EEG showed in AR at T1large shifts in cortical activation in temporo-occipital cortex (**Figure 1**), previously identified as the region mostly activated when PTSD symptoms disappear following successful EMDR therapy (Pagani et al., 2012, 2015) while in ED the activation state induced by both script listening and traumatic exposure was pretty similar in both conditions (**Figure 2**).

Similarly, metabolism in both subjects showed not only the prefrontal and anterior cingulate increase at T1 but increased in both conditions as compared to the control group in temporo-parietal regions (**Tables 3**, **5**) probably due to ruminating emotional thoughts during radiopharmaceutical administration and time before the scanning. In ED, the reduction of PTSD symptoms was associated with the disappearance of the hypometabolism in parahippocampal cortex and in the fusiform gyrus, regions known to be implicated in the pathophysiology of PTSD (**Table 4**).

In the case of PET, the metabolic changes were not assessed by a within-subject experimental design since the background noise (signal variability) in individual scan would have been excessive for a one-to-one scan comparison making the results of the analyses unreliable. We then chose to compare the data of the pre-EMDR PET scan of each subject to a set of scans of age-matched controls and run the same comparison again using the post-EMDR PET data. This kind of analysis was recently validated (Lange et al., 2016) and it is currently used in clinical setting to assist physicians in the diagnosis of neurodegenerative diseases (Gallivanone et al., 2017). In this way, we matched to the very same reference (eighteen control subjects) the individual scans pre- and post-EMDR being able to appreciate the changes occurring from the first to the second condition.

As the most of pilot studies, the present investigation suffers of some limitations, due to the inherent nature of the experiment (case reports). We did not include into the design of the study subjects undergoing the same traumatic event and not treated by EMDR. This prevented a controlled cause-effect link between the improvement of clinical condition and psychotherapy as well as the generalizability of our results to other cases of traumatic brain injury. Recruiting such individuals would have required an extensive retrospective screening identifying subjects with similar characteristic and duration of symptoms. It would have needed resources not available and was beyond the purpose of the present pilot investigation. However, the study was tailored for the two subjects according to their clinical condition and needs. Indeed, they were suffering since many years of post-traumatic symptoms related to the brain concussion as a result of traffic accident. We believe that the fact that EMDR could clearly mitigate the post-traumatic symptoms after more than 8 years in which they did not undergo any psychotherapy is a proof of concept of its effectiveness.

This limitation might be overcome by the recruitment in a prospective study of individuals suffering traumatic brain injury and randomized after the acute phase into two groups, one treated as usual and the other by EMDR. Such experimental design along with careful neuropsychological, neurophysiological and metabolic assessment of the respective outcomes might more reliably support the conclusions of the present pilot study. The hypothesis of this design would have to differ slightly from the present study. Because chronic PTSD would not have had time to develop, outcome measures would include incidence and severity of long-term psychological trauma in addition to comparative metabolic and electrophysiological changes in the two groups.

The two subjects showed a neurobiological response that was not directly comparable and, mainly at EEG, changes occurred in different regions. These inconsistencies derive firstly from the different individual response to emotional trauma exposition and to therapy, associated to the differences in pattern of injury between the two individuals underlying their neurocognitive state and secondly from the different neurological and anatomical functional deficits that each subject suffered as a result. Furthermore, the latter structural changes caused both PET and EEG to detect regional changes very likely deriving also from disrupted neuronal networks resulting in patterns of metabolism and cortical activation not applicable to a population of patients suffering of traumatic brain injury in which the anatomical damage and functional impairment vary from case to case.

Following the present promising pilot study in the next future attempts might be performed to investigate ^{18}F-FDFG-PET upon exposure to a psychological stress following a recent study in which olfactory stimulation was administered for about 10 min to the experimental subject (Chiaravalloti et al., 2015). Such experimental protocol would enable a direct correspondence upon traumatic exposure between electrical cortical activity and metabolic response allowing a better definition of the limbic and cortical regions implicated in the emotional process, due to the better spatial resolution of PET for sub-cortical structures as compared to EEG.

In conclusion, EMDR was proven to be clinically useful in two difficult cases of chronic PTSD due to severe physical trauma. This first ever investigation combining neuropsychological and psychopathological tests, EEG, PET, and EMDR yielded very promising results showing neurobiological changes following successful therapy as revealed by all measurements. The refinement of PET procedures allowing a dynamic assessment of the metabolic changes and the use of EEG instruments with larger number of sensors and more sophisticated software will in the future allow to more deeply investigate the association between electric cortical activity and metabolic changes.

AUTHOR CONTRIBUTIONS

MP, GC, IF and GD: study concept and design; PL, AD, LM, GD, AC, and FF: acquisition of data; MP, AC, AD, LM, GD, and FF: analysis and interpretation of data; MP, GC, AD, and FF: Drafting of the manuscript; MP, GC, AD, IF and AC: Critical revision of the manuscript for important intellectual content; MP and IF: obtained funding; AD, LM, FF, and AC: administrative, technical, and material support.

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Psychological and Brain Connectivity Changes Following Trauma-Focused CBT and EMDR Treatment in Single-Episode PTSD Patients

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Among the different therapeutic alternatives for post-traumatic stress disorder (PTSD), Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT) and Eye Movement Desensitization and Reprocessing (EMDR) Therapy have shown promising results in helping patients cope with PTSD symptoms. However, given the different theoretical and methodological substrate of TF-CBT and EMDR, a potentially different impact on the brain for the two interventions could be hypothesized, as well as an interaction between trauma-specific PTSD symptomatology and response to a given psychotherapy. In this study, we monitored psychological and spontaneous functional connectivity fMRI patterns in two groups of PTSD patients who suffered by the same traumatic event (i.e., natural disaster), before and after a cycle of psychotherapy sessions based on TF-CBT and EMDR. Thirty-seven (37) PTSD patients were enrolled from a larger sample of people exposed to a single, acute psychological stress (i.e., 2002 earthquake in San Giuliano di Puglia, Italy). Patients were randomly assigned to TF-CBT (n = 14) or EMDR (n = 17) psychotherapy. Clinical assessment was performed using the Clinician-Administered PTSD Scale (CAPS), the Davidson Trauma Scale (DTS) and the Work and Social Adjustment Scale (WSAS), both at baseline and after treatment. All patients underwent a fMRI data acquisition session before and after treatment, aimed at characterizing their functional connectivity (FC) profile at rest, as well as potential connectivity changes associated with the clinical impact of psychotherapy. Both EMDR and TF-CBT induced statistically significant changes in clinical scores, with no difference in the clinical impact of the two treatments. Specific changes in FC correlated with the improvement at the different clinical scores, and differently for EMDR and TF-CBT. However, a similarity in the connectivity changes associated with changes in CAPS in both groups was also observed. Specifically, changes at CAPS in the entire sample correlated with an (i) increase in connectivity between the bilateral superior medial frontal

gyrus and right temporal pole, and a (ii) decrease in connectivity between left cuneus and left temporal pole. Results point to a similar, beneficial psychological impact of EMDR and TF-CBT for treatment of natural-disaster PTSD patients. Neuroimaging data suggest a similar neurophysiological substrate for clinical improvement following EMDR and TF-CBT, involving changes affecting bilateral temporal pole connectivity.

Keywords: EMDR, fMRI, PTSD, connectivity, psychotherapy, MRI, CBT

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a psychiatric illness caused by traumatic events, usually developed after exposure to trauma such as physical or sexual assault, injury, combat-related trauma, natural disaster or death, but also after witnessing or indirect exposure (APA Association, 2013, October 3, 2013). It is estimated that, during lifetime, 60.7% of men and 51.2% of women experience at least one potentially traumatic event such as being taken hostage or being kidnaped, experiencing or witnessing sexual or physical assault, torture, a terrorist attack, a severe car accident, a natural disaster, war, or the unexpected death of a beloved person (Kessler et al., 1995). Of those experiencing potentially traumatic events, 10–40% develop psychiatric symptoms of clinical relevance (Breslau et al., 1999; Odonnell et al., 2008) such as affective disorders, substance abuse, or PTSD. PTSD is configured as a complex syndrome with pathognomonic symptomatology that includes re-experiencing of trauma-related aspects (i.e., flashbacks), avoidance of trauma-related situations, hyperarousal and emotional numbing, together with cognitive symptoms including impoverished auto-biographical memory for positive events (Harvey et al., 1998), attention and working memory deficits (Scott et al., 2015), enhanced arousal induced by trauma-related stimuli (Karl et al., 2006), as well as decreased social functioning (Fontana and Rosenheck, 2010). These features highlight the need for understanding the neurobiological basis of stress vulnerability (Brunetti et al., 2017), the impact of PTSD on the brain as well as the neural effect of treatment interventions.

Diverse pharmacological and psychotherapeutic approaches for PTSD treatment have been suggested, with psychotherapy being considered the gold standard, whereas pharmacological treatment is conceptualized as a form of symptoms control. Among the various alternatives, trauma-focused psychotherapeutic approaches such as trauma-focused cognitive behavioral therapy (TF-CBT), eye movement desensitization and reprocessing (EMDR), and exposure therapy (ET) are the most widely used (Gillies et al., 2012), with recent promising evidence also for mindfulness-based therapies (King et al., 2016a,b). Despite differences in session-to-session patient management and behavioral techniques, TF-CBT, EMDR and ET all focus on re-elaborating traumatic events or memories, favoring the emergence of new positive attitudes at the behavioral and cognitive level, leading to fear extinction and habituation. In particular, TF-CBT and EMDR further stress the cognitive component of therapeutic process, strengthening top-down cognitive control (Robertson et al., 2004). Specifically, TF-CBT helps patients to question and modify dysfunctional trauma-associated cognitions. *In vivo* or *in sensu* confrontation with trauma reminders helps patients to overcome their avoidance of trauma-related situations and thoughts, which leads to habituation and normalization of trauma memories. Besides habituation and conditioning, increased modulation of attentional processing and cognitive control are also associated to successful TF-CBT. Differently, during EMDR, patients mentally focus a trauma-associated disturbing image, memory, emotion, or cognition. As a specific feature of EMDR, the exposure is usually short and intermixed with saccadic eye movements initiated by the therapist (Herkt et al., 2014). The neurophysiological mechanism(s) behind the effect of saccadic movements is not clear, with hypotheses spanning from an unspecific, generalized relaxation achieved through activation of the parasympathetic system (followed by conditioning-based association with traumatic memories), to a decoupling between external attention and internal reprocessing of traumatic memories, which prevents patients from feeling overwhelmed (Davidson and Parker, 2001; Herkt et al., 2014).

Given the differences in treatment schedule and management, EMDR and TF-CBT could result in different therapeutic effects as well as different therapy-induced brain changes. Notably, multiple studies have addressed the impact of one or the other approach on both clinical and neurobiological patients' profile, using neuroimaging techniques such as functional and structural magnetic resonance imaging (MRI, fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) (Malejko et al. (2017). However, a direct comparison of the brain changes induced by the two interventions has not been performed. Most importantly, the type of trauma leading to PTSD has been shown to be a significant modulator of both patients' clinical and neuroimaging profile, leading to different physical and behavioral outcomes as well as different prevalence of PTSD. For instance, natural disaster/terrorism seems more associated with cardiovascular disease, gastrointestinal disease and arthritis, while combat-related trauma is not associated with any physical condition (Husarewycz et al., 2014). As for PTSD-related brain changes, morphometric and functional brain abnormalities in PTSD patients have been shown to follow different patterns for specific types of trauma as well (Meng et al., 2016).

In the present investigation we focused on monitoring the clinical and brain impact of TF-CBT and EMDR in a sample of PTSD patients who underwent the very same traumatic experience (i.e., natural disaster, ND). We collected data on a group of PTSD patients who survived an earthquake in Italy in 2002. Patients were screened at the Department of Psychiatry

of Le Scotte Hospital in Siena (Italy), and underwent both a clinical and a neuroimaging assessment based on MRI/fMRI. Patients were then assigned to a psychotherapy intervention based on either TF-CBT or EMDR. For the present study, we focused on assessing the impact of both TF-CBT and EMDR on patterns of functional connectivity (FC) as those measured via resting-state fMRI (rs-fMRI) analysis. Rs-fMRI evaluates regional spontaneous interactions that occur when a subject is not performing an explicit task, and has proved to be an informative and reliable research tool to understand individual differences in cognition (Biswal et al., 2010) as well as provide insights into the pathophysiology of neurological (Liao et al., 2010; Santarnecchi et al., 2012; Balthazar et al., 2013) and psychiatric conditions (Bassett et al., 2008; Anderson et al., 2011). Several studies have examined resting brain activity in PTSD patients (for a review see Wang et al., 2016), revealing significantly different spontaneous activity in cortical regions [e.g., superior temporal gyrus, medial prefrontal cortex (mPFC), inferior parietal lobule and middle occipital gyrus], limbic areas (e.g., the amygdala, hippocampus, insula, thalamus, and ACC), and even in the cerebellum. However, results are somehow inconsistent. For instance, some studies focusing on the insula have reported either increased (Yan et al., 2013), decreased (Yin et al., 2011; Zhu et al., 2014) or even no insula activation (Shin et al., 2009; Kim et al., 2012) in PTSD patients. As suggested above, differences in clinical profile, type of trauma and even neuroimaging analysis methods might be the cause of such variability. As for the latter, it is important to notice that several rs-fMRI studies have adopted *a priori* regions of interest (ROIs) based on theoretical models or previous reports, thus leading to inflation of positive results regarding one specific brain region or network to the detriment of a more comprehensive understanding of trauma-induced rearrangement of whole-brain connectivity. For instance, studies on the impact of PTSD on regions such as the amygdala usually report a strong support in the notion of PTSD being driven by hyper-excitability of such structure, but at the same time neglect potential changes in other structures yet to be included in models and theories (e.g., cerebellum, motor system, and thalamus). The vast majority of studies reporting amygdala-related alterations in PTSD are based on *a priori* defined ROI analysis (for a few example see Shin et al., 2005, 2009; Fonzo et al., 2010; Linnman et al., 2011; Sripada et al., 2012; Bruce et al., 2013; Stevens et al., 2013), i.e., they are explicitly looking just at the fMRI signal from the amygdala both during an emotion-provoking task or resting-state, neglecting activity in the rest of the brain. Additionally, to apply a ROI-based analysis also decrease the number of multiple comparisons and increases statistical power, resulting in a series of significant reports about one specific region that might be actually misleading for the comprehension of PTSD neurobiology.

Therefore, the present study explored the impact of EMDR and TF-CBT psychotherapy on PTSD patients' FC patterns by adopting a validated whole-brain anatomical atlas used in previous reports (Smith et al., 2004; Makris et al., 2006), providing a parcellation of the entire brain, including cortical, subcortical and cerebellar structures. Given the theoretical and, most importantly, methodological differences between EMDR and TF-CBT, we hypothesized that (i) EMDR and TF-CBT will induce different changes in functional connectivity fMRI patterns after psychotherapy, with (ii) more pronounced changes in connectivity involving the visual system and higher-order associative regions for, respectively, EMDR and TF-CBT.

MATERIALS AND METHODS

Study Participants and Group Assignment

In 2002, a devastating earthquake caused, among other tragedies, the collapse of an elementary school (1st–5th grade) in San Giuliano di Puglia (Campobasso, Italy). As a result, 27 children and a schoolteacher died. For the present study, 31 PTSD patients were recruited among the population affected by the earthquake, including survivors of the building collapse and victim's family members (parents, siblings). All subjects, recruited between January and March 2012, reported a symptomatology centered around a traumatic memory related to the event. None of the subjects did undergo any previous trauma-focused psychotherapy.

Two psychotherapeutic interventions were offered to the patients, namely EMDR and TF-CBT. The patients were given the opportunity to decide when to start the therapy according to their schedules, with four treatment cycles starting between March and May 2012. Assignment to EMDR and TF-CBT was pseudo-randomized across patients, based on patients' trauma severity at presentation. Perfect balance in severity across groups was not achieved due to the distribution of severity levels toward the third and fourth treatment cycle. The final sample of participants who completed the study (i.e., both clinical and MRI data acquired before and after psychotherapy) included 14 patients in the TF-CBT group (9 male, age = 37.7 $\pm$ 12) and 17 in the EMDR one (10 male, age = 35.4 $\pm$ 14), out of the 37 patients (83.7%) originally enrolled in the study (17/19 EMDR, 14/18 TF-CBT). Even though not significant, a difference in drop-outs for TF-CBT and EMDR was present, possibly due to the different average length of the two therapeutic interventions (10 $\pm$ 2 weeks and 4 $\pm$ 2 weeks, respectively). Please see dedicated paragraphs about each intervention for further details. Given the different protocol followed for EMDR and TF-CBT (and corresponding differences in timing of pre–post clinical and fMRI assessments), the interval between baseline and post-therapy assessments was included as a covariate in all the analyses. We did not use a fix interval for pre–post assessment and instead preferred scanning/evaluating patients right after each psychotherapy cycle, i.e., at the moment of highest probability of showing a beneficial effect on psychological dimensions and/or changes in FC patterns. The protocol was approved by the university of Siena School of Medicine institutional ethics committee. All patients were given a description of the procedures and were asked to sign a written informed consent to participate in the study in accordance with the Declaration of Helsinki. For more information about demographics and clinical information of the sample, see **Table 1**.

Study Design

The study included a clinical evaluation and a neuroimaging data acquisition, performed before and after the cycle of psychotherapy sessions. In both occasions, patients traveled to Siena and spent 2 days performing the clinical and neuroimaging evaluations at Le Scotte Hospital. Clinical evaluations were performed by trained psychiatrists (L.B., A.F.) at the department of Psychiatry. All subjects were interviewed via the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) and the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995), whose completion required about 2 h. All subjects were also given two self-administered psychological questionnaires, the Davidson Trauma Scale (DTS; Davidson et al., 1997) and the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002). Details about the neuro-psychiatric assessment as well as MRI data and analysis are reported in dedicated paragraphs below. The psychotherapy sessions were coordinated by one of the authors (P.LP.) and carried out by certified professionals in San Giuliano di Puglia. Psychotherapy was followed by the same clinical and neuroimaging evaluations performed in Siena.

EMDR Therapy

The therapy followed a standard EMDR protocol (Shapiro, 2014) and was composed by eight steps. The EMDR session began with the identification of patients' most disturbing memory of the traumatic event, as well as of any associated negative belief, disturbing emotion and its bodily location. Patients were then asked to focus on these traumatic events while following the bilateral finger movements performed by the therapist for about 30 s. After each set of horizontal movements, the patients were prompt to share any emotion/flashback/percept they have been noticing during the visual stimulation. When the patients reported no more erupting emotional burst or any other feeling related to the target memory, the therapist assessed patient's ability to elaborate on the target with no emotional distress. The process was completed when the patient reported to be able to think about the traumatic experience with no disturbing emotions or somatic reactions. Other targets were then selected and the same procedure (i.e., trauma identification, visual stimulation, assessment) was repeated. The EMDR treatment ended when patients were able to visualize themselves in a future scenario where they were able to face the re-elaborated targets while feeling no emotional discomfort. In the present sample, the EMDR required an average of 4 weeks (±2) of weekly sessions per patient. Each session lasted for approximately an hour. EMDR was performed by two certified EMDR therapists.

TABLE 1 | Demographic and Clinical information for the TF-CBT and EMDR groups.

	TF-CBT	EMDR
N	14	17
Age	37.7 ± 12	35.4 ± 14
Education	12.4 ± 3	13.6 ± 4
Gender	9 M	10 M
Age at trauma	26.3 ± 9	28.6 ± 12
Previous traumatic event	39%	45%
PTSD duration	10 years	10 years
CAPS	45.7	57.6
DTS	16.6	14.1
WSAS	15.7	17.4

Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT)

Trauma-focused cognitive behavioral therapy is an evidence-based treatment model designed to assist children, adolescents, and their families in overcoming the symptomatology resulting from the exposure to a traumatic experience (Mannarino et al., 2012). TF-CBT is a skills-based model, whose core components include, among others: Psychoeducation, Affective regulation, Cognitive processing of the trauma, Trauma narrative, *in vivo* mastery of trauma reminders, and Enhancing future safety and development. In order to allow the comparison of EMDR and TF-CBT interventions, an *ad hoc* TF-CBT protocol was implemented, following a standardized organization of between and within session procedures and targets. The first session included a narrative recollection of the traumatic event, with patients describing the event multiple times (at least two). The second session included an explanation of the therapeutic plan, relaxation exercises, trauma-focused psychoeducation and introduction to the upcoming exposure exercise. The third visit included recollection of traumatic events, exposure, and home assignments. Fourth-to-ninth visits started with (i) a review of home assignment, followed (ii) by relaxation exercises prior to exposure and (iii) psychoeducation, which included the differentiation between anxiety-based (psychological) and somatic responses to stress, strategies for managing intrusive thoughts and thoughts-blocking techniques. Tenth-to-twelfth visits included Systematic desensitization (i.e., graduate exposure therapy), with the creation of a hierarchy of stressful situation. TF-CBT required an average of 10 weekly visits (±2) to be completed in the study sample.

Clinical Evaluation

Structured Clinical Interview for DSM-IV (SCID)

The Structured Clinical Interview for DSM-IV (SCID-I/SCID-II) (First et al., 1997) is a semi-structured clinical interview administered by trained clinicians and designed to yield psychiatric diagnoses consistent with DSM-IV/DSM-IV-TR (American Psychiatric Association) diagnostic criteria. The SCID is composed by open-ended questions introducing content areas, followed by a series of scripted questions. The SCID was administered via consensus of two trained psychiatrists.

Clinician-Administered PTSD Scale (CAPS)

The CAPS measures frequency and intensity of PTSD symptoms rated for the last-week period (Blake et al., 1995). Seventeen items describe the classical PTSD cluster symptoms: re-experiencing, avoidance and numbing, and hyperarousal. In addition to assessing the twenty DSM-5 PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall

response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and de-realization). The CAPS total score ranges from 0 to 136, and classifies PTSD as: 0–19: asymptomatic/few symptoms; 20–39: mild PTSD/subthreshold; 40–59: moderate PTSD/threshold; 60–79: severe PTSD symptoms; and ≥80: extreme PTSD symptoms.

Davidson Trauma Scale (DTS)

The DTS is a 17-item self-report measure that assesses the 17 DSM-IV symptoms of PTSD. Respondents are asked to identify the trauma that is most disturbing to them and to rate, in the past week, how much trouble they have had with each symptom. Items are rated on 5-points frequency (0 = "not at all" to 4 = "every day") and severity scales (0 = "not at all distressing" to 4 = "extremely distressing"). The DTS can be used to make a preliminary determination about whether the symptoms meet DSM criteria for PTSD, and also provides scores for three separate subscales referring to specific symptoms related to re-experiencing, avoidance/numbing and hyperarousal. Validation work showed the DTS performed well at discriminating 67 individuals with PTSD from 62 without PTSD [area under the curve (AUC) = 0.88, *SE* = 0.02] diagnosed using a semi-structured interview (SCID; Spitzer et al., 1992).

Work and Social Adjustment Scale (WSAS)

The WSAS is a self-report scale of functional impairment attributable to an identified problem (Mundt et al., 2002). The WSAS is a short measure of work and social adjustment, with good validity and reliability in several patients populations (e.g., depression and anxiety) (Zahra et al., 2014). A WSAS score above 20 suggest moderately severe psychopathology. Scores between 10 and 20 are associated with significant functional impairment but less severe clinical symptomatology. Scores below 10 are usually associated with subclinical populations.

Changes in Clinical Scores After EMDR/TF-CBT

Scores obtained at CAPS, DTS, and WSAS before and after the EMDR/TF-CBT treatments were analyzed using a repeated measures Analysis of Covariance Model (rp-ANCOVA), using a p-value < 0.05 and including age, gender, pre–post interval and education as covariates. Models were built for global scores as well as for each subscale of the CAPS and DTS.

MRI Data Acquisition

The MRI data was acquired on a Philips Intera whole-body MRI scanner. Resting-state fMRI data included 178 volumes with 33 axial slices covering the whole brain, acquired via a T2 BOLD-sensitive multi-slice echo planar imaging (EPI) sequence (TR/TE = 2.5 s/32 ms; field of view = 22 cm; image matrix = 64 × 64; voxel size = 3.44 mm × 3.44 mm × 3.8 mm; flip angle = 75°). Structural imaging was performed using a whole brain T1-weighted Fast Field Echo 1 mm^3 sequence (TR/TE = 30/4.6 ms, field of view = 250 mm, matrix 256 × 256, flip angle = 30°, slice number = 150). T2-weighted Fluid Attenuated Inverse Recovery Images (FLAIR) were also acquired to assess participants white matter integrity. Participants were provided with earplugs. Particular care was taken to minimize head motion via vacuum cushions and custom-made padding.

fMRI Preprocessing

fMRI data preprocessing and statistical analyses were carried out using SPM8 software (Statistical Parametric Mapping[1]) and MATLAB 7.5 (the MathWorks, Natick, MA, United States). The first three volumes were discarded for each subject to allow for steady-state magnetization. EPI images were slice-time corrected using the interleaved descending acquisition criteria, and realigned and re-sliced to correct for head motion using a mean functional volume derived from the overall fMRI scans. Subject whose head motion exceeded 1.0 mm or rotation exceeded 1.0° during scanning were excluded. In order to obtain a better estimation of brain tissues maps, we implemented an optimized segmentation and normalization process using DARTEL (Diffeomorphic Anatomical Registration using Exponential Lie Algebra) (Ashburner, 2007) module for SPM8. Briefly, this approach is based on the creation of a customized anatomical template built directly from participants T1-weighted images instead of the canonical one provided with SPM (MNI template, ICBM 152, Montreal Neurological Institute). This allows a finer normalization into standard space and consequently avoids under- or overestimation of brain regions volume possibly induced by the adoption of an external template. Hidden Markov Random Field model was applied in all segmentation processes in order to remove isolated voxels. Customized tissue prior images and T1-weighted template were smoothed using an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. Functional images were consequently non-linearly normalized to standard space and a voxel resampling to (isotropic) 3 mm × 3 mm × 3 mm were applied. Linear trends were removed to reduce the influence of the rising temperature of the MRI scanner and all functional volumes were band pass filtered at (0.01 Hz $< f < 0.08$ Hz) to reduce low-frequency drift. Finally, a CompCor algorithm has been applied in order to control physiological high-frequency respiratory and cardiac noise (Behzadi et al., 2007).

Functional Connectivity Analysis

FC was calculated by computing the Pearson product-moment correlation coefficient between the average BOLD time series extracted from each brain region composing the Harvard-Oxford atlas, an anatomical atlas covering 112 cortical and subcortical structures (Smith et al., 2004). A connectivity matrix was built based on each pairwise connectivity between the 112 regions. Pre- and Post- EMDR/TF-CBT matrices were then compared using a repeated measures Analysis of Co-Variance (rp-ANCOVA) model, using a statistical threshold equal to $p < 0.05$ at the single edge (i.e., connection) level with a $p < 0.05$ False Discovery Correction (FDR) for multiple comparison. Additionally, according to the network-based statistics framework proposed by Zalesky et al. (2012), an additional threshold was applied in order to isolate regions of significant changes in connectivity not due to the

[1] www.fil.ion.ucl.ac.uk/spm/

intrinsic positive manifold among the entire connectivity set. Analysis was done by testing the effect of two factors, i.e., "Time" and "Treatment," respectively, representing the data acquired before and after the psychotherapeutic interventions (2 levels = Pre, Post) and the different therapeutic approaches (2 levels = EMDR, TF-CBT). All the analyses included age, gender, pre–post interval, education and total brain volume as covariates.

In order to identify a common substrate for clinical changes observed in patients receiving EMDR and TF-CBT, patterns of overlapping changes in FC across groups were explored. In the case of regions whose connectivity profile showed similar correlations with clinical scores in both EMDR and TF-CBT groups, an additional analysis aimed at increase spatial resolution was also performed, by looking at seed-based FC changes. Specifically, selected regions were used as a seed, with their average BOLD signal being correlated with that of any other voxel of the brain, thus producing spatial correlation maps not relying on any anatomical parcellation scheme (for an example see **Figure 5**). For seed-based analysis, a $p < 0.05$ at single-voxel level (FDR corrected) and a $p < 0.05$ (cluster-based corrected) were applied.

Correlation With Clinical Scales

Given the aim of identifying clinically relevant changes in functional connectivity induced by EMDR and TF-CBT, the simple comparison of FC patterns before and after psychotherapy might be informative but also misleading. Any change in connectivity at the group level might reflect individual differences in response to therapy, as well as daily habits and other factors not related to the clinical benefit of EMDR/TF-CBT. Therefore, changes in FC were considered with respect to changes in clinical scores, i.e., CAPS, DTS, and WSAS. Separate rp-ANCOVA models were built for EMDR and TF-CBT, looking at which specific change in connectivity significantly explain changes in clinical scores.

RESULTS

Demographic and Clinical Profile

The two groups did not differ with respect to age ($t = 0.502$, $p = 0.620$), gender distribution ($X^2 = 0.396$, $p = 0.668$) and education ($t = 1.527$, $p = 0.140$). At the time of the study a sub-sample of patients was taking psychotropic drugs (EMDR = 4, 23%; TF-CBT = 2, 14%), with no statistically significant differences among groups ($X^2 = 0.362$, $p = 0.639$). As for medical comorbidities, two participants in the TF-CBT and three in the EMDR group reported other not-neurological/psychiatric medical conditions and were prescribed with corresponding drug therapy. Comorbidities included hypertension, diabetes and dysthyroidism. Patients were not asked to withdraw their therapy during the EMDR/TF-CBT treatment. The average scores for the different clinical scales (CAPs, DTS, and WSAS) collected at baseline evaluation in both groups are reported in **Figure 1**. Additional demographic and clinical information are reported in **Table 1**.

Clinical Impact of EMDR/TF-CBT

Clinician-Administered PTSD Scale (CAPs)

As shown in **Figure 1**, no significant Treatment*Time interaction was reported for CAPS *total* [$F_{(1,13)} = 0.15$, $p = 0.9$], with both a main effect of Time [$F_{(1,13)} = 7.81$, $p = 0.015$] and Treatment [$F_{(1,13)} = 50.38$, $p < 0.001$]. However, a marginally significant Treatment*Time effect for CAPS "*intrusive thoughts*" subscale was found [$F_{(1,13)} = 3.95$, $p = 0.068$], with a marginally main effect of Time [$F_{(1,13)} = 3.39$, $p = 0.04$] and a significant main effect of Treatment [$F_{(1,13)} = 43.14$, $p < 0.001$]. CAPS *avoidance* showed no significant Treatment*Time interaction [$F_{(1,13)} = 0.1$, $p = 0.74$], with significant main effect of Time [$F_{(1,13)} = 21.94$, $p < 0.001$] and Treatment [$F_{(1,13)} = 50.17$, $p < 0.001$]. CAPS *hyperarousal* showed a similar trend, with no significant Treatment*Time interaction [$F_{(1,13)} = 0.003$, $p = 0.95$], a significant main effect of Treatment [$F_{(1,13)} = 21.79$, $p < 0.001$] and a marginally significant main effect of Time [$F_{(1,13)} = 3.88$, $p = 0.04$]. Overall, EMDR and TF-CBT did not show a significantly different impact on CAPS *total*, *intrusive thoughts*, *hyperarousal,* and *avoidance* scales (i.e., no significant Treatment*Time interaction). Differences in the intrusive thoughts scale showed difference between EMDR and TF-CBT trending toward statistical significance, suggesting a potential greater improvement for patients in the EMDR group (see **Figure 1**).

Davidson Trauma Scale (DTS)

Total DTS score showed no significant Treatment*Time interaction [$F_{(1,13)} = 0.002$, $p = 0.96$], with a significant main effect of Treatment [$F_{(1,13)} = 7.33$, $p = 0.018$] but no main effect of Time [$F_{(1,13)} = 2.87$, $p = 0.16$]. DTS *re-experiencing* showed no significant Treatment*Time interaction [$F_{(1,13)} = 0.26$, $p = 0.61$], with a significant main effect of Treatment [$F_{(1,13)} = 8.59$, $p = 0.012$] and a marginally main effect of Time [$F_{(1,13)} = 3.25$, $p = 0.04$]. DTS *avoidance/numbing* showed no significant Treatment*Time interaction [$F_{(1,13)} = 0.15$, $p = 0.69$], with a significant main effect of both Treatment [$F_{(1,13)} = 7.4$, $p = 0.018$] and Time [$F_{(1,13)} = 5.55$, $p = 0.035$]. Finally, DTS *hyperarousal* showed no significant Treatment*Time interaction [$F_{(1,13)} = 0.37$, $p = 0.55$], with a significant main effect of Treatment [$F_{(1,13)} = 7.19$, $p = 0.019$] but no significant main effect of Time [$F_{(1,13)} = 0.61$, $p = 0.44$]. Overall, EMDR and TF-CBT did not show a significantly different impact on DTS (i.e., no significant Treatment*Time interaction).

Work and Social Adjustment Scale (WSAS)

Total WSAS score showed a significant Treatment*Time interaction [$F_{(1,13)} = 3.36$, $p = 0.039$], with both a main effect of Time [$F_{(1,13)} = 16.56$, $p = 0.003$] and Treatment [$F_{(1,13)} = 9.44$, $p = 0.009$]. EMDR and TF-CBT did exert a different impact on WSAS scores after treatment, with TF-CBT inducing greater positive changes (see **Figure 1**).

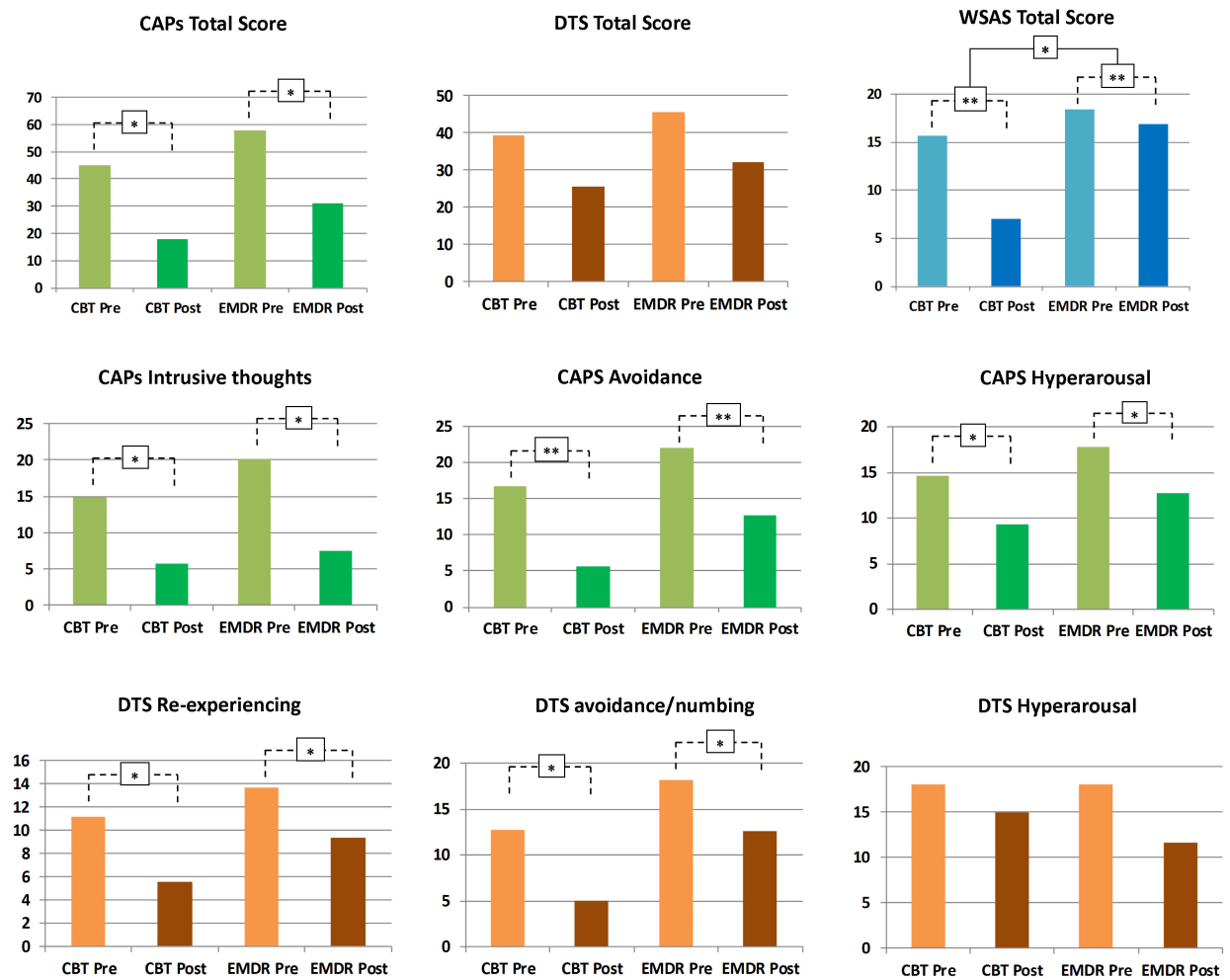

FIGURE 1 | Psychotherapeutic effects on PTSD symptomatology. Changes in psychological symptoms after EMDR and TF-CBT are displayed, for both CAPS, DTS, and WSAS total scores, as well as CAPS and DTS subscales. *$p < 0.05$, **$p < 0.01$.

Changes in FC and Predictors of Response to Psychotherapy

Changes in Symptomatology

Even though no statistically significant differences in clinical improvement between EMDR/TF-CBT were observed (except for the WSAS), different therapy-specific rearrangements of FC could have supported the observed clinical improvement. Indeed, fMRI analysis highlighted a differential pattern of increase and decrease in connectivity possibly supporting clinical changes observed at CAPs, DTS and WSAS, for patients receiving EMDR and TF-CBT. Results for both psychotherapies and each clinical score, including subscales, are reported in **Figures 2–4** and **Supplementary Figure S1**. Specifically, changes in pairwise FC explaining changes in CAPs score are reported in **Figure 2**; changes in DTS, **Figure 3**; changes in WSAS, **Figure 4**; changes in CAPs subscales (intrusive thoughts, avoidance, and hypervigilance), **Supplementary Figure S1**. To facilitate replication attempts, a complete list of the regions of interest included in the analyses and their corresponding MNI coordinates is reported in **Supplementary Table S1**.

Common Connectivity Changes in EMDR and TF-CBT

The two treatments displayed a significant heterogeneity in terms of connectivity modifications supporting changes in symptomatology. However, the analysis of overlapping regions/connections showing a similar change across the two interventions highlighted two main patterns, involving a decrease in connectivity between the left visual cortex (i.e., cuneus) and ipsilateral temporal pole [$F_{(1,29)} = 4.76$, $p < 0.0031$], as well as an increase in connectivity between bilateral superior frontal gyrus and right temporal pole structures [$F_{(1,29)} = 4.13$, $p < 0.015$] (**Figure 5**).

Connectivity-Based Predictors of Response to Therapy

Pre-existing structural and functional brain properties of each patient might contribute to the effectiveness of any given therapy

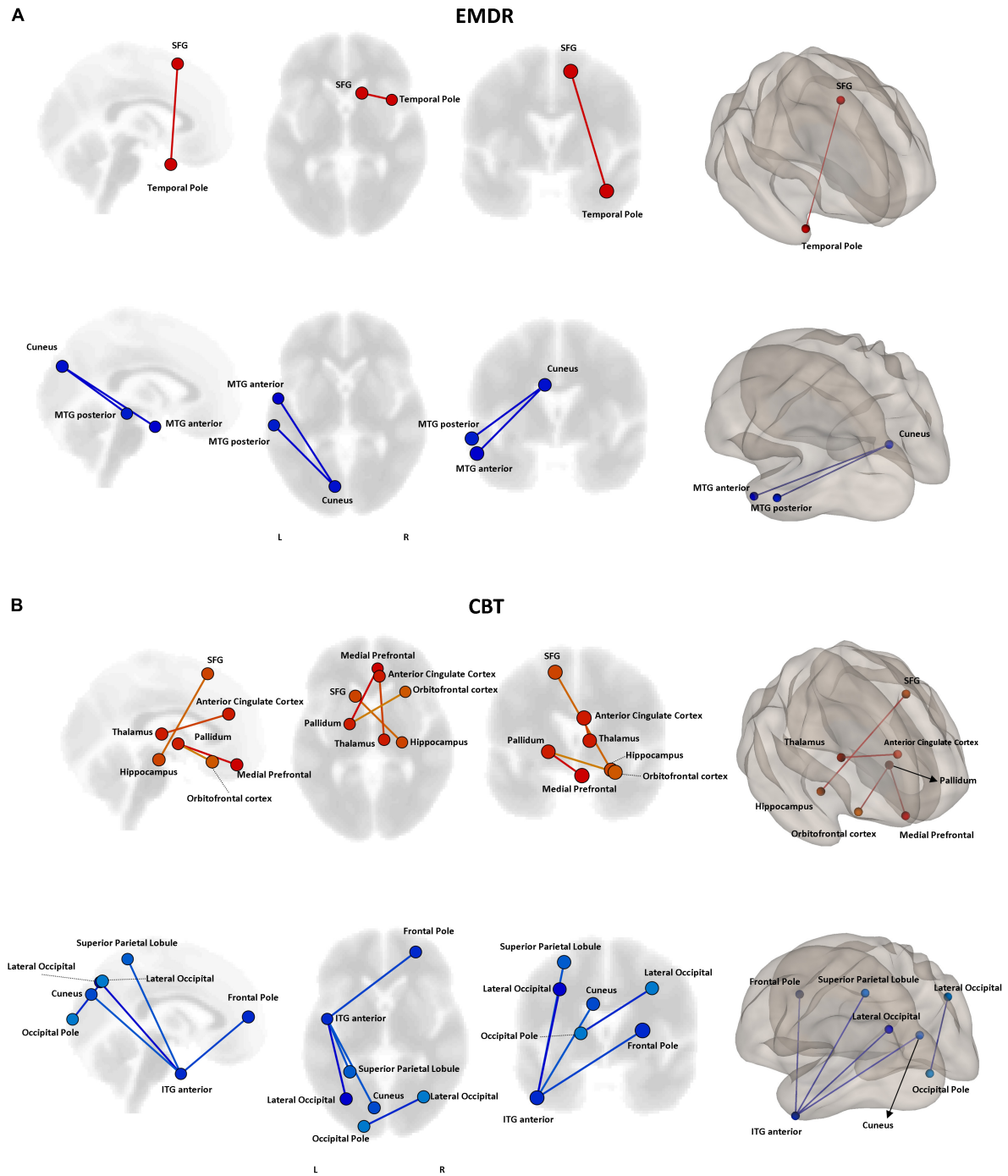

FIGURE 2 | Functional connectivity and CAPS changes. Results of the repeated measures ANCOVA on pairwise connectivity and CAPS total scores are displayed for patients receiving EMDR **(A)** and TF-CBT **(B)**. Significant changes are displayed separately for increased (red) and decreased (blue) connectivity, with edges representing connections at $p < 0.05$ (FDR corrected). The strength of pre–post changes in connectivity is color-coded for both edges and nodes (yellow → red, stronger increase in connectivity; cyan → blue, stronger decrease in connectivity). Images are displayed in neurological convention. SFG, Superior Frontal Gyrus; MTG, Middle Temporal Gyrus; ITG, Inferior Temporal Gyrus; FDR, False Discovery Rate.

(Drysdale et al., 2016). We tested whether specific patterns of FC might predict the response to EMDR and TF-CBT, identifying different set of connections (**Figure 6**). Specifically, EMDR patients with decreased FC between the precuneus and visual regions seem to display a greater benefit in terms of pre–post changes at CAPS [$F_{(1,29)} = 3.58$, $p < 0.023$]. Interestingly, patients showing a benefit at CAPS (after both EMDR and TF-CBT) showed a stronger positive connectivity between the

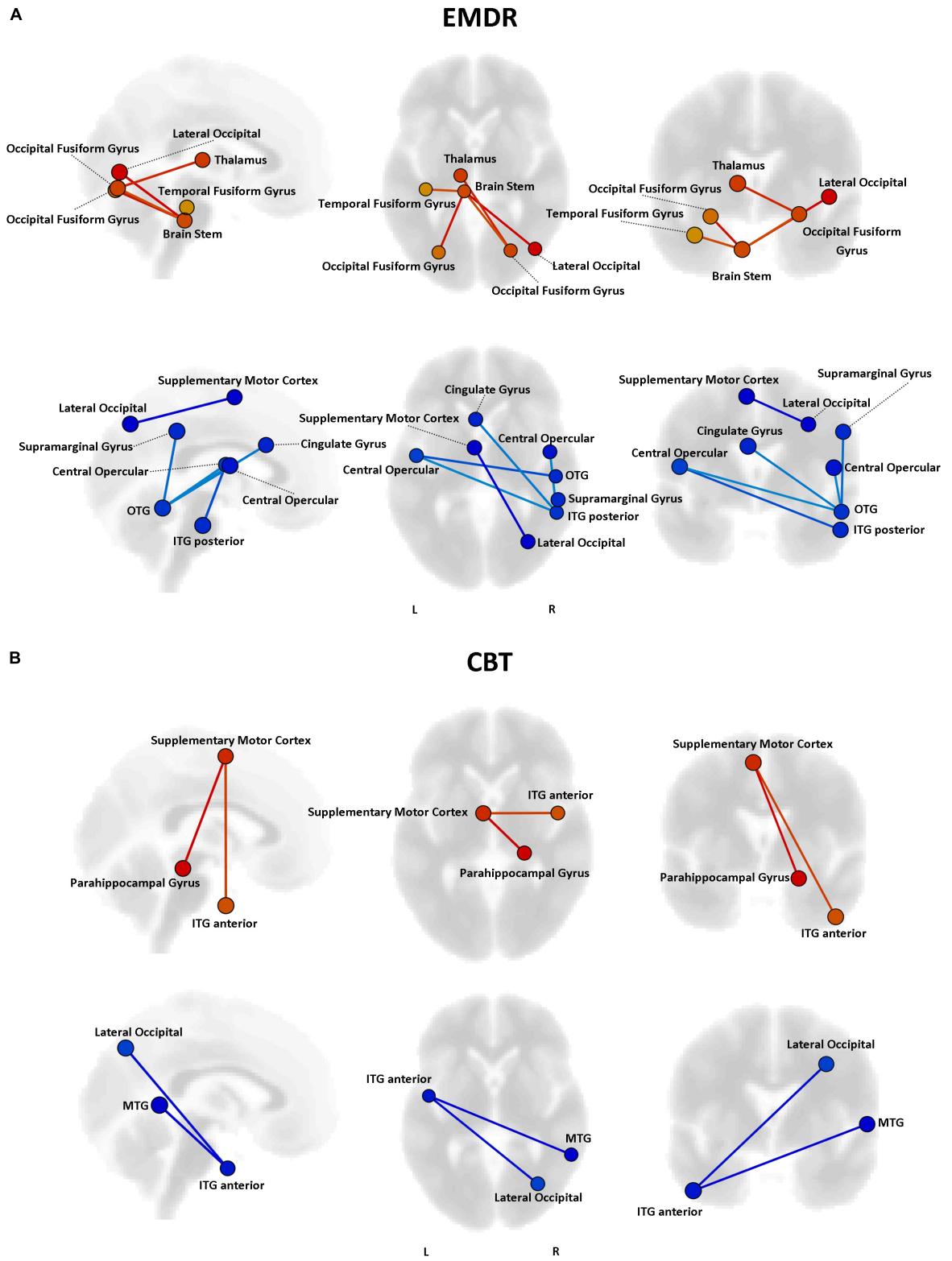

FIGURE 3 | Functional connectivity and DTS changes. Results of the repeated measures ANCOVA on pairwise connectivity and DTS total scores are displayed for patients in the EMDR **(A)** and TF-CBT **(B)** groups. Significant changes are displayed separately for increased (red) and decreased (blue) connectivity, with edges representing connections with a $p < 0.05$ FDR corrected. The strength of pre–post changes in connectivity is color-coded for both edges and nodes (yellow → red, stronger increase in connectivity; cyan → blue, stronger decrease in connectivity). Images are displayed in neurological convention. MTG, Middle Temporal Gyrus; ITG, Inferior Temporal Gyrus; OTG, Occipito-Temporal Gyrus; FDR, False Discovery Rate.

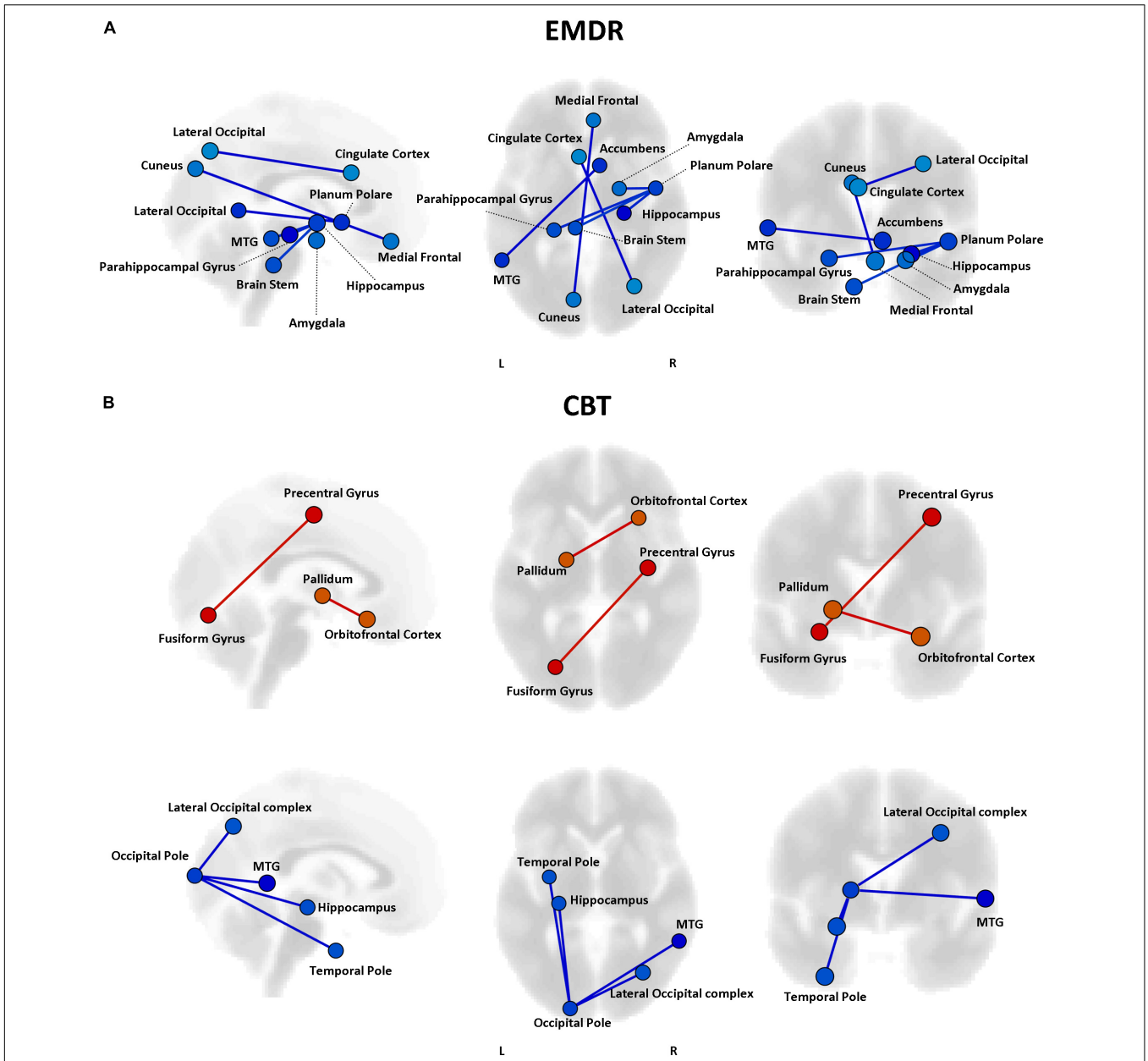

FIGURE 4 | Functional connectivity and WSAS changes. Results of the repeated measures ANCOVA on pairwise connectivity and WSAS scores are displayed for patients in the EMDR **(A)** and TF-CBT **(B)** groups. Significant changes are displayed separately for increased (red) and decreased (blue) connectivity, with edges representing connections with a $p < 0.05$ FDR corrected. No increase in connectivity accompanied changes in WSAS in the EMDR group. The strength of pre–post changes in connectivity is color-coded for both edges and nodes (yellow → red, stronger increase in connectivity; cyan → blue, stronger decrease in connectivity). Images are displayed in neurological convention. MTG, Middle Temporal Gyrus; FDR, False Discovery Rate.

right inferior frontal gyrus (pars triangularis) and regions of the temporal lobe (for EMDR) and somatosensory cortex (for TF-CBT) [$F_{(1,29)} = 3.49, p < 0.019$].

DISCUSSION

We investigated whether two psychotherapeutic approaches, EMDR and TF-CBT, might induce significant clinical benefit in a group of PTSD patients affected by the same trauma. By using functional MRI analysis, we also measured the corresponding impact of EMDR and TF-CBT on individual FC patterns, which might possibly represent the neurophysiological substrate of psychological healing in PTSD. While both EMDR and TF-CBT exerted a beneficial effect on PTSD symptomatology, the two psychotherapeutic approaches displayed both common and dissociable effects on brain connectivity, with the overlap being represented by decreased connectivity between visual cortex and

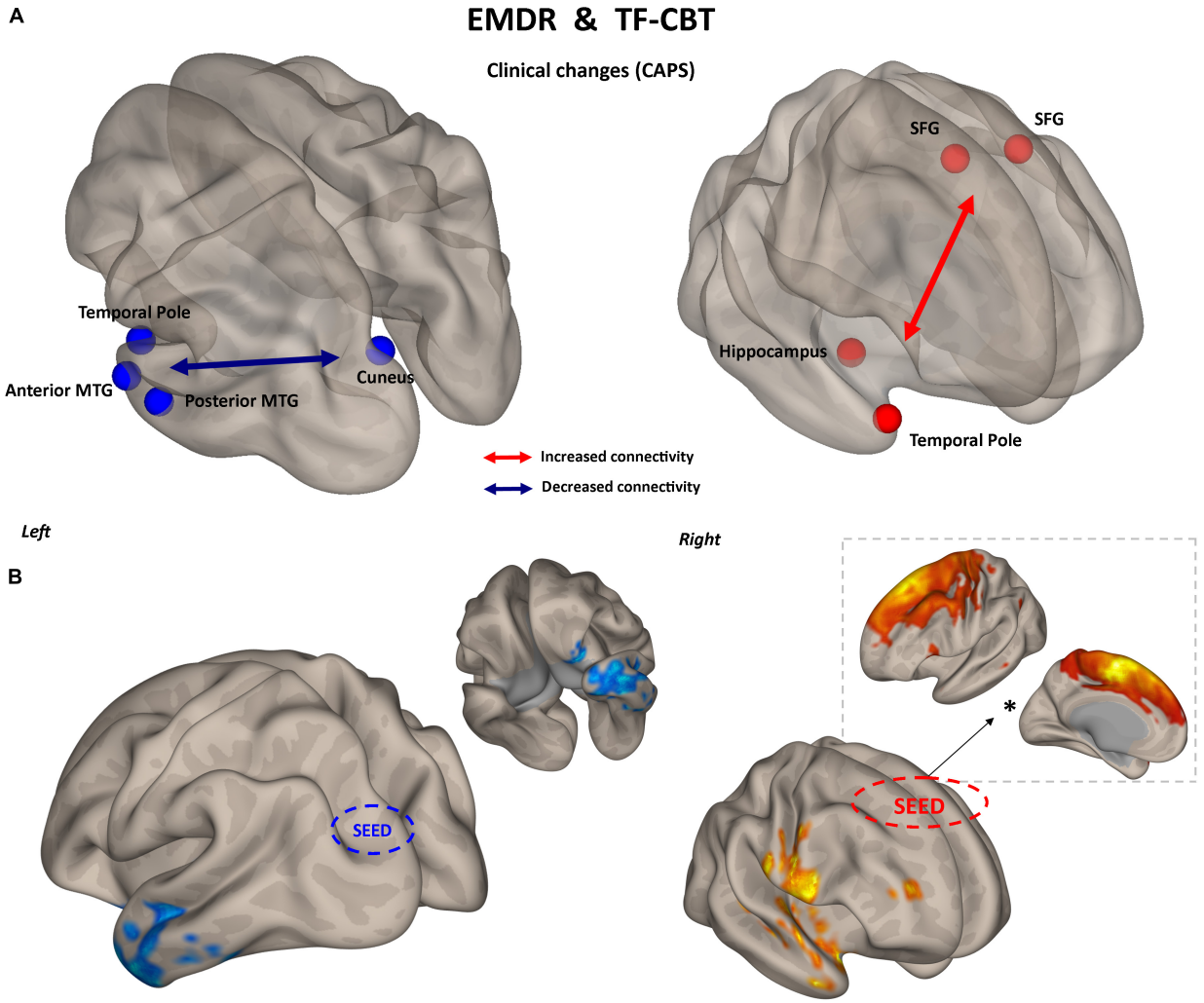

FIGURE 5 | Common substrate for psychological benefit. Changes in CAPS total score are accompanied by two patterns of FC changes after both EMDR and TF-CBT **(A)**. Increased connectivity between superior frontal gyrus and right temporal pole regions, and decreased connectivity between left visual cortex and left temporal pole, explain positive changes in CAPS after psychotherapy. Results are shown for the pairwise atlas-based analysis ($p < 0.05$, FDR corrected) **(A)** and confirmed with seed-based connectivity analysis ($p < 0.05$, cluster-based correction) **(B)**. The FC profile of the seed region located in the superior frontal gyrus is also displayed (*), highlighting its resemblance with the supplementary motor cortex. SFG, superior frontal gyrus; MTG, middle temporal gyrus; FDR, False Discovery Rate.

temporal lobe regions in the left hemisphere, and increased connectivity between bilateral superior frontal gyrus and right temporal pole regions.

Psychological Impact of EMDR and TF-CBT

No significant differences were observed in the impact of EMDR and TF-CBT on PTSD symptomatology, except for a significantly greater improvement in work and social impairment following TF-CBT intervention as compared to EMDR. This is in line with existing literature, showing no evidence of greater efficacy for a specific psychotherapeutic approach in the treatment of PTSD patients (Bradley et al., 2005), especially when therapies including elements of exposure such as TF-CBT and EMDR are compared (Bradley et al., 2005). This is not surprising, considering that many treatments for PTSD share not only factors common to all psychotherapeutic approaches (Bradley and Follingstad, 2001), but also some sort of exposure therapy. Exposure fosters habituation or extinction processes, while also providing an opportunity for a controlled re-elaboration of the traumatic event, which become a core element of the therapeutic process. Similarly, therapies focused on cognitive biases or maladaptive coping strategies sometimes include element of exposure. That being said, a difference in the effectiveness of the two interventions in terms of dose-response seems present, with EMDR and TF-CBT eliciting similar results at both the clinical and neuroimaging level even though EMDR included half the number of treatment sessions (4 weekly sessions ±2) compared to TF-CBT (10 weekly sessions ±2) and an overall shorter treatment

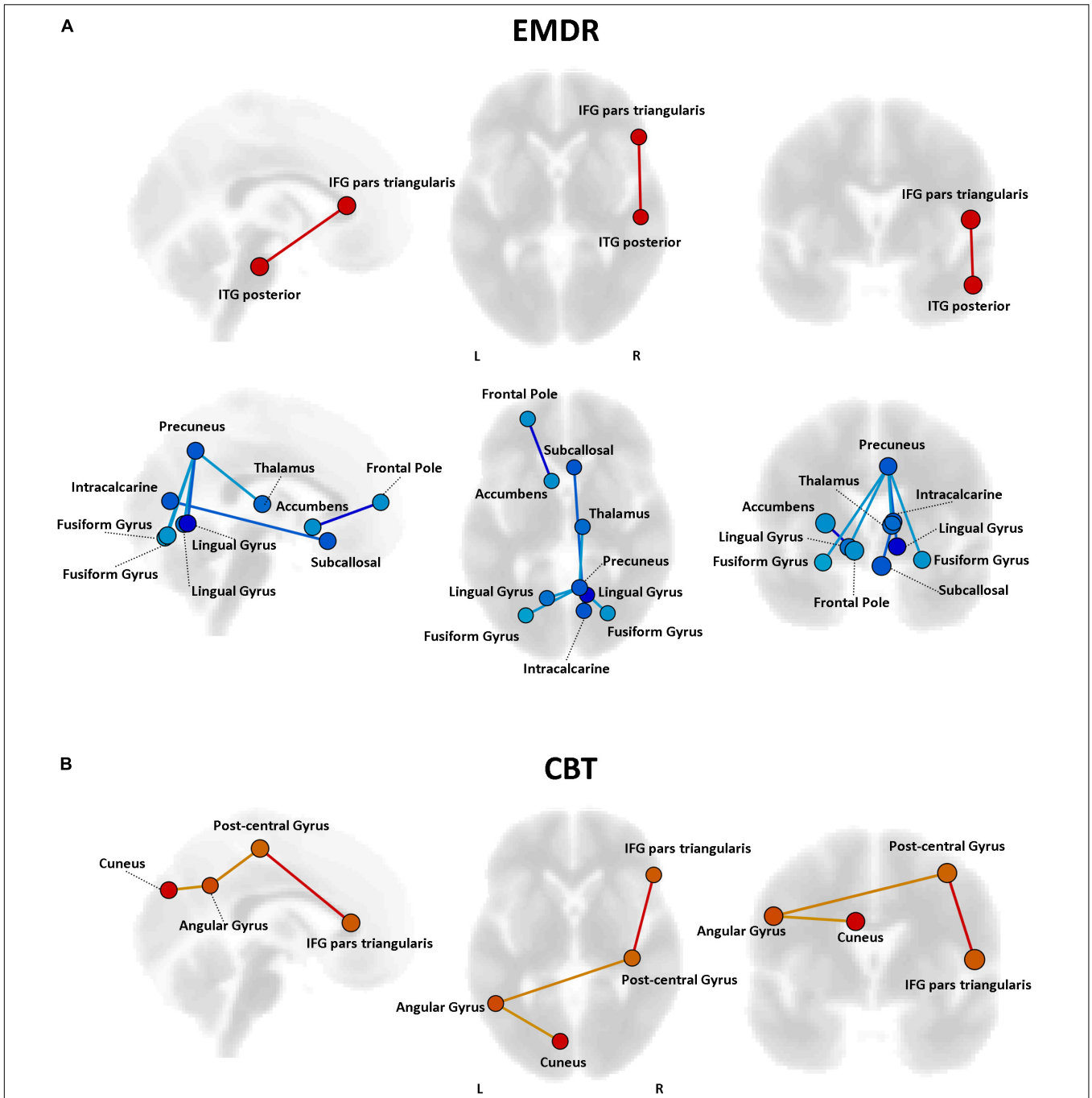

FIGURE 6 | Predictors of response to psychotherapy. For both EMDR **(A)** and TF-CBT **(B)**, a set of functional connections significantly predicting changes in CAPS total score were identified ($p < 0.05$ FDR corrected). The strength of the prediction weight is color-coded (yellow → red for positive predictors; cyan → blue for negative predictors). Images are displayed in neurological convention. ITG, Inferior Temporal Gyrus; ITG, Inferior Frontal Gyrus; FDR, False Discovery Rate.

period. The present data are not suitable for a proper analysis of dose-response effects across the two approaches, but results provide an interesting insight into this matter that should be considered in future studies.

Notably, the present study offers an original evidence of the non-differential effect of EMDR and TF-CBT in PTSD patients, by providing a quantitative estimate on the same patient population and trauma-type. Conversely, this also mean that any generalization of findings to other trauma types is strongly discouraged. More in general, both interventions elicited beneficial effects on patients' symptomatology, with a significant decrease in validated clinical scales such as CAPS and DTS. It must be noticed that, among PTSD based on different traumas, a significant variability in clinical efficacy of therapies exists, with

for instance lower effect sizes for treatments of combat-related PTSD as compared to natural disaster or interpersonal violence (Ford et al., 1997), suggesting again the non-generalizability of the present results.

Connectivity Changes Supporting Psychological Healing

The analysis of functional connectivity changes induced by EMDR and TF-CBT revealed both common and dissociable correlates for symptoms improvement recorded at the different various clinical scales. In general, both therapies seem to induce two main patterns of connectivity changes, pointing to a reduction of connectivity between regions of the visual cortex and of the left temporal pole, as well as an increase in connectivity between the superior frontal gyrus and right temporal pole. Interestingly, such changes characterize a decrease in CAPS scores in both patient groups, possibly due to the aforementioned methodological overlap between EMDR and TF-CBT for PTSD (Bradley et al., 2005).

In general, the changes in connectivity patterns highlight the involvement of the bilateral temporal pole. Changes in these structures have been extensively documented in PTSD patients (Shin, 2006; Cheng et al., 2015; Meng et al., 2016), including recent results about changes in hippocampal volume induced by EMDR treatment (Bossini et al., 2017). The specific decrease in connectivity between regions of the occipital cortex (e.g., cuneus) and the left temporal pole might point to a reduction of spontaneous synchronization between visual processing areas and re-elaboration of traumatic events (including flashbacks) which might be prompted by temporal lobe structures (Kroes et al., 2011). Interestingly, this correlation also appears to specifically characterize the intrusive thoughts subscale of CAPS, but not the avoidance and hyper-arousal ones. Models of (visual) flashbacks generation suggest a dominance of the activity in the dorsal visual stream, which includes posterior visual to superior parietal regions (including the cuneus and precuneus) and is responsible for processing of egocentric (i.e., own viewpoint) representations of experience. While the dorsal visual stream elaborates trauma-related representations associated with the insula and amygdala (reflecting emotional and body state responses), the ventral visual stream, including inferior and middle temporal regions, enables scenes to be visualized allocentrically (i.e., from alternative viewpoints), and provides memories with their context (Brewin et al., 2010). The observed therapy-related changes might suggest a modification of the ventral-dorsal stream balance.

An increase in connectivity between regions of the prefrontal cortex (i.e., superior frontal gyrus) and right temporal pole fits with the general neurocognitive theory about the beneficial effect of psychotherapy, which postulate an increase in top-down control as the main mechanism behind psychological healing in (among others) anxiety, trauma-related and addiction disorders (Robertson et al., 2004; Malejko et al., 2017). For instance, in PTSD in particular, impaired top-down cognitive control over limbic areas, which is frequently associated with hypo-activation in the dorsolateral prefrontal cortex, has been linked to the persistence of traumatic flashbacks as well as to worsening of attention (White et al., 2015). Increased connectivity between prefrontal and temporal pole regions might reflect a greater control of trauma-related contents, decreasing their intrusiveness during spontaneous mind wandering (Kroes et al., 2011). This also matches recent finding of resting-state fMRI networks alterations in PTSD patients with the same trauma-type as those enrolled in the present study (i.e., earthquake) (Shang et al., 2014). At a very general level, the authors reported modification of FC in various brain networks including the salience network (SN), central executive network (CEN), default mode network (DMN), somato-motor network (SMN), auditory network (AN), and visual network (VN). Differently from networks related to primary sensory systems (i.e., visual, auditory, and motor), activity in, e.g., DMN, SN, and CEN is associated with higher order cognitive dynamics, more specifically related to executive functioning (CEN), memory (CEN, DMN), attention (SN, CEN), monitoring of bodily sensation (SN) and mind wandering (DMN) (for a review see Zhang and Raichle, 2010). In general, this suggest changes in PTSD not being confined to sensorial processing, but also possibly involving cognitive networks. Interestingly, Shang and colleagues also observed that stronger connectivity involving the inferior temporal gyrus (ITG) and supplementary motor area (SMA) was negatively correlated with clinical severity in PTSD patients. The location of the superior frontal gyrus in our atlas highly resemble SMA (see **Figure 5**), while the ITG is one of the multiple temporal lobe regions showing increased connectivity with SMA after psychotherapy in our sample. This might be suggesting that both EMDR and TF-CBT work by re-normalizing such altered SFG/SMA $\longleftrightarrow$ temporal gyrus connectivity, confirming the potential pivotal role of this specific functional connection in PTSD patients' symptomatology.

The analysis of predictors of response to therapy highlighted different connectivity patterns for EMDR and TF-CBT, with some overlap for the inferior frontal gyrus, and higher predictive power for regions previously highlighted in relation to the response to therapy, e.g., the cuneus. Moreover, a role for decreased connectivity of the precuneus was also identified. It is important to note that all the potential predictors identified in the present analysis require a careful validation via ad-hoc studies investigating their correlation with cognitive and clinical scores, and are here discussed as additional exploratory findings. The finding about increased cuneus connectivity at baseline fits with the reduction in connectivity observed after therapy, suggesting that patients with higher connectivity of the visual cortex before therapy are possibly those observing a greater response to EMDR/TF-CBT. As for the precuneus –a crucial node of the DMN— multiple studies have pointed out alterations of precuneus connectivity (and of the DMN in general) in PTSD patients (Boccia et al., 2016). During memory retrieval –a crucial component for flashbacks generation— images are manipulated in terms of their content and point of view. Such conversion between egocentric and allocentric reference frames is assumed to be supported by the retrosplenial and posterior parietal

cortices, with imagery supported instead by the precuneus. Decreased connectivity between precuneus and areas of the visual cortex might point to the aforementioned ventral-dorsal stream framework, with a decrease in integration between precuneus and visual areas suggesting a less efficient shift from ego- to allo-centric images in patients before therapy. Finally, the IFG might be relevant for its role in inhibition processes, whose alterations have been reported in several studies on PTSD. For instance, decreased IFG activation during a proactive inhibition task in combat veterans as compared with a combat control group have been reported (van Rooij et al., 2014), while increased IFG resting-state fMRI activity has been recently suggested in a quantitative meta-analysis of fMRI findings in PTSD patients (Wang et al., 2016).

Insight for Further Combined Therapeutic Approaches

Non-invasive brain stimulation (NIBS), and transcranial electrical stimulation (tES) in particular, are becoming pivotal tools for the investigations of neuromodulatory intervention in both the healthy and pathological brain (Filmer et al., 2014; Bestmann et al., 2015; Santarnecchi et al., 2015). The possibility of applying low voltage electrical stimulation patterns to modulate –excite or inhibit— the activity of specific brain regions or entire networks constitutes an appealing scenario (e.g., using transcranial Direct Current Stimulation, tDCS) (Nitsche and Paulus, 2011), with potential applications for both the causal investigation of brain-function dualism [following the "virtual-lesion" approach (Pascual-Leone and Pridmore, 1995; Pascual-Leone et al., 1999)], as well as for the enhancement of individual cognitive functioning (Polania et al., 2012; Sela et al., 2012; Santarnecchi et al., 2013, 2016; Snowball et al., 2013). Additionally, recently developed techniques such as transcranial alternating current (tACS) and transcranial random noise (tRNS) stimulation offer the possibility to modulate brain activity by interacting with cortical excitability and/or specific brain oscillatory dynamics as those recorded via electroencephalography (EEG), exponentially multiplying potential available interventions (Thut et al., 2012). In this framework, with the increasing spatial resolution of current tES modeling works (Datta et al., 2009) and the potential to indirectly stimulate subcortical structure using Transcranial Magnetic Stimulation (TMS) (Wang et al., 2014), NIBS is becoming a valuable tool for the treatment of both neurological and psychiatric conditions, with FDA-approved protocols already available for conditions such as Depression and Obsessive Compulsive Disorder (Pascual-Leone et al., 1996). The present results, together with previously reported findings in PTSD patients, might suggest potential targets for both TMS and tES applications aimed at enhancing the therapeutic processes induced by psychotherapy. For instance, application of cathodal tDCS over the occipital lobe in PTSD patients might decrease local cortical excitability and modulate connectivity patterns (Callan et al., 2016; Hauser et al., 2016), and could be used to amplify the effect of each therapeutic session. Following the same logic, increase in excitability of prefrontal regions could be achieved by means of anodal tDCS, possibly increasing top-down control over subcortical regions. Given appropriate neurophysiological investigations aimed at defining the target EEG frequency band, a de-synchronization of occipital and temporal lobes activity in the left hemisphere could be hypothesized by applying tACS with opposite stimulation phase on the two lobes (i.e., 180* phase, "anti-phase"). Solutions targeting resting-state, large scale networks including the aforementioned target regions could also constitute valuable therapeutic solutions (Ruffini et al., 2018). Studies combining EEG and fMRI recording in patients before and after psychotherapy are needed to carefully defined stimulation patterns.

Limitations of the Study and Future Directions

Future investigations should include a placebo and/or wait-list control condition, and also compare EMDR and TF-CBT with other available approaches such as mindfulness-based therapies (King et al., 2016a), especially given the specific functional and structural effects of mindfulness practice on the brain (Holzel et al., 2011; Santarnecchi et al., 2014). The same comparison should also be explored in PTSD patients with different traumatic events.

Moreover, it should be noticed that, for different clinical scales, patients in both groups did show changes in connectivity of the thalamus (EMDR for DTS, TF-CBT for CAPs). Prior investigations using functional imaging have showed evidence of thalamic dysfunction in PTSD patients (e.g., Lanius et al., 2001; Francati et al., 2007). Future studies should look into the specific effects of psychotherapy on PTSD patients' thalamic function, with a finer characterization of FC patterns of different thalamic nuclei, and also including perfusion imaging data (arterial spin labeling – ASL).

Finally, the present investigation is based on a pseudo-randomized assignment to EMDR and TF-CBT across patients based on patients' trauma severity at presentation. While this might represent a reasonable solution to ensure a balanced comparison of treatment effects in a relatively small pilot study such as the present one, future investigation should adopt a fully randomized assignment in larger samples of PTSD patients.

CONCLUSION

Results point to a similar, beneficial psychological impact of EMDR and TF-CBT psychotherapeutic interventions for treatment of natural disaster-related PTSD patients. Also, fMRI data suggest a similar neurophysiological substrate for the observed clinical improvement following EMDR and TF-CBT, involving connectivity changes affecting bilateral temporal pole structures. This might point to the presence of a general psychological and neurophysiological effect of exposure- and reprocessing-based psychotherapy for natural-disaster PTSD, with a minor role played by therapy-specific components.

AUTHOR CONTRIBUTIONS

ES designed the study, acquired MRI data, analyzed the MRI data, and wrote the manuscript. LB designed the study and conducted the psychiatric assessment. GV acquired the MRI data. PLP coordinated the EMDR and TF-CBT sessions. GDL interpreted the results. AF, AS, SR, and AR interpreted the results and edited the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.00129/full#supplementary-material

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REVIEW
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Errors in the 2017 APA Clinical Practice Guideline for the Treatment of PTSD: What the Data Actually Says

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The American Psychological Association (APA) Practice Guidelines for the Treatment of Posttraumatic Stress Disorder (PTSD) concluded that there was strong evidence for cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and exposure therapy yet weak evidence for eye movement desensitization and reprocessing (EMDR). This is despite the findings from an associated systematic review which concluded that EMDR leads to loss of PTSD diagnosis and symptom reduction. Depression symptoms were also found to improve more with EMDR than control conditions. In that review, EMDR was marked down on strength of evidence (SOE) for symptom reduction for PTSD. However, there were several problems with the conclusions of that review. Firstly, in assessing the evidence in one of the studies, the reviewers chose an incorrect measure that skewed the data. We recalculated a meta-analysis with a more appropriate measure and found the SOE improved. The resulting effect size for EMDR on PTSD symptom reduction compared to a control condition was large for studies that meet the APA inclusion criteria (SMD = 1.28) and the heterogeneity was low (I^2 = 43%). Secondly, even if the original measure was chosen, we highlight inconsistencies with the way SOE was assessed for EMDR, CT, and CPT. Thirdly, we highlight two papers that were omitted from the analysis. One of these was omitted without any apparent reason. It found EMDR superior to a placebo control. The other study was published in 2015 and should have been part of APA guidelines since they were published in 2017. The inclusion of either study would have resulted in an improvement in SOE. Including both studies results in standard mean difference and confidence intervals that were better for EMDR than for CPT or CT. Therefore, the SOE should have been rated as moderate and EMDR assessed as at least equivalent to these CBT approaches in the APA guidelines. This would bring the APA guidelines in line with other recent practice guidelines from other countries. Less critical but also important, were several inaccuracies in assessing the risk of bias and the failure to consider studies supporting strong gains of EMDR at follow-up.

Keywords: PTSD, EMDR, American Psychological Association, treatment guidelines, data analysis

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INTRODUCTION

The American Psychological Association (APA) is acknowledged globally as an evidence based organization to support clinical practice. The organization aims to "*advance the creation, communication and application of psychological knowledge to benefit society and improve people's lives*" (American Psychological Association, 2017b) and has as one of its five core values "*Knowledge and its application based upon methods of science*" (American Psychological Association, 2017a). APA treatment guidelines are regularly referred to in the literature with some documents published by the organization having hundreds or even thousands of citations (American Psychological Association, 1995; Wilkinson, 1999; American Psychological Association Zero Tolerance Task Force, 2008). Therefore, it is crucial that the organization ensures that it maintains the highest standards in scientific methodology, and is unbiased and apolitical in it's reporting of guidelines for clinical practice. The latest guidelines do not meet those standards (Courtois et al., 2017, Unpublished).

The APA Practice Guideline Development Panel for the Treatment of Posttraumatic Stress Disorder (PTSD) was formed to review current data regarding the treatment of PTSD. The panel made recommendations based on a systematic review of the evidence for treatment for PTSD conducted by the Research Triangle Institute – University of North Carolina Evidence-Based Practice Center (RTI-UNC) (Jonas et al., 2013). The review found that EMDR was effective in decreasing PTSD symptoms, and achieving loss of diagnosis. EMDR was also effective in treating comorbid depression within the PTSD population. Despite this empirical support for EMDR, APA guidelines concluded that the strength of evidence (SOE) for EMDR to was low, while the SOE for other treatment approaches was classified as moderate to high. This paper identifies key methodological errors in the RTI-UNC paper with regards to the analysis of EMDR. Following this, additional analyses were conducted, correcting for these errors to give a more accurate view of the current empirical support for EMDR in treating PTSD.

AN INAPPROPRIATE MEASURE WAS USED TO DETERMINE EFFECT SIZE IN AN INCLUDED STUDY (Carlson et al., 1998)

The RTI-UNC review (Figure 17) referred to mean changes in PTSD symptoms for EMDR versus control comparisons. There are four studies listed and changes were assessed in each of the studies on identified primary measures. For example, in the Rothbaum et al. (2005) study, this was the Clinician Administered PTSD Scale (CAPS). The primary outcome measure for the Carlson et al. (1998) study was also the CAPS and this is reported in the original article for pre- and follow-up data. The effect size is large (Cohen's $d = 1.8$). However, CAPS scores were not collected at post-treatment. A battery of self-report measures were collected at post-treatment including the Mississippi Scale for Combat Related PTSD (M-PTSD) and the Impact of Events Scale (IES). In the RTI-UNC analysis, the IES was chosen above the M-PTSD. Why is difficult to fathom. The M-PTSD is more comprehensive than the IES and was designed specifically to assess PTSD in veteran populations, which is the population involved in the Carlson study, and similar to the CAPS it is based on the DSM. Also, two memories were treated in this study, and the status of the memory focused on in the IES is unknown. That is, one memory was treated until 0–2 SUD was reached, and then treatment began on the next memory, but not necessarily finished, during the 12 sessions. Hence, the more global measures -CAPS and M-PTSD- are more appropriate. Finally, a review article at the time recommended the M-PTSD above all other self-report measures for assessing PTSD (Watson, 1990).

Initially, when comparing relaxation to EMDR the RTI-UNC reviewers report that they conducted meta-analyses using both measures (see Table 7). However, when they were describing which studies were included in their analysis, and wanted to compare the severity of PTSD symptoms at baseline for each study, they chose the M-PTSD over the IES (see Tables 9, 18). Also later in the report when assessing the effectiveness of relaxation, they again use the M-PTSD (p. 70). Why they reverted to the IES in the middle of the report when assessing change in the PTSD symptom level for this study is perplexing.

Changing the outcome measure from the IES to the M-PTSD significantly effects the results with regards to PTSD symptom reduction following EMDR. We entered this corrected data into Comprehensive Meta-Analysis Software and showed if this adjustment was made the effect size, precision, and consistency are all improved [SMD, −1.28 (−1.81 to −0.74); $I^2 = 43\%$].

RTI-UNC guidelines define precision as the width of the confidence interval. Consistency is defined as the number of studies in the same direction and appears to take into account the heterogeneity (The RTI-UNC quote heterogeneity when discussing consistency in Appendix 1). Therefore heterogeneity at 43% for EMDR is better than mixed cognitive behavioral therapy (CBT), cognitive therapy (CT), and cognitive processing therapy (CPT) where heterogeneity was significant and ranged between 80 and 87%. In addition to EMDR being more consistent the precision improves to 1.07 (difference between lower and upper end of the confidence interval), which is better than both CPT (1.1) and CT (1.38). Therefore, there is no basis to argue SOE is better for these CBT therapies.

Changing the outcome measure analyzed to the more comprehensive measure of the M-PTSD provides a result more consistent with the rest of the data from the study. The effect size for the IES is small (SMD = −0.18) while the M-PTSD effect size is large ($d = 1.01$). The effect size for the CAPS at follow-up was large ($d = 1.82$) for the EMDR treatment compared to control condition, and there were large effect sizes for both depression and anxiety measures post-treatment in comparison to control, making the IES result at post-test an anomaly.

STRENGTH OF EVIDENCE USING ONLY THE DATA SUPPLIED IN THE RTI-UNC REPORT

There appears to be differences in how the consistency domain was rated with respect to SOE for PTSD symptom reduction in EMDR compared to other treatments. This section of our review refers to the analysis on the four studies included in the RTI-UNC report. This analysis excludes two important and relevant studies, which are described later in this report. With regards to PTSD symptom reduction, EMDR is rated in the RTI-UNC report as *Inconsistent*. This is based on the heterogeneity of the related studies ($I^2 = 70\%$), the direction of the effects and the magnitude of these effects. Examination of the impact of CT on PTSD symptom reduction suggests that there is even higher heterogeneity ($I^2 = 79.6\%$), as shown on Table G-2. However, rather than *Inconsistent*, the evidence was labeled as *Some Inconsistency*. The annotation of this table indicates that the '*Direction of effects were consistent; magnitude of effects ranged from very large to small*' (p. G-4). Similar annotations were made in Tables G-1, G-13 resulting in studies with high heterogeneity obtaining ratings of *Consistent* or *Some Inconsistency*.

These annotations have not been applied to the analysis of EMDR. With regards to impact on PTSD symptom reduction, while the heterogeneity of EMDR results is high ($I^2 = 70\%$), this is lower than the same measure for CT mentioned above. Further, the direction of the effects from EMDR studies is consistent and the magnitude of these effects ranged from 'almost small to very large,' which is similar to related results for CT. This suggests that the consistency domain for EMDR on PTSD symptom reduction should have been moved from *Inconsistent* to *Some Inconsistency*, to ensure uniformity in rating across therapies.

A change of the consistency domain would mean that the domains for PTSD symptom reduction following EMDR would be comparable to that for CT across all measures. Therefore the SOE for EMDR for PTSD symptom reduction should have been moderate rather than low.

It may have been argued that this annotation may not apply to the EMDR results with regards to symptom reduction as one of the studies (Carlson et al., 1998) had a confidence interval where the lower point falls below zero. However, two of the studies in CBT-Mixed Interventions (McDonagh et al., 2005; Johnson et al., 2011) have their confidence intervals falling below zero, and this intervention is still rated as consistent. Further, if the outcome measure analyzed for the Carlson et al. (1998) study was altered as suggested above from the IES to M-PTSD, then none of the EMDR studies would have had the lower point of the confidence interval falls below zero.

OMISSIONS OF RANDOMIZED CONTROLLED TRIALS RELEVANT TO THE RESEARCH QUESTIONS

An additional error in the analysis that occurred in the RTI-UNC report was the failure to include two studies relevant to the issue of whether EMDR leads to more symptom reduction than a control condition. The report purports to assess, as its first research question, the effectiveness of psychological treatments "compared with wait list, usual care (as defined by the study), no intervention, or a placebo," (pES-5). However, a study by van der Kolk et al. (2007) was omitted. This study assessed three treatment conditions. Participants were randomized to either EMDR or SSRI treatment condition, or a placebo control. This study is cited in the report, however, it is inexplicably missing from the meta-analysis that investigates mean changes in PTSD symptoms for EMDR vs. control comparisons. As placebo is clearly a control condition it should have been included.

This omission cannot be justified on a basis of methodological procedures because other studies that included multiple arms were utilized in more than one place in order to answer key questions. For example, Marks et al. (1998) appears in Table 9 when discussing coping skills trials, and again in Table 13, looking at the efficacy of exposure trials (Jonas et al., 2013). This suggests that there is no methodological issue that would result in the exclusion of the van der Kolk et al. (2007) data. The inclusion of this study into the analysis would change the conclusions on the SOE in the report. When we calculated the new confidence interval it was from −1.56 to −0.37, which is better precision than CPT. Heterogeneity also improved from the analysis of the four studies and continued to be better than CPT or CT.

Another important study omitted from the meta-analysis was published in 2015 (van den Berg et al., 2015). A problem with the APA guidelines is that they were based on the review by RTI-UNC published in 2013, however, the APA guidelines were published in 2017. This means that while readers may believe they are reading 2017 guidelines, they are actually reading guidelines that are 4 years out of date. Three recent randomized control trials (Capezzani et al., 2013; van den Berg et al., 2015; Acarturk et al., 2016) that support EMDR as evidence based are not considered in these conclusions. One study in particular, by van den Berg et al. (2015) meets a high methodological standard. Indeed, in the RTI-UNC appendices this study is highlighted. The APA committee in reviewing the RTI-UNC findings acknowledged that the addition of this study to the analysis was likely to narrow the confidence interval and therefore impact on precision and would also improve consistency. "*If a new meta-analysis were to be done. . . the confidence interval would be narrower and it is possible that the SOE might be upgraded from low to medium as a result.*" (Appendix p. F-11). However, seemingly paradoxically, after highlighting the impact of the addition of this study, they then conclude that there is insufficient evidence to determine whether the study would change the recommendation for EMDR. In contrast to this view, it is later purported that if the effect size stayed at medium/large, and given the increased sample size of including this study then the overall SOE for EMDR would probably change.

Actually testing this proposition is not difficult nor particularly time consuming. Again, we used Comprehensive Meta-Analysis

TABLE 1 | Comparative statistics on effect size, precision, and consistency analysis including changes when all relevant EMDR studies are included with appropriate comprehensive measures.

Treatment	PTSD symptom reduction	Difference	Heterogeneity
Cognitive processing therapy	SMD −1.40 (−1.95, −0.85)	1.10	87%
Cognitive therapy	SMD −1.22 (−1.91, −0.53)	1.38	80%
CBT-mixed	SMD −1.09 (−1.4, −0.78)	0.62	87%
EMDR (original report using IES for Carlson)	SMD −1.08 (−1.83, −0.33)	1.50	70%
EMDR (using M-PTSD for Carlson)	SMD −1.28 (−1.81, 0.74)	1.07	48%
EMDR with van der Kolk and van der Berg and using IES for Carlson	SMD −0.89 (−1.34, −0.44)	0.90	66%
EMDR with van der Kolk and van der Berg and using M-PTSD for Carlson	SMD−0.99 (−1.41, −0.58)	0.93	57%

SMD, standard mean difference; IES, Impact of Events Scale; M-PTSD, Mississippi Scale for Combat Related PTSD.

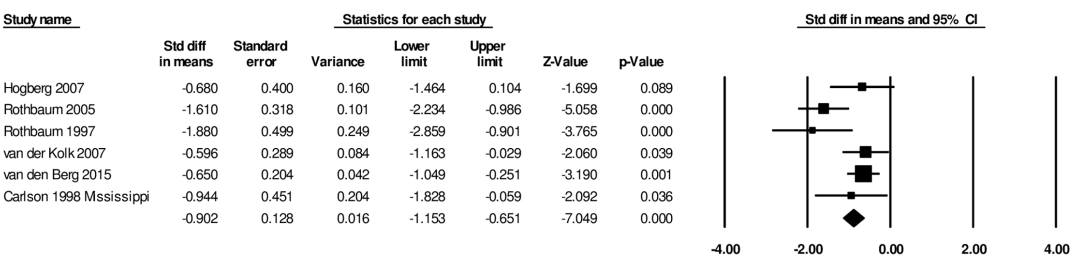
Software and input the same effect sizes reported from Figure 17 in the RTI-UNC report but added CAPS scores and confidence intervals from the studies of van der Kolk and van den Berg. The results are presented in **Table 1**. The effect size remained large SMD = −0.89 (−1.34, −0.44). The precision improved to a confidence interval difference of just 0.9. Using the RTI-UNC own guidelines of assessing SOE, EMDR is doing better than both CPT and CT in both consistency and precision. In fact, it is closer to mixed CBT in precision than CPT or CT. Even more compelling is the heterogeneity, which at 66% is better than mixed CBT, CT, and CP. The total N is also substantial at 284. Following, it is not possible from a science point of view to rate CPT and CT higher in SOE than EMDR.

Finally redoing the analysis for all six studies that compared EMDR to a control condition and using the more appropriate M-PTSD measure for the Carlson study the SMD is −0.99 and the confidence interval is from −1.41 to −0.58 ($I^2 = 57\%$) (see **Figure 1**). This is the best reflection of the state of the literature today. This is the result that should have been used by the APA. This data means that consistency for EMDR is better than CT, CPT and mixed CBT and EMDR has more precision than CT or CPT.

PAPERS INAPPROPRIATELY INCLUDED IN THE ANALYSIS

In examining the papers included from the analysis in the RTI-UNC review, there appear to be errors made in the inclusion of certain studies to the analysis of evidence. An example of this is the inclusion of Taylor et al. (2003), despite several significant validity concerns and concerns regarding the interpretation regarding psychometric properties.

In Table E1 of the RTI-UNC paper, there is a category that examines whether the participant groups in the study were equivalent at baseline. On page E-21, this category for the study by Taylor et al. (2003) was rated as yes. However, no pre-treatment test scores analysis for treatment conditions is reported. The only pre-treatment analysis reported suggests



Meta Analysis

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	6	-0.902	0.128	0.016	-1.153	-0.651	-7.049	0.000	11.749	5	0.038	57.444	0.146	0.168	0.028	0.382
Random	6	-0.994	0.211	0.045	-1.408	-0.580	-4.705	0.000								

FIGURE 1 | Results of the meta-analysis using all appropriate studies and measures.

no significant differences between dropouts and completers—regarding demographics and primary measures of interest. Furthermore, Figure 2 indicates that the participants in the exposure group reported less symptoms than those in the EMDR group at pre-treatment (Taylor et al., 2003). The confidence intervals on the bar graph show the mean score for the exposure group was outside the standard error of the EMDR group at pre-treatment for hyperarousal, re-experiencing, and avoidance symptoms.

The bias in the Taylor et al. (2003) study is further inflated as it relied on a treatment completer analysis rather than an intent-to-treat analysis. This is critical as while participants in the EMDR condition had more severe symptoms to begin with, the other CBT condition had a higher dropout rate (11% greater), resulting in an elevated chance of systematic bias.

An additional error in the rater's assessment of this study was the judgment that the providers of the therapy were masked. However, logic asserts that this assessment is not possible in a design comparing two psychological treatments. Given these errors in the risk of bias the Taylor et al. (2003) study should have been reclassified as high and the study excluded.

The results of the Taylor et al. (2003) study is at odds with other more methodologically sound studies. Removing this study changes the interpretation of the RTI-UNC report with regards to EMDR and PTSD symptom change. The conclusion that all studies '*. . .found a greater reduction in PTSD symptom scores for EMDR than for comparators*' (p. 67) still stands. However, Taylor et al.'s (2003) exclusion alters the effect size for '*PTSD symptom reduction for EMDR compared with relaxation*' (p. F-73) and '*Loss of PTSD diagnosis at 3-month follow-up for EMDR compared with relaxation*' (p. F-74), in favor of EMDR. The exclusion of this study also impacts the data comparing relaxation to exposure therapy.

PAPERS INAPPROPRIATELY EXCLUDED FROM THE ANALYSIS

In examining the papers excluded from the analysis in the RTI-UNC report (Jonas et al., 2013), there appears to be errors made in the exclusion of some studies from the analysis. Research by Lee et al. (2002) was assessed as a high risk of bias. However, as explained below, there appear to be errors in the examination of the results of this study.

In Table E1 on the RTI-UNC paper, there is a category that examines whether the participant groups in the study were equivalent at baseline. On page E-13, this category for the study by Lee et al. (2002) was rated as unclear. However, page 1077 of the Lee et al. (2002) article reports,

> *"Independent t-tests were used to investigate differences between the groups on pre-treatment measures. No differences were found for the IES [t(22) = 0.11, p = 91], BDI [t(22) = 1.05, p = 0.31], SI-PTSD [t(22) = 1.63, p = 0.12], or MMPI-K [t(22) = 1.31, p = 0.21]. Therefore, the groups appeared to be equivalent on major variables."*

Therefore, the raters made an error in asserting that the paper was not clear on whether there were differences at baseline. This is in sharp contrast to the Taylor et al. (2003) study where no baseline comparison data was analyzed.

The raters of Lee et al.'s (2002) study also marked it down saying that that the differential attrition data was unclear. However, the study clearly indicates that 24 participants entered the study, 12 were assigned EMDR and 12 were assigned to CBT, with three people dropping out, leaving 21 completers. On page 1075, it is stated that 21 participants completed the study, 11 for stress inoculation with prolonged exposure and 10 from EMDR. The article then describes how one of the EMDR non-completer was sent to prison. It does not make sense that the raters can claim that the attrition is not clear.

Given the above two errors, the risk of bias in the study deserves to be reclassified from high risk of bias to moderate. This inclusion strengthens the evidence base for a reduction in PTSD symptoms and for the loss of diagnosis for EMDR.

If correctly applying the RTI-UNC criteria to assess the evidence for EMDR to treat PTSD the APA should consider seven randomized controlled trials. Of these trials, four investigated EMDR compared to another manualized treatment and a waitlist or other minimal intervention control (Carlson et al., 1998; Rothbaum et al., 2005; van der Kolk et al., 2007; van den Berg et al., 2015), two compared EMDR treatment to a waitlist control only (Rothbaum, 1997; Högberg et al., 2008), and one trial compared EMDR to another manualized treatment only (Lee et al., 2002).

LACK OF ATTENTION TO FOLLOW UP DATA

In the RTI-UNC analysis, it states "*Our meta-analysis (Figure 17) found greater reduction in PTSD symptoms for EMDR than for controls. . .. Treatment gains were maintained for studies reporting follow up at 3, 6, or 9 months* (p. 67)." This statement ignores the considerable data that EMDR treatment gains are maintained far beyond end of treatment time points. At the very least the follow up study on the Högberg et al. (2008) data, which reported treatment gains for EMDR were maintained at 35 months, should have been mentioned. Other data, such as that presented in Wilson et al. (1995, 1997) papers, should also have been included. In this study, the researchers show that treatment gains made following just three EMDR sessions were maintained at follow-up (15 months) with large effect sizes.

EXCLUSION OF STUDIES TREATING PTSD WHERE SEVERITY OF SYMPTOMS DID NOT MEET THE FULL DIAGNOSTIC CRITERIA

The outcomes from the RTI-UNC review are based on studies with individuals who meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for PTSD (typically DSM-IV). However, there is a longstanding debate in the literature with

regards to the classification of mental health disorders, including PTSD (Haslam, 2003). Classification systems, such as the DSM, support a categorical classification system where by specific number of symptoms are provided in order to meet a diagnosis. Alternatively, a dimensional approach involves viewing mental health problems on a continuum without the arguable arbitrary cut of point that exists in a categorical classification (Brown and Barlow, 2005). The acknowledgment of the dimensional approach, and the inclusion of related studies, would significantly broaden the scope for the analysis and lead to more accurate data that is more meaningful to the practitioner (Luyten and Blatt, 2007). Typically practitioners would not refuse treatment to someone who wanted help in dealing with their trauma because they failed to meet all the diagnostic criteria from the DSM. Such a position is untenable especially as the diagnostic criteria changes over time and with different diagnostic systems. In the end, it is a science question. That is, where is the evidence of a differential effect of treatment on participants who make criteria and those who don't? With respect to PTSD at least one study reported no differences in the effect size on the outcome measures for those who met diagnostic criteria and those who did not (Wilson et al., 1995). Therefore to dismiss such studies as "wrong population" as cited in the RTI-UNC report lacks practical as well perhaps scientific credibility. There are three randomized controlled trials that were dismissed because of this position by the committee (Vaughan et al., 1994; Wilson et al., 1995, 1997; Scheck et al., 1998). All had solid methodology including assessing PTSD symptoms with a structured interview. These trials all found strong effects for EMDR over comparative treatments. There exclusion weakens the generalizability of the guidelines.

RESPONSE FROM THE APA WITH REGARDS TO THIS REVIEW

Prior to publication of the APA Practice Guidelines Development Panel for the Treatment of PTSD, an earlier version of this paper was submitted to the committee. The response of the Development Panel was to either ignore the main points of this paper or to respond with inaccurate information (Selected Representative Comments on PTSD Draft Document 1-24-17, American Psychological Association, forwarded as a personal communication by H. Kurtzman, 7 April 2017). For example, in response to the inappropriate measure issue in the Carlson et al. (1998) study, they stated that the IES was used as it is 'a more standard instrument' (p. 67) and that the M-PTSD was not used in any other study. However, as noted in this review they used the M-PTSD over the IES in other parts of their review. Regarding the failure to include the van der Kolk et al. (2007) study and the clear inappropriate inclusion of Taylor et al. (2003) study the panel simply failed to give any comments or responded by suggesting that no error had been made in with regards to the use of these studies. They do not directly address to the issues that were raised.

CONCLUSION

The APA guidelines are utilized worldwide and the accuracy of the document and the data it contains is crucial. This review highlights some serious inaccuracies regarding the way studies were handled in the statistical review of papers particularly with respect to evidence concerning EMDR. Therefore, the subsequent conclusions of the draft guidelines are flawed. Such failure to acknowledge errors explains why the proposed 2017 guidelines are at odds with other best practice guidelines from other countries and international based guidelines such as the World health Organization in 2013 (World Health Organization, 2013).

AUTHOR CONTRIBUTIONS

SD conducted all statistical analysis and reviewed the final version of the manuscript. CL initiated the writing of the article, provided the initial review of the RTI-UNC article and communicated directly with American Psychological Association regarding the content of this paper and relevant documents. Both authors contributed to the reviewing of the relevant papers and the studies they contained, and reviewing the draft versions of this manuscript.

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REVIEW
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The Use of Eye-Movement Desensitization Reprocessing (EMDR) Therapy in Treating Post-traumatic Stress Disorder—A Systematic Narrative Review

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Aim: There is an extensive body of research examining the efficacy of Eye-Movement Desensitization Reprocessing (EMDR) therapy in treatment of Post-traumatic Stress Disorder (PTSD). This systematic narrative review aimed to systematically, and narratively, review robust evidence from Randomized-Controlled Trials examining the efficacy of EMDR therapy.

Method: Eight databases were searched to identify studies relevant to the study aim. Two separate systematic searches of published, peer-reviewed evidence were carried out, considering relevant studies published prior to April 2017. After exclusion of all irrelevant, or non-robust, studies, a total of two meta-analyses and four Randomized-Controlled Trials were included for review.

Results: Data from meta-analyses and Randomized-Controlled Trials included in this review evidence the efficacy of EMDR therapy as a treatment for PTSD. Specifically, EMDR therapy improved PTSD diagnosis, reduced PTSD symptoms, and reduced other trauma-related symptoms. EMDR therapy was evidenced as being more effective than other trauma treatments, and was shown to be an effective therapy when delivered with different cultures. However, limitations to the current evidence exist, and much current evidence relies on small sample sizes and provides limited follow-up data.

Conclusions: This systematic narrative review contributes to the current evidence base, and provides recommendations for practice and future research. This review highlights the need for additional research to further examine the use of EMDR therapy for PTSD in a range of clinical populations and cultural contexts.

Keywords: eye movement desensitization and reprocessing (EMDR), EMDR therapy, trauma exposure, post-traumatic stress disorder, PTSD, review

INTRODUCTION

Eye-Movement Desensitization Reprocessing (EMDR) is a form of Psychotherapy developed by Shapiro (1995). Ostensibly, EMDR therapy is a trans-diagnostic, integrative psychotherapy that has been extensively researched and there is a growing empirical base for effective for the treatment of adverse life experiences, namely Post-traumatic Stress Disorder (PTSD) (Farrell, 2016). EMDR therapy utilizes a theoretical framework of Adaptive Information Processing (AIP), which posits that the primary source of psychopathology is the presence of memories of adverse life experiences inadequately processed by the brain (Felitti et al., 1998). There is much evidence examining the use of EMDR therapy as a treatment for trauma, however, much of this evidence centers upon non-Randomized Controlled Trials (RCTs).

This report intends to systematically, and narratively, review robust RCT evidence examining the efficacy of EMDR therapy.

METHODS

A systematic literature search of the databases was carried out, as outlined in **Figure 1**. After an initial scoping review of the literature, it became apparent that relevant meta-analyses of RCT studies were available. Therefore, the first systematic search gathered evidence of all systematic reviews and meta-analyses, which have synthesized and presented collective RCT evidence, examining the efficacy of EMDR therapy. All of the meta-analyses returned from this search specifically focused on the efficacy of EMDR therapy on PTSD symptoms - the most recent meta-analysis included papers prior to 2014. As a result, a second search was carried out to look at RCT studies investigating the efficacy of EMDR therapy on PTSD symptoms between 2014 and 2017, to ensure the most recent evidence was considered.

Search 1

A database search of published peer-reviewed systematic evidence relevant to the aim of this review was carried out, considering all relevant papers prior to April 2017 (**Table 1**). All databases were accessed using Northumbria University library's online subscription.

The Critical Appraisal Skills Programme tool (CASP, 2017a,b) for systematic reviews influenced the search strategy and was used to determine the quality of papers, and only those deemed of medium-high quality were included for review. Papers were excluded if they were not written in English, they reviewed non-Randomized-Controlled Trials (RCTs), they were not peer-reviewed, the review included RCTs including only children or adolescents, or EMDR therapy was not the focus of the report. A wildcard search strategy was utilized, to ensure that relevant papers were not excluded based on international spelling variations. A total of 24 papers were retrieved from the database search: ASSIA 2; CINAHL 2; Cochrane library 4; Medline 6; Psyc Articles 1; PubMed 0; Science Direct 1; Web of Science 8 (**Figure 2**). Fifteen papers were removed after an initial title and abstract search, and five papers were removed as duplicates. Four papers were read in full, and two papers were further removed as one was not written in English, and one involved children and adolescents only. A reference and citation search was conducted on all relevant papers to maximize the identification of relevant studies, however, no further papers were included as a result of this. A total of two papers were included in this review (**Table 2**).

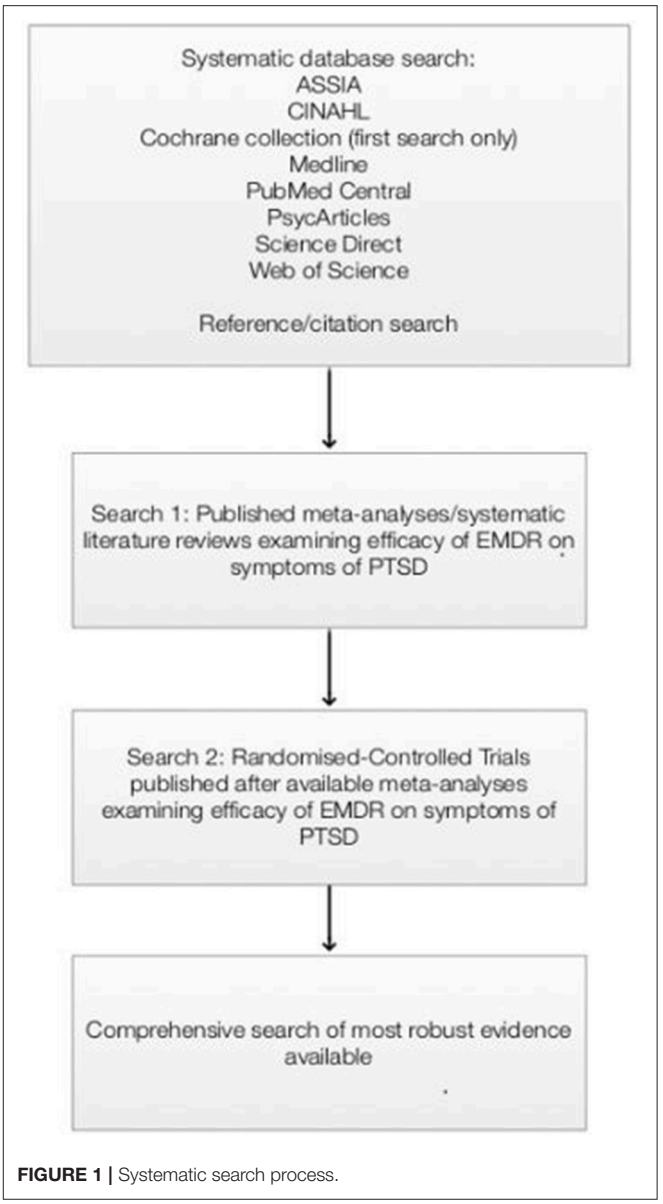

FIGURE 1 | Systematic search process.

Search 2

Search 2 aimed to examine the evidence underpinning the use of EMDR as a form of therapy that has been published since 2014. All databases, search fields, language and exclusion criteria were identical to those search 1, however search terms and year of publication differed (**Table 3**). All databases were accessed using Northumbria University library's online subscription.

TABLE 1 | Search strategy utilized for both systematic searches.

Source	ASSIA CINAHL Cochrane library Medline PsycARTICLES Pubmed central Science Direct Freedom Collection Web of Science
Search field	ASSIA (AB Abstract) CINAHL (AB Abstract) Cochrane library (Title, abstract, keywords) Medline (AB Abstract) PsycARTICLES (AB Abstract) Pubmed central (Abstract) Science Direct Freedom Collection (Abstract, title, keywords) Web of Science (Title)
Language	English only
Exclusion	Non-English language Non-RCTs Non-peer reviewed papers Pilot studies/RCT protocol data Studies including children/adolescents only EMDR not focus of report
Search terms	(eye movement desensitization reprocessing OR EMDR) AND (systematic review OR meta-analysis)
Year of publication	All papers published prior to April 2017

The most recent meta-analysis included evidence prior to 2014, therefore it is imperative that studies between 2014 and 2017 are also considered. A second database search was therefore carried out, considering RCT evidence of studies examining the efficacy of EMDR therapy on PTSD symptoms between January 2014 and April 2017. As with search 1 papers were excluded if they were not written in English, they were not RCTs, they were not peer-reviewed, they were a pilot study or reported protocol data, they involved only children/adolescents under 18 years old, or EMDR therapy was not the focus of the report. A wildcard search strategy was utilized, to ensure that relevant papers were not excluded based on international spelling variations. Again, the Critical Appraisal Skills Programme tool (CASP, 2017a,b) for RCT evidence was used to determine the quality of papers, and papers were excluded if they did not satisfy CASP criteria. A total of 72 papers were retrieved from the database search: ASSIA 4; CINAHL 1; Medline 5; Psyc Articles 2; PubMed 3; Science Direct 10; Web of Science 47 (**Figure 3**).

Sixty-five papers were removed after an initial title and abstract search, and three papers were removed as duplicates. Four papers were read in full. A reference and citation search was conducted on all relevant papers to maximize the identification of relevant studies, however no further papers were included as a result of this. A total of four papers were included in this review (**Table 4**).

RESULTS

Search 1

Two meta-analyses were included in this review (Chen et al., 2014, 2015). One was carried out in Taiwan (Chen et al., 2014) and one was carried out in China (Chen et al., 2015). One review focused on the use of EMDR therapy for adults with PTSD (Chen et al., 2015), whereas, one review included studies with both adults and children (5 of 26 RCTS involved children) (Chen et al., 2014). One meta-analysis focused on the efficacy of EMDR therapy compared to various interventions and control conditions (Chen et al., 2014) whereas, one study specifically focused on the efficacy of EMDR compared to CBT (Chen et al., 2015). Although this meta-analysis specifically compared EMDR therapy to CBT, many variants of CBT were included: image habituation training, trauma-treatment protocol, exposure plus cognitive reconstruction, prolonged exposure, stress inoculation training with prolonged exposure, imaginal exposure, brief eclectic psychotherapies, and "less standardized" CBT (Chen et al., 2015). Neither meta-analysis reported the length of follow-up for RCTs (Chen et al., 2014, 2015).

A total of 37 RCTs, and 1557 participants, were included over both meta-analyses. A total of seven RCTs were included in both of the reviews. It is evident that a vast number of comparator interventions and control conditions were used as comparisons to EMDR therapy. Furthermore, it is clear that there are severe inconsistencies between the outcome measures used to assess symptoms of PTSD, anxiety and depression, among other symptoms. Inconsistences also persist in use of scale sub-sections, as well as the scale version used.

Both meta-analyses followed PRISMA reporting guidelines (Chen et al., 2014, 2015). Meta-analyses provided in-depth, transparent evidence of their systematic search strategy. When examining the quality of RCTs, both studies utilized the Cochrane collaboration tool (Higgins and Green, 2011). The guidelines stipulate that a research quality score of 6–10 indicates an acceptable level of quality. One meta-analysis did not give quality indicators but described the quality assessment process (Chen et al., 2015), whereas, one meta-analysis stated that research quality of RCTs varied from 6 to 8 (Chen et al., 2014). Homogeneity among studies was measured in both meta-analyses (Chen et al., 2014, 2015) and publication bias was measured using funnel plot (Chen et al., 2014, 2015), Egger's test (Chen et al., 2014, 2015), and Begg's test (Chen et al., 2015). One study calculated effect size using Hedge's g and Cohen's d (Chen et al., 2014), and one study calculated effect size using Standard Mean Difference (Chen et al., 2015).

Both meta-analyses reported EMDR therapy as being significantly more effective in reducing PTSD symptoms than control conditions and other interventions, including CBT. Chen et al. (2014) conducted a meta-analysis specifically looking at the efficacy of EMDR therapy on the symptoms of PTSD (Chen et al., 2014). Twenty-two of the 26 studies examined

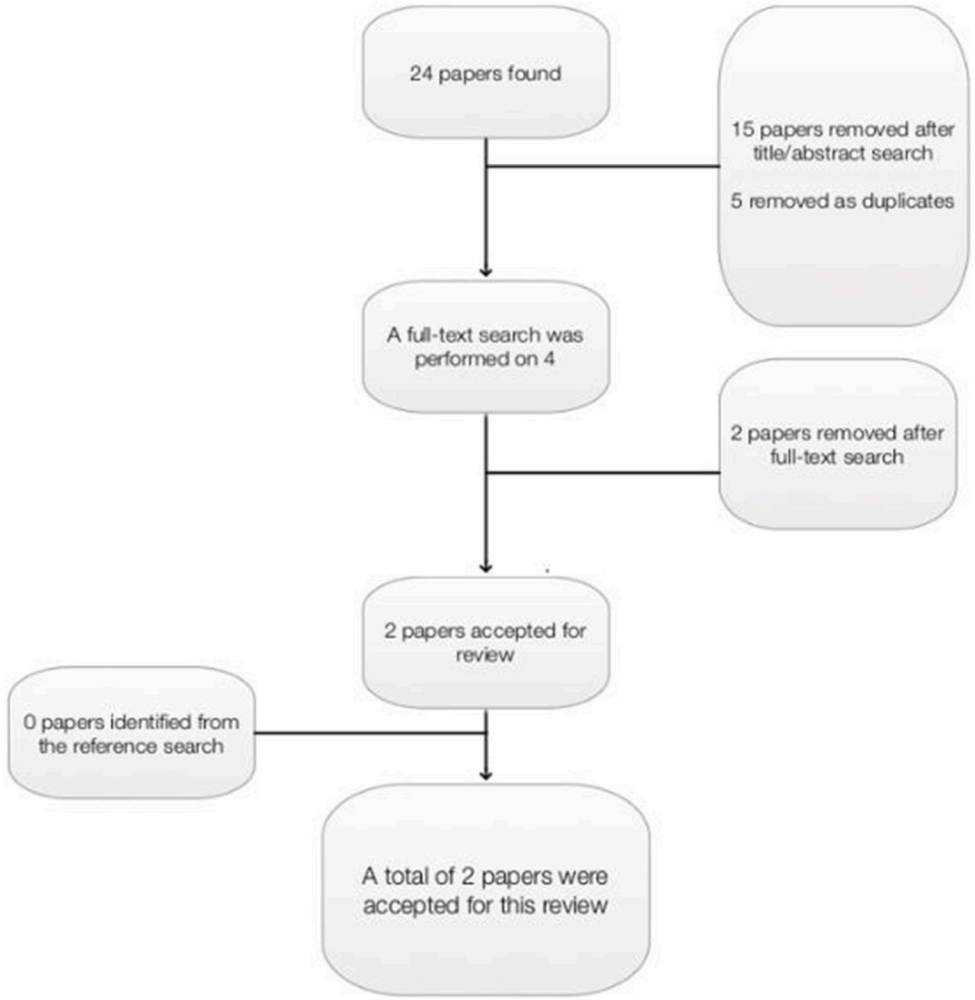

FIGURE 2 | Papers retrieved as part of first systematic search.

TABLE 2 | Characteristics of papers included in the first systematic search.

Author(s)	Aim	Design	Studies included (n =)	Total participants included (n =)	RCT quality assessment	Homogeneity measured	Publication bias	Effect size calculation	Location
Chen et al. (2014)	To examine the effects of EMDR on symptoms of PTSD, depression, anxiety, or subjective distress in PTSD patients	Meta-analysis	26	1,133	RCT requirements met by Cochrane collaboration (Higgins and Green, 2011)	Yes	Funnel plot Egger's test (Egger et al., 1997)	Hedge's *g* Cohen's *d*	Taiwan
Chen et al. (2015)	To examine the efficacy of EMDR compared to CBT for adults with PTSD	Meta-analysis	11	424	RCT requirements met by Cochrane collaboration (Higgins and Green, 2011)	Yes	Funnel plot Begg's test (Begg and Mazumdar, 1994) Egger's test (Egger et al., 1997)	Standard Mean Difference	China

TABLE 3 | Search strategy utilized as part of second systematic search.

Search terms	(eye movement desensitization reprocessing OR EMDR) AND (randomized controlled trial OR RCT) AND (post-traumatic stress disorder OR PTSD)
Year of publication	January 2014-April 2017

the effect of EMDR therapy on PTSD symptoms. The meta-analysis data reported that EMDR therapy significantly reduced PTSD symptoms overall ($p < 0.001$), with moderate effects sizes being evident ($g = -0.662$). In this instance, there were no reported publication biases, however, substantial heterogeneity was reported between studies.

Similarly, within the meta-analysis conducted by Chen et al. (2015) examining the efficacy of EMDR therapy to CBT, EMDR therapy was determined as being significantly more effective than CBT in reducing PTSD symptoms ($p = 0.05$)(Chen et al., 2015). No publication bias was reported, however, heterogeneity was high. Focusing on sub-scales of PTSD, EMDR therapy was also significantly more beneficial than CBT in reducing severity of intrusion ($p = 0.02$) and arousal ($p = 0.04$) (Chen et al., 2015). Only symptoms of avoidance failed to show a significant difference, and both EMDR therapy and CBT were comparable for this outcome ($p = 0.1$) (Chen et al., 2015). No publication bias was reported, however, heterogeneity ranged from moderate to high on all three sub-scales.

Further analyses within the meta-analysis carried out by Chen et al. (2014) revealed that group therapy carried out with experienced therapists showed a significantly larger effect size on PTSD symptoms than when carried out with an inexperienced therapist ($g = -0.753$; $g = -0.234$, respectively; $p = 0.007$)(Chen et al., 2014).

Chen et al. (2014) also investigated the efficacy of EMDR therapy on symptoms of depression and anxiety (Chen et al., 2014). Twenty of the 25 RCTs examined the effect of EMDR therapy on symptoms of depression, as the primary outcome. Findings from the meta-analysis report EMDR therapy as significantly reducing symptoms of depression overall ($p < 0.001$), with moderate effects being evident ($g = -0.643$) (Chen et al., 2014). Once more, no publication bias was reported, however, heterogeneity was moderate.

Sixteen of the 26 RCTs within the meta-analysis carried out by Chen et al. (2014) measured symptoms of anxiety as a primary outcome (Chen et al., 2014). EMDR therapy significantly reduced symptoms of anxiety ($p < 0.001$) with a moderate effect size being evident ($g = -0.640$)(Chen et al., 2014). No publication bias was reported, but heterogeneity was moderate. Finally, 12 of the 26 RCTs within the meta-analysis conducted by Chen et al. (2014) reported a significant reduction of subjective distress ($p < 0.01$) (Chen et al., 2014). A large effect size was evident illustrating the efficacy of EMDR therapy on subjective distress ($g = -0.956$) (Chen et al., 2014). Once more, no publication bias was reported but heterogeneity was moderate to high.

Chen et al. (2014) further reported that longer treatment sessions, of more than 60 min, were significantly more effective than shorter sessions for symptoms of depression ($p = 0.007$) and were also significantly more effective for symptoms of anxiety ($p = 0.045$). In this instance, homogeneity was reported over studies.

Summary Search 1

Both meta-analyses demonstrated the efficacy of EMDR therapy in treating symptoms of PTSD. Both studies concluded that EMDR therapy was more effective in treating symptoms of PTSD than various interventions and control conditions (Chen et al., 2014), including forms of CBT (Chen et al., 2015). Furthermore, Chen et al. (2014) demonstrated that EMDR therapy significantly reduced symptoms of depression, anxiety, and subjective distress (Chen et al., 2014). Chen et al. (2014) extrapolated further factors from RCT findings to determine that therapist experience of group therapy was a factor in reducing symptoms of PTSD. The meta-analysis identified that treatments lasting more than 60 min per session was a factor in improving symptoms of depression and anxiety (Chen et al., 2014).

There are however limitations to these studies. Both meta-analyses acknowledge that there is a lack of homogeneity between the RCTs reviewed, as variances exist between study design, interventions or control conditions used (including variations of CBT), sample sizes, and outcome measures including the use of various sub-scales or versions. The differences in study characteristics compromise the conclusions carried forward from these studies. Furthermore, one meta-analysis compares the efficacy of EMDR therapy to other interventions and control conditions, however, does not distinguish the differences of efficacy between these groups (Chen et al., 2014).

Search 2

All studies examined the efficacy of EMDR therapy with individuals diagnosed with PTSD (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016), with all but one study examining the impact of EMDR therapy on symptoms of PTSD (Acarturk et al., 2016; Carletto et al., 2016; ter Heide et al., 2016). Two studies examined the use of EMDR therapy with refugees diagnosed with PTSD (Acarturk et al., 2016; ter Heide et al., 2016), one study examined the use of EMDR therapy for symptoms of PTSD in patients diagnosed with multiple sclerosis (Carletto et al., 2016), and one study looked at effect of PTSD, depression and social functioning in patients with chronic psychotic disorders (de Bont et al., 2016). All studies used EMDR therapy as the intervention (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016). Two studies used additional intervention therapies; prolonged exposure (de Bont et al., 2016) and relaxation therapy (Carletto et al., 2016). Two studies included a waiting list group as a control measure (Acarturk et al., 2016; de Bont et al., 2016) and one study utilized stabilization as a control measure (ter Heide et al., 2016).

The number, and length, of sessions differed over the studies. One study did not provide details of treatment sessions (Acarturk et al., 2016), one study provided ten 60-min sessions (Carletto et al., 2016), one study provided eight sessions but provided no

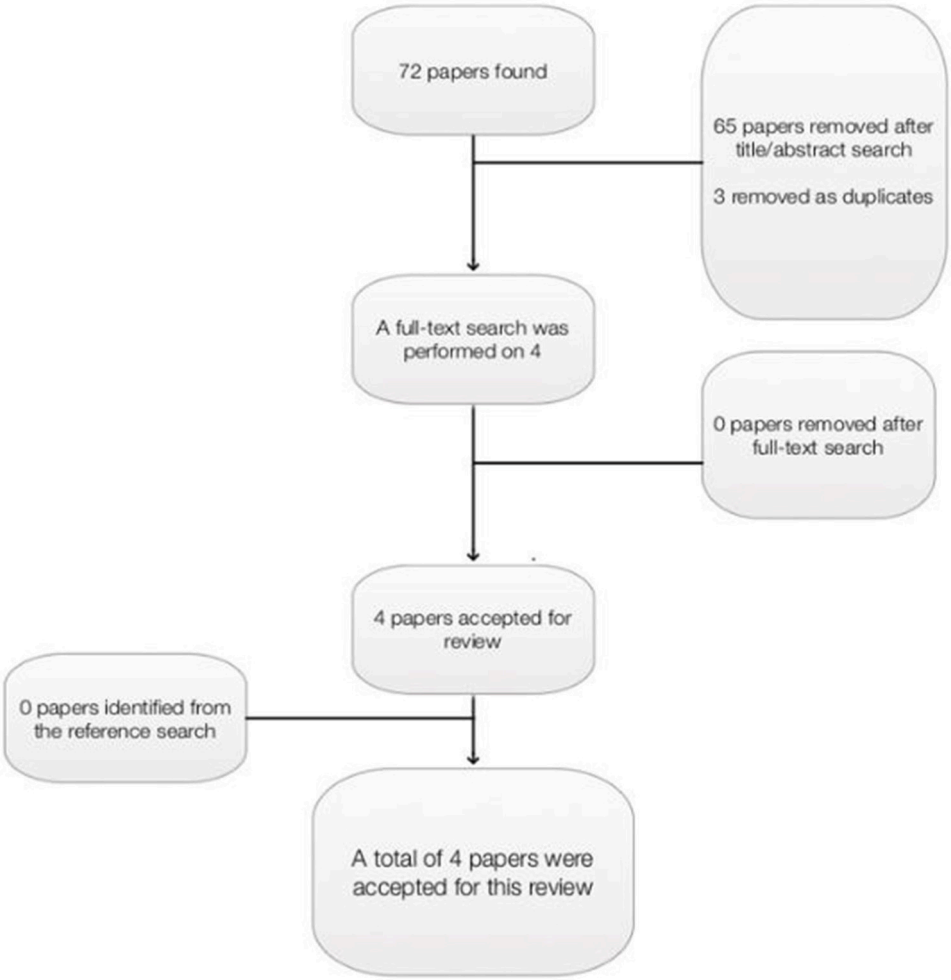

FIGURE 3 | Papers retrieved as part of second systematic search.

further detail (de Bont et al., 2016), and one study provided three 60-min sessions, followed by six 90-min sessions (ter Heide et al., 2016). Studies included between 50 and 155 participants (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016) and all studies reported a low dropout rate, with two of these studies reporting non-significant difference across conditions (Acarturk et al., 2016; ter Heide et al., 2016). All studies randomized participants to treatment groups (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016). In all studies, the treatment groups were blind to the assessor only (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016) as EMDR therapy is a healthcare treatment administered by a professional, therefore a blind or double blind study is inappropriate.

Only one study described power analyses, and indicated 80% power to detect medium effect size (ter Heide et al., 2016). All studies utilized different outcome measures to report symptoms of PTSD, depression, anxiety, and others, with 19 different measures being used of the four studies. The time of assessment, and follow-up, also differed between the studies. All studies reported pre-test measures, post-test measures were carried out between 1 and 12/15 weeks post-test, and follow-up also varied between 5 weeks to 6 months post-intervention. One study was carried out in Turkey (Acarturk et al., 2016), one was carried out in Italy (Carletto et al., 2016), and two were carried out in the Netherlands (de Bont et al., 2016; ter Heide et al., 2016).

All three studies directly measuring symptoms of PTSD found EMDR therapy significantly improved these symptoms (Acarturk et al., 2016; Carletto et al., 2016; ter Heide et al., 2016). One study reported EMDR therapy as being significantly more effective than another intervention therapy (Carletto et al., 2016), one reported EMDR therapy as being significantly more effective than a waiting list control-group (Acarturk et al., 2016), and one study found EMDR therapy to significantly improve some PTSD symptoms, but no more than a stabilization control group (ter Heide et al., 2016).

Carletto et al. (2016) utilized both EMDR therapy and relaxation therapy as intervention therapies to reduce PTSD

symptoms of individuals diagnosed with multiple sclerosis (Carletto et al., 2016). The study determined that 17 of 20 EMDR therapy participants no longer met PTSD diagnosis 12–15 weeks after treatment, and none of these 20 EMDR therapy participants met PTSD diagnosis at 6-month follow-up assessment. EMDR therapy was significantly more effective than relaxation therapy when considering post-treatment PTSD diagnosis ($p = 0.049$) (Carletto et al., 2016).

Acarturk et al. (2016) also concluded that EMDR therapy significantly reduced post-test PTSD diagnosis, compared to a waiting list control group ($p < 0.01$) (Acarturk et al., 2016). The study examined the efficacy of EMDR therapy for PTSD and depression among Syrian refugees. The results indicated that individuals in the waiting-list control group were 24.21 times more likely to be diagnosed with PTSD immediately post-test, compared to participants in the EMDR therapy group. Furthermore, the reduced likelihood of PTSD diagnosis remained significant at 1-month follow up, with individuals in the waiting-list control group being 23 times more likely to be diagnosed with PTSD, compared to EMDR therapy participants ($p < 0.01$)(Acarturk et al., 2016). Further analyses carried out by Acarturk et al. (2016) found EMDR therapy to significantly reduce the severity of PTSD compared to the waiting list control group ($p < 0.001$) and this effect was maintained over time. Specifically, there was a significant difference between EMDR therapy and control group for avoidance ($p < 0.01$), intrusion ($p < 0.01$), and hyper-arousal ($p < 0.01$). EMDR therapy also significantly improved reports of exposure of traumatic events compared to the control group condition ($p < 0.01$), and once more, this effect was maintained over time (Acarturk et al., 2016).

Similar to the study carried out by Acarturk et al. (2016), ter Heide et al. (2016) examined the efficacy of EMDR therapy for refugees diagnosed with PTSD (ter Heide et al., 2016). However, results were not as promising for the use of EMDR therapy in comparison. Over all of the reported primary and secondary outcomes, ter Heide et al. (2016) only reported significant improvement of trauma symptoms for both EMDR therapy and the stabilization control group ($p < 0.05$; $p < 0.05$), with no significant differences being reported between these conditions (ter Heide et al., 2016).

All four RCTs also considered the efficacy of EMDR therapy on symptoms of depression (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016), and three of these also considered its efficacy on symptoms of anxiety (Acarturk et al., 2016; Carletto et al., 2016; ter Heide et al., 2016). Carletto et al. (2016) identified that both EMDR therapy and relaxation therapy significantly improved anxiety symptoms ($p < 0.001$), depressive symptoms ($p < 0.001$) and mood ($p < 0.001$), although there were no significant difference between treatment efficacy (Carletto et al., 2016). EMDR therapy was also determined as being effective in reducing symptoms of depression and anxiety in the study carried out by Acarturk et al. (2016) (Acarturk et al., 2016). The study reported a significant difference between EMDR therapy intervention group and a waiting-list control group for the symptoms of depression ($p < 0.01$) and anxiety ($p < 0.01$), with both effects being maintained over time.

Although de Bont et al. (2016) utilized EMDR therapy as a treatment for individuals diagnosed with PTSD, the RCT did not report PTSD symptoms as an outcome measure (de Bont et al., 2016). Instead, de Bont et al. (2016) looked at the effect of EMDR therapy on symptoms of psychosis, depression and social functioning. The results presented by de Bont et al. (2016) are less favorable for the efficacy of EMDR therapy than other studies. The study reported prolonged exposure as being significantly more effective in reducing symptoms of depression than EMDR therapy (de Bont et al., 2016). The study showed that depressive symptoms for those in the prolonged exposure intervention, were significantly reduced compared to participants in a waiting-list control group at all follow-up points, and to EMDR therapy ($p < 0.05$) at both 6 month follow-up and over time (de Bont et al., 2016). Similarly, ter Heide et al. (2016) did not report statistically significant differences for symptoms of either depression or anxiety either over time, or between EMDR therapy and the stabilization control group (ter Heide et al., 2016).

Other outcome measures were also considered within these RCTs; paranoid thoughts (de Bont et al., 2016), social functioning (de Bont et al., 2016), functional assessment (Carletto et al., 2016), fatigue (Carletto et al., 2016), and quality of life (ter Heide et al., 2016). In addition to symptoms of depression, de Bont et al.'s (2016) main outcome measures were symptoms of psychosis and social functioning. This study demonstrated the impact of prolonged therapy exposure and EMDR therapy in reducing psychotic symptoms over the waiting list control condition (de Bont et al., 2016). EMDR therapy significantly reduced paranoid thoughts post-treatment ($p < 0.05$) and over time ($p < 0.05$), but interestingly not at 6-month follow up. Prolonged exposure was also significantly more effective in reducing paranoid thoughts compared to waiting list controls ($p < 0.05$) at all follow-up points. Neither EMDR therapy nor prolonged exposure significantly impacted auditory hallucinations or personal social performance compared to waiting list control group (de Bont et al., 2016). Carletto et al. (2016) also assessed the impact of EMDR therapy, and relaxation therapy, on functional assessment ($p = 0.001$) and fatigue severity ($p = 0.029$). Although both EMDR therapy and relaxation therapy were effective in improving these symptoms, there were no significant differences between reported between treatment groups (Carletto et al., 2016). ter Heide et al. (2016) examined quality of life, however, like other findings from this study, there were no significant outcomes for the efficacy of EMDR therapy, or for effects between the EMDR therapy intervention group, and the stabilization control group (ter Heide et al., 2016).

Summary Search 2

Four RCTs have been published between 2014 and 2017 examining the efficacy of EMDR therapy for individuals diagnosed with PTSD (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016). EMDR therapy was reported as significantly improving PTSD diagnosis and PTSD symptoms, over time, compared to relaxation therapy and a waiting-list control group (Acarturk et al., 2016;

TABLE 4 | Characteristics of papers included in the second systematic search.

Author(s)	Aim	Sample	Intervention (participants)	Randomization	Blindness	Power analyses	Drop-out rate	Outcome measures	Time of assessment	Location
Acarturk et al. (2016)	To examine effect of EMDR on symptoms of PTSD and depression in Syrian refugees	70 adult Syrian refugees with a PTSD diagnosis	EMDR ($n = 37$) Waiting list ($n = 33$) No further information provided	Randomly allocated to treatment but no details given	Blind to outcome assessor	Not discussed	EMDR ($n = 12$) Waiting list ($n = 16$) Non-significant across conditions	BDI-II IES-R HTQ HSCL-25 M.I.N.I	Pre-treatment 1-week post-treatment 5-weeks follow up	Turkey
Carletto et al. (2016)	To examine usefulness of EMDR and relaxation therapy as treatment for PTSD in patients with multiple sclerosis	50 adults diagnosed with multiple sclerosis	Ten 60-min EMDR sessions ($n = 20$) Ten 60-min sessions of relaxation therapy ($n = 22$)	Randomly allocated in 1:1 ratio	Blind to outcome assessor	Not discussed	EMDR ($n = 5$) Relaxation therapy ($n = 3$)	CMDI EDSS FAMS FSS HADS TAQ	Pre-treatment 12-15 weeks post-treatment 6-month follow up	Italy
de Bont et al. (2016)	To examine effects of prolonged exposure and EMDR for symptoms of PTSD in patients with chronic psychotic disorders	155 adults with chronic psychotic disorders	Eight EMDR sessions ($n = 55$) Eight sessions of prolonged exposure ($n = 53$) Waiting list ($n = 47$)	Randomly allocated to treatment but no details given	Blind to outcome assessor	Not discussed	EMDR ($n = 11$) Prolonged exposure ($n = 6$) Waiting list ($n = 8$)	BDI-II PRTS PSP PSYRATS SCI-SR-PANSS	Pre-treatment Post-treatment 6-month follow up	The Netherlands
ter Heide et al. (2016)	To examine safety and efficacy if EMDR in adult refugees with PTSD	72 adult refugees diagnosed with PTSD	Three 60-min; six 90-min EMDR sessions ($n = 43$) Twelve 60-min stabilization sessions ($n = 45$)	Blocked, simple randomization using a flipped coin	Blind to outcome assessor	80% power to detect medium effect size	EMDR ($n = 7$) Stabilization ($n = 9$) Non-significant across conditions	BREF CAPS HSCL HTQ WHOQOL-	Pre-treatment 2 weeks post-treatment 3-month follow up	The Netherlands

Carletto et al., 2016). EMDR therapy was also reported as significantly improving trauma symptoms (ter Heide et al., 2016).

All four RCTs also measured symptoms of depression and anxiety. EMDR therapy was reported as significantly reducing both depression and anxiety (Acarturk et al., 2016; Carletto et al., 2016). This effect was significant compared to control group (Acarturk et al., 2016) but there were no significant differences reported between EMDR therapy and relation therapy in reducing these symptoms (Carletto et al., 2016). Contradictory to this, one study did not report any differences in depression or anxiety symptoms between EMDR therapy and stabilization control group (ter Heide et al., 2016), and one study reported prolonged exposure as being significantly more effective in reducing symptoms of depression than EMDR therapy and waiting-list control group at post-test and over time (de Bont et al., 2016).

Finally, EMDR therapy and prolonged exposure therapies were reported as being an effective therapy to improve paranoid thoughts both at post-treatment assessment and over time (de Bont et al., 2016), but had not impact on auditory hallucinations or personal social performance compared to a waiting-list control group. Both EMDR therapy and relaxation therapy significantly improved functional assessment and fatigue severity (Carletto et al., 2016), however EMDR therapy was not effective in improving quality of life compared to a control stabilization group (ter Heide et al., 2016).

Study limitations were present. Similar to the meta-analyses reviewed, there was a lack of homogeneity across study design, intervention, control, outcome measures, and follow-up procedures. This makes it difficult to synthesize findings across studies, and reduces the impact of conclusions derived from the evidence. Furthermore, only one of the four studies reported power analyses which reduces the impact of the findings. Finally, only two of the four studies followed up at 6 months, therefore restricting the evidence of impact over time.

DISCUSSION

EMDR therapy is an empirically validated form of Psychotherapy (Shapiro, 2014), recommended by the World Health Organization to treat trauma (World Health Organisation, 2013). Meta-analysis and RCT data within this review evidence the efficacy of EMDR therapy in primarily treating symptoms of PTSD, depression and anxiety. Studies covered a wide range of counties including East and West affirming the effective delivery of EMDR therapy to differing cultures (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016). EMDR therapy significantly improved PTSD diagnosis (Carletto et al., 2016), and significantly reduced symptoms of PTSD (Chen et al., 2014, 2015; Acarturk et al., 2016; Carletto et al., 2016), and other trauma symptoms (ter Heide et al., 2016). Specifically, this review also evidenced EMDR therapy as significantly reducing symptoms of depression (Chen et al., 2014; Acarturk et al., 2016; Carletto et al., 2016), anxiety (Chen et al., 2014; Acarturk et al., 2016; Carletto et al., 2016), subjective distress (Chen et al., 2014), paranoid thoughts (de Bont et al., 2016), functional assessment (Carletto et al., 2016), and severe fatigue (Carletto et al., 2016). Despite the variations in methodology and analysis, the meta-analyses found EMDR therapy more effective than comparative interventions and control groups (Chen et al., 2014), resulting in PTSD below clinically significant levels. EMDR therapy was, however, more effective when delivered by more experienced therapists (Chen et al., 2015) and when sessions lasted more than 60 min (Chen et al., 2014). Overall, EMDR therapy was effective with a range of presenting problems and symptoms (Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016). Low drop-out rates across all studies indicates EMDR therapy is well tolerated by clients, including in comparison to prolonged exposure (Ironson et al., 2002; Evans, 2003; Bisson and Andrew, 2013; World Health Organisation, 2013; Shapiro, 2014; Acarturk et al., 2016; Carletto et al., 2016; de Bont et al., 2016; ter Heide et al., 2016). There were methodological limitations of the studies, which compromises the quality of data examined in this review. Initially, many of the RCT studies were low-powered due to small sample sizes used. Furthermore, studies reported limited follow-up data, and follow-up data that was reported was often differed between studies, limiting evidence of long-term efficacy. These limitations have been reported in other meta-analytic evidence examining PTSD therapies more widely, and it was acknowledged that these issues similarly hindered conclusions derived from the synthesized evidence (Bisson and Andrew, 2013).

Another limitation of the evidence to date is the lack of homogeneity between RCT evidence, due to the inconsistencies in study design, intervention characteristics, sample, outcome measures and follow-up procedures in each study. This lack of homogeneity limits comparability between data, and ultimately impacts conclusions. Furthermore, none of the retrieved studies reported economic factors of EMDR therapy, and this is seldom reported in wider EMDR therapy literature. It is acknowledged that EMDR therapy can reduce healthcare costs, whilst maintaining patient care, due to substantial patient improvement in relatively short time periods (Shapiro, 2014). However, evidence is required to examine these economic factors, specifically in comparison to similar therapies such as CBT.

Search Limitations

A strength of the review is that all papers were reviewed using the Critical Appraisal Skills Programme (CASP) tools for systematic reviews or RCTs, and studies were not included if they did not meet CASP criterion. It is also acknowledged that this review is limited to RCT evidence specifically of adults receiving EMDR therapy, a specific population with definite characteristics, and therefore findings cannot be more widely generalized. There were some limitations to the first literature search. Only meta-analyses and systematic searches with, EMDR, in their title were included as part of the first search. This was due to the refinement of the search strategy, which initially included syntheses of multiple forms of therapy. However, by including

evidence looking at multiple forms of therapy, some syntheses included only one or two studies investigating EMDR therapy, and often did not specifically analyse the efficacy of EMDR therapy as a stand-alone treatment. Therefore, limited evidence could be retrieved from these papers, and a decision was made to only examine papers directly investigating the efficacy of EMDR therapy. The second systematic search examined RCT evidence only as RCT evidence is considered gold standard evidence for the efficacy of healthcare interventions (Evans, 2003), and alternative evidence was therefore excluded from this report.

CONCLUSION

As the global burden of psychological trauma continues unabated, the need for more research and investigation into treatment interventions that are both effective and efficient is essential. It is clear from this extensive, robust evidence that EMDR therapy is an effective treatment to improve diagnosis of PTSD, and reduce symptoms of PTSD, and other trauma-related symptoms. More RCT evidence is required to further enhance our collective understanding of PTSD and co-morbid symptoms.

Recommendations for Practice

EMDR therapy should be available for adults who present with PTSD and co-morbid symptoms including depression and anxiety and EMDR therapy can be delivered effectively within the countries identified within this study.

Recommendations for Future Research

Further RCTs of EMDR therapy with larger sample sizes are required with a wide range of presenting mental health problems.

Additional research examining the differences between adult and child PTSD to ascertain which psychological treatment approaches for children and adolescents are more effective and efficient, as current evidence is weak. However emerging Practice-Based Evidence increasingly supports the utilization of Group Trauma Treatment Interventions (Jarero et al., 2013).

- More standardization of the normative outcome measures is required to facilitate comparison across studies.
- Studies need to include longitudinal evaluation beyond 6 months.
- Analysis is required of the economic benefits of EMDR therapy in comparison with other trauma-focused interventions.
- Comparative studies are needed of the efficacy of EMDR therapy across cultures.

AUTHOR CONTRIBUTIONS

GW carried out the systematic searches and synthesized the evidence. All authors contributed to the writing and editing of the paper. All authors approved the final manuscript.

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Efficacy of Eye Movement Desensitization and Reprocessing in Children and Adolescent with Post-traumatic Stress Disorder: A Meta-Analysis of Randomized Controlled Trials

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Background: Post-traumatic stress disorder (PTSD) can occur in both adults and children/adolescents. Untreated PTSD can lead to negative long-term mental health conditions such as depression, anxiety, low self-concept, disruptive behaviors, and/or substance use disorders. To prevent these adverse effects, treatment of PTSD is essential, especially in young population due to their greater vulnerability. The principal aim of this meta-analysis was to examine the efficacy of eye movement desensitization and reprocessing (EMDR) therapy for PTSD symptoms in children and adolescents. Secondary objectives were to assess whether EMDR therapy was effective to improve depressive or anxious comorbid symptoms.

Methods: We conducted a thorough systematic search of studies published until January 2017, using PubMed, Medline, Scopus, and ScienceDirect as databases. All randomized controlled trials with an EMDR group condition compared to a control group, such as treatment as usual or another psychological treatment, were included. Meta-analysis was conducted with MetaNSUE to avoid biases related to missing information.

Results: Eight studies (n = 295) met our inclusion criteria. EMDR therapy was superior to waitlist/placebo conditions and showed comparable efficacy to cognitive behavior therapy (CBT) in reducing post-traumatic and anxiety symptoms. A similar but non-statistically significant trend was observed for depressive symptoms. Exploratory subgroup analyses showed that effects might be smaller in studies that included more males and in more recent studies.

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Conclusion: Despite the small number of publications, the obtained results suggest that EMDR therapy could be a promising psychotherapeutic approach for the treatment of PTSD and comorbid symptoms in young individuals. However, further research with larger samples is needed to confirm these preliminary results as well as to analyze differences in the efficacy of EMDR therapy versus CBT.

Keywords: post-traumatic stress disorder, psychological trauma, EMDR, children, adolescents, meta-analysis

INTRODUCTION

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013), post-traumatic stress disorder (PTSD) is an anxiety disorder that can appear after an encounter with an unexpected traumatic event and can affect adults, adolescents, and children. The impact of an adverse life event with its negative effects will differ from one population to another depending on a number of factors such as the duration and intensity of the stressor, demographic variables, personality traits, and individual perception (Javidi and Yadollahie, 2012). Furthermore, when focusing on children and adolescents, the level of help and support given by the primary caregivers toward the victims, also plays an essential role in the potential negative consequences of the traumatic event (Javidi and Yadollahie, 2012). The variability of all these factors may be one of the reasons that contribute to the inconclusive evidence in PTSD rates, especially in children (Rodenburg et al., 2009); however, a recent meta-analysis revealed a prevalence around 16% in this population (Morina et al., 2016). Epidemiological studies show that the highest risk period for exposure to many potentially traumatic events is during adolescence, which include interpersonal violence and accidents or injuries among others (McLaughlin et al., 2013). Children, however, can also suffer highly stressful events like domestic violence, physical and/or sexual abuse, neglect, or chronic illnesses which can contribute to the development of a PTSD with or without a comorbid psychiatric disorder (Luthra et al., 2009). In fact, several studies have supported the hypothesis that the exposure to early stressful life events is associated with an increased vulnerability to major psychiatric disorders in adulthood including PTSD, personality disorders, substance use disorders, unipolar depression, bipolar disorder, and schizophrenia (Mclaughlin et al., 2012). Interestingly, there is also an increased risk of somatic illnesses such as obesity, migraines, cardiovascular disease, and diabetes (Javidi and Yadollahie, 2012; Nemeroff, 2016). Furthermore, it has been observed that patients with mood and anxiety disorders with a history of child abuse and neglect, show a worse prognosis of their mental health disorders and have a worse response to pharmacotherapy and/or psychotherapy (Nemeroff, 2016). Therefore, in light of the foregoing, the exposure to early life stressful events can be considered as a major risk factor for mental disorders, hence a rapid trauma orientated intervention is essential to prevent these adverse long term effects. This is especially true in children and adolescents due to their greater vulnerability during brain maturation.

To date, different forms of interventions for childhood PTSD have been used, including pharmacological agents such as tricyclic antidepressants, sertraline, or propranolol. Unfortunately, two systematic reviews concluded that these might be helpful in individual cases but the scientific support for the use of psychopharmacological interventions as a first-line treatment in PTSD in children is currently insufficient (Strawn et al., 2010; Keeshin and Strawn, 2014). Therefore, psychological interventions are the mainstay of treatment in traumatized children and adolescents. International guidelines, supported by several studies, recommend trauma-focused cognitive behavior therapy (TF-CBT) for the treatment of PTSD due to its efficacy to reduce PTSD symptoms and to improve a wide range of other mental health symptoms (Diehle et al., 2015; Morina et al., 2016). However, about a 16–40% of the treated children, continue to fulfill diagnostic criteria for PTSD after treatment (Diehle et al., 2015). Other approaches such as the prolonged exposure for adolescents (PE-A), the narrative exposure therapy (KIDNET), the child–parent psychotherapy (CPP) and the cognitive behavioral interventions for trauma in schools (CBITS), show some evidence of beneficial effects, but conclusions are not concise due an insufficient number of studies (Keeshin and Strawn, 2014; Morina et al., 2016).

A further form of trauma orientated therapy is eye movement desensitization and reprocessing (EMDR) therapy, which has been increasingly used in PTSD and has obtained promising results. This psychotherapeutic approach was developed in the late 80ies by Francine Shapiro. It is an eight-phase treatment approach based on a standardized protocol. Briefly, it consists of history taking, preparation, assessment, desensitization, installation, body scan, closure, and reassessment. This protocol facilitates a comprehensive evaluation of the traumatic memory picture, client preparation, and processing of (a) past traumatic events, (b) current disturbing situations, and (c) future challenges (Shapiro, 2014). One of the components used during the reprocessing phases, and considered as a key element in this therapy, is the bilateral stimulation by saccadic eye movements, tapping, or ear tones. The goal of EMDR therapy is to achieve an adequate processing of the negative experiences and to create new adaptive information. Its effectiveness for the treatment of PTSD in adults has been well-established by several independent meta-analysis (Davidson and Parker, 2001; Seidler and Wagner, 2006; Chen et al., 2014, 2015; Cusack et al., 2016). Numerous organizations, including the American Psychiatric Association, Department of Defense, and World Health Organization, recommend EMDR as an effective treatment for trauma victims (Shapiro, 2014). In the last decade, the number of the studies that have evaluated the efficacy of the EMDR in children or

adolescents with PTSD has increased. To date, a meta-analysis carried out by Rodenburg et al. (2009) has analyzed before the efficacy of EMDR in children. This meta-analysis included seven randomized controlled trials with a total sample of 109 children treated with EMDR therapy and 100 children in control conditions. The authors concluded that children receiving EMDR therapy benefited from the intervention and results suggested a small but significant advantage over CBT (Rodenburg et al., 2009). A further meta-analysis compared the evidence of various interventions, including EMDR, focused on man-made and natural disasters and found comparable positive effects of all interventions (Brown et al., 2017).

As new studies have been published, the principal aim of our meta-analysis of RCTs was to update the evidence of the efficacy of EMDR for the treatment of PTSD symptoms in children and adolescents. Secondarily, we also analyzed the effect of EMDR therapy on comorbid depressive and anxious symptoms.

METHODS

The meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and protocol outlined by the PRISMA Group (see Supplementary Table 1) (Moher et al., 2014).

Protocol and Registration

The protocol of this meta-analysis was registered with the International Prospective Register for Systematic Reviews (PROSPERO) (number CRD42017058769, available at www.crd.york.ac.uk/PROSPERO).

Eligibility Criteria

Criteria for inclusion for the meta-analysis were as follows: (a) studies that included children or adolescents who had suffered traumatic events and presented symptoms or a PTSD diagnosis; (b) studies that reported results of a RCT evaluating the efficacy of EMDR therapy against a control group, such as treatment as usual, waiting list or another psychological treatment; (c) studies that contained statistics and sufficient data for analyses.

Information Sources

Using PubMed, Medline, Scopus, and ScienceDirect two of the authors (AMA and ASE) conducted an independent systematic literature search to identify studies published until January 31th 2017 that used EMDR therapy for children or adolescent with trauma caused symptoms or PTSD diagnoses. Furthermore, manual searches of the references list of the previous meta-analysis and the retrieved articles were carried out.

Search

The search terms were selected from the thesaurus of the National Library of Medicine (Medical Subject Heading Terms, MeSH) and the American Psychological Association (Psychological Index Terms) and included the terms 'post-traumatic stress disorder,' 'PTSD,' 'psychological trauma,' 'EMDR,' 'eye movement desensitization reprocessing therapy,' 'children,' 'child*,' and 'adolescent.' The final search equation was defined using the Boolean connectors 'AND' and 'OR' following the formulation 'post-traumatic stress disorder' OR 'PTSD' OR 'psychological trauma') AND ('EMDR' OR 'eye movements reprocessing therapy') AND ('children' OR 'child*' OR 'adolescent').

Study Selection

After removing duplicates, AMA and ASE independently screened titles and abstracts and excluded studies that were considered non-pertinent. The final list was accepted by both authors. If inclusion criteria were met, the full text article was retrieved and screened to evaluate the available data for the analysis. Authors of the studies were contacted in case of any doubt (e.g., regarding the randomized process).

Data Collection Process

Data extraction was independently performed by two authors (DT and ASE). Disagreements were resolved via discussion with a third author (JR) until consensus was reached.

Data Items

For each article, we recorded the pre-treatment and post-treatment means and standard deviations of the symptoms measures, as well as the effect size of the between-group differences in the pre–post change of these measures. Related statistics (e.g., *t*-values) were also recorded to estimate missing information. PTSD and symptoms related to psychological trauma had been measured with the Peen Inventory for PTSD (Hammaiberg, 1992), the child reaction index (CRI) (Pynoos et al., 1987), the child report of post-traumatic symptoms (CROPS) (Greenwald and Rubin, 1999), the post-traumatic stress symptom scale for children (PTSS-C scale) (Ahmad et al., 2000), the child post-traumatic stress – reaction index (Child PTS-RI) (Frederick et al., 1992) and the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) (Nader et al., 1996). Depressive and anxiety symptoms had been measured with the Beck depression inventory (BECK) (Beck and Steer, 1993), the children's depression inventory (CDI) (Kovacs, 1992), the children's depression scale (CDS) (Lang and Tisher, 1983), the Depression Self Rating Scale (DSRS) (Birlenson, 1981), the Revised Child Anxiety and Depression Scale (RCADS) (Chorpita et al., 2000), the state-trait anxiety inventory (STAI) (Spielberg et al., 1983), the revised children's manifest anxiety scale (RCMAS) (Reynolds and Richmond, 1985) and the multidimensional anxiety scale for children (MASC) (March et al., 1996).

The following variables were also recorded: year of publication, sample size, participant's gender distribution, age, comorbid diagnoses (confirmed by clinical interview/clinician assessment), content of the active treatment and control conditions, treatment dose (operationalized as the number of therapy sessions and therapy hours provided), number of patients who dropped out of treatment during the treatment phase, and other clinical and methodological items objectively used to calculate the quality score of each study (see below).

Risk of Bias in Individual Studies

As recommended by the Cochrane Group (Higgins et al., 2011) we did not search for unpublished data to avoid the inevitable bias caused by dependence on investigators agreeing to provide data from unpublished studies. Included studies were assessed across six domains: adequate sequence generation, allocation concealment, outcome assessment blinding, management of incomplete outcome data, selective reporting and overall risk of bias. Each study was scored using three-item scale: low, high, or unclear risk of bias.

Quality of Individual Studies

In addition to checking the risk of bias of each study, we assessed their quality using the Jadad scale for randomized controlled trials (Jadad et al., 1996) through three domains: random assignment, double blinding, and the flow of patients. Each study was scored using a range from 0 to 5.

Summary Measures

Effect size of the difference in severity decrease between groups (Cohen's delta, i.e., the standardized difference in mean decrease) was directly retrieved from the papers or derived from the reported statistics. Missing data were multiply imputed when possible using the MetaNSUE approach (Radua et al., 2015).

Synthesis of Results

All effect sizes were corrected for small sample size (Hedges and Olkin, 1985) and separately meta-analyzed for each set of the multiple imputations using random-effects models, which take both intra-study and between-study variability into account. The latter, also called "heterogeneity," was estimated with the optimal restricted maximum likelihood (REML) technique (Viechtbauer, 2005).

Consistency of these differences was assessed by: (a) estimating the percentage of variability due to between-study heterogeneity (I^2) and the probability that this is statistically significantly different from 0% (so-called "Q test," but using an F statistic due to the multiple imputations); and (b) conducting leave-one-out jack-knife analyses (i.e., iteratively repeating the meta-analysis with all studies but one).

The multiple results originated from the different imputation sets were pooled taking imputation variability into account (Radua et al., 2015).

Separate meta-analyses were also conducted for post-traumatic, anxiety, and depression symptoms.

Drop-out Analysis

Possible differences in the number of patients who dropped out prematurely from treatment were investigated via a meta-analysis of the (logarithm-transformed) relative risk that a patient dropped out from the CBT group (as compared to the control group).

Risk of Bias across Studies

Potential bias was assessed by meta-regressing the effect sizes by their standard errors in order to detect whether studies with larger standard errors (due to e.g., small sample sizes) report larger effect sizes.

Analysis of Subgroups

For exploratory purposes, separate analysis were conducted for studies with <50% vs. >50% females, for studies comparing EMDR to CBT vs. other control groups, for studies applying <5 sessions vs. >5 sessions, for studies using <4 h per session vs. ≥4 h per session, for studies evaluating the patients before 3 months vs. at least 3 months after, for studies using an intention-to-treat analysis vs. studies using a per protocol analysis, and for studies published before 2008 vs. from 2008 onward. Subgroup analyses were only conducted when the two complementary subgroups included at least two studies each. No formal comparisons were conducted between each pair of subgroups due to the small numbers of studies.

Role of the Funding Source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the paper.

RESULTS

Study Selection and Study Characteristics

The PRISMA flowchart is shown in **Figure 1**. Eleven studies out of a total 136 were initially screened and analyzed for eligibility, leading to a total of eight final studies included in the review, comprising 295 participants with PTSD or trauma caused symptoms. All studies but one (Scheck et al., 1998) included exclusively children and adolescents with PTSD or trauma caused symptoms and involved individually delivered face-to-face EMDR sessions compared to no treatment (Soberman et al., 2002), pure waiting list (Chemtob et al., 2002; Ahmad et al., 2007; Kemp et al., 2010) active listening control (Scheck et al., 1998) or CBT (Jaberghaderi et al., 2004; de Roos et al., 2011; Diehle et al., 2015) (see **Table 1**).

Risk of Bias within Studies

Table 2 provides data on the risk of bias measured using the Cochrane Collaboration's Tool for Assessing Risk of Bias. Of the analyzed studies, five had unclear risk (Scheck et al., 1998; Chemtob et al., 2002; Soberman et al., 2002; Ahmad et al., 2007; Kemp et al., 2010) and three were considered to have low risk of bias (Jaberghaderi et al., 2004; de Roos et al., 2011; Diehle et al., 2015).

Quality of Individual Studies

Table 3 provides data on the quality of the studies using the Jadad Scale (0–5 points). Of the analyzed studies, one scored 2 points (Kemp et al., 2010), another 3 points (Soberman et al., 2002), two scored 4 points (Chemtob et al., 2002; Ahmad et al., 2007) and the rest of the studies scored 5 points (Scheck et al., 1998; Jaberghaderi et al., 2004; de Roos et al., 2011; Diehle et al., 2015).

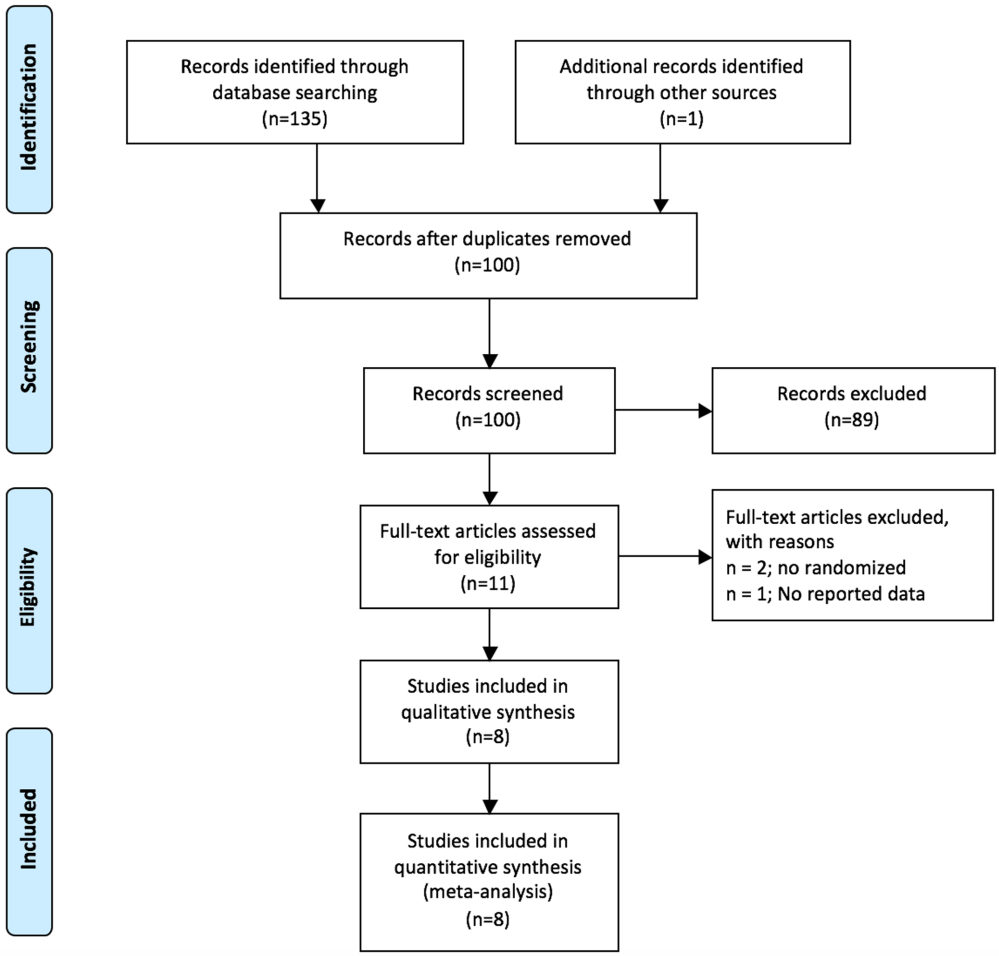

FIGURE 1 | Flow diagram of excluded and included studies according to the PRISMA guide.

TABLE 1 | Studies included in the meta-analysis.

Study	N		Age (years)	Females	Control group	Randomized	Blinded	Sessions		Months post	ITT analysis
	EMDR	Control						N	Hours		
Scheck et al., 1998	34	33	20.9	100%	ALC	Yes	Yes	2	3	3	No
Chemtob et al., 2002	19	15	8.4	NA	WL	Yes	Yes	3	NA	6	No
Jaberghaderi et al., 2004	10	9	12.5 [(a)]	100%	CBT	Yes	Yes	6.1	3	0.5	No
Ahmad et al., 2007	17	16	9.9	60.6%	WL	Yes	Yes	5.9	4.5	2	Yes
Soberman et al., 2002	14	15	13.0 [(a)]	0%	TAU	Yes	Yes	3	3	0.5	No
Kemp et al., 2010	13	14	8.9	44.4%	WL	Yes	No	4	4	12	No
de Roos et al., 2011 [(b)]	26	26	11.8	44.2%	CBT	Yes	Yes	3.2	3	3	Yes
Diehle et al., 2015	25	23	12.9	62.5%	CBT	Yes	Yes	8	8	NA	Yes

[(a)]*Average of age range;* [(b)]*only the ≥7-year old subsample was analyzed, values here are for the whole sample with the exception of the mean age which has been scaled to the ≥7-year old subsample. ALC, active listening control; CBT, cognitive behavioral therapy; EMDR, eye movement desensitization and reprocessing; ITT, intention to treat; NA, not available; TAU, treatment as usual; WL, waiting list.*

Post-traumatic Symptoms

The meta-analysis of post-traumatic symptoms included all studies, six of them with known effects and two with unknown non-statistically-significant effects. EMDR therapy decreased trauma-associated symptoms in a significant way ($d = -0.49$, $z = -2.5$, $p = 0.013$, 95% CI $= -0.87$ to -0.10). This analysis showed moderate but non-statistically-significant heterogeneity ($I2 = 52\%$, $p = 0.072$), without potential publication bias

TABLE 2 | Indicators of study quality based on the Cochrane collaboration's tool for assessing risk bias (Higgins et al., 2011).

Study (chronological order)	Adequate sequence generation	Allocation concealment	Blinding (outcome assessment)	Incomplete outcome data addressed	Free of selective reporting	Overall risk of bias
Scheck et al., 1998	Low	Low	Low	Low	Unclear	Unclear
Chemtob et al., 2002	Unclear	Unclear	Low	Low	Low	Unclear
Soberman et al., 2002	Unclear	Unclear	Low	Low	Low	Unclear
Jaberghaderi et al., 2004	Low	Low	Low	Low	Low	Low
Ahmad et al., 2007	Unclear	Unclear	Low	Low	Low	Unclear
Kemp et al., 2010	Unclear	Unclear	Unclear	Low	Low	Unclear
de Roos et al., 2011	Low	Low	Low	Low	Low	Low
Diehle et al., 2015	Low	Low	Low	Low	Low	Low

TABLE 3 | Jadad scale for randomized controlled trials (Jadad et al., 1996).

Study (chronological order)	Randomization	Blinding	An account of all patients	Total score (maximum points = 5)
Scheck et al., 1998	2	2	1	5
Chemtob et al., 2002	1	2	1	4
Soberman et al., 2002	1	1	1	3
Jaberghaderi et al., 2004	2	2	1	5
Ahmad et al., 2007	1	2	1	4
Kemp et al., 2010	1	0	1	2
de Roos et al., 2011	2	2	1	5
Diehle et al., 2015	2	2	1	5

($p = 0.860$). The Jackknife analysis suggested that the meta-analysis was not statistically significant after exclusion of either the study by Scheck et al. (1998) or the study by Ahmad et al. (2007) though effect sizes were still similar (from −0.58 to −0.36) (see **Table 4**).

Anxiety Symptoms

The meta-analysis of anxiety symptoms included five studies (Scheck et al., 1998; Chemtob et al., 2002; Kemp et al., 2010; de Roos et al., 2011; Diehle et al., 2015). Four of them had known effects and one had unknown non-statistically-significant effects. EMDR therapy proved to decrease significantly anxiety symptoms ($d = -0.44$, $z = -2.7$, $p = 0.006$, 95% CI = −0.76 to −0.13). Again, this analysis showed no heterogeneity (I2 = 1%, $p = 0.747$) and no potential publication bias ($p = 0.977$). Jackknife analysis showed that the meta-analysis was not statistically significant after exclusion of the study by Scheck et al. (1998), though effect sizes were still similar (from −0.55 to −0.37) (see **Table 4**).

Depression Symptoms

The meta-analysis of depressive symptoms included five studies (Scheck et al., 1998; Chemtob et al., 2002; Kemp et al., 2010; de Roos et al., 2011; Diehle et al., 2015). Four of the studies had known effects and one had unknown non-statistically-significant effects. EMDR therapy did not show a statistically significant decrease of depressive symptoms ($d = -0.27$, $z = -1.6$, $p = 0.118$, 95% CI = −0.61 to 0.07). This analysis showed no heterogeneity (I2 = 11%, $p = 0.416$), and no potential publication bias ($p = 0.366$). Jackknife analysis showed effect sizes in the range (−0.40, −0.11) (see **Table 4**).

Drop-out Analysis

No differences in the number of drop-out patients were detected between the EMDR and control groups (relative risk = 1.04, 95% CI = 0.97 to 1.12; $p = 0.287$).

Analysis of Subgroups

For post-traumatic symptoms, subgroup analyses showed that the effect size was nearly null (a) in studies that included mostly male patients ($d = -0.03$), (b) in studies that compared EMDR to CBT ($d = -0.09$) and (c) in studies published from 2008 onward ($d = -0.09$) (see **Table 4**).

For anxiety symptoms, subgroup analyses suggested that the effect size was small (a) in studies that included mostly male patients ($d = -0.12$), (b) in studies published from 2008 onward ($d = -0.23$), (c) in studies that compared EMDR therapy to CBT ($d = -0.25$) and (d) in studies that had applied an intention to treat analysis ($d = -0.25$) (see **Table 4**).

Finally, for depressive symptoms, subgroup analyses showed that the effect size was nearly null (a) in studies that included mostly male patients ($d = 0.04$), (b) in studies that compared EMDR therapy to CBT ($d = 0.08$), (c) in studies that had applied an intention to treat analysis ($d = 0.08$), (d) in studies published from 2008 onward ($d = 0.08$) and (e) in studies that had applied four or more sessions ($d = 0.11$) (see **Table 4**).

TABLE 4 | Meta-analysis of post-traumatic, anxiety, and depression symptoms.

	Post-traumatic		Anxiety		Depression	
	Effect size	***p*-value**	**Effect size**	***p*-value**	**Effect size**	***p*-value**
All studies	−0.49	0.013	−0.44	0.006	−0.27	0.118
Jackknife, study discarded:						
Scheck et al., 1998*	−0.46	0.057	−0.39	0.057	−0.11	0.593
Chemtob et al., 2002	−0.36	0.022	−0.37	0.043	−0.19	0.381
Jaberghaderi et al., 2004	−0.53	0.014				
Ahmad et al., 2007	−0.40	0.052				
Soberman et al., 2002	−0.51	0.014				
Kemp et al., 2010**	−0.51	0.016	−0.46	0.005	−0.28	0.134
de Roos et al., 2011	−0.58	0.005	−0.55	0.004	−0.40	0.037
Diehle et al., 2015	−0.57	0.010	−0.43	0.015	−0.33	0.078
Subgroup analyses:						
<50% females	−0.03	0.908	−0.12	0.694	0.04	0.883
>50% females	−0.48	0.016	−0.52	0.023	−0.31	0.338
Compared to CBT	−0.09	0.636	−0.25	0.336	0.08	0.747
Compared to other	−0.79	<0.001	−0.56	0.009	−0.51	0.014
<5 sessions	−0.52	0.068				
>5 sessions	−0.43	0.160				
<4 h per session	−0.30	0.135	−0.37	0.068	−0.27	0.379
≥4 h per session	−0.46	0.138	−0.36	0.332	0.11	0.765
Post < 3 months	−0.60	0.060				
Post ≥ 3 months	−0.58	0.080				
ITT analysis	−0.36	0.214	−0.25	0.336	0.08	0.747
Per protocol analysis	−0.60	0.025	−0.56	0.009	−0.51	0.016
Published before 2008	−0.84	0.001	−0.61	0.005	−0.55	0.010
Published from 2008	−0.09	0.662	−0.23	0.355	0.08	0.729

*Subgroup analyses only conducted when the two complementary subgroups included at least two studies each. * The only study included adults in the sample; ** the only non-blinded study. CBT, cognitive behavioral therapy; ITT, intention to treat.*

DISCUSSION

This is the third meta-analysis that explores the evidence of the efficacy of EMDR to treat trauma-associated symptoms in children and adolescents and the first one to assess its efficacy in depressive and anxiety symptoms associated with traumatic events. The main result of this meta-analysis is that patients treated with EMDR therapy present a reduction of their trauma-associated symptoms as compared to patients in the respective control conditions, this effect was also observed for comorbid anxiety symptoms ($d = -0.49$ and -0.44, $p < 0.013$). A similar but non-statistically-significant trend was observed for trauma-associated depressive symptoms ($d = -0.27$, $p = 0.118$).

Our results are similar to the previous meta-analysis carried out by Rodenburg et al. (2009), who also found that children treated with EMDR benefited from the treatment. That meta-analysis also found that EMDR was more effective than CBT ($d = 0.56$, $p < 0.001$) (Rodenburg et al., 2009), a finding that has not been detected in our updated meta-analysis. However, both meta-analyses are in line with recent meta-analytic studies analyzing EMDR therapy in adult samples, which showed that this psychotherapeutic approach reduces the symptoms of PTSD (Chen et al., 2014; Cusack et al., 2016) and is at least as effective as other techniques such as CBT (Davidson and Parker, 2001; Seidler and Wagner, 2006; Cusack et al., 2016).

Regarding comorbid depressive and anxiety symptoms, our meta-analysis is also in line with a meta-analysis carried out by Chen et al. (2014), which showed that EMDR therapy reduced depression and anxiety symptoms in adults with PTSD (Chen et al., 2014). The results of our meta-analysis reached statistical significance for the reduction of anxious symptoms but not for the reduction of depressive symptoms. However, the lack of statistical significance could be due to the small number of studies ($n = 5$) included in this analysis. More studies are needed to confirm these preliminary results.

Complementary analyses did not detect potential reporting bias, and the effect size was relatively similar throughout the jackknife iterations. In addition, no differences in the number of drop-out patients were detected between the EMDR and control groups. Conversely, exploratory subgroup analyses showed that the effect size was small or nearly null when studies with mostly male patients, comparative studies of EMDR to CBT, or studies published from 2008 onward were included only. The lack of effect of EMDR therapy in male patients is interesting, as current evidence suggests that girls are more likely to develop PTSD than boys (Alisic et al., 2014), especially when they have suffered interpersonal trauma. Regarding the lack of differences in the

efficacy of EMDR therapy compared to CBT, evidence in adults suggests -as stated before- that both approaches to treat PTSD are comparable (Davidson and Parker, 2001; Seidler and Wagner, 2006; Chen et al., 2015). However, subgroup analyses must be understood as exploratory given the small number of studies included in each subgroup. Our data are also in line with the second meta-analysis which included 34 studies and examined the effectiveness of EMDR, CBT, KIDNET and classroom-based interventions in children and adolescents after man-made and natural disasters (Brown et al., 2017). The authors did not reveal significant differences in pre–post scores within interventions. Importantly, six of the studies included in the meta-analysis applied group EMDR instead of individual sessions, a factor that might have reduced the efficacy of EMDR, as EMDR therapy was originally developed as an individual psychotherapy.

Eye movement desensitization and reprocessing is a complex psychotherapeutic approach that involves behavioral, cognitive, emotional, and psychical components in which each one plays an important role. Saccadic eye movements are elicited mainly to alleviate negative cognition, negative emotion, and unpleasant physical sensations associated with a traumatic memory and to reinforce positive cognition (Coubard, 2016). Despite EMDR has been validated as an effective treatment for PTSD based on controlled clinical research, the scientific community is divided about this intervention because its underlying neural mechanism is unknown (Coubard, 2016). Currently, several hypotheses have been proposed to explain the effectiveness of EMDR, related to orienting response, interhemispheric connection, visuospatial sketchpad and rapid eye movement (REM)-like movement (Novo et al., 2016), but none of them is sufficient to explain the effectiveness of EMDR.

The research about EMDR is still in its infancy, and more research is needed to understand better its mechanism of action and the underlying neural mechanism. More studies are also needed to confirm the preliminary results about the effectiveness of this psychotherapeutic approach in children and adolescents suffering from PTSD.

LIMITATIONS

Several limitations have to be taken into account before translating these results into clinical settings. First, the small number of studies included in this meta-analysis might have prevented the detection of some effects, such as the reduction of depressive symptoms. We included RCT only and discarded other types such as non-randomized, observational or case studies, which decreased statistical power but avoided possible biases. Secondly, the studies included in the meta-analysis used different control conditions, which reflects the heterogeneity of this field. Three studies used pure waiting list, three used CBT, one active listening and another one did not use any active control condition. Also, the number of EMDR sessions that participants received in some studies was relatively low, for instance patients only received two sessions in the study performed by Scheck et al. (1998). This could be insufficient bearing in mind the eight phases of the standard protocol and the complexity of trauma-associated and comorbid symptoms. Finally, the small number of studies prevented a multivariate analysis to discard whether the factors analyzed in the subgroup analyses may be confounding each other. Therefore, no strong conclusions should be taken regarding the effects of gender, the comparison with CBT or the publication year.

CONCLUSION

Despite the small number of publications, the results of this meta-analysis suggests that EMDR could be a promising psychotherapeutic approach for the treatment of PTSD and anxiety symptoms in children and adolescents. However, further research with larger samples is needed to confirm these preliminary results.

AUTHOR CONTRIBUTIONS

AM-A and BA had the idea of the project. AM-A and AS-E conducted the systematic literature search to identify studies published and the screening of the manuscripts. DT and AS-E performed data extraction. JR conducted the statistical analysis. AM-A, AV-G, and JR wrote the first draft of the manuscript. AM-A, DT, AV-G, AS-E, VP, BA, and JR contributed to the revisions and modifications of the manuscript and all have approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2017.01750/full#supplementary-material

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SYSTEMATIC REVIEW
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EMDR beyond PTSD: A Systematic Literature Review

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Background : Eye Movement Desensitization and Reprocessing (EMDR) is a psychotherapeutic approach that has demonstrated efficacy in the treatment of Post-traumatic Stress Disorder (PTSD) through several randomized controlled trials (RCT). Solid evidence shows that traumatic events can contribute to the onset of severe mental disorders and can worsen their prognosis. The aim of this systematic review is to summarize the most important findings from RCT conducted in the treatment of comorbid traumatic events in psychosis, bipolar disorder, unipolar depression, anxiety disorders, substance use disorders, and chronic back pain.

Methods : Using PubMed, ScienceDirect, and Scopus, we conducted a systematic literature search of RCT studies published up to December 2016 that used EMDR therapy in the mentioned psychiatric conditions.

Results : RCT are still scarce in these comorbid conditions but the available evidence suggests that EMDR therapy improves trauma-associated symptoms and has a minor effect on the primary disorders by reaching partial symptomatic improvement.

Conclusions : EMDR therapy could be a useful psychotherapy to treat trauma-associated symptoms in patients with comorbid psychiatric disorders. Preliminary evidence also suggests that EMDR therapy might be useful to improve psychotic or affective symptoms and could be an add-on treatment in chronic pain conditions.

Keywords: eye movement desensitization and reprocessing, PTSD, psychosis, bipolar disorder, chronic pain, unipolar depression, RCT

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INTRODUCTION

Eye Movement Desensitization and Reprocessing (EMDR) is a psychotherapeutic approach developed in the late 80s by Francine Shapiro (Shapiro, 1989) that aims to treat traumatic memories and their associated stress symptoms. This therapy consists of a standard protocol which includes eight phases and bilateral stimulation (usually horizontal saccadic eye movements) to desensitize the discomfort caused by traumatic memories and the aim of the therapy is to achieve their reprocessing and integration within the patient's standard biographical memories (Shapiro, 2005). The effectiveness of EMDR therapy in treating Post-traumatic Stress Disorder (PTSD) has undergone the scrutiny of several meta-analyses (Van Etten and Taylor, 1998; Bradley et al., 2005; Davidson and Parker, 2005; Seidler and Wagner, 2006; Benish et al., 2008; Jonas et al., 2013; Chen et al., 2014, 2015); this led to the final recognition by the World Health Organization (2013) as a

psychotherapy of choice in the treatment of PTSD in children, teenagers, and adults[1]. Moreover, the application of EMDR therapy is not restricted to the treatment of people with PTSD and its use is currently expanding to the treatment of other conditions and comorbid disorders to PTSD (de Bont et al., 2013; Novo et al., 2014; Perez-Dandieu and Tapia, 2014). In this context, it is important to note that traumatic events belong to the etiological underpinnings of many psychiatric disorders (Kim and Lee, 2016; Millan et al., 2017). In addition, a comorbid diagnosis of PTSD can worsen the prognosis of other psychiatric disorders (Assion et al., 2009). Therefore, investigation in EMDR therapy has increased beyond PTSD and several studies have analyzed the effect of this therapy in other mental health conditions such as psychosis, bipolar disorder, unipolar depression, anxiety disorders, substance use disorders, and chronic back pain. The aim of this systematic and critical review is to summarize the most important results of the available randomized controlled trials (RCT) conducted in this field.

METHODS

Using PubMed, ScienceDirect, and Scopus, we conducted a systematic literature search of studies published up to December 2016, which examined the use of EMDR therapy in other psychiatric disorders beyond PTSD. The search terms were selected from the thesaurus of the National Library of Medicine (Medical Subject Heading Terms, MeSH) and the American Psychological Association (Psychological Index Terms) and included the terms "EMDR," "schizophrenia," "psychotic disorder," "bipolar disorder," "depression," "anxiety disorder," "alcohol dependence," "addiction," and "chronic pain." The final search equation was defined using the Boolean connectors "AND" and "OR" following the formulation "EMDR" AND "schizophrenia", "psychotic disorder," "bipolar disorder," "depression," "anxiety disorder," "alcohol or substance dependence" OR "addiction," "chronic pain." The automatic search was completed with a manual snowball search using reference lists of included papers and web-based searches in an EMDR-centered library (https://emdria.omeka.net/). The search included English-published articles from 01/01/1997 to 31/12/2016 and did not include any subheadings or tags (i.e., search fields "All fields"). Furthermore, we performed a manual search of the references list of previous meta-analysis and the retrieved articles. Case reports, serial cases, unpublished studies, and non-randomized studies, were excluded from this systematic review. Due to the significant heterogeneity of the studies, a formal quantitative synthesis (i.e., meta-analysis) was not possible. Instead, a systematic review was conducted using the PRISMA guidelines as referenced above. Prisma 2009 checklist (Supplementary Datasheet) and flow chart (**Figure 1**), as well as the Jadad scale (Supplementary Table) for reporting RCT have been completed and included in the Supplementary Material.

[1]http://www.who.int/mediacentre/news/releases/2013/trauma_mental_health_20130806/es/2013.

Inclusion Criteria and Exclusion Criteria

The final selection of the articles was carried out using the following criteria: (i) RCT published in peer-reviewed journals, (ii) in adult populations (over 18 years) that (iii) examined the use of EMDR therapy in different psychiatric disorders (as previously described). The criteria for exclusion were: (i) articles that did not contain original research (i.e., reviews and meta-analyses and (ii) quasi-experimental designs (single case and/or no control group). The studies were selected by Alicia Valiente-Gómez and discrepancies were resolved by Ana Moreno-Álcazar and Benedikt L. Amann.

RESULTS

EMDR Therapy in Schizophrenia and Other Psychotic Disorders

Since 2010, five datasets of RCT have been published in patients with a psychotic disorder and a comorbid PTSD or traumatic events (see **Table 1**) (Kim et al., 2010; de Bont et al., 2013, 2016; van den Berg et al., 2015; Van Minnen et al., 2016). These consist of two pilot studies (Kim et al., 2010; de Bont et al., 2013) and one large RCT (van den Berg et al., 2015) with two further subanalysis (de Bont et al., 2016; Van Minnen et al., 2016).

A Korean group (Kim et al., 2010) carried out the first RCT including 45 acute schizophrenic inpatients. Patients were randomized to 3 weekly sessions of EMDR therapy (lasting 60 to 90 min) ($n = 15$), 3 weekly sessions of progressive muscle relaxation therapy ($n = 15$) (the first session lasted 90 min and the other two sessions lasted 60 min), and treatment as usual (TAU, $n = 15$). In the EMDR condition, the therapeutic treatment targets included stressful life events related with the current admission, traumatic incidents from childhood or adulthood, treatment-related adverse events (e.g., involuntary admission or seclusion), and the experience of distressing psychotic symptoms. All patients received TAU, which consisted of naturalistic psychopharmacological treatment, individual supportive psychotherapy, and group activities whilst being admitted. All groups showed an improvement of the symptomatic domains, which included psychotic, anxious, and depressive symptoms, measured by the Positive and Negative Syndrome Scale (PANSS), the Hamilton Depression Rating Scale (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A). The variance analysis (ANOVA), revealed a significant improvement over time in each of the treatment groups; however, there was no significant differences between treatment groups for the total PANSS ($F = 0.73$, $p = 0.49$), HAM-D ($F = 0.41$, $p = 0.67$), or HAM-A ($F = 0.70$, $p = 0.51$). Still, the effect size for negative symptoms was larger for the EMDR condition (0.60 for EMDR, 0.39 for PMR and 0.21 for TAU only, no significant differences).

A Dutch group published a small pilot RCT in patients with psychosis and PTSD in 2013 (de Bont et al., 2013). Patients were randomized to prolonged exposure (PE) ($n = 5$) or EMDR therapy ($n = 5$) to treat PTSD symptoms with a maximum of 12 weekly sessions of 90 min. The PTSD diagnosis was verified using the Clinical-Administered PTSD Scale (CAPS) and the

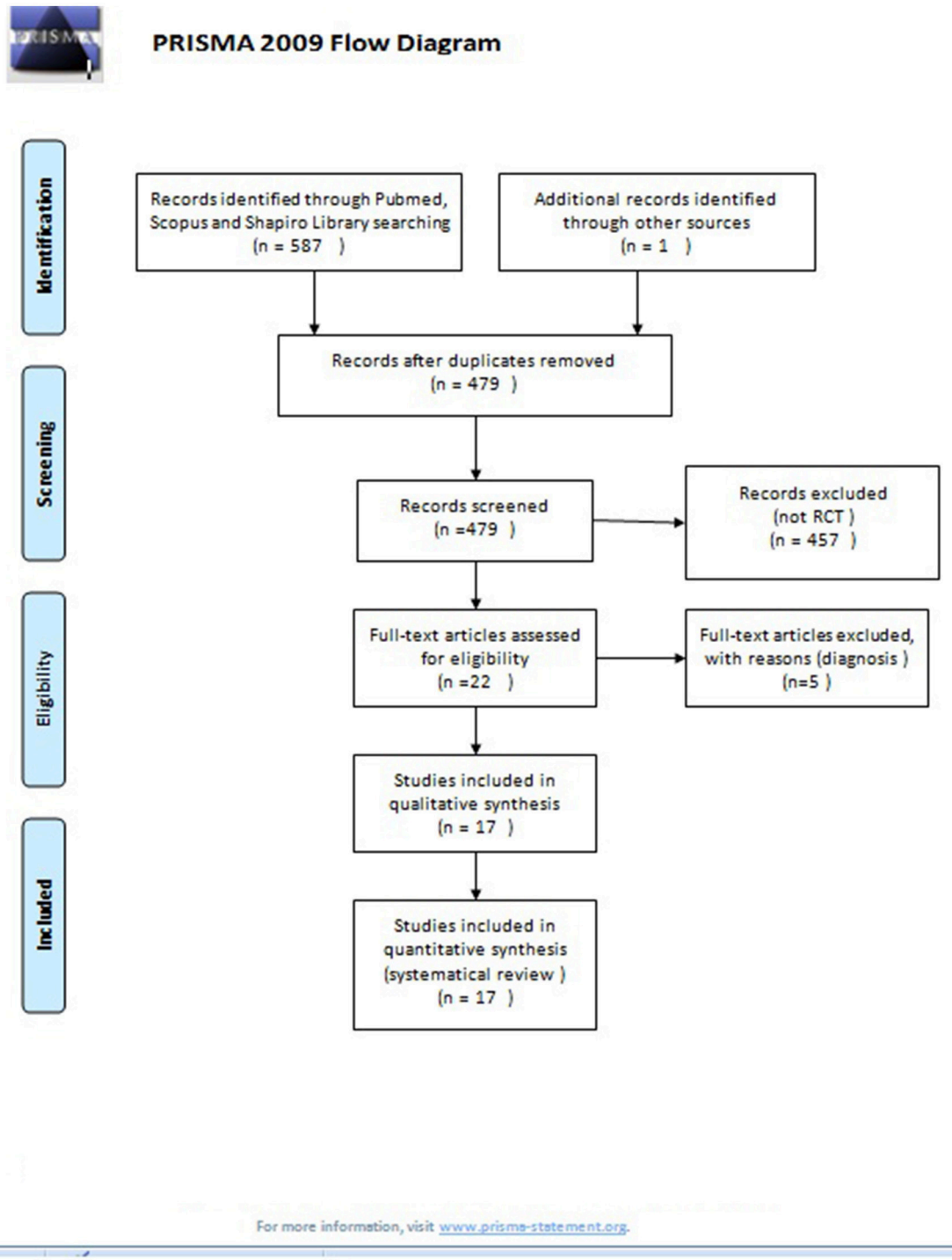

FIGURE 1 | PRISMA 2009 flow diagram. From Moher et al. (2009).

Post-traumatic Stress Symptom Scale Self-Report (PSS-SR). All patients were assessed with the Psychotic Symptoms Rating Scale interview (PSYRATS) and the Green Paranoid Thoughts Scale (GPTS) for psychotic symptoms. The mixed-model showed that in the intention to treat analysis, both groups reached a significant decrease of PTSD symptoms during the treatment phase ($p < 0.001$, $r = 0.64$), this effect was maintained in the post-treatment phase ($p < 0.001$, $r = 0.73$) and in the 3 months follow up phase ($p < 0.001$). The same group conducted a large single-blind RCT including a sample of 155 outpatients with

TABLE 1 | RCT of EMDR in psychotic disorder.

Title author, year	Sample (n)	EM/Full protocol	Control condition	Main findings	Conclusions
Kim et al., 2010	45	EMDR	PR or TAU	EMDR=PR=TAU, but EMDR>PR>TAU in negative symptoms.	No differences within all groups, except of advantage of EMDR in negative symptoms.
de Bont et al., 2013	10	EMDR	PE or WL	PE= EMDR>WL in trauma symptoms.	PTSD patients with schizophrenia benefit from trauma-focused treatment approaches.
van den Berg et al., 2015	155	EMDR	PE or WL	EMDR = PE> WL in trauma symptoms.	Both trauma-focuses treatments are effective and safe to treat PTSD symptoms in patients with chronic psychotic disorders.
Van Minnen et al., 2016*	108	DS	NDS	DS=NDS in trauma symptoms.	Trauma-focused treatments for DS should not be excluded from these treatments.
de Bont et al., 2016*	155	EMDR	WL or PE	PE = EMDR>WL In paranoid thoughts. PE>EMDR>WL in depressive symptoms.	No differences within all groups, except of advantage of EMDR in paranoid thoughts and PE in depressive symptoms.

*RCT, Randomized controlled trial; EMDR, Eye Movement desensitization and reprocessing; PR, progressive relaxation; TAU, treatment as usual; PE, Prolonged exposure; WL, wait-list control; PTSD, Post-Traumatic Stress Disorder; DS, Dissociative Subtype of PTSD; NDS, Non-Dissociative Subtype of PTSD.*These data sets corresponds to the clinical trial ISRCTN 79584912 of van den Berg et al. (2015).*

a psychotic disorder (schizophrenia or schizoaffective disorder) and a comorbid PTSD (van den Berg et al., 2015). Patients were randomized to three different groups (PE, EMDR, and Waiting-List Condition). Forty-seven patients were in the waiting-list condition (WL), for the other two conditions, PE ($N = 53$) and EMDR therapy ($N = 55$), patients received 8 weekly sessions of 90 min each. PTSD symptoms were evaluated with the CAPS, PSS-SR, and the Post-traumatic Cognitions Inventory (PTCI). The authors found that EMDR and PE therapy were both superior to the WL condition in reducing PTSD symptoms (PE effect size 0.78, $t = -3.84$, $p = 0.001$; EMDR effect size 0.65, $t = -3.26$, $p = 0.001$). No significant differences were detected between PE and EMDR therapy.

Two further subanalysis of the main study were published (de Bont et al., 2016; Van Minnen et al., 2016). The first subanalysis (de Bont et al., 2016) provided evidence, that the severity of paranoid thoughts assessed by GPTS, decreased in a significant way (PE $t = -2.86$, $p = 0.005$; EMDR $t = -2.68$, $p = 0.008$) and rates of remission for psychotic disorders increased for both treatment conditions in comparison to the WL arm (de Bont et al., 2016). In another secondary analysis with a subsample of 108 patients (Van Minnen et al., 2016), the authors evaluated the effectiveness of both trauma-focused treatment for patients with psychosis with and without the dissociative subtype of PTSD. This diagnosis was established regarding the items 29 (derealization) and/or 30 (depersonalization) (frequency $\geq$1 and intensity $\geq$2) on the CAPS. They though that, even though patients with a dissociative subtype of PTSD, showed significantly more severe PTSD symptoms at pre-treatment ($t = -0.29$, $p = 0.005$), the CAPS scores did no longer differ at post-treatment ($t = -1.34$, $p = 1.85$), when compared to patients without the dissociative subtype of PTSD.

In summary, one pilot study (Kim et al., 2010) found that EMDR therapy did not have a superior effect over progressive relaxation therapy or TAU in reducing trauma symptoms patients with PTSD and a psychotic disorder. In contrast, another preliminary study provided a comparable effect of EMDR therapy to PE (de Bont et al., 2013). This was confirmed by a large and well-designed study (van den Berg et al., 2015) that suggested that patients with a psychotic disorder and PTSD improved both with EMDR therapy and PE therapy (comparable to WL) in trauma-associated and paranoid symptoms, despite the impact and the high prevalence of comorbid PTSD in psychotic disorders, evidence of the use of EMDR therapy in psychosis and trauma is still scarce.

EMDR Therapy in Affective Disorders

EMDR Therapy in Bipolar Disorder

So far, only 1 RCT has investigated the efficacy of EMDR therapy in bipolar disorder (Novo et al., 2014). Twenty bipolar patients with subsyndromal symptoms and a history of traumatic events were randomly assigned to 12 weeks of treatment with EMDR therapy or TAU. The participants were re-assessed at the end of this period and after a further 12 weeks of follow-up. Results showed significant reductions in affective scores in favor of the EMDR group after treatment. Affective symptoms were assessed through the HAM-D ($F = 23.86$, $p = 0.001$) and the Young Mania Rating Scale (YMRS) ($F = 14.41$, $p = 0.004$). However, changes from baseline to 24 weeks follow-up did not reach statistical significance. Regarding trauma symptoms, assessed by the CAPS and the Impact Event Scale (IES), results showed significant improvement in the EMDR group after treatment in both measures (CAPS $F = 6.26$, $p = 0.03$; IES $F = 20.36$, $p = 0.001$). At the follow-up assessment, only the IES scores remained statistically significant ($F = 20.32$, $p = 0.003$). Functional impairment was also assessed, but no group differences were found (**Table 2**).

EMDR Therapy in Unipolar Depression

Two controlled studies in EMDR therapy have been performed in unipolar depressive disorders (Behnammoghadam et al., 2015; Hase et al., 2015). A matched pairs study (Hase et al., 2015)

TABLE 2 | RCTs of EMDR in affective disorder, substance use disorders and chronic pain.

Author, year	Diagnosis	Sample (n)	EM/Full protocol	Control condition	Main findings	Conclusions
AFFECTIVE DISORDERS						
Novo et al., 2014	Bipolar disorder	20	EMDR	TAU	EMDR>TAU in trauma, depressive and hypomanic symptoms.	EMDR can help to treat subsyndromal mood beyond trauma symptoms in bipolar patients.
Hase et al., 2015	Unipolar depression	16	EMDR+TAU	TAU	EMDR+TAU>TAU	EMDR has positive effects in the treatment of depression.
Behnammoghadam et al., 2015	Depression after myocardial infarction	60	EMDR	WL	EMDR>WL	EMDR is an efficient treatment to depression in patients with myocardial infarction.
SUBSTANCE USE DISORDERS						
Hase et al., 2008	Alcohol Dependence	34	EMDR+TAU	TAU	EMDR+TAU>TAU	EMDR might be a useful approach for treating addiction memory and craving of alcohol.
Perez-Dandieu and Tapia, 2014	Alcohol and other substance use disorders	12	EMDR+TAU	TAU	EMDR+TAU>TAU	PTSD symptoms can be successfully treated with EMDR in substance abuse patients.
CHRONIC BACK PAIN						
Gerhardt, 2016		40	EMDR	TAU	EMDR>TAU	Pain-focused EMDR might be useful for non-specific chronic back pain patients.

RCT, Randomized controlled trial; EMDR, Eye Movement desensitization and reprocessing; TAU, Treatment as usual; WL, waiting list.

was conducted with 32 inpatients currently suffering from mild-to-moderate depressive episodes related to recurrent depression according to the ICD-10 criteria. One group was treated with EMDR therapy ($N = 16$) in addition to TAU and matched by time of admission, gender and age with 16 controls who only received TAU. Usually, only one EMDR session was provided. In the case of an incomplete session, a second EMDR therapy session was added. EMDR therapy focused on disturbing memories related to the onset and course of the depressive disorder; however, most of the traumatic memories did not meet PTSD criteria. The TAU arm consisted of individual psychodynamic psychotherapy, group therapy sessions and five group sessions of psychoeducation. All patients were assessed by the Beck Depression Inventory (BDI), the Depression subscale of the Symptom Checklist 90 revised (SCL-90-R), and the SCL-90-R Global Severity Index (GSI). The authors found that TAU plus EMDR therapy was more effective than TAU by itself in reducing depressive symptoms [significant pre-post differences in SCL-90-R GSI score ($p = 0.015$) and in SCL-90-R Depression subscale score ($p = 0.04$)].

Regarding the second study, the efficacy of EMDR therapy on depression of patients with post-myocardial infarction was tested (Behnammoghadam et al., 2015). Sixty patients were randomized to EMDR therapy, receiving three sessions of 45–90 min per week during 4 months, or to a control group without any psychotherapeutic intervention. All participants were assessed by the BDI at the beginning and end of the study. The EMDR group showed significant differences in the depressive scores of the BDI before and after the EMDR therapy (27.26 ± 6.41 and 11.76 ± 3.71, $p < 0.001$). Mean scores of BDI also resulted significantly different between both groups at the end of the study (experimental group 11.76 ± 3.71 vs. control group 31.66 ± 6.09, $p < 0.001$). The authors concluded that EMDR therapy was an effective, useful, efficient and non-invasive method to treat depressive disorders in post-myocardial infarction patients (**Table 2**).

In summary, EMDR therapy has demonstrated preliminary positive evidence in one RCT as a promising therapy to treat depressive symptoms in unipolar depression (Hase et al., 2015). Furthermore, it might be a helpful tool to facilitate psychological and somatic improvement in patients with myocardial infarction who suffer subsequent depressive symptoms (Behnammoghadam et al., 2015).

EMDR Therapy in Anxiety Disorders

Six randomized studies have been carried out with EMDR therapy in anxiety disorders, beyond the diagnosis of PTSD (see **Table 3**) (Feske and Goldsteina, 1997; Goldstein et al., 2000; Nazari et al., 2011; Doering et al., 2013; Triscari et al., 2015; Staring et al., 2016).

The first study was carried out by Feske and Goldsteina (1997) in a sample of 43 patients with a diagnosis of panic disorder with agoraphobia. The diagnosis was established when symptoms were present for at least 1 year and at least one panic attack had occurred during the 2-week pre-test monitoring period. The subjects were randomized to EMDR therapy, eye fixation exposure and reprocessing therapy (EFER) (a version of EMDR omitting the ocular movements) or WL. The main aims of this study were to assess the efficacy of EMDR therapy in panic disorder and to analyze whether or not this correlates with the eye movements. Patients in both experimental groups, received five sessions over an average period of 3 weeks (one session of 120 min and four of 90 min). Authors found a significant improvement in post-treatment measures when comparing the EMDR group with the WL group ($p < 0.05$). ANCOVAS test revealed that the EMDR group was superior to the EFER group on 2 out of 5 primary measures of anxiety, specifically in the Agoraphobia-Anticipated Panic-Coping Composite ($F = 7.65$, $p = 0.009$) and

TABLE 3 | RCTs of EMDR in anxiety disorders.

Author, year	Diagnosis	Sample (*n*)	EM/Full protocol	Control condition	Main findings	Conclusions
Feske and Goldsteina, 1997	Panic disorder with agoraphobia	43	EMDR	WL or EFER	EMDR>WL in panic-related symptoms. EMDR=EFER	This study provides initial support for EMDR in the treatment for panic disorder.
Goldstein et al., 2000	Panic disorder with agoraphobia	45	EMDR	TAU and WL	EMDR=TAU>WL for anxiety, severity and agoraphobia. EMDR=WL<TAU for panic attack frequency and anxious cognitions.	EMDR partly effective but did not reduce panic attack frequency.
Doering et al., 2013	Dental phobia	31	EMDR	WL	EMDR>WL in dental anxiety and avoidance behavior.	EMDR effective in processing memories of past dental events in patients with dental phobia.
Triscari et al., 2015	Flying anxiety	65	EMDR+CBT	CBT-SD or CBT-VRET	EMDR+CBT=CBT-VRET=CBT-SD	Trauma focuses approaches are effective to treat patients with flying anxiety.
Staring et al., 2016	Anxiety disorders	47	EMDR	COMET	COMET>EMDR in self-esteem in anxiety disorders.	EMDR did not improve self-esteem in patients with anxiety disorders.
Nazari et al., 2011	OCD	90	EMDR	CTP	EMDR>CTP	EMDR can be more useful in short term than medication in improvement of OCD symptoms.

RCT, Randomized controlled trial; EMDR, Eye Movement desensitization and reprocessing; WL, wait-list control; EFER, Eye fixation exposure and reprocessing; TAU, treatment as usual; CPT, Citalopram; BDORT, Bi-Digital-O-Ring-Test; CBT, Cognitive Behavioral therapy; CBT-SD, Cognitive Behavioral Therapy integrated with systematic desensitization; VRET, Cognitive Behavioral Therapy +virtual reality exposure therapy; COMET, Competitive Memory Training.

General Anxiety-Fear of Panic Composite ($F = 5.28$, $p = 0.028$), on secondary measures of depression (BDI $F = 4.96$, $p = 0.033$), and on social adjustment, measured by the Social Adjustment Scale, Self-Report ($F = 5.96$, $p = 0.020$). However, at 3 months follow up, results did not remain significant.

Goldstein et al. aimed to replicate these results in 46 outpatients with a panic disorder and agoraphobia. Patients were randomized to EMDR therapy (6 sessions lasting 90 min conducted along 4 weeks), a credible attention-placebo control group or to a WL condition (Goldstein et al., 2000). The attention-placebo condition, consisted in a combination of 30–45 min of progressive muscle relaxation training and 45–60 min of association therapy. Compared to the WL condition, patients in the EMDR group showed a significant improvement on the measures of severity of anxiety, panic disorder and agoraphobia ($F = 9.91$, $p \leq 0.01$), but the authors did not find significant changes in panic attacks frequency ($F = 1.3$, $p \geq 0.05$) nor in anxious cognitions ($F = 2.69$, $p \geq 0.05$). They found that EMDR therapy was superior to WL with a medium to large effect for all anxiety measures. ANOVAs test did not show any significant differences between EMDR therapy and the credible attention-placebo control condition (all measures: cognitive measures, panic and agoraphobic severity, diary and panic frequency were $p > 0.13$). Although EMDR therapy was superior to the WL condition, they concluded, based on their results, that EMDR therapy should not be the first-line treatment for panic disorder with agoraphobia.

One RCT so far has compared EMDR therapy with other psychotherapies to treat flight anxiety (Triscari et al., 2015). Of 65 patients, 22 patients were randomized to cognitive behavioral therapy integrated with systematic desensitization (CBT-SD), 22 patients to CBT with EMDR therapy (CBT-EMDR) and 21 patients to CBT combined with virtual reality exposure (CBT-VRET). All patients were assessed with the Flight Anxiety Situations Questionnaire and with the Flight Anxiety Modality Questionnaire. They received 10 weekly sessions of 2 h duration. No mean differences were found between the three groups after treatment or at follow-up, but all interventions showed efficiency in reducing fear of flying, demonstrating a high effect size (Cohen's *d* ranged from 1.32 to 2.23).

Another RCT has been performed in dental phobia (Doering et al., 2013). Sixteen patients were randomized to 3 weekly sessions of EMDR therapy, 90 min each, and 15 patients to a non-interventional WL. All patients were assessed with the Dental Anxiety Scale (DAS) and the Dental Fear Survey (DFS), secondary measures were assessed with the Brief Symptom Inventory and the Clinical Global Impression Score. Anxiety and depressive symptoms were assessed with the German Version of Hospital Anxiety and Depression Scale, symptoms of PTSD with the Impact of Event Scale-Revised and dissociative symptoms with the German Version of Dissociative Experiences Scale. The EMDR group demonstrated a significant decrease of dental anxiety scales with an effect size of 2.52 and 1.87 in DAS and DFS, respectively ($p < 0.001$). The effect sizes after 3 months (DAS 3.28 and DFS 2.28) and after 12 months (DAS 3.75 and DFS 1.79) persisted among the follow-up ($p < 0.001$). The most important result of this study was that a high number of patients overcame their avoidance behavior and visited the dentist regularly following treatment.

Furthermore, a recent trial compared EMDR therapy and competitive memory training (COMET) in the treatment of anxiety disorders with the purpose to improve self-esteem (Staring et al., 2016). The authors included 47 patients with a primary anxiety disorder and low self-esteem, which were

assessed by the Rosenberg Self-esteem Scale, the Self-esteem Rating Scale-short Form and the STAI. Depressive symptoms were evaluated with BDI-II. Patients were randomized in a crossover design. Twenty-four patients received 6 EMDR therapy sessions and then 6 COMET sessions, the other 23 patients received firstly 6 COMET sessions and then 6 EMDR therapy sessions. COMET was more effective in improving self-esteem than EMDR therapy (effect sizes of 1.25 vs. 0.46, respectively). When EMDR therapy was applied before COMET, the effects of COMET on self-esteem and depression were significantly reduced. It could be hypothesized that EMDR therapy could diminish the effectiveness of the COMET intervention.

Finally, 1 RCT was performed in obsessive–compulsive disorder (OCD) (Nazari et al., 2011). They recruited a sample of 90 patients who were randomized to a treatment condition with Citalopram (a selective serotonin reuptake inhibitor) or EMDR therapy during 12 weeks. All subjects were assessed with the Yale-Brown Obsessive-Compulsive Scale before and after the treatment. They observed that both treatments were effective to treat obsessive symptoms, but the EMDR therapy group showed a faster improvement of obsessive and compulsive symptoms than the group treated with Citalopram ($p = 0.001$).

In summary, EMDR therapy has demonstrated in 4 RCT a positive effect on anxious and OCD symptoms (Feske and Goldsteina, 1997; Nazari et al., 2011; Doering et al., 2013; Triscari et al., 2015), whereas 1 RCT in panic disorder with agoraphobia was in part negative (Goldstein et al., 2000) and another study failed in improving self-esteem in patients with anxiety disorders (Staring et al., 2016).

EMDR Therapy in Substance Use Disorders

Two studies so far have explored the efficacy of EMDR therapy in substance use disorders (Hase et al., 2008; Perez-Dandieu and Tapia, 2014). In a first study, 34 alcohol addicted patients were randomly assigned to TAU or TAU plus two sessions of EMDR therapy (Hase et al., 2008). The overall aim was to assess the craving intensity for alcohol via the Obsessive Compulsive Drinking Scale (OCDS) at pretreatment, post-treatment, and follow-up at 1 and 6 months. Likewise, other variables such as depression or anxiety symptoms were analyzed. Compared to pretreatment, post-treatment scores of craving and depression revealed a significant improvement in the experimental group (OCDS $t = 10.7$, $p < 0.001$; BDI $t = 4.0$, $p = 0.001$), while only a small reduction in both measures was noticed in the control group (OCDS $t = 1.1$, $p = 0.29$, BDI $t = 0.9$, $p = 0.37$). Between both groups, the difference in OCDS scores post-treatment was statistically significant ($p < 0.001$). These differences were maintained at 1-month follow-up ($p < 0.05$) but not at 6 months.

In a second study, 12 alcohol and/or drug addicted women with PTSD were randomized to TAU or TAU plus eight sessions of EMDR therapy (Perez-Dandieu and Tapia, 2014). Outcome criteria were PTSD symptoms, addiction symptoms, depression, anxiety, self-esteem [measured with Coopersmith's Self-esteem Inventory (SEI)] and alexithymia [assessed by Toronto Alexithymia Scale (TAS)]. Compared to pretreatment, PTSD scores showed a significant improvement in the experimental group compared to the control group (TAU+EMDR $t = 4.22$, $p = 0.008$; TAU $t = -0.94$, $p = 0.38$). Between both groups, the difference in the post-treatment PTSD scores, was also statistically significant ($p < 0.01$). Regarding addiction symptoms, no differences between both groups were detected. Finally, regarding the measures of depression, anxiety, self-esteem, and alexithymia, the experimental group showed a significant improvement in all of them except in the TAS (BDI $t = 4.38$, $p = 0.007$; STAI $t = 2.65$, $p = 0.04$; SEI $t = -3.37$, $p = 0.01$). On the contrary, the control group showed no significant differences in any measure. Between both groups, only the difference in post-treatment BDI scores were statistically significant ($t = 14.13$, $p < 0.004$).

Considering the results of both studies, EMDR therapy could be a useful therapy to use in substance use disorders with a history of traumatic life events in order to improve the prognosis of these patients (Perez-Dandieu and Tapia, 2014). Besides, EMDR therapy could help as an adjuvant psychotherapy to standard treatment of alcohol dependence directly decreasing craving (Hase et al., 2008; **Table 2**).

EMDR Therapy and Chronic Pain

One RCT has investigated so far the efficacy of EMDR therapy in the treatment of patients suffering from chronic pain (see **Table 2**; Gerhardt, 2016). Forty patients with chronic back pain and psychological trauma were randomized to 10 sessions of EMDR therapy in addition to TAU or TAU alone. The participants were re-assessed 2 weeks after study completion and also at 6 months follow-up after the end of the treatment. The primary outcome was its efficacy in pain reduction, measured by pain intensity, disability and treatment satisfaction. Estimated effect sizes between groups for pain intensity and disability were $d = 0.79$ ($Ci_{95\%}$:0.13, 1.42) and $d = 0.39$ ($CI_{95\%}$:−0.24, 1.01) at post-treatment and $d = 0.50$ ($CI_{95\%}$:0.14, 1.12) and $d = 0.14$ ($Ci_{95\%}$:−0.48, 0.76) at 6 months follow-up. Evaluation on treatment satisfaction from the patient's perspective showed that about 40% of the patients in the EMDR group in addition to TAU improved clinically and also rated their situation as clinically satisfactory, whilst in the control group, no patients showed clinical improvement. In view of these results, the authors concluded that EMDR therapy is a safe and effective therapeutic strategy to reduce pain intensity and disability in patients with chronic back pain.

DISCUSSION

This systematic review aimed to describe briefly the current evidence regarding EMDR therapy in patients with psychiatric conditions beyond PTSD but with a history of comorbid traumatic events. Even though RCT of EMDR therapy in severe mental disorders beyond PTSD are still scarce, an increased trend of publications at last decade has been observed. In general terms, we can conclude that there is currently insufficient evidence to recommend EMDR therapy as a treatment of choice in psychotic disorders and, so far, the same occurs with bipolar disorders (Kim et al., 2010; de Bont et al., 2013; Novo et al., 2014; van den Berg et al., 2015; Van Minnen et al., 2016). However, a large

trial is being currently conducted in order to reach more accurate conclusions (Moreno-Alcazar et al., 2017).

The largest RCT of EMDR therapy in other psychiatric disorders has been performed in patients suffering from a psychotic disorder and a comorbid PTSD (van den Berg et al., 2015). Trauma-associated symptoms but also paranoid thoughts improved equally in both active comparators, EMDR and PE, when compared to WL. Both interventions were considered as safe. Both treatments were also effective in reducing PTSD symptoms with no significant differences between them in terms of effect or safety. The lack of superiority of EMDR therapy over the other treatment condition might be due to the fact that this study only applied 3 EMDR therapy sessions, which might be insufficient and infratherapeutic considering the symptomatic complexity of the sample, suffering from both schizophrenia and PTSD. In the subanalysis of the study, the authors pointed out that patients with a dissociative subtype of PTSD had a similar and favorable response to trauma focused treatments than those without the dissociative subtype, so this subgroup could benefit from this treatment and should not be excluded. These results are clinically relevant considering that patients with a psychotic disorder frequently suffer from comorbid adverse events/PTSD which affects in a negative way the course of the illness. Unfortunately, this is rarely taken into account when clinicians develop a personalized therapeutic plan, as therapists often believe treating traumatic events might deteriorate the patient's psychopathological state.

Similar to psychotic disorders, bipolar patients experience comorbid PTSD with a prevalence of 20% approximately (Hernandez et al., 2013; Passos et al., 2016; Cerimele et al., 2017). PTSD symptoms as well as life events cause more affective episodes (Simhandl et al., 2015). Therefore, trauma-orientated interventions need to be integrated in treatment strategies for bipolar patients. Positive evidence of trauma-orientated therapies, such as CBT and cognitive restructuring, exist in both psychotic and bipolar disorders with comorbid PTSD, these interventions have proven to be effective and safe (Mueser et al., 2008, 2015). Additionally, EMDR therapy has also been tested to treat traumatic symptoms in this population. Hereby in a pilot RCT including patients with a bipolar disorder (types I and II) with subsyndromal symptoms and a history of traumatic events, the authors found that patients showed an improvement in comparison to the TAU condition (Novo et al., 2014) and did not develop any mood episode related to the EMDR therapy. Given these results, EMDR therapy could be a promising and safe therapeutic strategy to reduce trauma symptoms and stabilize mood in traumatized bipolar patients, which is why a specific EMDR bipolar protocol has been suggested (Batalla et al., 2015). Currently, this EMDR protocol is being tested vs. supportive therapy in a large multicenter RCT including bipolar patients with a history of traumatic events (Moreno-Alcazar et al., 2017).

In depressive disorders, one study demonstrated the effectiveness of EMDR therapy compared to psychodynamic psychotherapy, group therapy, and psychoeducation therapy (Hase et al., 2008). EMDR therapy improved memories of stressful life events at onset of depressive episodes, emotional cognitive processing and long-term memory conceptual organization (Hase et al., 2008).

Within anxiety disorders, conflicting results were found in panic disorders with agoraphobia as it seems that EMDR therapy decreases severity of anxiety, panic disorder, and agoraphobia but not panic attacks frequency and anxious cognitions. Authors recommended EMDR therapy as an effective alternative to treat panic disorder with agoraphobia when other evidence-based treatments, such as exposure therapy or cognitive-behavior therapy, had failed. Nevertheless, panic disorder studies were not able to demonstrate an effect of EMDR therapy on anxious cognitions, as you would expect to find after applying the therapy. In OCD or phobias studies we did not find this fact. Further larger trials are needed to answer whether or not EMDR therapy is a valid therapeutic option as first line treatment in anxiety disorders and OCD.

Evidence of RCT so far suggests that EMDR therapy is a useful tool in the treatment of specific phobias, like flight anxiety or dental phobia, whether or not related to PTSD symptoms (Doering et al., 2013; Triscari et al., 2015).

In substance use disorders, EMDR therapy has been tested mainly in alcohol use disorders (Hase et al., 2008). EMDR therapy appears hereby to be useful as it decreases craving and drinking behavior (Hase et al., 2008; Perez-Dandieu and Tapia, 2014).

Finally, EMDR therapy was also effective in a first RCT for the treatment of chronic back pain (Gerhardt, 2016). This is not surprising as the impact of stress on both mental and physical health has been acknowledged for many years (Schneiderman et al., 2005). Pain as consequence of a traumatic event has been hereby identified as a risk factor for the development of PTSD (Norman et al., 2008) and often PTSD and chronic pain are concomitant (Beckham et al., 1997; Beck and Clapp, 2011; Moeller-Bertram et al., 2012). Again, further trials are needed to confirm the efficacy of EMDR therapy in this complex and often difficult to treat population.

The main limitation of this review is that RCT are scarce so far; however, as the use of EMDR therapy is increasing and gaining popularity, this systematic review is timely. Another limitation is that some of the included studies had very few therapeutic sessions. The high heterogeneity in number and duration of EMDR therapy sessions could have a negative effect on the results, so these must be taken cautiously (Hase et al., 2008, 2015; Kim et al., 2010; Behnammoghadam et al., 2015).

In general, EMDR therapy seems a safe intervention (Feske and Goldsteina, 1997; Hase et al., 2008, 2015; Doering et al., 2013; Novo et al., 2014; Perez-Dandieu and Tapia, 2014; Triscari et al., 2015; van den Berg et al., 2015; Gerhardt, 2016). This is of importance as it allows clinicians to consider EMDR therapy as an appropriate treatment in various psychiatric comorbid conditions without causing side effects.

AUTHOR CONTRIBUTIONS

AV has performed the bibliographic search and has elaborated the first draft of the manuscript. AM has participated in the selection of included studies, resolved methodological doubts

of possible studies, and helped in the first version of this manuscript. DT helped in the development of this review and revised the manuscript as native speaker. CC has collaborated in methodological aspects of this article. VP and FC have contributed in the improvement of the manuscript and BA had the idea of this work and revised the last version of this article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2017.01668/full#supplementary-material

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Cognitive Behavioral Therapy vs. Eye Movement Desensitization and Reprocessing for Treating Panic Disorder: A Randomized Controlled Trial

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Objective: Cognitive Behavioral Therapy (CBT) is an effective intervention for patients with panic disorder (PD). From a theoretical perspective, Eye Movement Desensitization and Reprocessing (EMDR) therapy could also be useful in the treatment of PD because: (1) panic attacks can be experienced as life threatening; (2) panic memories specific to PD resemble traumatic memories as seen in posttraumatic stress disorder (PTSD); and (3) PD often develops following a distressing life event. The primary objective of this Randomized Controlled Trial (RCT), was to compare EMDR therapy with CBT for PD and determine whether EMDR is not worse than CBT in reducing panic symptoms and improving Quality Of Life (QOL).

Methods: Two-arm (CBT and EMDR) parallel RCT in patients with PD ($N = 84$). Patients were measured at baseline (T1), directly after the last therapy session (T2), and 3 months after ending therapy (T3). Non-inferiority testing (linear mixed model with intention-to-treat analysis) was applied. Patients were randomly assigned to 13 weekly 60-min sessions of CBT ($N = 42$) or EMDR therapy ($N = 42$). Standard protocols were used. The primary outcome measure was severity of PD at T3, as measured with the Agoraphobic Cognitions Questionnaire (ACQ), the Body Sensations Questionnaire (BSQ), and the Mobility Inventory (MI). The secondary outcome measure was QOL, as measured with the World Health Organization Quality of Life short version (WHOQOL-Bref), at T3.

Results: The severity of PD variables ACQ and BSQ showed non-inferiority of EMDR to CBT, while MI was inconclusive (adjusted analyses). Overall QOL and general health, Psychological health, Social relationships, and Environment showed non-inferiority of EMDR to CBT, while Physical health was inconclusive.

Conclusion: EMDR therapy proved to be as effective as CBT for treating PD patients.

Trial Registration: Dutch Trial Register, Nr. 3134 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3134

Keywords: EMDR, CBT, Panic disorder, psychotherapy, RCT

INTRODUCTION

Panic disorder (PD) is characterized by recurrent, unexpected panic attacks and hyperarousal symptoms such as palpitations, pounding heart, chest pain, sweating, trembling, or shaking (Frances, 2004). These symptoms are often experienced as catastrophic and can have a great impact on daily life (Frances, 2004). Prevalence rates of PD are around 2.1% (Batelaan et al., 2006). Women are twice as likely to develop PD compared to men. Up to 50% of patients meet the criteria of agoraphobia (Weissman et al., 1997). In addition, widowed, lower educated, and divorced persons are more likely to experience panic attacks (Batelaan et al., 2006).

Several controlled treatment effect studies have shown that cognitive behavioral therapy (CBT), particularly interoceptive exposure, is the most effective intervention for PD (Barlow et al., 1989, 2000; Öst et al., 2004; Furukawa et al., 2007). Typical for this approach is that patients are exposed to exercises that evoke the physical sensations associated with a panic attack, such as hyperventilation, in order to experience that the worst expected outcome (e.g., dying) does not occur (i.e., "expectancy violation"). Approximately 40-90% of patients treated with CBT are panic free directly after treatment (Bakker et al., 1999). Variations in treatment effects are strongly determined by the selected study population (e.g., with/without comorbidity) and the content of CBT (e.g., whether in vivo exposure is offered) (Bakker et al., 1999; Rief et al., 2000). Furthermore, several studies have shown that the quality of life (QOL) for patients with PD improves after CBT (Telch et al., 1995; Davidoff et al., 2012). Nevertheless, a group of patients still needs additional treatment after CBT because some patients do not benefit, while others do not make a full recovery or develop other affective disorders (Van Balkom et al., 1996; Bakker et al., 1999). Eye Movement Desensitization and Reprocessing (EMDR) therapy is a treatment procedure for patients who suffer from past traumatic experiences in the present (Shapiro, 2002). In EMDR therapy the focus is on resolving disturbing memories of distressing or traumatic events by focusing on the memory while making eye movements at the same time. Besides CBT, EMDR is recommended as a first-line treatment for psychological trauma (Bisson et al., 2007). Despite the well-examined efficacy of EMDR for Post-Traumatic Stress Disorder (PTSD), the applicability of EMDR for other anxiety disorders, like PD, has hardly been examined (De Jongh and ten Broeke, 2009). There are several reasons why EMDR could be useful in the treatment of PD. Firstly, panic attacks likely occur unexpectedly, are experienced as distressing, cause a subjective response of fear or helplessness, and can be considered life threatening (McNally and Lukach, 1992; Hagenaars et al., 2009). Secondly, there are indications that panic memories in PD resemble traumatic memories as seen in PTSD (Hagenaars et al., 2009). Thirdly, there are indications that PD often develops after one or more distressing life events (Faravelli and Pallanti, 1989; Horesh et al., 1997). The few available studies on EMDR as PD treatment (Goldstein and Feske, 1994; Feske and Goldstein, 1997; Goldstein et al., 2000), all performed by the same research group, found a decrease in panic complaints and anticipatory anxiety in most EMDR-treated patients (Goldstein and Feske, 1994). Goldstein et al. (2000) showed that EMDR was superior to the waitlist condition on panic and agoraphobia severity, albeit no significant change was apparent on cognitive measures or on panic attack frequency. Importantly, these studies only included a short EMDR procedure and some essential parts of the current EMDR protocol (e.g., the installation of a "future template") were lacking (De Jongh and ten Broeke, 2009). More recently, a pilot study comparing 12 sessions of EMDR to CBT for PD, found no differences between both treatments, except that EMDR resulted in significantly less frequent panic attacks (Faretta, 2013). Although the effect of EMDR on QOL in PD patients was not examined, QOL seems to be an important outcome measure as PD is a very stressful condition (Trompenaars et al., 2005).

In conclusion, CBT has been found to be effective for a considerable number of patients suffering from PD. The treatment of PD with EMDR seems plausible, but previous studies are limited and replications are needed. This is the first randomized controlled trial (RCT) that directly compares CBT and EMDR therapy in PD patients regarding PD severity and QOL.

The primary aim of this RCT was to examine if EMDR therapy is not worse than CBT among patients with PD on symptom severity and QOL 3 months post-treatment. It is hypothesized that EMDR is not worse than CBT.

MATERIALS AND METHODS

Design

The study was approved by the Medical Ethical Board of the St. Elisabeth hospital in Tilburg, the Netherlands and was registered in the Dutch Trial Register (www.trialregister.nl, NTR 3134). All included patients gave their written consent before enrollment. This study is a two-arm parallel RCT, including CBT and EMDR therapy.

Participants

Patients were recruited, assessed, and treated at the department of psychiatry, St. Elisabeth hospital, Tilburg, the Netherlands between February 2010 and December 2013. Advertisements were placed in a local newspaper to inform people about the existence of our study. When someone wanted to participate he or she had to visit his or her general

practitioner. Patients were referred to the hospital by general practitioners.

Inclusion criteria were: (1) age between 18 and 65 years old; (2) the presence of a SCID-I primary diagnosis of PD (First et al., 1997); and (3) sufficient knowledge of the Dutch language.

Exclusion criteria were: (1) comorbid diagnosis of dementia, psychosis, severe depression, bipolar disorder, and/or another psychiatric disorder that was more prominent than the PD; (2) use of more than 20 standard units of alcohol a week; and (3) use of benzodiazepines and/or other sedative agents (De Jongh and ten Broeke, 2006). This last criterion was added because benzodiazepines or other sedative agents are likely to interfere with the level of arousal that is needed for EMDR therapy to be effective (Little et al., 2017). Patients who use modern antidepressants (e.g., Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) and/or classic antidepressants (e.g., Tricyclic Antidepressants (TCA) were required to be on a stable medication dose (i.e., unchanged dosage of medication), 6 weeks prior to trial until the end. Patients were not allowed to attend any form of therapy during the whole trial. Patients not eligible for participation were offered treatment as usual.

Measures

The primary outcome measure was the severity of the PD, assessed with the Agoraphobic Cognitions Questionnaire (ACQ), which measures the degree of catastrophic cognitions when feeling anxious or tense (Chambless et al., 1984). The two subscales have a good internal consistency. The discriminant validity and construct validity are also good (Chambless et al., 1985).

The Body Sensations Questionnaire (BSQ) measures anxiety about bodily sensations and consists of two questionnaires; while the BSQ1 assesses the amount of fear, the BSQ2 measures how often the sensations are experienced when the patient feels anxious or tense (Chambless et al., 1984). The internal consistency and the test-retest reliability of the BSQ are good. Furthermore, the BSQ has good discriminant- and construct validity (Chambless et al., 1985).

The Mobility Inventory (MI) measures the degree to which places or situations are avoided with a trusted companion (MI-ac) and when the patient is alone (MI-al) (Chambless et al., 1985). Both subscales have a good internal consistency, discriminant validity and construct validity (Chambless et al., 1985). For ACQ, BCQ, and MI, lower scores indicate better outcomes.

The secondary outcome measure, QOL, was assessed with the World Health Organization Quality of Life short version (WHOQOL-Bref) (De Vries and van Heck, 1995). This measure consists of one generic facet (Overall quality of life and general health) and four domains (i.e., "Physical health," "Psychological health," "Social relationships," and "Environment") (De Vries and van Heck, 1995). Higher scores indicate better QOL. The WHOQOL-Bref is sensitive for changes over time and for treatment influences. The psychometric properties of the WHOQOL-Bref are also good (Trompenaars et al., 2005).

Procedure

All patients were first screened by a psychiatrist who conducted a regular psychiatric interview, including the registration of the participants' medical status and medication use. Participation was voluntary and patients could withdraw from the study at any time without specifying a reason. After referral by a psychiatrist and before randomization, patients were screened with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 1997). The SCID-I was conducted by independent clinicians who were trained intensively during a 2-day workshop.

Patients eligible for participation were randomized to one of two treatment groups. Randomization was carried out by an independent secretary, who had 84 sealed envelopes, of which 42 contained a note with "EMDR" written on it, and 42 included a note with "CBT" on it. In both groups, a standardized treatment protocol was used. For each eligible patient, random assignment of sealed envelopes was performed. Before randomization, patients signed an informed consent. Patients were measured at baseline (T1), post-treatment (T2), and 3 months follow-up (T3), and received no financial compensation for participation.

Treatment

In total, six licensed clinical psychologists (three men, three women) performed the EMDR and CBT treatments. In both groups, standardized treatment protocols were used. Therapists who performed EMDR therapy (one man, one woman) were both accredited practitioners by the European association. Therapists performing CBT treatment (three men, two women) were accredited CBT therapists by the Dutch National CBT Association.

The CBT protocol is the Dutch version of Craske and Barlow's (2008) and consists of 13 weekly sessions lasting about 60 min each (Craske and Barlow, 2008). During the first part (psycho-education), the patient is informed about panic attacks and PD. The second part consists of teaching and applying relaxation exercises which help the patient to reduce general anxiety. The third part consists of interoceptive exposure exercises in order to become accustomed to, and to cope with, the fear of bodily sensations. The fourth part is cognitive therapy in which the patients learn to recognize their automatic, anxious thoughts and formulate alternative, more adaptive thoughts. Finally, *in vivo* exposure consisted of learning patients to cope with the anxiety experienced during situations or activities that are feared and avoided by using an anxiety hierarchy (Kampman et al., 2004).

The EMDR treatment protocol is the Dutch version (De Jongh and ten Broeke, 2006) of Shapiro's EMDR protocol (Shapiro, 2001) and consists of 13 weekly sessions lasting about 60 min each. In this protocol, a patient is first informed about EMDR therapy, traumatic memories are identified, and the course of current symptoms is evaluated. In the present study the case conceptualization was conducted according to the "first method" of the "Two Method Approach" that deals with symptoms whereby memories of the etiological and/or aggravating events were meaningfully specified on a time line. To this end, the memories of the distressing events that were assumed to play a key role in the acquisition and maintenance of the condition and

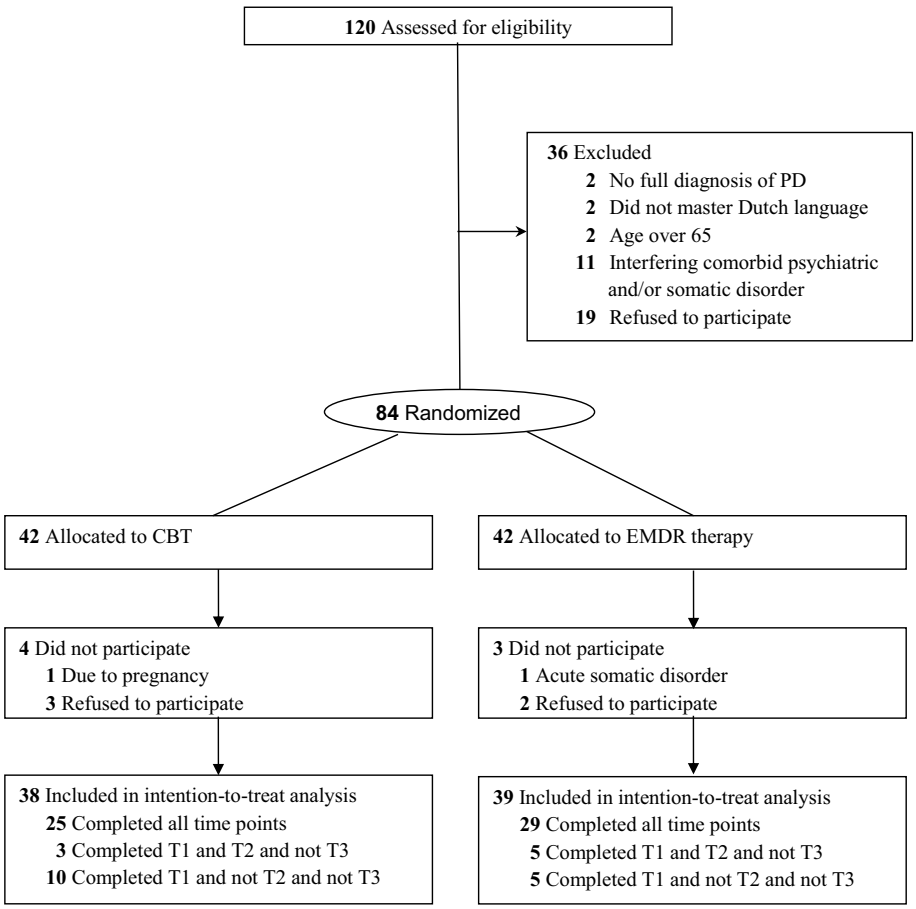

FIGURE 1 | Flow of participants through the trial.

evoked distress, were determined. Subsequently, the memories that evoked the most disturbance, e.g., the first or worst panic attack, were reprocessed first using working memory taxation by listening to alternating audio tones. Subsequently, other memories that were considered to contribute to a patient's current symptoms were targeted in the same way (De Jongh et al., 2010). During EMDR therapy, patients are asked to report what associations come to mind and the patient is guided to refocus on that association. This is continued until the patient no longer reports any distress related to the target image. Afterwards, the patient is asked to formulate a positive belief regarding the target image.

Supervision and Treatment Integrity

To each treatment group, 20 h of group supervision by an independent qualified EMDR or CBT supervisor were given. Additional supervision by telephone or e-mail was provided on request. All patients were asked permission to make video recordings of the treatment sessions, to ensure that therapists adhered to the treatment protocol. During the study, therapists had supervision sessions in which adherence to the therapist protocol was evaluated and discussed to maintain quality and homogeneity of the intervention protocol.

Statistical Analysis

According to the method of Faul et al. (2009), a sample size calculation was performed using G-Power 3.1.7 which showed that in total, 102 patients would be needed (non-inferiority test, effect size Cohen's $d = 0.5$, one-sided alpha $= 0.05$, power $= 0.80$). Anticipating 20% drop out, 128 patients were needed. For each outcome variable, linear mixed models (with ML estimation) were specified including main effects of group, time (categorical), and interaction effect group*time. The dependence of the repeated measures was taken into account by using the unstructured error covariance pattern model. Covariates (i.e., age, gender, education, marital status, duration of complaints, number of axis I diagnoses, received previous treatment, and antidepressant treatment) were added to obtain adjusted results under the missing at random assumption.

Non-inferiority testing was used to determine whether EMDR is not worse than CBT (Piaggio et al., 2006, 2012). For ACQ, BCQ, and MI, the null hypothesis is (EMDR - CBT) $> \delta$, and the alternative hypothesis is (EMDR - CBT) $\leq \delta$, where δ is the

margin that is set at minimal clinical relevance. If the upper bound of confidence interval of 90% is below δ, it is concluded that EMDR is non-inferior to CBT. For ACQ and BCQ, the margin was $\delta = 5$, and for MI, the margin was $\delta = 8$. The margins of these questionnaires were determined by clinical experts. For WHOQOL-BREF, the non-inferiority was reversed and the margin was $\delta = -1$ (Den Oudsten et al., 2013).

Group differences were analyzed at T3. Intention-to-treat approach was used on the patients that started treatment, while per-protocol approach was used as a sensitivity analysis on patients that completed all treatments (Piaggio et al., 2006, 2012). For effect size measure, Cohen's d was computed as mean difference divided by baseline pooled standard deviation. Statistical analyses were performed in SPSS version 19.0.

RESULTS

Figure 1 shows the patient flow through the trial. Despite an extended inclusion period, in total, 120 patients could be assessed for eligibility, from which 36 were excluded. Accordingly, were randomized to both treatment groups: 42 patients to CBT and 42 to EMDR therapy. **Table 1** displays the baseline and clinical characteristics of both groups. No significant differences in age, gender, education, marital status, and number of axis I diagnoses at baseline were found. However, patients in the CBT group had experienced significantly shorter duration of PD and received significantly less previous treatment than those in the EMDR group. Significantly more patients in the EMDR group received antidepressant treatment than those in the CBT group.

Seven patients (8%) did not start the first treatment session and were unaware of treatment allocation (**Figure 1**). Completers of all time points did not significantly differ from non-completers (i.e., missing at least one time point) on gender, education, and years of complaints. No unintended effects were found in both treatment groups.

Primary Outcome Measures

Information on observed outcome means and effect sizes for both treatment groups for all time points, are presented in **Table 2**. The intention-to-treat analyses at T3 were performed on 39

TABLE 1 | Baseline demographic and clinical characteristics.

Characteristics	CBT (*N* = 42)	EMDR (*N* = 42)	Total sample (*N* = 84)	*P*
Age, mean (SD), year	40.9 (12.1)	37.0 (10.7)	39.0 (11.5)	0.126[a]
Gender, No.				0.491[b]
Male	16	13	29	
Female	26	29	55	
Education, No. (%)				0.143[b]
Low (<10 years)	9 (21%)	13 (31%)	22 (26%)	
Middle (10–14 years)	24 (57%)	15 (36%)	39 (46%)	
High (>14 years)	9 (21%)	14 (33%)	23 (27%)	
Marital status, No. (%)				0.078[b]
Unmarried	20 (48%)	28 (67%)	48 (57%)	
Married	22 (52%)	14 (33%)	36 (43%)	
Duration of PD, No. (%)				0.027[b]*
<2 years	25 (60%)	12 (29%)	37 (44%)	
2–5 years	8 (19%)	12 (29%)	20 (24%)	
5–10 years	2 (5%)	8 (20%)	10 (12%)	
>10 years	7 (17%)	9 (22%)	16 (19%)	
Missing	0	1	1 (1%)	
DSM-IV-TR Axis I diagnoses[a], mean (SD)	2.5 (1.1)	2.5 (1.1)	2.5 (1.1)	0.766[a]
Agoraphobia[I], No. (%)	33 (80%)	28 (68%)	61 (74%)	0.161[b]
Received previous treatment for PD, No. (%)				0.001[b]**
Yes	18 (43%)	33 (79%)	51 (61%)	
No	24 (57%)	9 (21%)	33 (39%)	
Received antidepressant treatment No. (%)				0.026[b]*
Yes	12 (29%)	22 (52%)	34 (40%)	
No	30 (71%)	20 (48%)	50 (60%)	

CBT, cognitive behavioral therapy; EMDR, eye movement desensitization and reprocessing; PD, Panic Disorder; SCID-I, Structured Clinical Interview for DSM-IV Axis I disorders; SD, standard deviation.

[I]Measured using SCID-I.

[a]Independent two-sampled t-test.

[b]Pearson Chi-Square.

**p < 0.05.*

***p < 0.01.*

TABLE 2 | Observed outcome means (standard deviation) for both treatment groups EMDR and CBT for baseline (T1), after treatment (T2), and 3 months follow up (T3).

Outcome	CBT					EMDR				
	T1 (*N* = 38)	T2 (*N* = 28)		T3 (*N* = 25)		T1 (*N* = 39)	T2 (*N* = 34)		T3 (*N* = 29)	
	Mean (SD)	Mean (SD)	d^a	Mean (SD)	d^b	Mean (SD)	Mean (SD)	d^a	Mean (SD)	d^b
SYMPTOMS[a]										
ACQ	34.1 (9.6)	24.7 (8.8)	−0.86	27.5 (10.7)	−0.60	36.8 (12.1)	23.6 (10.5)	−1.21	25.1 (10.2)	−1.07
BSQ1	47.0 (11.8)	29.1 (9.4)	−1.44	34.1 (12.1)	−1.04	50.2 (13.0)	28.5 (10.4)	−1.74	30.2 (11.5)	−1.60
BSQ2	48.3 (11.2)	34.5 (9.9)	−1.25	40.3 (10.9)	−0.72	52.5 (10.7)	33.0 (12.4)	−1.77	36.3 (14.0)	−1.47
MI-ac	51.9 (18.8)	33.3 (9.7)	−0.99	35.2 (11.2)	−0.89	51.8 (19.1)	36.6 (16.9)	−0.80	36.2 (15.8)	−0.83
MI-al	62.2 (22.8)	41.3 (14.8)	−0.85	43.3 (17.3)	−0.77	68.1 (26.0)	42.0 (21.7)	−1.06	41.4 (17.5)	−1.09
QOL[b]										
OQOL/GH	10.8 (3.6)	14.4 (2.4)	1.00	13.0 (3.8)	0.62	10.6 (3.5)	14.7 (3.8)	1.16	15.3 (2.7)	1.33
Physical health	11.9 (2.6)	14.4 (2.4)	0.91	14.0 (2.7)	0.75	11.2 (3)	14.7 (3.1)	1.26	14.5 (2.5)	1.18
Psychological health	11.0 (2.5)	13.3 (1.8)	0.91	12.9 (2.7)	0.78	11.0 (2.6)	14.3 (2.8)	1.32	14.5 (2.1)	1.39
Social relationships	13.4 (2.8)	15.0 (2.6)	0.55	14.6 (2.3)	0.42	14.1 (3.0)	15.6 (3.0)	0.55	15.0 (2.5)	0.32
Environment	14.0 (2.3)	15.7 (1.9)	0.70	15.5 (2.1)	0.62	13.8 (2.5)	16.4 (2.4)	1.05	15.9 (1.9)	0.88

ACQ, Agoraphobic Cognitive Questionnaire; BSQ1, Body Symptoms Questionnaire (amount of fear); BSQ2, Body Symptoms Questionnaire (how often sensations are experienced); CBT, Cognitive Behavioral Therapy; EMDR, Eye Movement Desensitization and Reprocessing; MI-ac, Mobility Inventory (when accompanied); MI-al, Mobility Inventory (when alone); QOL, Quality Of Life; OQOL/GH. Overall Quality Of Life and General Health; d, Mean difference divided by pooled (CBT + EMDR) baseline standard deviation; d^a, d(T2-T1); d^b, d(T3-T1).

TABLE 3 | Non-inferiority effects EMDR vs. CBT at T3.

Outcome	Unadjusted			Adjusted[f]		
	B (EMDR-CBT)	Lower 90%CI	Upper 90%CI	B (EMDR-CBT)	Lower 90%CI	Upper 90%CI
SYMPTOMS[a]						
ACQ[c]	−2.68	−7.11	**1.75***	−3.05	−7.92	**1.82***
BSQ1[c]	−4.09	−9.26	**1.08***	−3.40	−9.08	**2.28***
BSQ2[c]	−4.50	−9.98	**0.98***	−6.02	−11.97	**−0.06***
MI-ac[d]	0.74	−5.09	**6.58***	2.83	−3.61	**9.28**
MI-al[d]	−0.28	−7.56	**7.00***	2.44	−5.21	**10.09**
QOL[b]						
OQOL/GH[e]	1.95	**0.53***	3.37	1.25	**−0.23***	2.74
Physical health[e]	0.51	**−0.58***	1.61	−0.07	**−1.27**	1.13
Psychological health[e]	1.55	**0.47***	2.62	1.41	**0.29***	2.54
Social relationships[e]	0.41	**−0.64***	1.45	0.47	**−0.66***	1.60
Environment[e]	0.47	**−0.42***	1.36	0.02	**−0.97***	1.01

ACQ, Agoraphobic Cognitive Questionnaire; B, unstandardized effect estimate; BSQ1, Body Symptoms Questionnaire (amount of fear); BSQ2, Body Symptoms Questionnaire (how often sensations are experienced); CBT, Cognitive Behavioral Therapy; CI, Confidence Interval; EMDR, Eye Movement Desensitization and Reprocessing; MI-ac, Mobility Inventory (when accompanied); MI-al, Mobility Inventory (when alone); QOL, Quality Of Life; OQOL/GH, Overall Quality Of Life and General Health.

[a] Lower scores indicates better for patient.

[b] Higher scores indicates better for patient

*[c] Noninferiority test: **upper bound 90% CI** < 5.*

*[d] Noninferiority test: **upper bound 90% CI** < 8.*

*[e] Noninferiority test: **lower bound 90% CI** > (−1).*

[f] Adjusted for age, gender, education, marital status, duration of complaint, received previous treatment, number of axis I diagnoses and antidepressant.

**Indicates non-inferiority.*

EMDR patients and 38 CBT patients. Scores on questionnaires measuring severity of PD (ACQ, BSQ1, BSQ2, MI-ac, and MI-al) showed non-inferiority of EMDR to CBT in the unadjusted analysis (**Table 3**, **Figure 2A**). In the adjusted analysis, this was also the case for ACQ, BSQ1, and BSQ2, whereas MI-ac and MI-al were inconclusive.

Secondary Outcome Measures

For the facet 'Overall QOL and general health' and the four QOL domains, EMDR appeared to be non-inferior to CBT at T3 in the unadjusted analysis (**Table 3**, **Figure 2B**). For the adjusted analyses, only "physical health" was inconclusive.

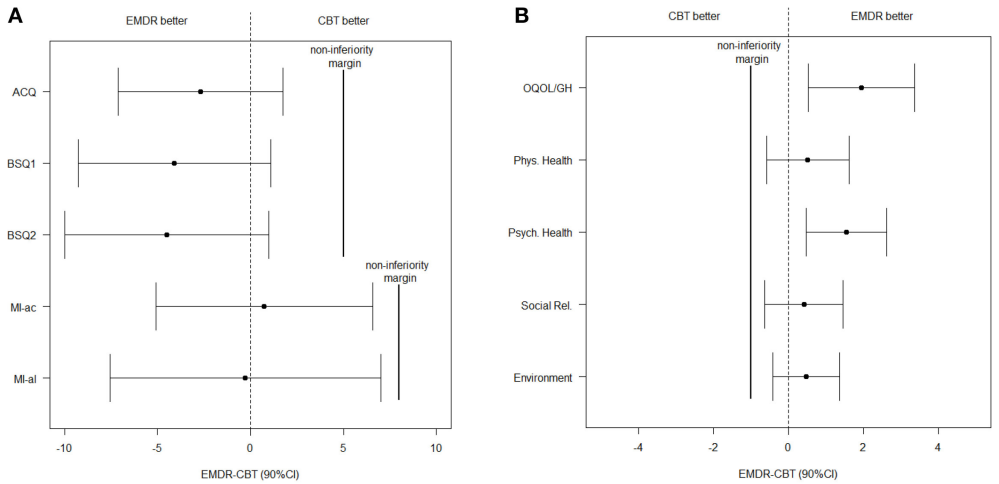

FIGURE 2 | Unadjusted effects and 90% CI of **(A)** the symptoms and **(B)** the quality of life facet and domains at T3. ACQ, Agoraphobic Cognitive Questionnaire; BSQ1, Body Symptoms Questionnaire (amount of fear); BSQ2, Body Symptoms Questionnaire (how often sensations are experienced); CBT, Cognitive Behavioral Therapy; CI, Confidence Interval; EMDR, Eye Movement Desensitization and Reprocessing; MI-ac, Mobility Inventory (when accompanied); MI-al, Mobility Inventory (when alone); QOL, Quality Of Life; OQOL/GH, Overall Quality Of Life and General Health.

Sensitivity Analyses

Per-protocol analyses included the 62 patients that had T1 and T2 measurement (10 patients were removed in the CBT group and five in the EMDR group). All conclusions were similar to the intention-to-treat analyses, except for QOL domain "Environment" in which the unadjusted analysis at T3 was now inconclusive (lower bound −1.09).

DISCUSSION

This is the first RCT that tested whether EMDR is no worse than CBT (i.e., the "gold standard" for the treatment of PD). The results show that EMDR is no worse (i.e., non-inferior) than CBT with regard to severity of a wide range of PD symptoms, including anxiety related cognitions, fear of bodily sensations, as well as quality of life. Concerning the behavioral aspects of the condition, the tendency to avoid certain situations, the results were inconclusive. Intriguingly, despite both treatments were comparable in terms of effects, from face value the procedures seem to be opposed. That is, the CBT procedure for panic disorder entails specific exposures to patient's physical sensations (i.e., sensory experiences associated with anxiety, i.e., the conditioned stimuli), while disturbing memories of past events (the unconditioned stimuli, e.g., the first panic attack), that may have laid the groundwork for the panic disorder, are left untreated. In contrast, in EMDR therapy only memories of the latter type of events are targeted and processed, whereas the protocol only indirectly deals with the stimuli that normally would evoke a panic attack.

A strength of the current study is the use of manualized treatment protocols, including a relatively long therapeutic track consisting of 13 sessions making generalizability to clinical practice more feasible.

A limitation of the current study is the use of audio tones as the modality by which the memory taxation was performed. Laboratory studies provide evidence that audio tones are less optimal or appeared even less effective when compared to eye movements in diminishing the emotionality of memories underlying PTSD and other mental health problems (Van den Hout et al., 2012; De Jongh et al., 2013). This implies that when eye movements would have been applied in the present study the results might have been more profound. Furthermore, the determined sample size was not reached. Therefore, the study was underpowered given the expected effect size. Nonetheless, results showed larger effects sizes than a-priori expected, particularly for EMDR therapy. Concerning our randomization, it appeared that the two treatment groups differed on three aspects. Patients receiving CBT had a shorter PD duration, less previous treatment, and less antidepressant treatment compared to patients receiving EMDR. With regard the dropout rate, this was higher than expected, especially in the CBT group. This might partly be explained by the fact that Dutch law states that patients' decision to participate in scientific studies is voluntary, which means that patients may withdraw from the study at any time without specifying a reason. Therefore, we cannot provide a definite explanation for all patients. Another reason could be that patients who used benzodiazepines or other sedative agents were asked to stop medication so they could enter the study when clean. When patients asked for support, they were offered a clinical detox. Several patients refused to stop medication and therefore, received treatment as usual, and stopped participating in the study. Finally, no fidelity measure was used for CBT interoceptive exposure. To our knowledge, no such measure exists and developing and validating such a measure was beyond the scope of the current research. For EMDR fidelity measures do exist, but reporting this on its own seemed inappropriate.

Future long-term studies may provide more insight into the stability of the effects. This study has focused directly on comparing CBT with EMDR in the treatment of PD. Concerning the small sample size and the inconclusive results with regard to the MI, future studies may focus on combining both therapies, and especially on *in vivo* exposure with EMDR.

In conclusion, the present results provided evidence suggesting that EMDR therapy is as effective as CBT for patients with PD and may, therefore, be considered as a useful alternative to a conventional CBT treatment of PD patients.

AUTHOR CONTRIBUTIONS

FH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: FH, BD, WZ, AdJ, JL, and JD. Acquisition, analyses or interpretation of data: FH, BD, WZ, AdJ, JL, and JD. Drafting of the manuscript: FH, BD, WZ, AdJ, JL, and Jd. Critical revision of the manuscript for important intellectual content: FH, BD, WZ, AdJ, JL, and JD. Statistical analyses: FH, WZ, and JD. Administrative, technical, or material support: FH, BD, WZ, AdJ, JL, and JD.

STUDY SUPERVISION

Veronique Boelaars (CBT) and Indra Spierts (EMDR).

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The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Effect of EMDR and CBT on Low Self-esteem in a General Psychiatric Population: A Randomized Controlled Trial

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Although low self-esteem has been found to be an important factor in the development and maintenance of psychopathology, surprisingly little is known about its treatment. This study investigated the effectiveness of Eye Movement Desensitization and Reprocessing (EMDR) therapy and Cognitive Behavioural Therapy (CBT), regarding their capacities in enhancing self-esteem in a general psychiatric secondary health care population. A randomized controlled trial with two parallel groups was used. Participants were randomly allocated to either 10 weekly sessions of EMDR (n = 15) or CBT (n = 15). They were assessed pre-treatment, after each session, post treatment and at 3 months follow-up on self-esteem (Rosenberg Self-esteem Scale and Credibility of Core Beliefs), psychological symptoms (Brief Symptom Inventory), social anxiety, and social interaction (Inventory of Interpersonal Situations) (IIS). The data were analyzed using repeated measures ANOVA for the complete cases (n = 19) and intention-to-treat (n = 30) to examine differences over time and between conditions. Both groups, EMDR as well as CBT, showed significant improvements on self-esteem, increasing two standard deviations on the main parameter (RSES). Furthermore, the results showed significant reductions in general psychiatric symptoms. The effects were maintained at 3 months follow-up. No between-group differences could be detected. Although the small sample requires to exercise caution in the interpretation of the findings, the results suggest that, when offering an adequate number of sessions, both EMDR and CBT have the potential to be effective treatments for patients with low self-esteem and a wide range of comorbid psychiatric conditions. This study was registered at www.trialregister.nl with identifier NTR4611.

Keywords: self-esteem, EMDR, CBT, psychiatric population, randomized controlled trial

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INTRODUCTION

Self-esteem has been defined as a person's overall evaluation of his or her own worth (Hewitt, 2009). Low self-esteem is involved in a wide range of psychiatric conditions, including depression (Brown et al., 1990), anxiety disorders (Sowislo and Orth, 2013), personality disorders (Lynum et al., 2008) obsessive compulsive disorder (Ehntholt et al., 1999), eating disorders (Gual et al., 2002), chronic pain (Soares and Grossi, 2000), substance abuse (Silverstone and Salsali, 2003),

and psychosis (Barrowclough et al., 2003). Research suggests that low self-esteem increases the susceptibility for development of these psychiatric disorders, and that, in turn, the presence of a psychiatric condition negatively influences someone's self-esteem (Silverstone and Salsali, 2003). There is also considerable evidence to support the notion that in general self-esteem is a reliable predictor of treatment outcome, in that higher initial self-esteem is significantly associated with better treatment outcomes (Johnson et al., 2000; Parker et al., 2013). It can be concluded that low self-esteem is an important factor in relation to psychiatric disorders in general.

Over the past several years a variety of therapeutic interventions has been developed for changing low self-esteem, predominantly with a cognitive behavioral background. These interventions mostly aim at changing core beliefs underlying patients' low self-esteem (Padesky, 1994; Beck, 1995; Fennell, 1999). Several case studies (Fennell, 1998; McManus et al., 2009) and clinical trials (Rigby and Waite, 2006; Waite et al., 2012) suggest that these interventions are effective in enhancing self-esteem. However, only a few studies have compared Cognitive Behavioural Therapy (CBT) to an active or passive control group using a randomized controlled trial. One study examined the effectiveness of CBT on improving implicit and explicit self-esteem in patients with a social anxiety disorder, comparing this to psychodynamic therapy using 25 sessions (Ritter et al., 2013), and found a positive treatment effect for both treatments. Another study found a positive effect of CBT being significantly more effective in changing self-esteem in comparison to a waitlist control condition (Waite et al., 2012). Some studies have also addressed the effectiveness of group CBT on individuals' self-esteem, mostly using protocols designed by Fennell (1998), showing significantly positive treatment effects, including a reduction of symptoms of depression and anxiety (Rigby and Waite, 2006; Morton et al., 2012; Pack and Condren, 2014). Hence, research thus far found support for the effectiveness of CBT for individuals suffering from low self-esteem.

It is an observation in clinical practice that when treating low self-esteem in patients with psychiatric comorbidities or more severe symptoms of psychiatric conditions, the application of cognitive interventions may not always be sufficient to effectively change patient's core beliefs. Patients frequently report that they still "feel" bad about themselves, albeit rationally believing that their core beliefs are not true (Young et al., 2002; Sanders and Ten Broeke, 2011). This suggests that a treatment that would intervene in a different manner, perhaps on a more affective level, and make patients actually "feel" more worthy, could be more effective, or at least be an additional tool for enhancing self-esteem.

Eye Movement Desensitization and Reprocessing (EMDR) therapy is considered to be a treatment method that intervenes on a more affective level (Shapiro, 2001). EMDR therapy is a protocolized psychotherapeutic treatment that is used to treat symptoms caused by distressing and unprocessed life events through reducing the vividness and disturbance of the memories of such events (Shapiro, 2007; Solomon and Shapiro, 2008). Although EMDR is mainly used for treating posttraumatic stress disorder (PTSD), it has been argued that EMDR therapy might also be an effective therapy for changing low self-esteem (De Jongh et al., 2010). Assuming that core beliefs underlying the low self-esteem developed as a consequence of subsequent learning experiences, EMDR may be used to reprocess emotionally charged memories that the patient considers to be "evidence" for his or her core belief (De Jongh et al., 2010). According to this case conceptualization, processing these memories using EMDR would make it possible to re-evaluate the present meaning of those experiences, thereby positively influencing their self-esteem.

Several case studies have shown a positive effect of EMDR on low self-esteem (Dziegielewski and Wolfe, 2000; Shapiro, 2001; Maxwell, 2003; Sanders and Ten Broeke, 2011). The results of a randomized controlled trial among 26 adolescents with self-esteem and behavioral problems showed that EMDR was effective in enhancing their self-esteem (Wanders et al., 2008). The researchers used four sessions EMDR therapy and compared this to four sessions of CBT, which contained strategies to teach children practical skills, to identify negative feelings and unhelpful thoughts, to replace these with more positive thoughts and to face and overcome their problems and challenges. Although both therapies where found to be effective, EMDR resulted in significantly more behavioral changes than CBT. Recently, Staring et al. (2016) used a randomized controlled trial with a crossover design among 47 adults with anxiety disorders to compare six sessions EMDR therapy with an equal number of sessions Competitive Memory Training (COMET) that aims to activate positive representations for enhancing self-esteem. They found that EMDR improved self-esteem, but they found a significantly stronger effect of COMET compared to EMDR therapy. Thus, the few studies that investigated the effectiveness of EMDR applied on self-esteem have so far shown mixed results. There are some explanations for these contradicting findings. First, until now, only a few sessions (4–6) of EMDR therapy have been used. It is conceivable that for changing individuals' long existing negative core beliefs, a wide array of memories would have to be targeted, "proving" that the person is bad or worthless. Furthermore, it could be argued that in the study of Staring et al. (2016) the memories that were targeted with EMDR, and that were deemed to contribute to patients' low self-esteem, could have been relatively low in emotional charge and, consequently, less sensitive to EMDR (Littel et al., 2017). Therefore, it could be hypothesized that especially patients with severe pathology and multiple diagnoses, associated with lower self-esteem (Silverstone and Salsali, 2003), might have memories underlying their low self-esteem with higher emotional charge, making them more likely to benefit from EMDR therapy.

The purpose of the current study was to test the effectiveness of EMDR therapy in adults with low self-esteem in a secondary mental health care population, by comparing it to a cognitive behavioral approach, using a randomized controlled trial. We hypothesized a significant improvement in self-esteem after 10 weekly sessions of treatment. It was hypothesized that the results associated with both interventions would be maintained at 3 months follow-up. The second aim of the study was to examine the difference in effectiveness between both treatments.

MATERIALS AND METHODS

Design

The protocol of the study was approved by the Medical Ethics Committee (NL49421.044.14) and was registered on May 27th, 2014 (www.trialregister.nl) with identifier NTR4611. It used a randomized controlled trial (1:1 allocation ratio) with two parallel groups, i.e., an EMDR condition and a CBT condition. Randomization was executed (with concealment of allocation) through central randomization performed by an independent randomizer (http://www.randomizer.org) using random assignment with "a two blocked design" (to keep sample size equal across conditions) in order of date of entry of the study.

Participants

The study participants were recruited at a health care center for secondary mental health. During the study period (i.e., from October 2014 through July 2016), a total of 82 patients were referred for self-esteem treatment and were informed about the study. Thirty patients met the inclusion criteria and were willing to participate. They were included and randomized to either EMDR therapy ($n = 15$) or CBT ($n = 15$). **Figure 1** shows the flow of patients through the study. During the study 10 patients (four in the EMDR and six in the CBT condition) dropped out for various reasons, for example due to a sudden loss in the family, acute suicidality before starting treatment, a preference for a certain treatment condition while not being included in that condition, or wanting to follow other treatments for more prominent disorders. Ultimately, 20 patients underwent the full treatment protocol, i.e., 11 patients in the EMDR condition and nine in the CBT condition. One patient in the CBT condition was lost to follow-up. Baseline characteristics of the sample are shown in **Table 1**.

The inclusion criteria of the study were an age between 18 and 65 years, a reference by their therapist for the treatment of their self-esteem, having a low self-esteem as indexed by a score below the cut-off point (<16) on the Rosenberg Self-esteem Scale, having an Axis I and/or Axis II disorder according to the DSM-IV-TR (American Psychiatric Association, 2000) diagnosed by their referring therapist, other than a PTSD, sufficient mastery of the Dutch language, and being capable of doing homework. During the study period patients were not allowed to receive other treatments.

Procedure

The study participants, already diagnosed with an Axis I and/or II disorder, were referred for self-esteem treatment by their mental health professional. They were screened for low self-esteem with the Rosenberg Self-esteem Scale (RSES) and assessed for PTSD with the MINI-International Neuropsychiatric Interview (Van Vliet and De Beurs, 2007). When patients met the inclusion criteria they were informed about the study, verbally and in writing. One week later, one of the researchers had telephone contact about participating, answered possible questions and formally invited the patient to participate. After the informed consent form was signed, the baseline assessment and randomization to the EMDR or CBT condition took place. Patients were assessed at baseline (T0) regarding self-esteem (RSES and Credibility of Core Beliefs), psychological symptoms (Brief Symptom Inventory) and both social anxiety and social interaction IIS. Before treatment, the negative core belief that was most representative of patients' low self-esteem was selected using the "Downward arrow technique" (Beck, 1995). In contrast, a positive alternative belief was formulated by the patient in reaction to the question as to what they would rather believe instead of their negative core belief. The affective credibility of the beliefs was scored on a Visual Analogue Scale (VAS) ranging from 0 to 100% credibility (Credibility of Core Beliefs). After each of the 10 treatment sessions, patients were assessed with the Credibility of Core Beliefs and with the Rosenberg Self-esteem Scale. After 10 weeks of treatment (T1), and at 3 months follow-up (T2) all patients were assessed again on all the outcome measures.

Assessment Measures

It was hypothesized that the treatments would enhance self-esteem, reduce psychiatric symptoms in general, reduce social anxiety, and would increase social interaction.

Rosenberg Self-esteem Scale

The RSES was used as primary outcome measure for self-esteem. This widely used questionnaire (Schmitt and Allik, 2005) is a 10-item self-report measure to assess global self-esteem by asking the respondents to reflect on their current feelings on a four-point scale (0 = "strongly disagree" 3 = "strongly agree"; Rosenberg, 1965; Franck et al., 2008). Total scores range from 0 up to 30, with higher scores indicating a higher global self-esteem. The cut-off for inclusion was 16, so that participants at baseline all scored at least 1 standard deviation ($SD = 4$) below the mean of 20 (Franck et al., 2008). The Dutch version of the RSES has good internal consistency and test–retest reliability (Everaert et al., 2010).

Credibility of Core Beliefs

The affective credibility of the negative core belief (CNCB) and the credibility of the positive alternative belief (CPAB) were scored on a visual analog scale ranging from 0 to 100% credibility.

Brief Symptom Inventory

The Brief Symptom Inventory (BSI) is an abbreviated version of the SCL-90-R questionnaire, consisting of 53-items, and is an index for severity of psychological symptoms (Derogatis and Melisaratos, 1983). The BSI rates the extent to which individuals have been bothered (0 = "not at all" to 4 = "extremely") in the past week by various symptoms. In the present study the BSI Total Score was used as outcome measure which represents the overall degree of mental illness. The reliability of the Total Score is sufficient and the discriminant validity of the Dutch version is good (De Beurs and Zitman, 2006).

Inventory of Interpersonal Situations

The Inventory of Interpersonal Situations (IIS) is a Dutch self-report questionnaire measuring social anxiety and social interaction (Van Dam-Baggen and Kraaimaat, 2004). The

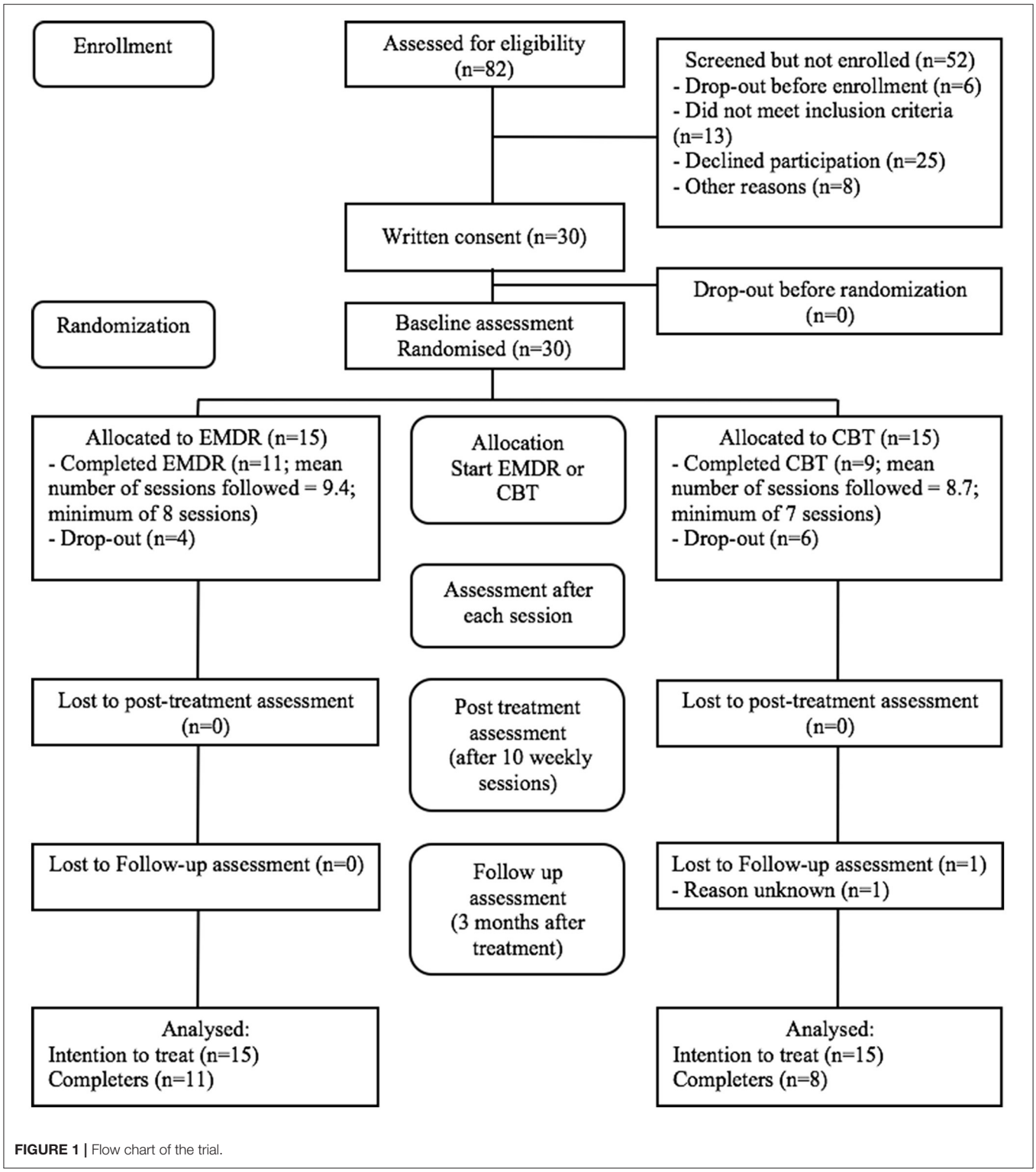

FIGURE 1 | Flow chart of the trial.

questionnaire consists of two parts, the first part determining the extent to which discomfort is experienced in certain social situations and the second part determining the frequency of the social interaction. The questionnaire consists of 35 items ranging from 1 to 5 (part 1; 1 = "not at all" 5 = "very much", part 2; 1 = "never" 5 = "always"). Several studies support the high predictive validity and the reliability of the IIS Discomfort and Frequency scales (Van Dam-Baggen and Kraaimaat, 1999).

TABLE 1 | Demographic and Diagnostic Characteristics of Intention-to-Treat and Treatment Completer Samples, divided by group allocation.

Variable	Intention-to-Treat		Completers	
	EMDR ($n = 15$)	CBT ($n = 15$)	EMDR ($n = 11$)	CBT ($n = 8$)
Mean age	38,8	28,6	41,5	32,1
SEX				
Male	2	3	2	2
Female	13	12	9	6
MOOD DISORDER				
Depressive disorder	7	5	6	2
Dysthymic disorder	5	4	4	1
ANXIETY DISORDER				
Social phobia	1	2	1	2
Specific phobia	1	–	1	–
Panic disorder with agoraphobia	1	2	1	1
Panic disorder without agoraphobia	1	–	1	–
Agoraphobia without history of panic disorder	1	–	–	–
Generalized anxiety disorder	3	3	3	–
Obsessive compulsive disorder	–	1	–	1
Anxiety disorder NOS	2	–	1	–
DEVELOPMENTAL DISORDER				
Autistic spectrum disorder	–	2	–	1
ADHD	3	3	2	1
SOMATOFORM DISORDER				
Undifferentiated somatoform disorder	–	1	–	1
EATING DISORDER				
Eating disorder NOS	1	2	1	–
SUBSTANCE RELATED DISORDERS				
Alcohol dependence	1	1	–	1
Cannabis dependence	–	1	–	–
Sedative-, hypnotic-, or anxiolytic related disorder	1	–	–	–
ADDITIONAL CODES				
Partner relational problem	–	1	–	1
Identity problem	1	–	1	–
Psychological factors affecting medical condition	1	–	1	–
PERSONALITY DISORDER				
Borderline personality disorder	3	3	1	1
Avoidant personality disorder	2	1	2	1
Personality disorder NOS	4	3	3	2
Personality disorder deferred	5	5	4	3
No diagnosis on Axis II	2	2	2	1
CO-MORBIDITY				
Multiple Axis I diagnosis	11	10	9	4
Axis I and Axis II diagnosis or deferred	13	13	9	7
Multiple Axis II diagnosis or deferred	1	–	1	–

Diagnosis according to the Diagnostic Statistical Manual-IV-TR (DSM-IV-TR).

Treatments

EMDR Condition

Patients received 10 weekly sessions of 75 min each. For the case conceptualizations addressing patients' self-esteem the "second method" was used (De Jongh et al., 2010). The underlying principle of this method of case conceptualization is that negative events leave memory traces causing and maintaining dysfunctional core beliefs. According to this method, five of the most relevant memories that contributed to the formation and the present credibility of the selected negative core belief were identified. More specifically, in the present study the patient was requested to select the memories that subjectively "proved" that the belief was true and to describe the content of these memories in a few sentences. EMDR therapy, using the Standard protocol (De Jongh and Ten Broeke, 2003), started with the memory which, according to the patient, was considered providing the strongest "proof" for the negative core belief; that is, the memory associated with the dysfunctional meaning (e.g., "I'm worthless"). Next, a more functional belief about the person (e.g., "I'm okay"; Shapiro, 2002) was installed. When the memory was effectively treated, meaning the Subjective Units of Distress scale (SUD) reported by participants was at least 2 or lower (range 0–10), the next memory that provided the most evidence for the negative core belief was selected and processed. This was repeated for the other memories.

CBT Condition

Patients received 10 weekly group sessions of CBT of 120 min each including a 15 min break. The CBT group, consisting of 6 to 10 patients, was based on the "Whitebook Method" described by De Neef (2010) that uses "positive data logging" (Padesky, 1994) to specifically focus on evidence that is contradictory to the negative core belief. Patients received psycho-education about how information that is contradictory to the negative core belief is usually discounted and distorted leading to not noticing and evaluating exceptions to their negative core belief. Patients kept a positive data log to write down positive events and positive qualities of themselves. Additionally they investigated pro's and cons of negative thoughts, received information and training about receiving criticism and they discussed how to prevent relapse.

Treatment Integrity

All EMDR and CBT sessions were videotaped. Feedback on adherence to the EMDR or CBT protocol and the competence of the therapists was given by licensed EMDR or CBT supervisors to optimize the quality and equality of the treatments. Case conceptualizations of each patient in the EMDR condition were checked and evaluated with the therapists by two EMDR supervisors before commencing treatment. The EMDR therapists were trained to perform EMDR for low self-esteem, using the "Second method," whereas the group therapists received extensive general training in CBT and were qualified to perform the CBT protocol for low self-esteem as described by De Neef (2010).

Statistical Analysis

All analyses were conducted with SPSS for Windows version 23.0. Independent samples *t*-tests and Chi-square tests were performed to analyse differences between treatment conditions pre-treatment. This was done for both the intention-to-treat sample ($n = 30$) and the complete cases ($n = 19$), i.e., patients who finished the whole research protocol. For the variables that

were not normally distributed, the Mann-Whitney U test was used. In the Chi-square analyses the Yates' correction was used (Yates, 1934) to prevent overestimation of statistical significance for small groups. Using descriptive statistics, the scores on the self-esteem measures over the course of sessions (RSES and CCB) were explored.

A repeated measures ANOVA was performed for each of the outcome variables on all complete cases (patients who completed the full research protocol) to examine the effect of treatment condition on self-esteem, psychological symptoms, social anxiety, and frequency of social interaction (GLM: general linear model, repeated measures). Time (pre-treatment, post treatment and follow-up) was used as a within-subject variable and treatment (EMDR vs. CBT) as a between-subject variable. To determine to what extent patients showed improvement over time a Helmert contrast was used to directly compare pre-treatment (T0) to post treatment (T1) and follow-up (T2) and post treatment (T1) with follow-up (T2). Not all variables were normally distributed but ANOVA is considered fairly robust to such a violation (Stevens, 2002). Since the assumption of sphericity was violated in most of the variables (Mauchly's Test of Sphericity $p < 0.05$), the Greenhouse Geisser correction was applied. For all comparisons effect sizes were calculated (small effect: $\eta_p^2 = 0.01$; medium effect: $\eta_p^2 = 0.06$; large effect: $\eta_p^2 = 0.14$) (Fritz et al., 2012). Furthermore, an intention-to-treat analysis was performed, using the last observation carried forward method, and a non-parametric analysis, using the Friedman test, was performed to examine the robustness of the ANOVA results in the complete cases.

A reliable change (RC) index was calculated to determine which patients' RSES, BSI, and IIS scores changed beyond a level that could be attributed to measurement error (Evans et al., 1998). For this purpose, the standard error of measurement of the difference (SEdiff) was used, which takes account of the 2 measurements (pre-treatment and post treatment). The formula is $SE_{diff} = SD_1\sqrt{2}\sqrt{1-\alpha}$, where SD1 is the standard deviation of the baseline observations and alpha is the reliability of the measure (Cronbach alpha coefficient). It is assumed that change that exceeds 1.96 times this standard error (i.e., the RC index) is unlikely to occur more than 5% of the time by unreliability of the measure alone (Evans et al., 1998). In addition, a clinical significant change criterion was calculated to determine which patients' RSES, BSI, and IIS scores changed to a level that could be considered clinically meaningful. The cut-off point was determined according to "criterion C," i.e., where the likelihood of the patient being in the normative distribution was greater than being in the clinical distribution after treatment (Evans et al., 1998). The cut-off point was set at where the SD's of the clinical and normative data were equal: $\frac{(mean_{clin} \times SD_{norm}) + (mean_{norm} \times SD_{clin})}{SD_{norm} + SD_{clin}}$ (Evans et al., 1998).

RESULTS

Participants and Randomization

Considering the demographic characteristics (intention-to-treat), there was a significant age difference between the two treatment conditions [$t(28) = 2.81$, $p = 0.01$], the mean age of the EMDR condition being significantly higher ($M = 38.8$, $SD = 11.83$) than in the CBT condition ($M = 28.6$, $SD = 7.64$). The sex ratio in sample did not differ from expectation [Chi-square = 0.21 (1), $p = 0.65$]. As for diagnoses, no significant differences between groups were found, with the only exception that the prevalence of mood disorders within the complete cases was significantly [Chi-square = 7.21 (1), $p = 0.01$] higher in the EMDR condition (10) than in the CBT condition (3). For the baseline measures of all the outcome variables there were no significant pre-experimental differences in scores measuring self-esteem, psychological symptoms, social anxiety, and social interaction between the EMDR and the CBT condition. This was the case for the intention-to-treat as well as the complete cases.

Treatment Participation

No significant between-group difference in the number of sessions that were completed was found [$t = 1.42(28)$, $p = 0.17$]. For the complete cases, patients in the EMDR condition completed at least 8 of the 10 sessions ($M = 9.36$, $SD = 0.81$), whereas in the CBT at least seven sessions of the 10 sessions were completed ($M = 8.67$, $SD = 1.32$). In the EMDR condition, the mean of the SUD scores of the selected targets before desensitization was 7.6 (scale 0–10). In the EMDR condition, a mean of 4 memories were reprocessed to a SUD score of 2 or lower.

Changes in Self-esteem over Sessions

As to the scores on the CNCB over the sessions, the mean scores of the patients in the EMDR condition dropped below 50% credibility in session #7 and this was maintained throughout session #8, #9, and #10. Looking at individual scores, more than half of the patients in the EMDR condition (6 patients) dropped below 50% credibility in session #5. For the CBT condition the mean score on CNCB dropped below 50% credibility, being more not true than true, in session #8 and this was maintained in session #9 and #10. Also in session #8, more than half of the patients in the CBT condition (5 patients) reached an individual score below 50% credibility.

For the positive alternative belief, credibility exceeded 50% credibility in session #7 for the EMDR and in session #10 in the CBT condition. More than half of the patients in each group exceeded 50% credibility in session #5 for the EMDR and in session #9 for the CBT condition. **Figures 2** and **3** show the mean scores on the CNCB and the positive alternative belief per group over the course of the treatment.

When looking at the scores on the RSES over the sessions, the mean of the patients in the EMDR condition reached a score of 16 (cut-off) or higher in session #9. This was also the case in session #9 in the CBT condition. More than half of the patients reached a score of 16 or higher in session #9 in the EMDR condition, this was in session #10 for the CBT condition. **Figure 4** shows the mean scores on the RSES per group over the course of treatment.

Treatment Effects

Table 2 displays the means and standard deviations for the various outcome measures, measurement times, and therapy

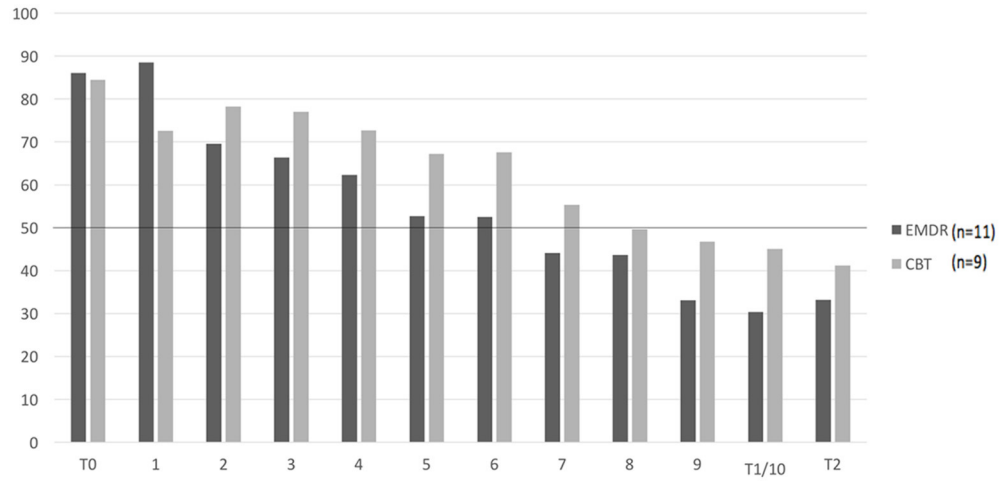

FIGURE 2 | Mean scores on the CNCB per condition over the course of treatment ($n = 20$). CNCB, Credibility of Negative Core Belief. T0: pre-treatment, T1: post-treatment, T3: months follow-up. 1–10: weekly sessions. 0–100%: credibility of core belief. Missing values were imputed with last observation carried forward.

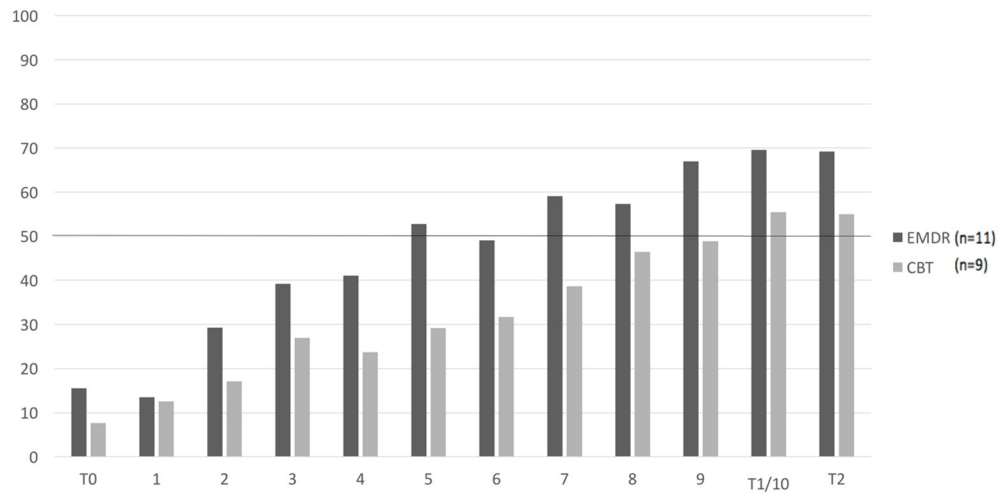

FIGURE 3 | Mean scores on the CPAB per condition over the course of treatment ($n = 20$). CPAB, Credibility of Positive Alternative Belief. T0: pre-treatment, T1: post-treatment, T3: months follow-up. 1–10: weekly sessions. 0–100%: credibility of core belief. Missing values were imputed with last observation carried forward.

types. The ANOVA analysis for the complete cases showed a significant improvement over time on all the outcome measures as shown in **Table 3**. Regarding all measures the interaction between time and treatment condition was, however, not significant, congruently showing very small effect sizes. This indicates that there were no significant differences between the EMDR and CBT condition on any of the measures. Yet, significant increases of self-esteem and social interaction as well as decreases of psychological symptoms and social anxiety were seen for both treatment conditions. The Friedman test yielded similar results for the self-esteem measures and the measure for psychological symptoms except for social anxiety, whereas social interaction significantly increased over time in the CBT condition, but not in the EMDR condition. The intention-to-treat analysis showed significant improvements that for all outcome measures from pre-treatment (T0) compared to post-treatment (T1) and follow-up (T2). For the complete cases, no differences were found between T1 and T2, indicating that the treatment results that were achieved in both the EMDR and CBT condition between T0 and T1 were maintained at T2. The intention-to-treat analysis showed similar results. For more detailed information on the intention-to-treat sample, we refer to **Table A1** in Appendix.

Reliable and Clinical Change

The self-esteem measure (RSES) showed the highest percentage clinically relevant change (60%), followed by social anxiety (40%), social interaction (35%), and finally psychological symptoms (25%). For the specific percentages in the different treatment groups, see **Table 4**.

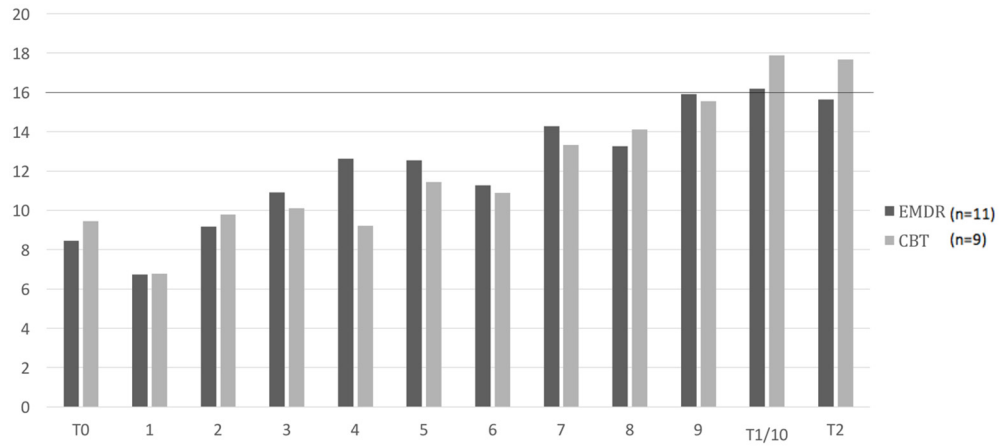

FIGURE 4 | Mean scores on the RSES per condition over the course of treatment ($n = 20$). RSES, Rosenberg Self-esteem Scale. T0: pre-treatment, T1: post-treatment, T3: months follow-up. 1–10: weekly sessions. Cut-off score 16. Missing values were imputed with last observation carried forward.

TABLE 2 | Means (SD) of the outcome measures.

	Condition 1; EMDR			Condition 2; CBT		
	T0 ($n = 11$)	T1 ($n = 11$)	T2 ($n = 11$)	T0 ($n = 8$)	T1 ($n = 8$)	T2 ($n = 8$)
RSES	8.45	16.18	15.64	9.00	18.13	17.88
	(4.44)	(10.17)	(9.09)	(3.51)	(7.24)	(8.37)
CNCB	86.09	30.36	33.18	90.75	47.50	43.12
	(17.46)	(37.42)	(37.99)	(7.78)	(32.20)	(36.52)
CPAB	15.55	69.55	69.18	7.75	57.38	56.88
	(19.31)	(36.97)	(36.06)	(6.16)	(33.49)	(33.27)
BSI	1.73	1.27	1.17	1.78	1.09	1.13
	(1.03)	(1.19)	(1.16)	(0.95)	(0.70)	(0.83)
IIS DISC	112.45	95.18	88.91	110.63	86.00	83.63
	(31.83)	(39.73)	(38.37)	(25.43)	(26.40)	(24.85)
IIS FREQ	82.73	92.18	95.27	85.13	100.63	109.38
	(11.47)	(30.06)	(27.55)	(17.72)	(22.52)	(19.98)

RSES, Rosenberg Self-esteem Scale; CNCB, Credibility of Negative Core Belief; CPAB, Credibility of Positive Alternative Belief; BSI, Brief Symptom Inventory; IIS DISC, Inventory of Interpersonal Situations, Discomfort in Social Interactions; IIS FREQ, Inventory of Interpersonal Situations, Frequency of Social interaction; T0, Pre-treatment; T1, Post treatment; T2, 3 months follow-up.

DISCUSSION

The results of the present study suggest that both EMDR therapy and CBT have the potential to be an effective treatment alternative for patients who suffer from low self-esteem in co-occurrence with a wide range of psychiatric disorders.

Patients improved not only more than two standard deviations on the primary outcome measure (Rosenberg Self-esteem Scale), the treatments also led to significant reductions in general psychiatric symptoms and social anxiety, as well as to a significant increase of social interactions. All treatment effects were maintained at 3 months follow up. These results were held after an intention-to-treat analysis was performed that included all patients who dropped out early in treatment. For the majority of the patients (60%), the amount of 10 therapy sessions resulted in a clinically significant improvement in self-esteem. No significant differences could be detected between the two therapies.

The results of this study are in line with the study of Wanders et al. (2008) who found similar effects in adolescents, in that EMDR therapy and CBT proved equally effective in changing low self-esteem. Conversely, the results are at odds with those of Staring et al. (2016) who found EMDR to be less effective in treating low self-esteem than COMET. Patients in the current study showed a larger improvement on self-esteem compared to Staring et al. (2016). This difference in results may be explained by the amount of sessions provided, in that Staring et al. (2016) used six sessions whereas the patients in the current study received ten sessions. Also it is likely that the memories targeted with EMDR in the current study with patients with multiple psychiatric diagnoses, were more emotionally charged and hence more susceptible for processing using EMDR therapy (Littel et al., 2017). Concerning CBT, in contrast to Ritter et al. (2013), who used 25 sessions of CBT to treat low self-esteem, we found that 10 sessions of CBT were sufficient to establish changes in self–esteem in the majority of the patients. The effectiveness of CBT in changing low self-esteem found in the present study (effect size on the RSES $\eta_p^2 = 0.49$), is in line with former studies on group CBT (Rigby and Waite, 2006; Morton et al., 2012; Pack and Condren, 2014).

This study had several strengths. Firstly, it is one of the first RCTs explicitly focussed on the effectiveness of EMDR therapy for low self-esteem in adults, and also one of the first RCTs examining the efficacy of CBT in treating low self-esteem. In contrast to former studies examining the effect of EMDR on low self-esteem (Wanders et al., 2008; Staring et al., 2016), the current study explicitly excluded patients with PTSD, making it more likely that the EMDR therapy was in fact effective in changing self-esteem instead of treating trauma related symptomatology. Secondly, regarding self-esteem treatment, the present study was one of the first to include a diverse patient group with

TABLE 3 | ANOVA analysis for the complete cases ($n = 19$).

	Effect Time			Effect time × condition			T0 vs. T1 and T2			T1 vs. T2		
	F	*P*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
RSES	16.30	0.00	0.49	0.15	0.77	0.01	18.80	0.00	0.53	0.21	0.65	0.01
CNCB	28.56	0.00	0.63	0.34	0.59	0.02	29.92	0.00	0.64	0.12	0.74	0.01
CPAB	36.30	0.00	0.68	0.07	0.81	0.00	37.54	0.00	0.69	0.06	0.81	0.00
BSI	10.51	0.00	0.38	0.29	0.68	0.02	13.45	0.00	0.44	0.10	0.76	0.01
IIS DISC	10.40	0.00	0.38	0.19	0.76	0.01	12.75	0.00	0.43	1.30	0.27	0.07
IIS FREQ	5.74	0.01	0.25	0.56	0.55	0.03	7.59	0.01	0.31	1.79	0.20	0.10

RSES, Rosenberg Self-esteem Scale; CNCB, Credibility of Negative Core Belief; CPAB, Credibility of Positive Alternative Belief; BSI, Brief Symptom Inventory; IIS DISC, Inventory of Interpersonal situations; Discomfort in Social Interactions, IIS FREQ, Inventory of Interpersonal Situations; Frequency of social interaction; T0, Pre-treatment; T1, Post treatment; T2, 3 months follow-up.

TABLE 4 | Percentage of patients showing reliable and clinical significant changes on self-esteem, psychological symptoms and social interaction ($n = 20$).

		Total group ($n = 20$) reliable change		EMDR ($n = 11$)		CBT ($n = 9$)	
		Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
CLINICAL CHANGE							
RSES (>14)	60%						
		55	5	55	0	56	11
BSI (<0.80)	25%						
		15	10	27	0	0	22
IIS DISC (<86)	40%						
		30	10	36	9	22	11
IIS FREQ (>95)	35%						
		35	0	27	0	44	0

RSES, Rosenberg Self-esteem Scale; BSI, Brief Symptom Inventory; IIS DISC, Inventory of Interpersonal Situations; Discomfort in Social Interaction; IIS FREQ, Inventory of Interpersonal Situations, Frequency of Social Interaction.

various psychiatric disorders. The results suggest that EMDR as well as CBT are effective for treating low self-esteem in such a difficult population. Finally, this study used a follow-up measure to examine the treatment outcomes over time, showing that the treatment effects of both EMDR and CBT were maintained.

While the present study results are encouraging, there are a number of limitations that need to be acknowledged. First, given the relatively small sample size, it cannot be ruled out that the fact that no differences between groups were found were due to the fact that this study was underpowered. Secondly, because the EMDR treatment was delivered individually whereas the CBT treatment was given in a group setting, it could be argued that the experience of being accepted within a group and meeting other people who share similar difficulties, would be therapeutic for individuals with low self-esteem. Conversely, patients in the EMDR condition could have profited more from the individual attention of the therapist, feeling perhaps more comfortable in this context to display their deepest feelings and beliefs. Thirdly, there was a significant difference in age between patients in the EMDR and CBT condition. However, age differences in self-esteem generally appears to be relatively small compared to interindividual differences, like personality traits, and measurement error (Pullman et al., 2009; Orth et al., 2010). This is in line with the pre-treatment measurements as found in the current study in that despite the difference in age between both groups differences on self-esteem measures were lacking. Finally, this study lacked a passive control group, so it cannot be ruled out, however unlikely, that patients improved simply because of getting attention from the therapist and not because of the specific treatments methods.

Looking at an individual level, not all patients benefited equally from treatment. This was the case for the CBT as well as for the EMDR condition. Given that both treatments were effective at group level, specific patient groups might have benefited more or less from different kinds of interventions. Likewise, while for the majority of the patients ten sessions were enough to reach a clinical significant improvement in self-esteem, for the non-responders perhaps more sessions may have been needed, or perhaps they would have benefited more from another treatment method. The fact that no significant differences were found between groups does not support the hypothesis that EMDR might intervene on a more affective level than CBT. However, the results of this study indicate that EMDR can be used as an effective alternative for CBT in treating low self-esteem. Further research is warranted to examine whether certain patient groups might benefit more from one or the other treatment method, or a combination of both.

In conclusion, the present study is the first RCT examining the effectiveness of EMDR therapy and CBT on treating low self-esteem in a general psychiatric, adult, population. Despite the small sample size, the results suggests that, when using 10 sessions, both therapies seem effective for treating low self-esteem in patients with a wide range of psychiatric disorders in secondary mental health care. Future research will be needed to examine whether these findings can be replicated in a larger patient group, preferably using a waiting list control group. Furthermore, future studies should aim at

examining which method for treating self-esteem works best for whom.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Medical Ethics Committee Twente with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Ethics Committee Twente.

AUTHOR CONTRIBUTIONS

BG and AvdV designed the study, collected the data and wrote the manuscript; BG performed the data analysis; IdG and AdJ made substantial contributions to the conception and design of the study and edited and revised the manuscript. All authors read and approved the final manuscript.

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AdJ receives income for published books on EMDR therapy and for the training of postdoctoral professionals in this method.

APPENDIX

TABLE A1 | Means (SD) of the outcome measures of intention to treat sample.

	Condition 1; EMDR			**Condition 2; CBT**		
	T0 ($n = 15$)	**T1 ($n = 15$)**	**T2 ($n = 15$)**	**T0 ($n = 15$)**	**T1 ($n = 15$)**	**T2 ($n = 15$)**
RSES	9.33	15.07	14.67	8.00	12.93	12.67
	(4.25)	(8.92)	(8.00)	(4.38)	(8.70)	(8.92)
CNCB	87.07	41.47	42.93	87.93	63.73	62.67
	(15.31)	(41.27)	(41.59)	(17.41)	(34.23)	(37.88)
CPAB	16.60	60.80	60.60	7.13	37.87	35.60
	(18.80)	(39.84)	(39.23)	(6.29)	(35.21)	(34.65)
BSI	1.77	1.39	1.33	1.91	1.52	1.61
	(0.90)	(1.09)	(1.07)	(0.86)	(0.91)	(1.02)
IIS DISC	106.27	94.00	88.80	109.67	96.87	96.40
	(30.64)	(34.89)	(34.11)	(26.32)	(31.93)	(33.68)
IIS FREQ	87.07	94.73	95.80	88.47	96.80	101.33
	(12.46)	(26.14)	(23.40)	(16.73)	(20.19)	(20.52)

RSES, Rosenberg Self-esteem Scale; CNCB, Credibility of Negative Core Belief; CPAB, Credibility of Positive Alternative Belief; BSI, Brief Symptom Inventory; IIS DISC, Inventory of Interpersonal Situations, Discomfort in social interactions; IIS FREQ, Inventory of Interpersonal Situations, Frequency of social interaction; T0, Pre-treatment; T1, Post treatment; T2, 3 months follow-up.

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EMDR as Add-On Treatment for Psychiatric and Traumatic Symptoms in Patients with Substance Use Disorder

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Background: Substance use disorders (SUD) are patterns of substance use leading to severe impairment on social, working and economic levels. *In vivo* and clinical findings have enhanced the role of the brain's stress-related system in maintaining SUD behaviors. Several studies have also revealed a high prevalence of post-traumatic symptoms among SUD patients, suggesting that a trauma-informed treatment approach could lead to better treatment outcomes. However, only few studies have evaluated the use of eye movement desensitization and reprocessing (EMDR) in SUD without consistent results. The aim of the present pilot study was to assess the efficacy of a combined trauma-focused (TF) and addiction-focused (AF) EMDR intervention in treating post-traumatic and stress-related symptoms of patients with SUD.

Methods: Forty patients with different SUD were enrolled in the study. Twenty patients underwent treatment as usual (TAU), the other 20 patients were treated with TAU plus 24 weekly sessions of EMDR. All patients were assessed before and after intervention for several psychological dimensions using specific tools (i.e., BDI-II, DES, IES-R, STAI, and SCL-90-GSI). A repeated measure MANOVA was performed to evaluate both between groups (TAU + EMDR vs. TAU) and within group (pre- vs. post-intervention) effects and interactions. A secondary outcome was the dichotomous variable yielded by the urine drug testing immunoassay (yes/no).

Results: The RM-MANOVA revealed both a significant pre–post main effect ($p < 0.001$), and a significant group-by-time main effect ($p < 0.001$). Significant improvements on IES-R, DES, and SCL-90-GSI scales were shown in both groups according to time effects ($p < 0.05$). However, significant greater effects were found for TAU + EMDR group than TAU group. No differences were found between TAU and TAU + EMDR groups in terms of urine drug immunoassay results before and after the interventions.

Conclusions: The TAU + EMDR group showed a significant improvement of post-traumatic and dissociative symptoms, accompanied by a reduction in anxiety and

overall psychopathology levels, whereas TAU group showed a significant reduction only in post-traumatic symptoms. Although our results can only be considered preliminary, this study suggests that a combined TF- and AF- EMDR protocol is an effective and well-accepted add-on treatment for patients with SUD.

Keywords: eye movement desensitization and reprocessing, substance use disorder, traumatic stress, dissociation, anxiety, depression, psychiatric symptoms, adverse childhood experiences

INTRODUCTION

Substance use disorders (SUD) are pathological patterns of behaviors related to substance use leading to severe impairment of familial, social and working relationships as well as of economic conditions (American Psychiatric Association, 2013).

Although the neurobiological circuitry that is associated with drug reward has been broadened in recent years, the meso-cortical-striatal dopamine system is still the most important pathway involved in the rewarding properties of almost all drugs (Koob and Volkow, 2016).

However, *in vivo* and clinical findings have also enhanced the role of brain's stress-related system in maintaining SUD behaviors: the chronic administration of all major drugs with dependence or abuse potential is associated with corticotropin-releasing factor variation leading to both hypothalamic-pituitary-adrenal axis and brain stress system dysregulation (Koob, 2013).

The increase of corticotropin-releasing factor, dynorphin, and norepinephrine recruited in the extended amygdala contributes to the development of negative emotional states during acute withdrawal (such as chronic irritability, dysphoria, and loss of motivation; Koob and Volkow, 2016).

From an epidemiologic point of view, patients having any lifetime SUD showed higher risk of also having a post-traumatic stress disorder (PTSD; OR = 1.6, 95% CI = 1.27–2.10, Grant et al., 2016) with a prevalence of current PTSD ranging from 15 to 42% (Mills et al., 2005; Reynolds et al., 2005, 2011; Driessen et al., 2008).

Moreover, some studies conducted on SUD showed that 67–92% of the patients report having experienced at least one traumatic event according to the DSM-IV PTSD criterion A (Dragan and Lis-Turlejska, 2007; Reynolds et al., 2011).

Furthermore, several studies have also reported a strong relationship between exposure to severe stress in childhood and substance abuse (Dube et al., 2003; Green et al., 2010). One of the most important studies, conducted by the Center for Disease Control along with the Kaiser Hospital in San Diego, released the landmark Adverse Childhood Experience (ACE) study, showing that individuals who experienced four or more types of ACEs were at a four to 12-fold increased risk of developing alcohol or drug abuse problems (Felitti et al., 1998).

Research has shown that substance abuse treatment using a trauma-informed approach could lead to better treatment outcomes, such as greater symptom reduction and increased retention in treatment (Amaro et al., 2007; LeTendre and Reed, 2017).

Such involvement of stress systems, trauma, and PTSD in SUD suggested a possible role of intervention possibly impacting on traumatic and stress disorders in the treatment of patients with SUD.

Among the different psychological approaches, eye movement desensitization and reprocessing (EMDR) has emerged as an evidence-based therapy for the treatment of psychological sequelae of traumatic events and other negative stressful experiences (Shapiro, 2014).

EMDR is a psychotherapeutic approach that focuses on trauma elaboration. It is guided by the adaptive information processing (AIP) model, that posits that stressful events not fully processed and integrated into the already existing memory networks are stored in a dysfunctional way. A distinct characteristic of EMDR therapy is the use of alternating bilateral stimulation (eye movements, tactile, or audio), which appears to produce a physiological effect promoting accelerated reprocessing of dysfunctionally stored information related to the traumatic event (Jeffries and Davis, 2013; Carletto et al., 2017; Pagani et al., 2017).

EMDR is considered one of the elective psychotherapeutic treatments for PTSD, according to several meta-analyses and clinical guidelines (Van Etten and Taylor, 1998; Davidson and Parker, 2001; Bradley et al., 2005; National Collaborating Centre for Mental Health, 2005; Bisson et al., 2013; WHO, 2013; Chen et al., 2014, 2015) and its neurobiological effects are also supported by neuroimaging findings (Pagani et al., 2012, 2015; Boukezzi et al., 2017).

Furthermore, in recent years the use of EMDR has expanded beyond PTSD and several studies have reported its efficacy for treatment of trauma-associated symptoms in patients with other psychiatric conditions (for a review see Valiente-Gómez et al., 2017). Among these, several protocols of treatment were developed in order to address traumatic experiences of SUD patients.

The clinical application of trauma-focused EMDR (TF-EMDR) in some studies resulted in EMDR being efficacious in the treatment of traumatic symptoms, but not in addiction behavior severity (see reviews by Roberts et al., 2015 and Markus and Hornsveld, 2017). Subsequently, some authors focused on the role of TF-EMDR in patients with SUD without PTSD, considering different types of outcomes even in relation to the addiction with fairly positive results but without conclusive findings.

Finally, as a third possible application of EMDR in SUD, there were some proposals of addiction-focused EMDR (AF-EMDR) protocols, such as the desensitization of triggers and urge reprocessing (DeTUR) protocol by Popky (2005), the feeling-state addiction protocol (FSAP) by Miller (2010) and the craving extinguished (CravEx) protocol by Hase et al. (2008). All these

protocols were specifically focused on the addiction rather on trauma but only the CravEx was clinically evaluated in a randomized clinical trial. Comparing treatment as usual (TAU) with CravEx plus TAU in a sample of patients with alcohol use disorder, Hase et al. (2008) have found a significant reduction in craving and depression severity up to 1 month after treatment.

To the best of our knowledge, no studies have yet evaluated the efficacy of both trauma and addiction-focused protocols on the relapse rate and stress-related symptoms of patients with SUD. Therefore, the aim of the present pilot study was to assess the efficacy of a combined trauma-focused and addiction-focused EMDR protocol in treating post-traumatic and stress-related symptoms of patients with SUD. We hypothesized that this combined adjunctive EMDR intervention would be more effective than a TAU intervention.

MATERIALS AND METHODS

Design

This was a quasi-experimental study investigating the efficacy of an additional EMDR treatment as compared with TAU alone in patients diagnosed with SUD.

Setting

The participants were recruited in two settings: an outpatient territorial service for drug addiction in northern Italy (Ser.T. of Limbiate, MI) and a residential facility in central Italy (Comunità di Capodarco di Fermo, FM) from March 2015 to May 2016.

The study was approved by the Medical Ethics Committee of Azienda Territoriale dei Servizi of Brianza (MB, Italy) and by the Board of Directors of Capodarco (FM, Italy). Informed written consent was obtained from all the participants.

Participants

The subjects of the study were patients with a diagnosis of SUD, who were referred to one of the two above-mentioned centers for drug addiction treatment.

Inclusion criteria were as follows: (1) a diagnosis of SUD, according to DSM-5; (2) age between 18 and 65 years; (3) fluent Italian language; (4) legal capacity to consent to the treatment; (5) maintenance of psychotropic medications throughout the study.

Exclusion criteria were as follows: (1) having a pathological gambling disorder without comorbidity with other SUDs; (2) presence of other severe psychiatric disorders such as psychosis or bipolar disorder; (3) cognitive disorders such as overt dementia; (4) suicide attempts; (5) current pregnancy.

Assessment

The recruitment of participants was carried out by a psychiatrist and psychologist who proposed participation in the research protocol to patients during a clinical visit in the outpatient setting and during the first visit after admission in the inpatient setting. The research protocol was proposed to consecutive patients who met the inclusion criteria, with an explanation of the aims of the study, and patients were asked whether they were willing to receive an additional psychotherapeutic intervention (EMDR) other than TAU. Patients could choose the group to which they wanted to be assigned (TAU or TAU + EMDR). On reaching the maximum number of patients in the TAU + EMDR group, the remaining patients were assigned to the TAU alone group.

The psychological assessment was performed by psychologists independent of the research protocol, using the same timing and tools, i.e., at baseline before the first session of treatment (T0), and after the end of treatment (T1).

The following psychological self-report questionnaires were administered:

Impact of Event Scale—Revised (IES-R). The IES-R (Weiss and Marmar, 1997) is a 22- item self-report questionnaire consisting of three subscales (eight items relate to intrusions, eight items evaluate avoidance, and six items assess hyperarousal). The scale assesses subjective distress caused by traumatic events. An IES-R score equal to or >33 represents the best cut-off for a probable diagnosis of PTSD. The IES-R was found to be highly internally consistent (Cronbach's alpha, $\alpha = 0.96$; Creamer et al., 2003).

State-Trait Anxiety Inventory (STAI-Y). The STAI-Y (Spielberger et al., 1983) is used to measure the presence and severity of current symptoms of anxiety (state anxiety; STAI-1) and a generalized propensity to be anxious (trait anxiety; STAI-2). Range of scores for each subtest is 20–80, the higher score indicating greater anxiety. A cutoff point of 39–40 has been suggested to detect clinically significant symptoms for the state anxiety scale. The STAI-Y has shown an adequate to excellent internal reliability ($\alpha = 0.86$–0.95).

Beck Depression Inventory-II (BDI-II). The BDI-II (Beck and Steer, 1993) is a 21-item self-report instrument that assesses the presence and severity of depression symptoms. A score above 13 indicates presence of depression symptoms. The internal consistency of the BDI-II is good to excellent ($\alpha = 0.83$–0.96; Wang and Gorenstein, 2013).

Symptom Checklist 90 Items revised version (SCL-90- R) (Derogatis et al., 1973; Derogatis, 1994) is a 90-items self-report questionnaire that evaluates a broad range of psychological problems and symptoms of psychopathology. For the purpose of this study we chose to utilize the Global Severity Index (GSI), as it represents the best global indicator of the intensity of psychic distress reported by the subject and it demonstrated a high Cronbach's alpha value ($\alpha = 0.97$; Prinz et al., 2013). This global index combines information about the number of reported symptoms and the intensity of perceived discomfort. A score between 55 and 65 indicates a distress level of moderate intensity, while a score above 65 reveals a severe intensity of discomfort, beyond the threshold of clinical attention.

Dissociative Experiences Scale (DES) (Bernstein and Putnam, 1986; Frischholz et al., 1990) is a brief, 28-item, self-report inventory of the frequency of dissociative experiences. It represents a reliable and valid measure for determining the contribution of dissociation to various psychiatric disorders and a screening instrument for dissociative disorders. High levels of dissociation are indicated by scores of 30 or more. The DES has an excellent internal consistency, with Cronbach's alpha ranging from 0.96 to 0.97 (Dubester and Braun, 1995).

The *Adverse Childhood Experience Questionnaire (ACE)* (Felitti et al., 1998) is a 10-item self-report measure developed

for the ACE study to identify childhood experiences of abuse and neglect. The internal consistency of the ACE questionnaire is adequate ($\alpha = 0.88$; Murphy et al., 2014). This questionnaire was administered only at baseline.

Treatments

Treatment as Usual

All patients received TAU, which consisted of standard treatment for recovery from SUD in the National Health Service in Italy. TAU included clinical interviews with the addiction specialist and administration of medications appropriate for each patient (e.g., alcohol craving, heroin substitute treatment). Comorbid psychiatric conditions such as depression or anxiety disorders were treated in accordance with the patient's needs, including appropriate medication.

Lastly, TAU included psychological treatment (both individual and group sessions) and participation in psycho-educational group sessions.

Eye Movement Desensitization and Reprocessing

Participants received 24 weekly EMDR sessions over a period of 6 months. The EMDR treatment used in this study incorporated both elements of the classic TF-EMDR protocol (Shapiro, 2001) and of the existing AF-EMDR protocols (Hase, 2010; Knipe, 2010; Miller, 2010; Popky, 2010), in accordance with the Palette of EMDR Interventions in Addiction (PEIA; Markus and Hornsveld, 2017).

The EMDR treatment steps were as follows:

1) Building a positive therapeutic relationship;
2) Information gathering (trauma history, addiction history);
3) Strengthening the motivation for treatment through positive and achievable therapeutic goals and enhancing personal resources;
4) Desensitization of traumatic events in chronological order;
5) Desensitization of the "first time" memory and the dependence of precipitating factors;
6) Desensitization of the level of urge;
7) Desensitization of the recall of the relapse;
8) Desensitizing triggers of triggering behavior;
9) Installing a positive state for each triggering factor.

EMDR treatment was provided by four clinical psychotherapists specialized in EMDR therapy (who at least had completed the Level II EMDR program). The EMDR therapists were supervised monthly by an EMDR consultant.

Statistical Analyses

Data were processed and analyzed using the Statistical Package for Social Sciences (SPSS version 22.0; Chicago, IL, USA).

Both parametric and nonparametric tests were used, in accordance with Shapiro–Wilk as a test for normality. Baseline group differences were assessed using Student's *t*-test or Mann–Whitney *U*-test to compare the two groups for continuous measures and Fisher's Exact Test for categorical measures.

GLM repeated measures multivariate ANOVA (RM-MANOVA) was used to analyze the main pre- and post-intervention effects and interactions both between and within TAU + EMDR and TAU groups. Pairwise comparison between groups were made by simple contrast and are reported as means difference with the Sidak correction 95% confidence interval (95%CI) for multiple comparisons.

A $p < 0.05$ was considered statistically significant throughout all of the analyses.

RESULTS

A total of 40 patients were enrolled in the study: 20 were assigned to the TAU + EMDR intervention and the other 20 patients were assigned to the TAU treatment. We did not register any dropout from the treatments.

Table 1 presents the sociodemographic characteristics of these patients at baseline. There were no significant differences in demographics between the two groups at baseline (T0), except for adverse childhood experiences, which were more frequent in the TAU + EMDR group (**Table 1**).

There were several differences between the two groups at baseline. Overall, patients in the TAU + EMDR group showed higher post-traumatic stress and anxiety symptoms and more psychiatric symptoms.

We evaluated whether the different psychotherapy treatments (TAU + EMDR or TAU) administered to the patients had a different impact on the psychological variables of interests. A repeated-measures MANOVA was performed on the pre- and post-intervention clinical scores (IES-R, DES, SCL-90-GSI,

TABLE 1 | Demographic data of participants at baseline.

	EMDR ($N = 20$) Mean (*SD*)/ Median (IQR)	TAU ($N = 20$) Mean (*SD*)/ Median (IQR)	*p*
Age (years)	32 (8)	32 (19)	0.820[a]
Years of substance use	19.40 (7.98)	21.10 (9.59)	0.546[b]
Adverse Childhood Experiences	4 (5)	2 (2)	0.004[a]
	***n* (%)**	***n* (%)**	
Gender			0.487[c]
Female	2 (10)	0 (0)	
Male	18 (90)	20 (100)	
Marital status			0.410[c]
Single	17 (85)	14 (70)	
Married	1 (5)	4 (20)	
Separated/divorced	2 (10)	2 (10)	
Level of education			0.198[c]
Primary school	0 (0)	3 (15)	
Low secondary school	9 (45)	10 (50)	
High secondary school	11 (55)	7 (35)	

EMDR, Eye Movement Desensitization and Reprocessing group; TAU, Therapy As Usual group.

[a] *Mann–Whitney U-test.*

[b] *Pearson's independent samples t-test.*

[c] *Fisher's exact test.*

STAI-1, STAI-2, BDI-II), comparing group and time effects and interactions between group and time.

The RM-MANOVA yielded a significant pre–post main effect [$F_{(6, 33)} = 10.102$, $p < 0.001$; $\eta^2_p = 0.647$], and a significant interaction between the pre–post measures and the treatment condition [$F_{(6, 33)} = 7.830$, $p < 0.001$; $\eta^2_p = 0.587$].

Significant time effects were found across both groups for all variables except for STAI-1 and STAI-2, indicating that the mean participant scores improved from time 0 (pre-intervention) to time 1 (post-intervention) on all variables except for anxiety symptoms (**Table 2**).

Group-by-time interaction effects were found for IES-R, DES, SCL-90-GSI, STAI-1, and STAI-2 total scores, indicating that clinical improvements regarding these variables were different in the two treatment groups. No group-by-time interaction was found for BDI-II, showing that change on this measure was similar for both treatment groups (**Table 2**).

Planned *post-hoc* analyses of simple effects of pre–post were conducted for all variables with a significant group-by-time effect (DES, IES-R, SCL-90-GSI, STAI-1, STAI-2,) by GLM pairwise comparisons using the Sidak adjustment for multiple comparisons.

The two groups significantly differ for IES-R scores at baseline, with participants in the TAU + EMDR group showing higher post-traumatic symptoms than those in the TAU group (**Table 2**). The analysis of simple effects over time indicated both groups had an improvement in post-traumatic symptoms (**Table 3**), but the TAU + EMDR group scored significantly lower compared to the TAU group at post-treatment (**Table 2**).

As regards the DES score, there was no significant difference between groups at baseline (**Table 2**). Results indicated that the group-by-time effect is explained by the significant difference between dissociative pre- and post-treatment scores for participants who underwent EMDR intervention (**Table 3**).

Moreover, there was also a difference between groups at baseline for the SCL-90-GSI score, with more severe psychiatric symptoms in the TAU + EMDR group (**Table 2**). The comparison between pre- and post-treatment indicated a significant improvement in the TAU + EMDR group between T0 and T1, while there was no difference in the TAU group (**Table 3**).

In the case of STAI-1, results indicated that there was a significant difference between the two groups at baseline, as the STAI-1 scores at baseline in TAU + EMDR group were significantly higher than those in TAU group (**Table 2**). Concurrently, there was a significant difference between STAI-1 pre- and post-treatment scores in the TAU group but not in the TAU + EMDR group. This indicates that the group-by-time effect was due to the significant difference between groups at baseline and to the significant worsening of state anxiety symptoms in patients in the TAU group (**Table 3**).

With regard to STAI-2, a significant difference between the two groups at baseline was found, as STAI-2 scores at baseline in TAU + EMDR group were significantly higher than those in TAU group (**Table 2**). Moreover, there was a significant reduction of STAI-2 scores in the TAU + EMDR group that was not present in the TAU group. This indicates that the improvements over time on trait anxiety were registered only in the TAU+ EMDR treatment group (**Table 3**).

No differences were found before and after treatment in the urine drug testing immunoassays, which showed a similar increase of negative results after the interventions (TAU group from 65% at baseline to 85% at T1; TAU + EMDR group from 70% at baseline to 80% at T1; $\chi^2 = 0.067$, $p = 0.795$).

DISCUSSION

Overall, all SUD patients included in the study improved their clinical condition with a significant reduction of post-traumatic, dissociative and psychiatric symptoms, regardless of the type of treatment.

Both TAU and TAU + EMDR interventions had a significant effect in reducing post-traumatic symptoms, but the add-on EMDR proved to have a significant greater effect, allowing a shift from baseline levels above the clinical cut-off to post-treatment normal levels. This finding is in line with those of previous studies (Perez-Dandieu and Tapia, 2014; Brown et al., 2015), which showed that adding EMDR to TAU has a significant effect on post-traumatic symptoms.

In the same way, according to the results of the present study, the add-on EMDR has an important effect in reducing

TABLE 2 | Comparison of clinical variables for the two groups (TAU and TAU + EMDR).

	Pre-treatment		*p*	Post-treatment		*p*	Effect Time			Effect Time × Group		
	TAU (*N* = 20)	TAU + EMDR (*N* = 20)		TAU (*N* = 20)	TAU + EMDR (*N* = 20)		*F*	*P*	η^2_p	*F*	*P*	η^2_p
BDI-II	11.60 (7.45)	18.35 (14.08)	0.066	10.10 (7.58)	11.65 (12.54)	0.639	8.646	0.006	0.185	3.477	0.070	0.084
STAI-1	41.95 (4.17)	46.35 (5.26)	0.006	46.25 (5.28)	43.50 (5.31)	0.109	0.459	0.502	0.012	11.160	0.002	0.227
STAI-2	42.05 (2.69)	45.65 (5.49)	0.012	43.20 (3.14)	42.60 (7.61)	0.746	1.476	0.232	0.037	7.212	0.011	0.160
DES	10.93 (8.07)	15.69 (14.05)	0.196	8.53 (6.67)	6.72 (7.13)	0.411	15.766	<0.001	0.293	5.279	0.027	0.122
IES-R	23.90 (15.35)	39.65 (23.12)	0.015	12.30 (11.76)	6.05 (5.88)	0.040	48.282	<0.001	0.560	11.438	0.002	0.231
SCL-90-GSI	62.65 (10.39)	73.90 (2.94)	<0.001	61.95 (11.55)	63.25 (12.37)	0.733	14.378	0.001	0.275	11.050	0.002	0.225

Data are mean (SD).

TAU, Therapy As Usual group;

TAU + EMDR, Eye Movement Desensitization and Reprocessing in addition to TAU group.

TABLE 3 | Comparison between T0 and T1 of clinical variables for the two groups (TAU and TAU + EMDR).

	TAU				TAU + EMDR			
	T0	T1	Mean difference (95%CI)	*p*	T0	T1	Mean difference (95%CI)	*p*
BDI-II	11.60 (7.45)	10.10 (7.58)	−1.500 (−5.492; 2.492)	0.452	18.35 (14.08)	11.65 (12.54)	−6.700 (−10.692; −2.708)	0.002
STAI-1	41.95 (4.17)	46.25 (5.28)	4.300 (1.236; 7.384)	0.007	46.35 (5.26)	43.50 (5.31)	−2.850 (−5.914; 0.214)	0.067
STAI-2	42.05 (2.69)	43.20 (3.14)	1.150 (−1.089; 3.389)	0.305	45.65 (5.49)	42.60 (7.61)	−3.050 (−5.289; −0.811)	0.009
DES	10.93 (8.07)	8.53 (6.67)	−2.395 (−6.493; 1.703)	0.244	15.69 (14.05)	6.72 (7.13)	−8.973 (−13.071; −4.874)	<0.001
IES-R-Total	23.90 (15.35)	12.30 (11.76)	−11.600 (−20.912; −2.288)	0.016	39.65 (23.12)	6.05 (5.88)	−33.600 (−42.912; −24.288)	<0.001
SCL-90 Total	62.65 (10.39)	61.95 (11.55)	−0.700 (−4.985; 3.585)	0.743	73.90 (2.94)	63.25 (12.37)	−10.650 (−14.935; −6.365)	<0.001

Data are mean (SD).
TAU, Therapy As Usual group;
TAU + EMDR, Eye Movement Desensitization and Reprocessing in addition to TAU group.

dissociative symptoms, probably due to the well-recognized effect of EMDR on the reintegration of previous dysfunctionally stored memories (Nardo et al., 2013; van der Hart et al., 2013).

As regards the effect of EMDR on stress-related psychiatric symptoms, a significant improvement in the global severity of psychiatric symptoms was observed in patients who received add-on EMDR as compared to TAU alone, suggesting that EMDR also has a beneficial impact on a wide range of symptoms of clinical relevance, beyond post-traumatic symptoms.

In terms of anxiety, our results show a significant effect of add-on EMDR in improving trait anxiety that is not shown in TAU alone. In spite of its tendency to be stable over time, a number of studies revealed that trait anxiety can improve as a result of a psychological intervention over time (Vøllestad et al., 2011; Lee et al., 2015). Our results suggest that EMDR intervention might also affect the trait-like tendency to experience anxiety over time and across situations. Another interesting finding of our study is that state anxiety worsened in the TAU alone group, whereas in the TAU + EMDR group it remained stable. An increase of anxiety levels, mediated by adrenocorticotropic hormone, corticosterone, and amygdala corticotrophin releasing factor (CRF), is commonly observed during acute withdrawal stages of substance treatment and recovery programs (Koob and Volkow, 2016). It would seem that the TAU alone does not impact on this increase in anxiety levels, whereas the add-on of an EMDR intervention seems to be able to counterbalance this physiological elevation of anxiety related to abstinence.

With regard to depressive symptoms, no significant change was observed in either group, although our findings suggest a trend toward improvement in the group that received add-on EMDR, partially confirming previous findings (Hase et al., 2008; Perez-Dandieu and Tapia, 2014).

This study presents a methodological limitation that may moderate the interpretation of the results outlined so far. The non-randomized design led to the significant differences between the two groups at baseline. In fact, participants who received EMDR treatment showed higher baseline levels of symptoms compared to the group receiving only TAU treatment. These differences at baseline could limit a conclusive interpretation of the results of the study, as the improvements obtained by the group that received EMDR in addition to TAU could also be due to a spontaneous reduction of symptoms linked to the fact that higher reductions are observed when there are higher starting levels.

At the same time, the findings of the present study suggest that EMDR may be more useful in subjects who experienced more adverse childhood experiences and higher levels of symptoms, in order to strengthen standard treatment that otherwise would only be partially effective, especially on withdrawal-related anxiety. Consistent with previous literature reporting that adverse childhood events have significant implications for substance abuse treatment and that a trauma-informed approach to SUD leads to better treatment outcomes (Felitti et al., 1998; LeTendre and Reed, 2017), our findings suggest that exposure to adverse childhood experiences should be routinely assessed in treatment settings, in order to provide specific interventions to reduce traumatic burden associated with SUD. Future randomized controlled studies with larger samples should better investigate these aspects.

Another limit of the present study is that aspects related to craving and abstinence were not specifically investigated. The results of our study are in line with previous studies, which show that EMDR has beneficial effects on symptoms related to the traumatic history and only limited effects on additional outcomes (Markus and Hornsveld, 2017). The present study aimed to focus on post-traumatic and associated aspects linked to the relationship between addiction and traumatic burden, but future studies on similar populations should also take into account addict-related aspects.

This study also has some strengths. The results of the study confirm that EMDR could be a viable and well-accepted add-on treatment for patients with SUD, with some evidence of both efficacy and good compliance. Moreover, to the best of our knowledge this is the first study evaluating the clinical impact of an add-on EMDR intervention focused on both traumatic and addiction-related memories, and it found the first promising evidence of the efficacy of this combined TF- and AF-EMDR protocol. Further studies could evaluate the usefulness of combining TF- and AF-EMDR protocols in different clinical samples.

Although our results can only be considered preliminary, this study suggests that add-on EMDR is more effective

than TAU alone in improving post-traumatic and dissociative symptoms, accompanied also by a reduction in anxiety and overall psychopathology levels.

The findings of this study underline the importance of assessing ACEs and other traumatic experiences in this population because they may contribute to the onset and maintenance of SUDs and lead to a worsening of psychopathological severity. As a clinical consequence, it could be useful to offer these patients specific add-on treatments addressing both ACEs and traumatic experiences related to addiction, in adjunction to standard treatments.

Future studies, such as that designed by Markus et al. (2015) on alcohol-dependent patients, would be better to investigate not only the effectiveness of an EMDR add-on treatment but also the mediators, moderators, and predictors of treatment outcome, in order to be able to delineate effective interventions for these disorders, which represent a major public health problem.

AUTHOR CONTRIBUTIONS

MB is the national coordinator of the research. MB, IF, and MP were responsible for the conception and the design of the study. MB, TA, AC, PM, CR, and IF were responsible for data collection and for clinical treatments. SC and FO were responsible for the data analysis. IF, MB, LO, and MP contributed to the interpretation of data. SC and FO wrote the article, which was critically revised by all the others authors. All authors have approved the final version of the manuscript.

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Comparison of Eye Movement Desensitization Reprocessing and Cognitive Behavioral Therapy as Adjunctive Treatments for Recurrent Depression: The European Depression EMDR Network (EDEN) Randomized Controlled Trial

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Background: Treatment of recurrent depressive disorders is currently only moderately successful. Increasing evidence suggests a significant relationship between adverse childhood experiences and recurrent depressive disorders, suggesting that trauma-based interventions could be useful for these patients.

Objectives: To investigate the efficacy of Eye Movement Desensitization and Reprocessing therapy (EMDR) in addition to antidepressant medication (ADM) in treating recurrent depression.

Design: A non-inferiority, single-blind, randomized clinical controlled trial comparing EMDR or CBT as adjunctive treatments to ADM. Randomization was carried out by a central computer system. Allocation was carried out by a study coordinator in each center.

Setting: Two psychiatric services, one in Italy and one in Spain.

Participants: Eighty-two patients were randomized with a 1:1 ratio to the EMDR group (n = 40) or CBT group (n = 42). Sixty-six patients, 31 in the EMDR group and 35 in the CBT group, were included in the completers analysis.

Intervention: 15 ± 3 individual sessions of EMDR or CBT, both in addition to ADM. Participants were followed up at 6-months.

Main outcome measure: Rate of depressive symptoms remission in both groups, as measured by a BDI-II score <13.

Results: Sixty-six patients were analyzed as completers (31 EMDR vs. 35 CBT). No significant difference between the two groups was found either at the end of the interventions (71% EMDR vs. 48.7% CBT) or at the 6-month follow-up (54.8% EMDR vs. 42.9% CBT). A RM-ANOVA on BDI-II scores showed similar reductions over time in both groups [$F(6,59) = 22.501$, $p < 0.001$] and a significant interaction effect between time and group [$F(6,59) = 3.357$, $p = 0.006$], with lower BDI-II scores in the EMDR group at T1 [mean difference = –7.309 (95% CI [–12.811, –1.806]), $p = 0.010$]. The RM-ANOVA on secondary outcome measures showed similar improvement over time in both groups [$F(14,51) = 8.202$, $p < 0.001$], with no significant differences between groups [$F(614,51) = 0.642$, $p = 0.817$].

Conclusion: Although these results can be considered preliminary only, this study suggests that EMDR could be a viable and effective treatment for reducing depressive symptoms and improving the quality of life of patients with recurrent depression. Trial registration: ISRCTN09958202.

Keywords: EMDR, CBT, depression, traumatic stress, anxiety, quality of life, antidepressants, randomized controlled trial

INTRODUCTION

Depression is one of the most common mental disorders, affecting more than 300 million people (WHO, 2017). The consequences of this disorder in terms of health loss are huge. WHO has ranked depression as "the single largest contributor to global disability, accounting for 7.5% of all years lived with disability in 2015" (WHO, 2017).

Although over the last 20 years the options for depression therapy have increased significantly, the optimism that initially accompanied the use of new antidepressant medications (ADMs), such as selective reuptake inhibitors of serotonin (SSRIs), disappeared rapidly (Pampallona et al., 2002). In fact, several meta-analyses have concluded that ADMs have only a modest advantage over placebos (Kirsch et al., 2008; Khan and Brown, 2015), though with greater benefits in the case of severe depression (Fournier et al., 2010).

Depression treatment also involves the use of psychotherapeutic interventions, which have proved effective not only in mild and moderate depression but also in severe chronic depression (Nemeroff et al., 2003).

Guidelines indicate that for people with moderate or severe depression the most effective treatment is a combination of ADMs and a high-intensity psychological intervention (National Collaborating Centre for Mental Health [UK], 2010). Cognitive Behavioral Therapy (CBT) is one of the best known, empirically supported treatments for depression (National Collaborating Centre for Mental Health [UK], 2010). CBT is based on the premise that maladaptive cognitions contribute to the onset and maintenance of depression. According to Beck's model, a change in these maladaptive cognitions can lead to changes in emotional regulation and dysfunctional behaviors (Beck, 1979).

In recent years, much evidence has accumulated highlighting the role of stress and its neurobiological correlates in both the occurrence and development of major psychiatric disorders, including depression (Nemeroff, 2016). The exposure to adverse childhood experiences (ACEs), which includes physical and sexual abuse as well as emotional neglect (Felitti et al., 1998; Norman et al., 2012; Infurna et al., 2016), is associated with a marked increase in the risk of developing depression in adulthood (Kendler et al., 1995; Anda et al., 2006; American Psychiatric Association, 2013; Lindert et al., 2014; Khan et al., 2015; Infurna et al., 2016; Kendler and Gardner, 2016; Nemeroff, 2016; Hughes et al., 2017).

Compared with individuals who have not experienced adverse events in childhood, those with a history of such experiences are at greater risk of having a depressive episode in their lifetime (Kessler, 1997). A graded relationship between the number of ACEs and the probability of lifetime and recent depressive disorders has also been highlighted (Chapman et al., 2004; Anda et al., 2006).

Moreover, several studies have shown that ACEs are associated with a poorer clinical course of depression, including earlier age of onset, greater severity of symptoms, co-morbidity, and episode persistence and recurrence (Heim and Nemeroff, 2001; Wiersma et al., 2009; Scott et al., 2012; Tunnard et al., 2014; Paterniti et al., 2017).

Several studies have investigated the effect of ACEs on the course of major depressive disorder (MDD), pointing out

a strong association between a history of adverse events in childhood and the course of depression in adulthood (Widom et al., 2007; Infurna et al., 2016; Li et al., 2016). Also, a recent meta-analysis (Nanni et al., 2012) has suggested that childhood maltreatment is associated with an elevated risk of the recurrence and persistence of depressive symptoms. In addition, Chen J. et al. (2014) recently showed a significant association between childhood sexual abuse and recurrent major depression, with earlier age of onset and longer depressive episodes for depressed women who experienced sexual abuse in their childhood.

The clear recognition that patients with major depression who have experienced ACEs exhibit an unfavorable course of depression and a poor response to standard treatments, thereby incurring a greater risk of recurrent and persistent depressive episodes, suggests that it is essential to develop novel therapeutic approaches specifically tailored to treating traumatic experiences (Nanni et al., 2012; van Nierop et al., 2015; Nemeroff, 2016; Williams et al., 2016).

Eye Movement Desensitization and Reprocessing (EMDR) therapy was originally developed by Francine Shapiro in the late 1980s to treat traumatic memories (Shapiro, 1989). It is now widely recognized as an empirically supported treatment for post-traumatic stress disorder (PTSD) (National Collaborating Centre for Mental Health [UK], 2005; Bisson and Andrew, 2007; Chen Y.-R. et al., 2014).

EMDR therapy is guided by the Adaptive Information Processing (AIP) model (Shapiro, 2001). One of the key aspects of the AIP model is that stressful events that have not been fully processed and integrated into already existing memory networks are stored in a dysfunctional way. These stressful events do not necessarily fulfill Criterion A for PTSD and are the basis of several mental disorders, including PTSD, affective disorders, chronic pain, and addiction (Shapiro, 2014; Hase et al., 2017). A recent study (Hase et al., 2017) proposed a link between dysfunctionally stored memory and the theory of pathogenic memory, previously described by Centonze et al. (2005).

The reactivation of a pathogenic memory induced by various internal and external stimuli, also exerting vegetative arousal, could lead to subsequent maladaptive responses, which in the long-term could contribute to the onset of various psychiatric disorders (Hase et al., 2017). From this perspective, it could be hypothesized that pathogenic memories contribute to the onset and maintenance of recurrent depression episodes. By promoting the reprocessing of pathogenic memories, EMDR may represent a promising approach and thus could broaden the range of effective interventions for this disorder.

In recent years, the application of EMDR beyond PTSD has expanded rapidly. It is currently being used as a treatment for a wide range of disorders that follow distressing life experiences (Shapiro and Maxfield, 2002). Several books, conference presentations, and case reports suggest its applicability in treating depression too (Wood and Ricketts, 2013; Luber, 2016).

Two studies reviewing the literature on the application of EMDR to depression as primary diagnosis concluded that EMDR showed preliminary promise as a therapy for treating this disorder, although further research was required (Wood and Ricketts, 2013; Valiente-Gómez et al., 2017).

More recently, other studies have reported evidence of EMDR efficacy in patients with depression (Hofmann et al., 2014; Behnammoghadam et al., 2015; Hase et al., 2015; Mauna Gauhar, 2016), while a specific EMDR therapy protocol for the treatment of depressive disorders has been published (Hofmann et al., 2016). Moreover, a recently published study has shown the feasibility of using EMDR treatment in patients with recurrent and/or long-term depression (Wood et al., 2017).

In 2010, a group of European researchers founded the European Depression EMDR Network (EDEN) with the purpose of evaluating the efficacy of EMDR in this disorder in different contexts and with different methodologies. The underlying hypothesis is that EMDR therapy could directly address memories of adverse and traumatic experiences that are significant contributors to the onset and maintenance of depressive episodes.

The present study represents one of the Network's research projects, its aim being to assess whether patients with recurrent depressive disorders benefit from a trauma-adapted psychotherapeutic intervention (EMDR) compared with a more classical intervention (CBT), in addition to standard clinical management and medication.

The primary aim of the study was to evaluate the efficacy of EMDR compared with CBT in terms of response rates and time frame of depressive symptoms remissions. A secondary aim was to compare the efficacy of both treatments on associated symptoms and quality of life.

MATERIALS AND METHODS

Design

This study was a non-inferiority, randomized controlled clinical trial investigating the efficacy of EMDR treatment compared with CBT intervention in patients with recurrent depressive disorder already undergoing "treatment as usual" (TAU).

The study is registered in the ISRNCTN registry as ISRCTN09958202.

Setting

The study was a multicenter trial, and therefore patients were consecutively recruited between 2014 and 2016 from two settings: in Italy, participants were recruited from the psychiatric services affiliated with the University Hospital San Luigi Gonzaga of Orbassano, Turin; in Spain, patients were enrolled at the Assistens Clinic, A Coruña.

This study was approved by the Research Ethics Committee of the University Hospital San Luigi Gonzaga and by the Ethical Committee of Clinical Research of Galicia. Informed written consent was obtained from all participants.

Participants

The participants in the study consisted of 82 patients with recurrent depressive episodes, who had been referred to one of the two above-mentioned specialized clinical services and

were already receiving TAU (ADMs and psychiatric visits, with stabilized ADMs for at least four weeks).

Participants were pre-screened using the Beck Depression Inventory-II (BDI-II; Beck and Steer, 1993) during a routine clinical visit. Those with a score on BDI-II greater than 13 (considered the clinical cut-off for screening of depression symptoms) were assessed using the Mini-International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998) clinical interview, in order to confirm the diagnosis.

Inclusion criteria were as follows: (1) a diagnosis of recurrent depressive disorder (F33.x or F33.x + F34.1 "double depression")— this could be chronic depression (of at least two years' duration); (2) aged between 18 and 65 years; (3) a score of at least 13 on Beck's Depression Inventory-II (BDI-II); (4) having received ADM treatment for at least four weeks; (5) legal capacity to consent to the treatment.

Exclusion criteria were as follows: (1) a history of psychotic symptoms or schizophrenia; (2) bipolar disorder or dementia; (3) cluster A and B severe personality disorders; (4) dissociative disorders (DES score >25%); (5) any substance-related abuse or dependence disorder (except those involving nicotine) in the 6 months prior to the study; (6) a serious, unstable medical condition; (7) being pregnant; (8) undergoing parallel legal processes or applications for pension or social security.

Recruitment and Measures

The recruitment of participants was carried out by psychiatrists, who proposed their participation in the research protocol to patients during a routine clinical visit.

The research protocol and aims of the study were explained to patients who met the inclusion/exclusion criteria. They were also told that if they took part in the study they would be randomly assigned to one of two treatment conditions, both employing the same timing and assessment tools, for the period of the study. If they agreed they signed the informed consent, were randomized, and then asked to proceed with the psychological assessment.

The following psychological self-report questionnaires were administered:

Beck Depression Inventory-II (BDI) (Beck and Steer, 1993)

This is a 21-item self-report instrument that assesses the presence and severity of depressive symptoms, based on DSM-IV criteria. The total score ranges from 0 to 63, with higher scores indicating higher levels of depression. A score greater than 13 is considered the cut-off for the presence of depressive symptoms (14−19: mild depression; 20−28: moderate depression; ≥29: severe depression).

Beck Anxiety Inventory (BAI) (Beck and Steer, 2013)

This is a 21-item self-report measure that assesses cognitive, somatic, and affective anxiety symptom severity. The total score ranges from 0 to 63, with higher scores indicating higher levels of anxiety. A score above 9 suggests the presence of clinical anxiety (10−16: mild anxiety; 17−29: moderate anxiety; ≥30: severe anxiety).

Impact of Event Scale-Revised (IES-R) (Weiss and Marmar, 1997)

The IES-R is a 22-item self-report questionnaire consisting of three subscales (eight items relate to intrusions, eight items evaluate avoidance, and six items assess hyperarousal). The overall scale assesses subjective distress caused by traumatic events.

WHO-Quality of Life Bref (WHOQOL-Bref) (Murphy et al., 2000)

The WHOQOL-Bref consists of 26 items that measure the following broad domains: physical health (WHO-Phys); psychological health (WHO-Psychol); social relationships (WHO-Social); and environment (WHO-Env).

Global Assessment of Functioning Scale (GAF) (American Psychiatric Association, 2000)

This scale is included in the V Axis of DSM-IV and is used by mental health providers to rate patients' social, occupational, and psychological functioning. Scores range from 100 (extremely high functioning) to 1 (severely impaired).

The following tools were administered at the beginning of the study only:

The Dissociative Experiences Scale (DES) (Bernstein and Putnam, 1986; Frischholz et al., 1990)

It is a brief, 28-item self-report inventory of the frequency of dissociative experiences. It is a reliable and valid measure for determining the contribution of dissociation to various psychiatric disorders and a screening instrument for dissociative disorders. In this study, a score above 25 was considered an exclusion criterion.

The Trauma Antecedent Questionnaire (TAQ) (Luxenberg et al., 2001)

It is a self-administered instrument that gathers information about ACEs and other life experiences, assessed at four different age periods: early childhood (birth to 6 years), latency (7 to 12 years), adolescence (13 to 18 years), and adulthood. For each item of the TAQ, respondents are asked to rate the extent to which they have had a particular experience during each developmental period on a scale from 0 to 3. Presence of ACE is calculated when at least one adverse experience of an intensity of at least 2 is reported.

Randomization and Assessment Points

Patients were randomly allocated to one of the two conditions: TAU+EMDR or TAU+CBT. Patients were randomized at a 1:1 ratio, using a block-wise randomization sequence (block size of four). The sequence was determined by an independent statistical consultant, blind to the initial assessments in order to ensure that allocation remained unknown, using a centralized randomization algorithm.

In each center, treatment allocation was communicated to the patients by the study coordinator to ensure that evaluators remained blind to their allocation.

The psychological assessment was performed by psychologists independent of the research protocol, using the same tools and at the same time periods for both groups: at baseline (T0), at the end of the treatment (T1), and 6 months after the end of the treatment (T2).

In order to assess the trend of depressive symptoms, four clinical management visits were also scheduled for each patient during the treatment phase. The first assessment (Assess-1) was scheduled after the first two treatment sessions, and each successive assessment (Assess-2, Assess-3, and Assess-4) was conducted every four treatment sessions. During these intra-treatment assessments, psychiatrists independent of the research protocol administered the Beck Depression Inventory-II only.

Interventions

The clinical psychologists conducting the clinical assessments were both independent and blind to the interventions.

All patients in the study continued to receive Treatment as Usual, which comprised ADMs and the clinical management provided by each center.

The number of adjunctive EMDR or CBT individual sessions was allowed to vary between 12 and 18 (15 ± 3). This relatively flexible range of sessions was chosen with a twofold aim: (1) to avoid any large disparity in treatment between patients and centers, as no therapist would be allowed to schedule a number of sessions <12, or >18; (2) to allow therapists to schedule the appropriate number of sessions for each patient, albeit within the defined range, according to patients' needs.

The sessions were scheduled on a weekly basis where possible. The duration of the intervention depended mainly on the number of sessions completed by each patient. Overall, it varied from between three and 6 months (e.g., when a period of vacation interrupted the treatment phase or logistical difficulties made it difficult for a patient to maintain a weekly schedule).

Eye Movement Desensitization and Reprocessing

The EMDR treatment followed the DeprEnd protocol; that is, the manual for EMDR in the treatment of depressive patients (see Hofmann et al., 2016 for a detailed explanation).

Eye Movement Desensitization and Reprocessing therapy intervention started with a stabilization phase consisting of two stages: in the first two sessions, the Safe Place procedure (Shapiro, 2001) and the Absorption technique (Hofmann, 2009) were used. The second phase, lasting for the following three sessions, was based on Self-care procedures (Gonzalez-Vázquez and Mosquera-Barral, 2012).

The remaining sessions focused on trauma reprocessing. EMDR targets were selected taking into account four factors that play a major role in the emergence, maintenance, and recurrence of depressive episodes. Depending on the individual life history of the patient, one or all of the following forms of pathogenic memory networks became a focus of EMDR treatment:

(1) Episode triggers of the current depressive episode (and earlier episodes): when depressive episodes appear to be triggered for the most part by either traumatic (PTSD Criterion A) or non-traumatic (not fulfilling Criterion A) events;
(2) Belief systems: when a patient undergoes a series of repeated experiences (mostly non-Criterion A events, like humiliation) that become crystallized in the form of belief systems, increasing vulnerability and the maintenance of depressive episodes;
(3) Depressive states: when patients experience earlier, longer, more intense, or repeated depressive episodes that can be remembered in a state-specific way;
(4) Depressive and suicidal states: when the memory of depression and/or suicidality itself (or suicide attempts) has created a memory structure of its own.

The EMDR targets were prioritized according to the clinical state of the patient.

In each center, EMDR was provided by three psychotherapists specializing in Level II EMDR and with a minimum of three years of experience in treating patients with depression. They received extensive training and supervision in the manualized protocol established for the study, from a certified senior EMDR instructor.

Cognitive Behavioral Treatment

The CBT treatment followed the manual of cognitive therapy for depression (Beck, 1979). The therapy works systematically with dysfunctional beliefs and teaches self-monitoring of negative emotions and their influence on behaviors. In addition, it includes decision-making training and targeted work on how to increase the frequency and quality of pleasant experiences. Homework assignments help patients to improve social skills in their everyday life.

In each center, CBT treatment was performed by three psychotherapists with certified training in CBT techniques and a minimum of three years' experience in treating patients with depression. They received regular CBT supervision to ensure that the quality of their CBT treatment was maintained.

Sample Size

Given the trial's non-inferiority design [Null hypothesis H_0: $\pi_2 - \pi_1 \leq -0{,}2$ (non-inferiority)], sample size estimation was based on the formula of Farrington and Manning, the maximum likelihood method (Farrington and Manning, 1990), and implemented by ADDPLAN 4.0.3 software [Adaptive Design and Analyses, ADDPLAN 4.0.3. ADDPLAN GmbH, 2002 Cologne].

In the analysis, a single stage (fixed sample size) design and an allocation ratio $(n_2/n_1) = 1$ were considered.

For specified $\alpha = 0.05$, rates $\pi_1 = 0.3$, and $\pi_2 = 0.4$ (odds ratio of 1.556), 62 patients (31 per group) were needed to reach a power $(1-\beta)$ equal to 80.0%. In order to take 25% of dropouts and loss to follow up into account, we planned to include a total number of 82 patients.

Statistical Analyses

Data were processed and analyzed using the Statistical Package for Social Sciences (SPSS version 22.0; Chicago, IL, United States).

Both parametric and non-parametric tests were used, in accordance with Shapiro–Wilk, as a test for normality. Baseline group differences were assessed using Student's *t*-test or Mann–Whitney *U* test to compare the two groups on continuous measures, and Fisher's Exact Test for categorical measures.

The primary outcome of the study was the rate of depressive symptoms remission in both groups, as measured by a BDI-II score <13. Based on the BDI-II score, patients were classified as either asymptomatic or symptomatic (BDI-II score <13/≥13, respectively) and with or without symptoms remission (BDI-II score <9/≥9, respectively), while the difference between the EMDR and CBT groups at T1 and T2 was analyzed using Fisher's Exact Test.

Another primary aim was to compare the time frame of depressive symptoms reduction in the two groups. A GLM repeated measures ANOVA (RM-ANOVA) was used to analyze the effects of time and the interaction between time and groups (EMDR vs. CBT) for BDI-II levels across the multiple assessment points.

A secondary outcome of the study was to compare the efficacy of both treatments on associated symptoms and quality of life. A GLM repeated measures multivariate ANOVA (RM-MANOVA) was used to analyze the main pre- and post-intervention effects and interactions both between and within EMDR and CBT groups for the other clinical variables (BAI, IES-Total, WHO, GAF).

The results are shown as F (υ1, υ2), with υ1 and υ2 as numerator and denominator degrees of freedom, respectively.

Pairwise comparison between both groups and times was achieved by simple contrast and reported as means difference with Sidak correction 95% Confidence Interval (95%CI) for multiple comparisons.

Finally, an exploratory intention-to-treat analysis (ITT) was performed on the primary outcome only (i.e., BDI-II scores), with missing data accounted for using Multiple Imputation models (Howell, 2008).

A $p < 0.05$ was considered statistically significant for all the analyses.

RESULTS

Figure 1 shows a flow diagram with the number of participants at each assessment stage. A total of 159 patients were screened using the BDI-II; 56 patients were excluded on the basis of the inclusion/exclusion criteria (35.2%); and 21 refused to participate (refusal rate: 20.4%); reasons given for refusal were mainly the distance of patients' place of residence from the place of treatment and the inability to attend the psychiatric and psychotherapeutic sessions). Eighty-two patients were randomized: 40 were assigned to the EMDR intervention and 42 to the CBT intervention. Four patients did not begin the treatment (three in the EMDR group and one in the CBT group), and five patients (three in the EMDR group and two in the CBT group) attended fewer than half of the treatment sessions. These patients refused to continue with the assessment at post-treatment and follow-up assessments and therefore it was not possible to include them in the statistical analysis. Moreover, seven patients were lost to the follow-up evaluation.

Therefore, a total of 66 patients (31 in the EMDR group and 35 in the CBT group) were included in the per-protocol statistical analysis.

Table 1 presents the socio-demographic and clinical characteristics of these patients at baseline. There were no significant differences in demographics or clinical characteristics between the two groups at baseline (T0). In particular, both groups reported a high proportion of ACEs in the 0−18 years age period (96.7% in the EMDR group and 94.3% in the CBT group; $p = 1.000$). At the same time, no patient reported any co-morbidity with PTSD, as assessed by the MINI-Plus clinical interview at baseline.

The number of individual treatment sessions was similar for both groups (EMDR: $M = 15.1$, $SD = 1.11$; CBT: $M = 14.6$, $SD = 1.77$; $p = 0.209$).

First, for our primary outcome measure we examined the proportion of patients who no longer had a BDI-II score above the cut-off (i.e., BDI-II score > 13) at the end of the treatment (T1) and at follow-up assessment (T2). At T1 we found that 22 out of 31 patients (71.0%) in the EMDR group and 17 out of 35 patients (48.7%) in the CBT group did not have a score above the clinical cut-off for depression. At T2 we found that 17 out of 31 (54.8%) in the EMDR group and 15 out of 35 patients (42.9%) in the CBT group did not have a BDI-II score above the clinical cut-off. No significant difference between the two groups was found at either T1 or T2.

We also examined the proportion of patients who recorded a BDI-II score below 9, which is considered the clinical threshold for complete symptoms remission. At T1, 18 out of 31 patients (58.1%) in the EMDR group and 11 out of 35 patients (31.4%) in the CBT group had a BDI-II score <9, with a statistically significant difference in favor of the EMDR group ($\chi^2 = 4.735$, $p = 0.046$). At T2 we found that 13 out of 31 patients (41.9%) in the EMDR group and 13 out of 35 patients (37.1%) in the CBT group had a BDI-II score below 9, with no significant difference between the two groups.

We then investigated whether the different psychotherapy treatments (EMDR or CBT) had a different impact on BDI-II trend over time. A repeated-measures ANOVA was performed comparing group and time effects as well as interactions between group and time for BDI-II scores across the seven assessment points (i.e., baseline, four assessments during treatments, post-treatment, and 6-month follow-up). Descriptive scores are shown in **Figure 2**. The RM-ANOVA yielded a significant time main effect [$F(6,59) = 22.501$, $p < 0.001$], showing significantly reduced BDI-II scores over time for both groups. The RM-ANOVA also revealed a significant interaction effect between time and group [$F(6,59) = 3.357$, $p = 0.006$]. Planned *post hoc* analyses of simple effects with Sidak correction showed a significant difference between the two groups at post-treatment (T1), with lower BDI-II scores in the EMDR group ($M = 10.55$, $SE = 2.006$) compared

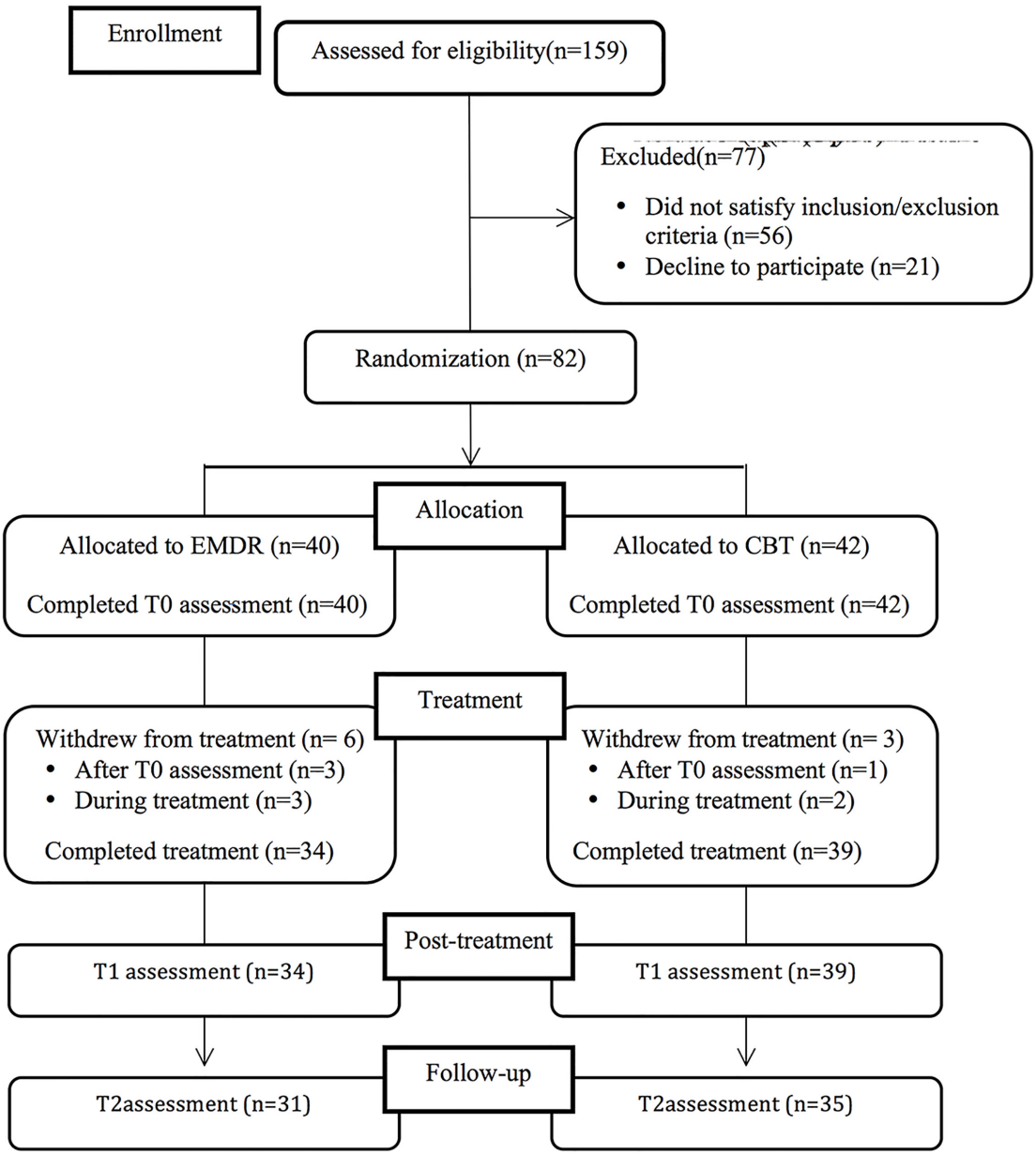

FIGURE 1 | Participants flow diagram.

with those in the CBT group (M = 17.86, SE = 1.888), with mean difference = –7.309 (95% CI [–12.811, –1.806]), p = 0.010 (**Figure 2**). *Post hoc* analysis of simple effects also showed a similar trend of reduction in both groups until Assessement-2, with both showing a significant difference between baseline and Assessment-2 (EMDR: mean difference = 6.161 (95%CI [1.186, 11.136]), p = 0.005; CBT: mean difference = 7.543 (95%CI [2.861, 12.225]), $p < 0.001$). Thereafter, the trends of the two groups differed: the CBT group showed no statistically significant difference between Assessment-2 and post-treatment (T1), mean difference = 1.806 (95%CI [–4.159, 6.331]), p = 1.000, while in the EMDR group there were a significant reduction in BDI-II scores between Assessment-2 and post-treatment (T1), mean difference = 11.194 (95%CI [5.620, 16.767]), $p < 0.001$ (**Figure 2**).

An ITT analysis based on Multiple Imputation models of BDI-II trend over time was also performed on the whole randomized sample, confirming the finding obtained in the completers analysis of a significant difference between EMDR and CBT at T1 (p = 0.011).

Moreover, for our secondary outcome we examined whether the different psychotherapy treatments (EMDR or CBT) administered to the patients had a different impact on psychological variables relating to depression. A

TABLE 1 | Demographic and clinical data of participants at baseline.

	EMDR (*N* = 31) Mean (SD)/Median (IQR)	CBT (*N* = 35) Mean (SD)/Median (IQR)	*p*
Age (years)	48.23 (9.66)	47.54 (12.90)	0.810[a]
Education (years)	13.00 (6.3)	12.00 (7)	0.446[b]
Age onset depression diagnosis	24.50 (21.3)	28.00 (24.5)	0.382[b]
DES	11.00 (12)	9.00 (13.5)	0.113[b]
	n(%)	*n*(%)	
Gender			0.290[c]
Female	25 (80.65)	31 (88.57)	
Male	6 (19.35)	4 (11.43)	
Employment status			0.505[c]
Unemployed	5 (16.13)	4 (11.43)	
Employed	22 (70.97)	24 (68.57)	
Pensioned	4 (12.90)	6 (17.14)	
Student	0 (0)	1 (2.86)	
Marital status			0.893[c]
Single	9 (29.03)	8 (22.86)	
Married/Cohabitee	20 (64.52)	25 (71.42)	
Separated/divorced	1 (3.225)	1 (2.86)	
Widowed	1 (3.225)	1 (2.86)	
Depression diagnosis			0.706[c]
Chronic depressive disorder	3 (9.675)	6 (17.15)	
Double depression	3 (9.675)	4 (11.43)	
Recurrent depressive disorder	25 (80.65)	25 (71.42)	
TAQ			
0-6	21 (67.74)	25 (71.43)	0.793[c]
7-12	28 (90.32)	30 (85.71)	0.713[c]
13-18	30 (96.77)	33 (94.28)	1.000[c]
Adult	31 (100)	35 (100)	–

EMDR, Eye Movement Desensitization and Reprocessing group; CBT, Cognitive Behavioral Therapy group; DES, Dissociative Experience Scale; TAQ, Trauma Antecedent Questionnaire. [a]Pearson's independent samples t-test. [b]Mann-Whitney U test. [c]Fisher's exact test.

repeated-measures MANOVA was performed on baseline, post-treatment, and follow-up secondary outcome scores (i.e., BAI, IES-R, WHO-Phys, WHO-Psychol, WHO-Social, WHO-Env, GAF), comparing group and time effects as well as interactions between group and time. This analysis yielded a significant time main effect [$F(14,51) = 8.202$, $p < 0.001$], while no significant interaction was found between time and group [$F(614,51) = 0.642$, $p = 0.817$]. The mean participant scores of all secondary outcome variables improved from baseline (T0) to post-treatment (T1) and follow-up evaluation (T2), without significant differences between the groups (**Table 2**).

Planned *post hoc* analysis using Sidak correction showed that in the EMDR group all the clinical scores showed improvement both between T0 and T1 and between T0 and T2, while in the CBT group similar improvement was observed for all variables except WHO-Social and WHO-Env, which showed significant improvement between T0 and T2 but not between T0 and T1 (**Table 2**).

DISCUSSION

Depression is the condition considered to bear the greatest responsibility for health decrements worldwide, due to its prevalence and its chronic and recurrent nature (WHO, 2017). Therefore, understanding its etiology and identifying effective and lasting treatments is a global health priority.

Antidepressant medication are the current standard of treatment in clinical practice, but they appear to be symptom-suppressive rather than curative (Hollon et al., 2002) and do not appear to maintain their effectiveness in terms of reducing future risk of depressive episodes once their course is completed (DeRubeis et al., 2008).

Therefore, identifying additional interventions that are effective in treating depression and reducing the risk of its recurrence to lasting effect, is of the utmost importance.

To the best of our knowledge, this is the first randomized controlled trial to evaluate the efficacy of EMDR in comparison with CBT in patients affected by recurrent depression and treated with ADM.

The most significant result highlighted by this study is that the majority of patients were able to significantly reduce their depression symptoms level after only 15 therapy sessions, and to sustain this clinical benefit 6 months after the end of the psychotherapeutic intervention.

Eye Movement Desensitization and Reprocessing therapy treatment was shown to be as effective as CBT in reducing the proportion of patients with a level of depressive symptoms above the clinical threshold, both at the end of the treatment and 6 months later, with response rates similar to those reported in previous studies (DeRubeis et al., 2005; Hollon et al., 2005).

At the same time, EMDR exceeded CBT in terms of the proportion of patients who could be considered to be in remission after the end of the interventions. In addition, the results for depressive symptoms trend showed that both interventions were effective in reducing clinical levels of depression, with a significant difference in favor of EMDR treatment at the end of the intervention phase. This difference was no longer present at the 6-month follow-up, although in the EMDR group there was a tendency to remain below the clinical threshold that was not apparent in the CBT group.

Interestingly, EMDR and CBT showed a similar trend of clinical improvement in depressive symptoms in the initial phase of the intervention (i.e., until Assessment-2), but then exhibited different trajectories between Assessment-2 and post-treatment (T1). In this second phase, EMDR continued to significantly reduce depression levels until the end of the intervention, while CBT only maintained the gains made in the first phase. It is possible to interpret this result by looking in-depth at the contents of the treatment sessions. In the first four to five sessions, EMDR treatment focused on assessment and stabilization, thus exerting a similar effect to that of CBT. After EMDR's specific

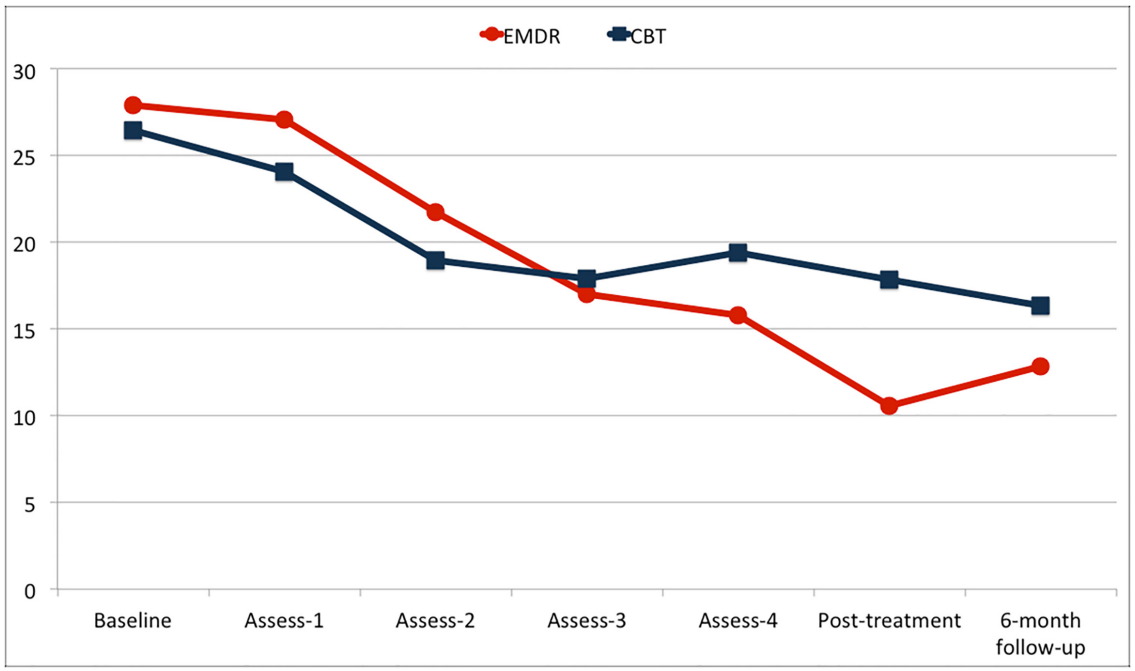

FIGURE 2 | Trend of BDI-II scores for the two groups [Eye Movement Desensitization and Reprocessing group (EMDR) and Cognitive Behavioral Therapy group (CBT)].

TABLE 2 | Comparison of clinical variables between T0, T1, and T2 for the two groups (EMDR and CBT).

	Pre-treatment (T0)		Post-treatment (T1)		6 month follow-up (T2)		Time effect*
	***EMDR* (*N* = 31)**	***CBT* (*N* = 35)**	***EMDR* (*N* = 31)**	***CBT* (*N* = 35)**	***EMDR* (*N* = 31)**	***CBT* (*N* = 35)**	
BAI	23.23 (10.77)	27.94 (13.69)	13.55 (10.47)	19.03 (12.80)	12.61 (9.82)	17.80 (13.55)	$F(2,128) = 33.549$, $p < 0.001$; $\eta_p^2 = 0.344$
IES-R	39.29 (20.74)	37.49 (23.39)	23.00 (21.81)	26.97 (22.77)	20.23 (17.92)	24.49 (21.88)	$F(2,128) = 27.421$, $p < 0.001$; $\eta_p^2 = 0.300$
WHO-Phys	11.34 (2.31)	11.92 (2.32)	13.05 (2.28)	13.08 (2.53)	13.27 (2.10)	13.31 (2.79)	$F(2,128) = 13.457$, $p < 0.001$; $\eta_p^2 = 0.174$
WHO-Psychol	9.53 (1.83)	9.24 (1.46)	12.02 (2.25)	10.69 (2.54)	11.99 (2.47)	11.05 (2.50)	$F(2,128) = 28.945$, $p < 0.001$; $\eta_p^2 = 0.311$
WHO-Social	10.92 (2.52)	11.16 (2.46)	12.60 (2.38)	11.70 (2.19)	12.73 (2.62)	12.53 (3.09)	$F(2,128) = 9.395$, $p < 0.001$; $\eta_p^2 = 0.128$
WHO-Env	12.37 (2.11)	12.26 (2.20)	13.42 (1.74)	12.74 (2.12)	13.29 (1.77)	13.09 (2.29)	$F(2,128) = 8.405$, $p < 0.001$; $\eta_p^2 = 0.116$
GAF	68.10 (11.90)	63.66 (16.93)	77.90 (10.97)	74.60 (17.84)	77.87 (13.09)	74.94 (10.72)	$F(2,128) = 23.557$, $p < 0.001$; $\eta_p^2 = 0.269$

*Data are mean (SD). EMDR, Eye Movement Desensitization and Reprocessing group; CBT, Cognitive Behavioral Therapy group; BAI, Beck Anxiety Inventory; IES-R, Impact of Event Scale-Revised; WHO-Phys, WHO-Quality of Life Bref-Physical health; WHO-Psychol, WHO-Quality of Life Bref-Psychological health; WHO-Social, WHO-Quality of Life Bref-Social relationships; WHO-Env, WHO-Quality of Life Bref-Environment; GAF, Global Assessment of Functioning scale. *Significant time effect, independent of the type of treatment (EMDR or CBT).*

work on trauma reprocessing started (around Assessment-3), EMDR showed an increase in effectiveness while CBT effects remained virtually unchanged.

The upturn in depression levels recorded at follow-up in the EMDR group may have been due to the low volume of EMDR provided. It might be hypothesized that a greater number of EMDR sessions would have facilitated more reprocessing of the pathogenic memories underlying depressive symptoms and thus the upturn could have been prevented.

As regards the secondary outcome of the study, both treatments were effective in reducing anxiety and post-traumatic symptoms even after just a limited number of sessions, with the benefits still apparent 6 months after the end of the psychological treatment. EMDR and CBT have both been proven to be efficacious in treating anxiety and post-traumatic symptoms, and therefore these results are in agreement with previous literature (Kar, 2011; Hofmann et al., 2012; Chen Y.-R. et al., 2014).

Furthermore, both treatments were able to significantly improve Quality of Life (QoL) and global functioning, the benefits here too persisting beyond the end of the intervention. The benefits associated with social and environmental QoL appeared to became apparent faster for the EMDR group, which also showed considerable improvement in these variables at the end of therapy, while the CBT group appeared to gain these benefits at a later stage. This difference could be due to the different focus of the two psychotherapeutic interventions;

while CBT focuses mainly on maladaptive beliefs underlying depression, in EMDR therapy the reprocessing of dysfunctionally stored memories can lead to changes in different symptoms or in the impairment of functioning connected to the reprocessed memory, as proposed in the AIP-Model of EMDR therapy.

Moreover, the majority of patients in our study reported previous adverse childhood experiences and stressful life events (e.g., sexual and physical abuse, traumatic mourning, abandonment, and serious neglect). This finding is in line with the hypothesis that stressful life events play a significant role in both the onset and the risk of recurrence of depressive episodes (Chapman et al., 2004; Nanni et al., 2012; Pietrek et al., 2013; Nemeroff, 2016).

This study has a number of strengths. It is the first study to compare the efficacy of EMDR with that of CBT for patients with depressive disorder treated with ADMs using a randomized controlled design and evaluating the effects on associated symptoms and QoL.

Limitations

The number of patients treated with EMDR and CBT included in the study is not large. As this is the first study attempting to investigate the non-inferiority of EMDR compared with CBT, it is possible that actual differences between the two groups were not revealed due to the design and sample size of the study; future superiority clinical trials are needed to broaden this investigation. Moreover, in this study a self-report measure (BDI-II) was used as the primary outcome measure. Future studies should also include a clinician report measure administered by an independent rater in order to overcome this limitation.

Another limitation is that the 6-month follow-up evaluation was not long enough to examine the recurrence rate of subsequent depressive episodes. Therefore, longer follow-ups (e.g., at 1 year or longer) are needed in order to identify possible differences between the two interventions in reducing the risk of recurrence of depressive episodes. Lastly, another limitation of this study was the inclusion of ITT analysis for the primary outcome only.

Although our results can only be considered preliminary, this study suggests that EMDR could be as effective as CBT in reducing depressive symptoms in patients suffering from recurrent depressive disorder and treated with ADMs. Both EMDR and CBT as adjunctive interventions to ADMs are effective in reducing anxiety and post-traumatic symptoms and increasing QoL, even over a limited number of treatment sessions.

AUTHOR CONTRIBUTIONS

AH, LO, MC, IF, MH, and AG-V were responsible for the conception and design of the study. MC, PB-G, AJ-A, ML, FO, SR-E, and VT were responsible for data collection. SC, GM, and FO were responsible for the data analysis. MP, RT, and GDL contributed to the interpretation of data. LO and SC wrote the article, which was critically revised by all the others authors. All authors approved the final version of the manuscript.

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Eye Movement Desensitization and Reprocessing Versus Treatment as Usual in the Treatment of Depression: A Randomized-Controlled Trial

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Eye movement desensitization and reprocessing (EMDR) is a well-established treatment for post-traumatic stress disorder. Recent research suggested that it may be effective in treating depressive disorders as well. The present study is part of a multicenter randomized-controlled trial, the EDEN study, in which a homogenous group of 30 patients was treated to test whether EMDR plus treatment as usual (TAU) would achieve superior results compared to TAU only in a psychosomatic-psychotherapeutic inpatient treatment setting. Both groups were assessed by the Beck Depression Inventory-II (BDI-II) and the Global Severity Index and depression subscale of the Symptom Checklist 90-Revised. The EMDR + TAU group improved significantly better than the TAU group on the BDI-II and Global Severity Index, while a marginally significant difference favoring the EMDR + TAU group over the TAU group was found on the depression subscale. In the EMDR + TAU group, seven out of 14 patients improved below nine points on the BDI-II, which is considered to be a full remission, while four out of 16 in the TAU group did so. These findings confirm earlier suggestions that EMDR therapy may provide additional benefit in the treatment of depression. The present study strengthens the previous literature on EMDR therapy in the treatment of depression due to the randomized-controlled design of the EDEN study.

Keywords: depression, eye movement desensitization and reprocessing, randomized-controlled trial, Beck Depression Inventory, symptom checklist 90-revised

INTRODUCTION

According to the often-considered study of the World Health Organization (World Health Organization [WHO], 2012), depressive disorders belong to the most prevalent and disabling diseases of all: At least 350 million people are affected by depressive disorders worldwide, almost one million of which commit suicide every year (Murray and Lopez, 1996; Greden, 2001).

Due to their frequency and severity, depressive disorders thereby belong to the biggest worldwide challenges of the psychiatric profession.

Treatment options for depressive spectrum disorders are partially favorable, but also partially problematic. Although pharmacological as well as psychotherapeutic treatment approaches are available, incomplete remission and high long-term relapse rates remain for many patients. Research has shown that psychotherapeutic interventions can be helpful – not only in mild and moderate depression, but also in cases of severe and chronic depression (Nemeroff et al., 2003). In a meta-analysis by Vittengl et al. (2007), however, 29% of those who responded to acute-phase cognitive-behavioral therapies relapsed after 1 year, and 54% relapsed after 2 years. Furthermore, the available pharmacological treatments for depressive disorders are associated with several issues. Although these treatments improved in the last 20 years, the optimism associated especially with recent antidepressants like the SSRI class (e.g., Fluoxetine) has faded due to meta-analyses on antidepressant pharmacotherapy showing only a slight advantage over placebo. The greatest treatment success was shown in a study with predominantly severe depression (Fournier et al., 2010), wherein antidepressant treatment was often associated with side effects (e.g., weight gain and other problems lasting over time; Hirschfeld, 2003; Kripalani et al., 2007; Reid and Barbui, 2010). Though a systematic review based on 31 randomized studies has shown that relapse rates may be reduced by 50% with antidepressant medication (of all classes; Geddes et al., 2003), the very high likelihood of depressive relapses often leads to lifelong medication. Incidentally, depressive symptoms remaining after treatment and the degree of treatment resistance relating to the previous depressive episode are considered risk factors for a relapse (Reid and Barbui, 2010). Additionally, it is noteworthy that between 10 and 20% of depressive episodes become chronic or are considered treatment resistant to standard depression treatments. Furthermore, the danger of relapsing increases not only when specific personality traits, dysfunctional beliefs, and/or cognitive schemas are present, but also in response to experience of trauma or critical life events. In summary, the current treatment effects and especially the high relapse rates in acute depressive episodes are unsatisfactory. However, adjunctive psychotherapeutic treatment has been found to reduce the risk of relapse by 22% when compared with pharmacological antidepressant treatment alone (Vittengl et al., 2007).

In order to further improve treatment effects and lower relapse rates, it may be necessary to put greater emphasis on the importance of traumatic experiences and adverse life events for the development and progression of depression. For instance, it is a well-known clinical observation that depression may be triggered and maintained by stressful life events. Recent research indicates that chronic and acute stressors like traumatic experiences and other adverse life experiences like loss, hurt, and humiliation can trigger depressive disorders (Heim and Nemeroff, 2001; McFarlane, 2010). Especially so-called primary episodes are often closely linked with a specific psychosocial stressor, while later depressive episodes may be triggered by far smaller events or even come about without any noticeable stressor (Post, 1992). Risch et al. (2009) could also show the strong influence of stressful life events in a large meta-analysis: According to their analysis, stressful life events are the only risk factor to be significantly correlated with the onset of depression. For instance, a serotonin transporter gene polymorphism as a neurobiological vulnerability factor alone, or in combination with adverse life events, did not significantly correlate with the occurrence of depressive episodes. Similarly, a large case-control study found an association in which the risk for depression doubled when violent victimization was experienced in early life (Wise et al., 2001). Furthermore, Mandelli et al. (2015) found that childhood emotional abuse and neglect correlate with the highest risk for experiencing depressive disorders in adulthood, even when compared to other forms of childhood trauma like physical abuse or sexual abuse. Some researchers have also brought up the notion that adverse life events could have similarly severe effects on depression as the far more stressful traumatic experiences described in the type A criterion definition of the DSM (Gold et al., 2005). This is also supported by data from a survey of 832 people (Mol et al., 2005), which showed that stressful life events can generate at least as many post-traumatic stress disorder (PTSD) symptoms as classical traumatic events according to the type A criterion. For stressful life events dating up to 30 years back, the PTSD symptomatology was more pronounced than for traumatic events that corresponded with the type A criterion.

In light of the previously presented research, it makes sense to develop complementary therapy strategies. Eye movement desensitization and reprocessing (EMDR) therapy is a promising candidate for such a complementary strategy that could provide an additional benefit in the treatment of depression. The treatment was first developed by Shapiro (1989, 2001) after a serendipitous observation of the relaxing effect of horizontal saccadic eye movements was initially used to treat PTSD, and has proven its effectiveness in this field (Bisson and Andrew, 2007). It targets memories of critical life events as well as traumatic experiences and enables the psychotherapeutic focus on maladaptive cognitive patterns. Though Shapiro (1989, 2001) at first observed the therapeutic effectiveness of EMDR in PTSD, she increasingly observed effects on other symptoms (e.g., anxiety), which led to EMDR being used to treat other disorders that may also be based on, or exacerbated by, unprocessed and maladaptively stored memories of stressful life events. The main principle of EMDR therapy thus is the reprocessing of maladaptively stored (pathogenic) memories that produce symptoms when activated by sensory cues (Centonze et al., 2005). The effectiveness of EMDR has also been shown by neurobiological research showing a normalization of brain activity in the sense of more adaptive information processing (AIP) after EMDR treatment (Pagani et al., 2013). The reprocessing part of EMDR is initiated and maintained by bilateral stimulation – mainly through eye movements, but alternatively also through bilateral alternating auditory or tactile stimulation.

While its efficacy as a PTSD treatment has been well-researched, the effectiveness of EMDR in the treatment of depression has only recently begun to receive systematic research

attention (Hofmann et al., 2014; Hase et al., 2015). Previously, what stood out in studies of PTSD was that EMDR concomitantly improved comorbid depressive symptoms along with the main PTSD symptomatology. For instance, several case reports showed that depressive patients could be successfully treated with either EMDR therapy alone or with EMDR therapy as an adjunct to other approaches (Manfield, 1998; Tinker and Wilson, 1999; Sun et al., 2004; Broad and Wheeler, 2006; Shapiro and Grand, 2009; Rosas Uribe et al., 2010; Grey, 2011). For instance, two adolescents with major depression were successfully treated with EMDR therapy only (three and seven sessions, respectively) and showed stable improvements in a 3-month follow-up examination (Bae et al., 2008). In both cases, EMDR was successfully applied in the processing of relationship losses or changes. Such events (relationship losses or negative changes) also seem to be a specific risk factor for depressive disorders. In a large retrospective study, losses, separation events, and humiliating events were strongly associated with an increased risk for depressive episodes (Kendler et al., 2003). Going beyond case reports, van der Kolk et al. (2007) conducted a randomized clinical trial comparing the effectiveness of fluoxetine with EMDR treatment and placebo in a PTSD population and found the EMDR group to have significantly lower depression scores than the fluoxetine group. This led them to conclude that once ". . .the trauma is resolved, other domains of psychological functioning appear to improve spontaneously" (van der Kolk et al., 2007, p. 8). This result had previously been found by similar controlled studies, such as a study of Power et al. (2002) in which PTSD patients were either treated with cognitive behavioral therapy (CBT) or with EMDR (there was a wait list control group). Both treatment groups experienced significant improvements in PTSD and comorbid depression symptoms, which also showed at 6-month follow-up.

Out of these research results, the idea emerged that EMDR therapy may be a helpful adjunct treatment in the treatment of depression. To test this, a larger study investigated whether different results may be obtained in depressive patients without an explicit trauma history when adding additional EMDR therapy in comparison with CBT treatment (Hofmann et al., 2014). In this study with a group of 42 depressive patients, one group was treated with CBT (21 patients) and the other one with CBT + EMDR (seven additional EMDR sessions). The CBT + EMDR group showed more complete remissions and a greater reduction in Beck Depression Inventory (BDI) scores than the CBT only group. In another matched-pairs study in a clinical setting (Hase et al., 2015), 11 out of 16 patients (68%) in the EMDR group showed a complete remission of depressive symptomatology at the end of treatment. The EMDR group also showed a greater reduction of depressive symptoms than the CBT only group. However, it should be noted that the generalizability of the findings was limited due to the small sample and lack of a randomized-controlled design.

On the whole though, these previously mentioned studies provided first empirical indications that EMDR therapy may have significant positive effects in the treatment of depressive episodes and recurrent depressive disorders. This provided an incentive to conduct higher-quality clinical studies like the present study, which presents the first randomized-controlled clinical trial looking at adjunctive EMDR therapy in the treatment of depression. In this study, we proposed the following hypotheses:

(1) EMDR therapy produces an additional benefit over treatment as usual in the treatment of patients with acute depressive episodes.
(2) EMDR therapy increases the proportion of complete remissions in the treatment of patients with acute depressive episodes.

MATERIALS AND METHODS

Study Setting and Study Participants

The study was part of a Europe-wide multicenter study (EDEN) examining the effects of EMDR in the treatment of depressive disorders. The aim of the study was to replicate previous results showing that EMDR contributes to the improvement of depressive disorders in a larger patient group. The study also aims to show, via the analysis of follow-ups recorded in the EDEN study, whether the number of depressive relapses can be reduced. The study was carried out in accordance with the recommendations of the ethical guidelines of the Declaration of Helsinki with written informed consent being obtained from all participants. The protocol was approved by the ethics committee of the University of Kiel.

Table 1 presents sample demographic information. The sample consisted of 30 inpatients of a psychiatric and psychosomatic rehabilitation clinic receiving treatment for a moderate to severe depressive episode. The treatment as usual (TAU) group comprised 16 patients and the EMDR + TAU group comprised 14 patients. Included ICD-10 diagnoses were F32.1 (three in TAU, four in EMDR + TAU group), F33.0 (one in TAU, none EMDR + TAU group), F33.1 (ten in TAU, nine in EMDR + TAU group), F33.2 (one in TAU, one in EMDR + TAU group), and F33.4 (one in TAU, none in EMDR + TAU group). All participants were patients (privately insured through the German Armed Forces) in the department of psychosomatic medicine and psychotherapy at the Diana rehabilitation center clinic, Bad Bevensen, Germany. In the context of standard admission procedures with clinical anamnesis and gathering of existing psychopathology according to AMDP, the diagnosis of depression (ICD-10 F32.x and F33.x) was made. Patients that were eligible for the study were extensively informed about the chances and risks of an additional treatment with the EMDR method and gave their written informed consent. In the case of consent, they were added to the EDEN database and concomitantly randomized in one of the two treatment groups (see below). The EMDR treatment was administered according to manualized EMDR procedures (Shapiro, 2001) and the EDEN study protocol (Hofmann et al., 2016).

Inclusion criteria were: The presence of a depressive episode or a recurrent depressive disorder according to clinical diagnostic findings, at least mild depression with a BDI-score of more than 12, and current psychopharmacological antidepressant treatment.

TABLE 1 | Sample demographics by treatment group.

		TAU (%)	EMDR + TAU (%)	Sig.[1]
Children	None	11 (69)	7 (50)	0.30
	One or more	5 (31)	7 (50)	
Education	Post-secondary	5 (31)	4 (29)	0.93
	Post-secondary (vocationally restricted)	1 (6)	1 (7)	
	Secondary	9 (56)	7 (50)	
	Lower secondary	1 (6)	2 (14)	
Marital status	Unmarried	9 (56)	3 (21)	0.13
	Married	6 (38)	8 (57)	
	Divorced/Separated	1 (6)	3 (21)	
Sex	Male	14 (88)	13 (93)	1.00
	Female	2 (13)	1 (7)	
Age		39.23 (10.02)	40.32 (9.25)	0.78

Frequencies with corresponding percentages (rounded to the closest integer) given in parentheses. For Age, mean and standard deviations (in parentheses) are provided instead of frequencies and percentages. [1]*The p-value for the Children by Treatment Group comparison was derived from a chi-squared test. The p-values for Education by Treatment Group and Marital Status by Treatment Group were derived from Fisher's exact test as expected cell totals below five occurred in the respective contingency tables. The p-value for Age by Treatment Group was derived from an independent-samples t-test.*

Exclusion criteria were: Acute suicidality, detected comorbidities like, for example, personality disorders or addiction disorders, psychotic symptomatology, complex PTSD, and a pronounced dissociative symptomatology (detected with scores of >25% in the standardized questionnaire "DES-II," disorders of the eye (e.g., acute retinal detachment or recent eye surgery), or simultaneously running judicial trials or statutory pension insurance scheme applications to prevent external obstacles to a successful treatment. The only dropout criteria were the emergence of acute suicidality or the withdrawal of informed consent.

In the early diagnostics, complex PTSD was selected as an exclusion criterion to minimize risks and side effects in the study. As was shown in multiple studies (Frustaci et al., 2010; Rosas Uribe et al., 2010; Hofmann et al., 2014), EMDR treatment is well tolerated when controlling for contraindications. All study participants were offered the opportunity to receive up to two outpatient follow-up care visits in the rehabilitation center, if needed.

Procedure of Data Collection

The beginning of the data collection started with the admission to the inpatient psychosomatic treatment in the department of psychosomatic medicine and psychotherapy of the Diana clinic. For randomization, the EDEN database was used. The EDEN database was developed for the EDEN study, which has been running since 2012 as a multicenter study in six centers in four European countries (Italy, Germany, Spain, and Turkey). In this study, the EDEN database randomized participants into the control group (TAU) and the treatment group (TAU + EMDR). The project also focuses on the research question of whether the number of relapses may be reduced by EMDR treatment through a planned follow-up taking place 1 and 2 years after treatment. The measurements with the instruments described below were partly taken on a weekly basis (BDI), and partly only at beginning and end of treatment (SCL-90-R, see below). An assessor who was blind to participants' assigned conditions administered all of these measurements, which were computer-based.

Beck Depression Inventory II

The Beck Depression Inventory II (BDI-II; Hautzinger et al., 2006) is a self-report instrument to assess of the severity of depressive symptomatology and its change in response to treatment (the study comparison considers admission and end-of-treatment scores). The sum score of this test can range from 0 to 63 points. If the patient checks multiple answer options in one item, the highest selected number of points will count toward the sum score. A score of less than nine points falls into the normal range. Scores between nine and 13 indicate a minimal severity of depressive symptoms. Scores between 14 and 19 indicate a mild depressive disorder. Scores of 20 or higher are considered clinically relevant, with scores between 20 and 28 indicating a moderate depressive disorder, and scores higher than 29 indicating severe depression. The BDI-II maps a wide spectrum of depressive symptomatology (Beck et al., 1961) and features high reliability and validity. Moderate to high correlations show concurrent validity with different depression scales. Albeit no exact value is listed for the diagnosis of a depressive disorder, a comparing statement is possible.

SCL-90-R

The Symptom-Check-List 90 Items Revised-Version (SCL-90-R; Derogatis et al., 1973) is an instrument to record subjective impairment due to physical and mental symptoms within a time frame of 7 days. The test is also suitable for checking the course of a disorder. The Global Severity Index (GSI) gives an indication of the overall burden for any given patient with symptoms on all scales. Of the nine factorial scales, the depression subscale was additionally used in the study. Measurements are given in the form of standardized *t*-values here. They fall within the normal population when they are between 40 and 60. The mean score is thus 50 (SD = 10). Values of 60–64 are considered to be slightly elevated, 65–69 considerably elevated, 70–74 strongly elevated, and 75–80 very strongly elevated.

Treatment Methods

The TAU group comprised 16 patients with depressive symptomatology satisfying the in- and exclusion criteria listed above. These patients were treated in the usual clinical setting with a psychodynamic or behavioral group therapy (participation twice or 90 min per week) and a standard individual therapy. They all received antidepressant medication (which is listed as an inclusion criterion above).

The EMDR + TAU group comprised 14 patients that were treated in the same clinical setting as the TAU group, receiving the same TAU treatment including antidepressant pharmacotherapy. In addition, it was planned to process one unprocessed memory

with EMDR per week, which requires one to two sessions per week. It is important to highlight that the EMDR group did not receive as many standard individual therapy sessions as the TAU group due to the administration of EMDR. The EMDR + TAU group received between 4 and 12 EMDR sessions in total ($M = 8.5$, $SD = 2.41$).

The so-called EMDR standard protocol is split into eight treatment phases. In the application of the EMDR therapy, the work is usually conducted in the three domains of past, present, and future. In the domain of the past, dysfunctionally stored pathogenic memories are being reprocessed. In the domain of the present, experience-related nightmares, triggers, and also abnormal behaviors are targets of the EMDR treatment. In the domain of the future, the therapy targets the change of avoidance behavior and the development of respective behavioral alternatives, and anxiety concerned with a possible future depressive relapse. In all areas, dysfunctionally stored and unprocessed information is the target of the EMDR treatment. The eight treatment phases according to the EMDR standard protocol are ideally structured as:

Phase 1: History and Treatment Planning – In phase 1, the precise anamnesis and clinical history are recorded. In doing this, it is especially important to give an indication for or against the EMDR method, which also means it is about the exclusion of contraindications. This is also done with the help of specific test diagnostics.

Phase 2: Preparation – In phase 2, a precise treatment plan is made and the patient receives extensive information about the method. If necessary, the learning of relaxation or imaginative techniques, as well as pharmacological treatment may take place at this point to ensure sufficient stabilization.

Phase 3: Assessment – In phase 3, the dysfunctional stressful memory in question is activated in its affective, sensory, and cognitive components. In doing this, the entire pathogenic memory is activated through the controlled and fractional activation of partial networks (according to LeDoux, 2001).

Phase 4: Desensitization – The method then proceeds to the central phase of the processing work, where the patient connects with the memory. At the same time, bilateral stimulation is applied here, mostly by therapist-guided eye movements. From here on, the process typically proceeds idiosyncratically and individually. The quick associative succession of changing affective and sensory impressions and thoughts is characteristic here. This often leads to a notable relief in the patient, although intensively experienced affects or physical symptoms (affective or somatic reactions) may also be registered in the meantime. The gradual relief experienced in this offers a great advantage for the processing in the patient. The pressure generated by the mobilized memory material remains well-manageable therapeutically.

Phase 5: Installation – Once the degree of stress has sufficiently decreased in phase 4 and the positive cognition that was identified in phase 3 has clearly gained strength (as checked by the therapist), a strengthening of the positive cognition is enforced by bilateral stimulation. In doing so, it appears to be sustainably cognitively installed.

Phase 6: Body Scan – The body scan serves to search for potentially persisting sensory memory. In case any of them are encountered, they will be reprocessed by adding bilateral stimulation.

Phase 7: Closure – Since the experience that the patient makes from phase 4 to phase 6 is typically very impressive, it is extensively discussed with the therapist afterwards. The possibility of reprocessing material that surfaced during the session or was not completely processed is also presented to the patient.

Phase 8: Re-evaluation – This phase serves as a platform for patient feedback about changes after previous sessions.

Statistical Analysis

An analysis of covariance (ANCOVA) was run for BDI-II, SCL-90-R GSI, and SCL-90-R depression subscale scores as dependent variables with treatment group as the main independent variable. The analyses controlled for type of diagnosis (single/recurrent depression), patient age, total number of days in treatment, and the score on the respective dependent variable at the beginning of treatment. Interactions between treatment group and the covariates type of depression, patient age, and total number of days in treatment were included in the model. A simple contrast with the TAU group as the reference group was used to examine potential differences between the two groups.

RESULTS

There were no statistically significant differences between the scores on the recorded outcome measures (BDI-II, SCL-90-R depression subscale, and SCL-90-R GSI) and age between the two groups at the beginning of treatment. **Table 2** presents descriptive statistics for said outcome measures and patient age at the beginning and at the end of treatment, grouped by treatment.

Table 3 presents descriptive statistics and correlations between variables of interest. The distribution of single and recurrent depressive episodes was not significantly different between TAU and EMDR + TAU (Fisher's exact test: $p = 0.68$). **Table 4** presents the results of the ANCOVA of BDI-II scores at the end of treatment. The analysis controlled for the type of depression (single versus recurrent episode), patient age, total number of days in treatment, and BDI-II scores at the

TABLE 2 | Mean and standard deviations for both groups.

		Baseline	End of treatment
BDI-II	TAU	23.02 (5.86)	16.59 (11.35)
	EMDR + TAU	22.43 (8.75)	12.21 (11.23)
SCL-90R depression subscale	TAU	72.06 (6.53)	65.07 (9.23)
	EMDR + TAU	69.79 (8.20)	59.71 (13.71)
SCL-90R GSI	TAU	70.63 (6.00)	62.40 (8.97)
	EMDR + TAU	66.71 (6.01)	58.79 (12.91)

Standard deviations are given in parentheses. $N_{TAU} = 16$, $N_{EMDR + TAU} = 14$.

TABLE 3 | Descriptive statistics and correlation matrix.

	M	*SD*	1.	2.	3.	4.	5.	6.	7.	8.
1. BDI-II (Beginning)	22.74	7.22								
2. BDI-II (End)	14.55	11.32	0.58**							
3. SCL-90-R depression subscale (Beginning)	71.00	7.32	0.62***	0.68***						
4. SCL-90-R depression subscale (End)	62.48	11.72	0.55**	0.88***	0.73***					
5. SCL-90-R GSI (Beginning)	68.80	6.22	0.59**	0.64***	0.85***	0.62***				
6. SCL-90-R GSI (End)	60.66	11.00	0.59**	0.86***	0.74***	0.95***	0.71***			
7. Treatment group			−0.04	−0.20	−0.16	−0.23	−0.32	−0.17		
8. Age	39.74	9.52	−0.49**	−0.45*	−0.36*	−0.53**	−0.20	−0.48**	0.06	
9. Total number of days in treatment	53.97	16.34	0.52**	0.14	0.15	0.29	0.03	0.31	0.33	−0.33

*N = 30, M = Mean, SD = Standard deviation. Significance denoted by *p < 0.05; **p < 0.01; ***p < 0.001.*

beginning of treatment. A significant effect of treatment group [$F(1,21) = 6.30$, $p < 0.05$, $\eta_p^2 = 0.23$] was examined by a simple contrast, which showed that the EMDR + TAU group scored significantly lower than the TAU group on adjusted end of treatment BDI-II scores (contrast value = 74.97, $p = 0.02$, $\eta_p^2 = 0.23$). **Figure 1** illustrates this contrast. Furthermore, a significant covariate effect was found for BDI-II scores at the beginning of treatment [$F(1,21) = 8.85$, $p < 0.05$, $\eta_p^2 = 0.30$]. Additionally, a significant interaction between treatment group and patient age was found [$F(1,21) = 6.40$, $p < 0.05$, $\eta_p^2 = 0.23$]. This interaction can be interpreted as the difference between EMDR + TAU and TAU concerning the magnitude of the association between age and end-of-treatment BDI-II scores. Precisely speaking, the association between patient age and end-of-treatment BDI-II scores is more positive in the TAU group than in the EMDR + TAU group. It is presented in **Figure 2**.

Table 5 displays the results of the ANCOVA of SCL-90-R depression subscale scores at the end of treatment. The analysis controlled for the type of depression, patient age, total number of days in treatment, and SCL-90-R depression subscale scores at the beginning of treatment. A marginally significant effect for treatment group [$F(1,20.87) = 3.44$, $p = 0.08$, $\eta_p^2 = 0.14$] was examined by a simple contrast, which showed that the EMDR + TAU group had marginally significantly lower end-of-treatment SCL-90-R depression subscale scores than the TAU group (contrast value = 46.02, $p = 0.08$, $\eta_p^2 = 0.15$). **Figure 3** illustrates this contrast.

Moreover, significant covariate effects for patient age [$F(1,20) = 5.66$, $p < 0.05$, $\eta_p^2 = 0.22$] and beginning-of-treatment SCL-90-R depression subscale scores were found [$F(1,20) = 13.41$, $p < 0.01$, $\eta_p^2 = 0.40$]. Apart from that, a significant interaction between treatment group and patient age was found [$F(1,20) = 6.78$, $p < 0.05$, $\eta_p^2 = 0.25$]. This interaction can be interpreted as the difference in magnitude of the association between patient age and beginning-of-treatment SCL-90-R depression subscale scores. After examining the respective coefficient, it emerged that the association between patient age and SCL-90-R depression subscale scores was more positive in the TAU group than in the EMDR + TAU group. **Figure 4** illustrates this.

Table 6 displays the results of the ANCOVA of SCL-90-R GSI scores at the end of treatment. The analysis controlled for the type of depression, patient age, total number of days in treatment, and SCL-90-R GSI scores at the beginning of treatment. A significant effect for treatment group [$F(1,20.95) = 4.37$, $p < 0.05$, $\eta_p^2 = 0.17$] was examined by a simple contrast, which showed that the EMDR + TAU group scored significantly lower on the SCL-90-R GSI than the TAU group (contrast value = 47.47, $p < 0.05$, $\eta_p^2 = 0.18$). **Figure 5** displays this graphically. Moreover, significant covariate effects for patient age [$F(1,20) = 6.27$, $p < 0.05$, $\eta_p^2 = 0.24$] and beginning-of-treatment GSI scores were found [$F(1,20) = 21.04$, $p < 0.001$, $\eta_p^2 = 0.51$]. Apart from that, a significant interaction effect between treatment group and patient age was found [$F(1,20) = 8.00$, $p < 0.05$, $\eta_p^2 = 0.29$]. This interaction can be interpreted as the difference in magnitude of the association between patient age and beginning-of-treatment SCL-90-R GSI scores. After examining its coefficient, it turned out that the association between patient age and SCL-90-R GSI scores was more positive in the TAU group than in the EMDR + TAU group. **Figure 6** illustrates this.

The results consisted of the changes between the beginning and the end of the treatment regarding psychological tests (BDI-II, SCL-90-R depression subscale, and SCL-90-R GSI). In the EMDR + TAU group, a relatively more clear improvement compared to the TAU group showed. In seven of the 14 patients in the EMDR + TAU group, the BDI-II score dropped below nine points, falling within the normal range and being considered a full remission. In four patients, a clear improvement showed with scores dropping below 20, which is considered a slight depressive symptomatology. One patient showed mild improvement, remaining in the range of moderate depressive symptoms. In two patients, no improvements showed according to the BDI-II.

Of the 16 TAU group patients, four patients improved below nine points on the BDI-II, which can be considered a full remission. In five patients, an improvement showed, letting their scores drop below 14 into in the range of a minimally depressive symptomatology. In two patients, an improvement showed that put them in the mildly depressive symptom range (below 20 points). One patient improved to fall within 20 to 28 points, which classifies as moderately severe depressive symptomatology. Two patients remained without improvement in the severely depressed range with

TABLE 4 | ANCOVA of BDI-II (End).

Source	Mean square	*F*	Significance	η_p^2
Treatment group	456.43	6.30	0.02	0.23
Type of diagnosis	100.91	13.44	0.24	0.95
Age	89.68	1.22	0.28	0.06
Total number of days in treatment	50.75	0.69	0.42	0.03
BDI-II (Beginning)	650.58	8.85	0.01	0.30
Treatment group*age	470.47	6.40	0.02	0.23
Treatment group*total number of days in treatment	291.36	3.96	0.06	0.16
Treatment group*type of diagnosis	8.67	0.12	0.74	0.01

N = 30.

scores higher than 29. In two patients, the BDI-II worsened from the moderately severe to the severe range (over 29 points).

This means that 50% of the 14 patients who received EMDR + TAU showed a complete remission at the end of treatment. In the TAU group with 16 patients, only 25% of scores indicated a complete remission. The EMDR + TAU group thus showed a greater reduction of depressive symptoms than the TAU group, exhibiting significantly lower BDI-II scores at the end of treatment (see **Figure 1**). Furthermore, a significant interaction between treatment group and patient age was found. The effect indicated age was more strongly negatively related with end-of-treatment BDI-II scores in the EMDR + TAU group than in the TAU group. This suggests that older people may have benefited more from EMDR treatment than younger people.

On the SCL-90-R depression subscale, the EMDR + TAU group also showed lower end-of-treatment scores than the TAU group. In the EMDR + TAU group, 12 out of 14 patients showed a mild to marked improvement of those scores. One patient showed a mild worsening, and one patient scored the same as at the beginning of treatment. In the TAU group, 11 patients showed a mild to marked improvement. In three patients, no improvement showed relative to their scores at the beginning of treatment. One patient in this group missed this testing session. Hence, the EMDR + TAU group showed a somewhat greater reduction of depressive symptoms on the SCL-90-R depression subscale than the TAU group, albeit only marginally statistically significant in the ANCOVA analysis. This difference is shown in **Figure 3**.

An interaction effect similar to the one found in the BDI-II score analysis showed on the SCL-90-R depression subscale. It involved patient age and treatment group, indicating that higher age was more strongly associated with lower SCL-90-R depression subscale scores in the EMDR + TAU group than in the TAU group.

In the SCL-90-R GSI score analysis, the EMDR + TAU group (14 patients) showed mild to marked improvements at the end

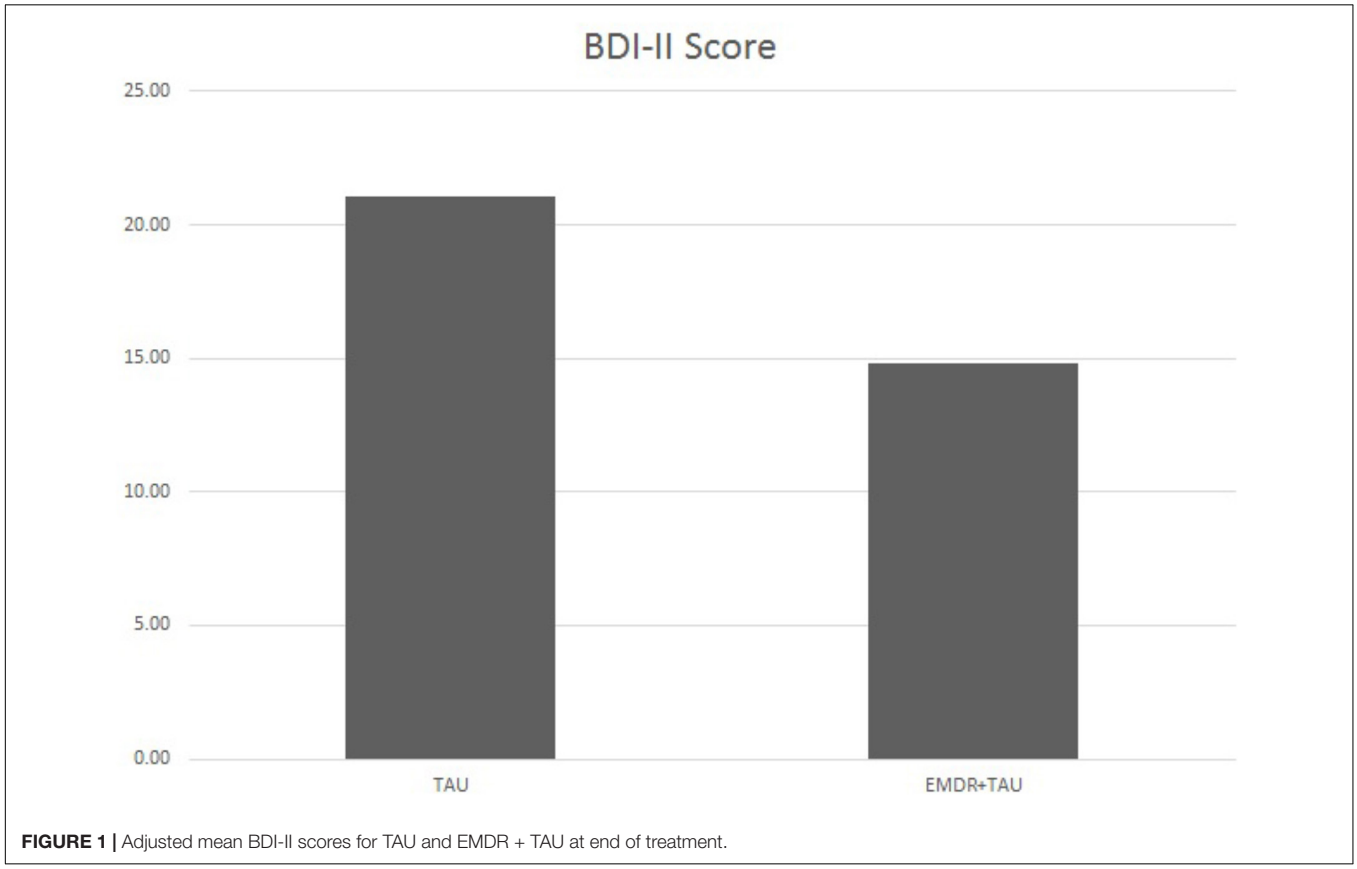

FIGURE 1 | Adjusted mean BDI-II scores for TAU and EMDR + TAU at end of treatment.

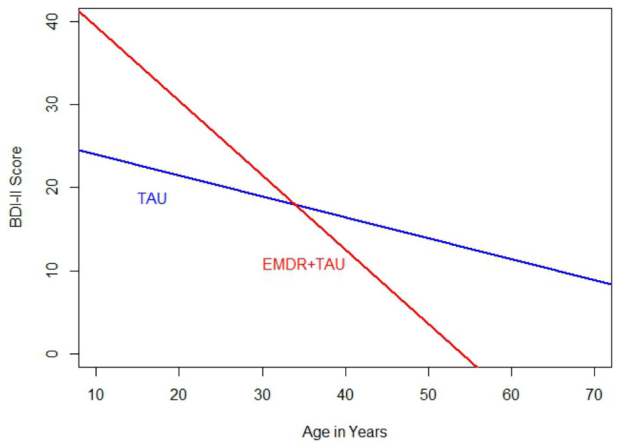

FIGURE 2 | Comparison of regression slopes for age and BDI-II (end of treatment) between the two treatment groups.

TABLE 5 | ANCOVA of SCL-90-R depression subscale (End).

Source	Mean square	*F*	Significance	η_p^2
Treatment group	143.37	3.44	0.08	0.14
Type of diagnosis	112.60	1.57	0.41	0.58
Age	233.34	5.66	0.03	0.22
Total number of days in treatment	98.34	2.38	0.14	0.11
SCL-90-R depression subscale (Beginning)	553.21	13.41	<0.01	0.40
Treatment group*age	279.73	6.78	0.02	0.25
Treatment group*total number of days in treatment	41.62	1.01	0.33	0.05
Treatment group*Type of diagnosis	75.31	1.83	0.19	0.08

N = 29.

of treatment in 13 patients and a worsening of global symptom severity in one patient. In the TAU group with 16 patients, 13 patients showed mild to marked improvements, as measured by lower SCL-90-R GSI scores at the end of treatment. In two patients, stagnation showed with scores remaining unchanged from beginning to end of treatment. One patient missed the final testing, leading to missing data on this outcome.

Both groups thus showed improvements in SCL-90-R GSI scores from the beginning to the end of treatment. Like on the BDI-II, the SCL-90-R GSI scores in the EMDR + TAU group were lower than in the TAU group. Similar to the BDI-II and SCL-90-R depression subscale analyses, an interaction emerged in the analysis of SCL-90-R GSI scores between age and treatment group. This effect indicated that the negative relationship between age and end-of-treatment SCL-90-R GSI scores was stronger in the EMDR + TAU group than in the TAU group.

No side effects were reported during the treatment in the context of the study. This indicates that the EMDR treatment was well tolerated by the patients. Hyperarousal was hardly observed in the sessions. Intense affect was experienced in some sessions, but could be stabilized and reprocessed. The time frame of a maximum of 60 min per session was sufficient to process most of the treated stressful memories.

DISCUSSION

The present study is embedded in the larger context of the EDEN multicenter study, which investigates whether EMDR treatment has a beneficial effect in the treatment of depression. Moreover, the collection of catamnesis data helps to examine whether EMDR may reduce the number of relapses. This research is necessary due to the high worldwide prevalence of depressive disorders and the not yet satisfactory outcomes in the treatment of depression that are characterized by high relapse rates. Furthermore, the present study is relevant because it represents the first study of higher methodological quality regarding this topic, reporting on a randomized-controlled clinical trial. In order to provide more homogenous treatment conditions, the use of antidepressant medication was an inclusion criterion in the study, leading to a more naturalistic sample.

The results of this study show that patients suffering from depression benefit from adjunctive EMDR in the acute depression treatment. In the experimental group (EMDR + TAU), there was a significantly better improvement of BDI-II scores than in the control group (TAU only). Of 14 patients in the experimental group, the BDI-II score of seven patients improved below nine points, which equals a complete remission. This compares to four patients improving below nine points in the control group with 16 patients. The experimental group also showed better results on the SCL-90-R depression subscale. A mild to clear improvement was shown in 12 out of 14 patients. In the slightly larger control group, mild to clear improvements showed in 11 patients. Finally, the SCL-90-R GSI scores also showed a clearly more positive result in the experimental group than in the control group. In the experimental group, 13 patients showed mild to clear improvements. In the control group, mild to clear improvements showed for 12 patients.

The interaction between treatment group and patient age that was observed on all outcome variables (BDI-II, SCL-90-R depression subscale, and SCL-90-R GSI) showed that there was a greater age effect in the experimental group than in the control group, meaning that older patients tended to have relatively lower symptom scores than younger patients in the experimental group than in the control group. Possible explanations for this could be the greater life experience of older patients, the decreasing number of foreign missions for soldiers as they get older, the often higher rank of older soldiers within the armed forces, or the proximity to retirement. Regarding this, it would be interesting to compare this sample with patients from a different health care provider (e.g., a public health insurance provider).

The model of AIP (Shapiro, 2001) offers a potential explanation for the beneficial effects of EMDR therapy observed in the present study. The AIP model postulates that stressful events may be dysfunctionally stored and that these stressful memories may consequently form the basis of mental disorders

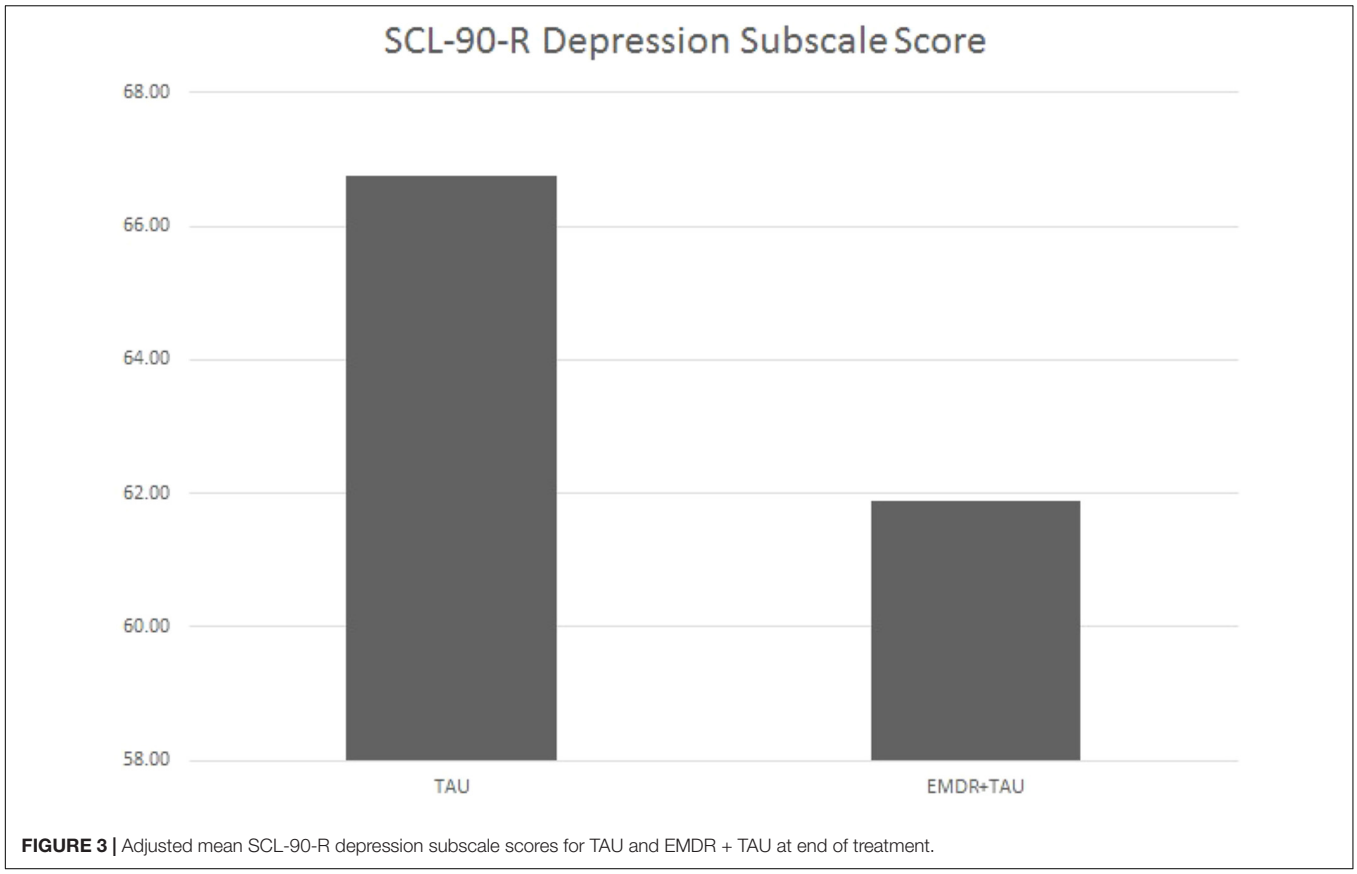

FIGURE 3 | Adjusted mean SCL-90-R depression subscale scores for TAU and EMDR + TAU at end of treatment.

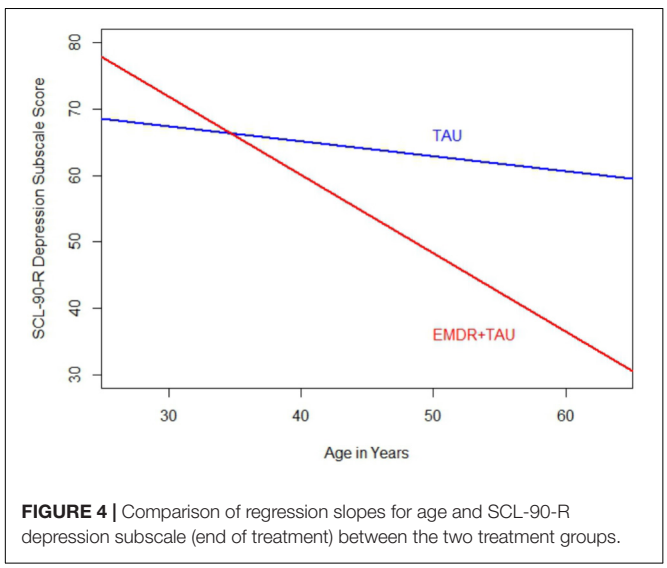

FIGURE 4 | Comparison of regression slopes for age and SCL-90-R depression subscale (end of treatment) between the two treatment groups.

TABLE 6 | ANCOVA of SCL-90-R GSI scores (End).

Source	Mean square	*F*	Significance	η_p^2
Treatment group	161.93	4.37	0.05	0.17
Type of diagnosis	17.63	0.21	0.72	0.16
Age	227.62	6.27	0.02	0.24
Total number of days in treatment	80.21	2.21	0.15	0.10
GSI (Beginning)	764.16	21.04	<0.001	0.51
Treatment group*Age	290.46	8.00	0.01	0.29
Treatment group*total number of days in treatment	28.58	0.79	0.39	0.04
Treatment group*type of diagnosis	89.62	2.47	0.13	0.11

N = 29. Scores were rounded to two decimals. The exact significance value for treatment group was below 0.05 (p = 0.048).

such as depression. This means that even non-A criterion types of stressful memories can be dysfunctionally stored in memory networks. It also postulates that in reprocessing patients' dysfunctionally stored stressful memories, they ultimately get adaptively integrated into memory networks. Many of these stressful memories in depressive disorders were memories of losses, separations, or humiliations, but also experiences of childhood emotional abuse and neglect, which are typical forms of stressful memories that appear to be related with the occurrence of depressive disorders (Mandelli et al., 2015). This fits well with studies that showed that victims of adverse life events do not remember A criterion events as more traumatic than other adverse life events (Gold et al., 2005) or in other terms, that the so-called type A criterion events were not perceived as more stressful than the so-called non-type A criterion events. In summary, the AIP model suggests a profound effect of EMDR therapy due to the processing

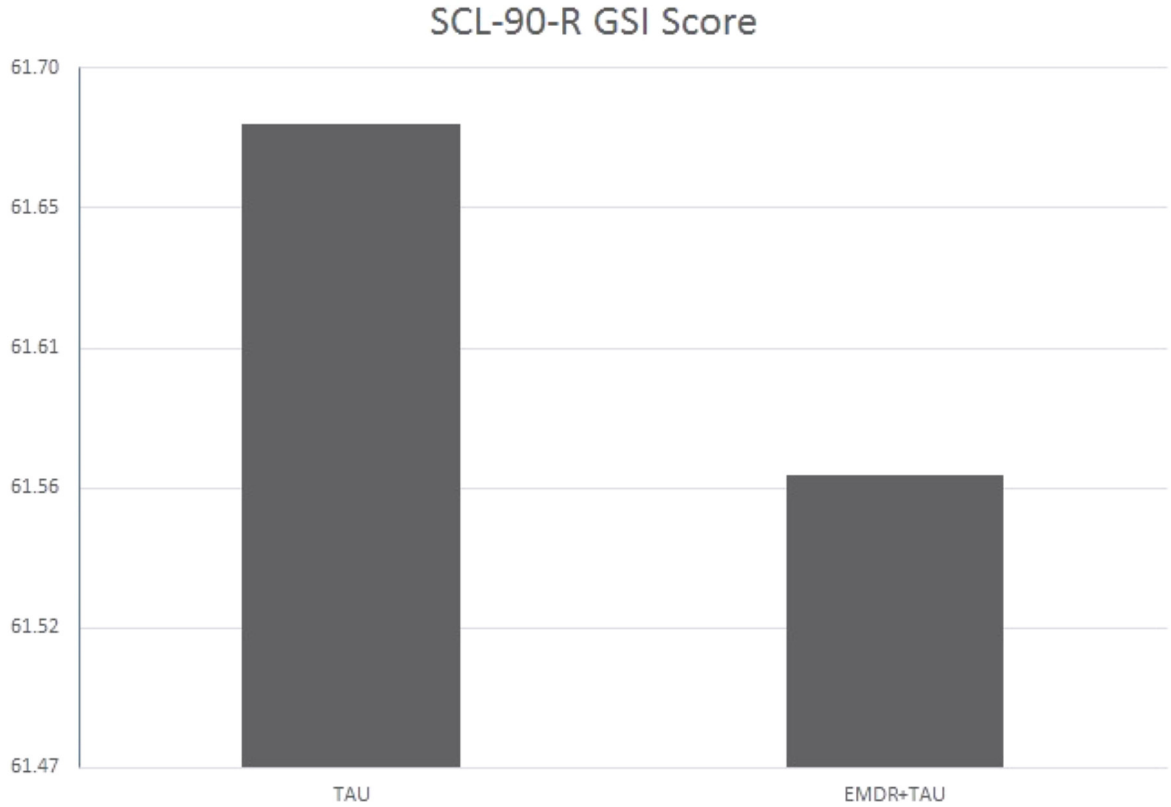

FIGURE 5 | Adjusted mean SCL-90-R GSI scores for TAU and EMDR + TAU at end of treatment.

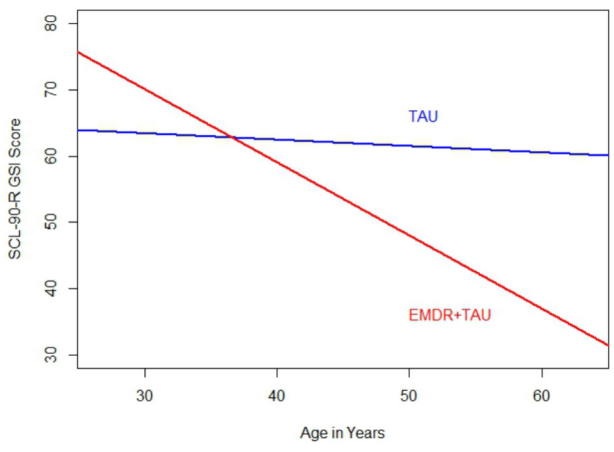

FIGURE 6 | Comparison of regression slopes for age and SCL-90-R GSI scores (end of treatment) between the two treatment groups.

of pathogenic memories, as described by Centonze et al. (2005).

The present study contributes to the literature not only by showing the beneficial effect of EMDR in the treatment of depression, but also by corroborating previous findings with a stronger research design. For example, compared with a previous matched-pair study (Hase et al., 2015), the present study was advantageous with regard to the randomized-controlled design. Furthermore, a disadvantage of the matched-pair study was that the BDI-II tests were only given to the 11 patients of the experimental group. This precluded the comparison of both groups regarding the rate of complete remissions, as the BDI-II tests were not given to the control group due to limited resources. Thus, the study was unable to make a scientific comparison and could only hint at the effectiveness of adjunctive EMDR treatment of depressive patients. The somewhat older, similar study of Hofmann et al. (2014) did not randomize the sample, either. It may also have been limited by the limited clinical experience of the psychotherapists in both groups and the fact that the control group consisted of patients who received CBT in the same clinic at the same time, but did not constitute a randomized treatment group. A further possible disadvantage was the unequally distributed use of antidepressants in the patients of the study. In the control group, 6 of 21 patients received antidepressants, while nine of 21 in the experimental group received antidepressant medication. The literature around EMDR therapy in the treatment of depression is likely to be strengthened by further studies using strong methodologies to examine the effect of EMDR in the treatment of depression in the context of the EDEN multicenter study.

There are several limitations to the present study. First, its low sample size limits the generalizability of the results and requires

replication in order to see whether the present findings would show again in a larger sample, for example, in a multicenter study comparison, which is also planned for the EDEN study. Second, this study sampled a population of patients that were insured by the armed forces, leading to an over-representation of men. In order to account for this limitation and include more female participants, future research could sample patients insured by health care companies other than those exclusively working with military personnel. A third limitation concerns the fact that patients self-reported the severity of their depressive symptoms. More objective measures, or independent observer ratings of depressive symptoms could have strengthened the findings of this study.

In future research, one could study the efficacy of EMDR in the treatment of depression without concomitant antidepressant medication in an outpatient sample. This would be possible in mildly to moderately depressed patients. Furthermore, the expected meta-analysis of the EDEN multicenter study remains a prospect for the further scientific investigation of EMDR therapy in the treatment of depressive disorders. This will also show whether the positive effects of EMDR found in the present study can be supported in a greater population. Lastly, one could still examine the hypothesized beneficial effect of EMDR therapy in reducing the depressive relapse rate at follow-up.

CONCLUSION

Given the predicted worldwide increase of depression and the limited success of TAU, it is important to develop adjunctive therapy strategies. The present randomized study examined whether EMDR therapy produces a positive effect in the treatment of depression beyond TAU. On the BDI-II and the GSI score of the SCL-90-R, additional EMDR treatment produced significant improvements over the effects of TAU, while it produced marginally significant improvements over TAU on the depression subscale of the SCL-90-R. Given the previously high rate of non-responders to TAU, the present study thus suggests that EMDR may improve treatment outcomes when added to TAU. The present study significantly contributes to the knowledge base in the field as it is the first to have used a randomized-controlled study design to examine the efficacy of EMDR in the treatment of depression. However, its low sample size reduces the generalizability of the results and calls for larger future studies to replicate the effects found in this study. Follow-up comparisons to the present study will reveal whether adjunctive EMDR therapy also produced more sustainable treatment effects as manifested by fewer depressive relapses at follow-up.

AUTHOR CONTRIBUTIONS

MH and JP acted as center and data manager in the study and share first authorship. AdH contributed the statistical analysis. LO and ArH acted as study manager and internal reviewers. RB assisted in participant recruitment and further contributed by reviewing the literature. CH took responsibility as senior author.

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Conflict of Interest Statement: MH and ArH offer education in EMDR therapy for licensed psychotherapists.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Non-randomized Controlled Trial of EMDR on Affective Symptoms in Patients With Glioblastoma Multiforme

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Glioblastoma multiforme (GBM) is a highly aggressive brain cancer and its survival after diagnosis is less than 2 years. Therefore, GBM patients are especially prone to co-occurring psychological conditions such as anxiety and depressive disorders. Furthermore, aggressive medical therapies affect patients' lives, undermining their sense of meaning and coherence. The main aim of this study was to determine the effectiveness of Eye Movement Desensitization and Reprocessing (EMDR) therapy on anxiety, depression and sense of coherence in patients with GBM. Thirty-seven GBM-diagnosed women were included in this trial and received standard medical care. Of those, 18 patients were treated during 4 months with 10–12 individual EMDR sessions (60–90 minutes each). Nineteen GBM patients were used as a non-randomized control group as they consented to psychological evaluations but not to a psychotherapeutic intervention. The groups were homogeneous in terms of gender, age, educational level and treatment, but not in anxiety and depressive levels at baseline. All patients were evaluated at baseline, after treatment (4 months) and at follow-up (further 4 months) by the Hospital Anxiety and Depression Scale (HADS-M) and the Sense of Coherence Scale (SOC-29). Caregivers in both groups were interviewed by the Patient Caregiver Questionnaire after 4 months follow-up. Statistical analyses were conducted using ANOVA statistics, correlation and regression analysis. Results showed a statistically significant decrease in the EMDR group in anxiety, depression and anger, when compared to the experimental group. EMDR therapy also had a positive impact upon the sense of coherence level in the experimental group, whereas in the control group this declined. Finally, the caregivers reported beneficial outcomes of the EMDR therapy with less anxiety- and anger-related behaviors in patients in the experimental group compared to the control group. This study is the first to show beneficial effects of EMDR therapy in alleviating affective symptoms and improving coherence in a severe medically ill population with GBM.

Keywords: EMDR therapy, brain cancer, coherence, anxiety, depression, anger

INTRODUCTION

Cancers of the brain are among the greatest challenges of today's medicine. Brain tumors, which are the most difficult to treat, are included in the Grade 4 group of cancers and are determined as high grade glioma (HGG) (Woehrer et al., 2013). Glioblastoma multiforme (GBM) belongs to this group and is the most malignant. It is responsible for around 3–4% of the mortalities among cancer patients (Carlsson et al., 2014; Razavi et al., 2016), with an average survival after diagnosis of approximately 15–17 months (Li et al., 2010; Huang et al., 2017). Only 5% of patients survive 5 years from diagnosis (Carlsson et al., 2014). Treatment strategies such as surgical intervention, chemotherapy, radiotherapy or steroid therapy with their well-known side-effects represent a further burden for the patients beyond the diagnosis.

As a consequence, anxiety and depressive symptoms appear frequently and are a widely occurring reaction to a cancer diagnosis (Kadan-Lottick et al., 2005; Kandasamy et al., 2011; Andersen et al., 2014; Sharpe et al., 2014; Lyon and Wang, 2016). Given time, these affective symptoms usually result in a major depressive disorder (MDD) or anxiety disorder on long-term (Archer et al., 2012; Pereira et al., 2012; Salvo et al., 2012). A meta-analysis of 62 studies conducted by Pinquart and Duberstein (2010) demonstrated that depressive symptoms could result in a diagnosis of MDD over time in patients with various types of cancer. Interestingly, a study conducted by Pelletier et al. (2002) demonstrated that intensification of depressive symptoms in patients with brain tumors is even significantly higher than in patients with other types of cancer. Approximately 40% of examined patients were diagnosed with MDD, whereas this was true in 15 to 30% in the case of other cancer types. Other studies of brain cancers indicate that depressive disorders affect 15–38% of patients (Pangilinan et al., 2007), with 28% patients fulfilling diagnosis of MDD (Wellisch et al., 2002). Furthermore, it has been proposed that in case of a GBM diagnosis, subjects experience this as a severe traumatic, life-threatening event which influences the meaningfulness, comprehensibility, and manageability of their lives, defined as "sense of coherence" by Antonovsky (1979). Thus, appropriate psychological assistance and psychotherapy should accompany subjects recently diagnosed with GBM. One potential therapeutic option is Eye Movement Desensitization Reprocessing (EMDR) therapy which was developed by Francine Shapiro almost three decades ago for the treatment of post-traumatic stress disorder (PTSD). The therapy aims, via bilateral stimulation, to reprocess traumatic memories through reinterpretation and inclusion in the existing memory network, using an eight-phase EMDR protocol (Shapiro, 2002; Boukezzi et al., 2017). The efficacy of EMDR for PTSD has undergone the scrutiny of various meta-analyses (Van Etten and Taylor, 1998; Davidson and Parker, 2001; Bradley et al., 2005; Seidler and Wagner, 2006; Bisson and Andrew, 2007; Benish et al., 2008; Jonas et al., 2013; Chen et al., 2014, 2015; Cusack et al., 2016). In 2013 it was also recommended by the World Health Organization as a first line treatment of PTSD (World Health Organization [WHO], 2013). So far, three pilot studies have investigated the effect of EMDR in oncological patients suffering from various types of cancer (Capezzani et al., 2013; Faretta et al., 2014; Jarero et al., 2015) but none have included GBM patients.

The present trial aimed to study, for the first time in a controlled design, the effect of EMDR therapy on anxiety, depression and sense of coherence in a sample of female patients suffering from GBM. The hypothesis of this trial was that GBM patients would improve with EMDR in affective symptoms and sense of coherence when compared to the control group.

MATERIALS AND METHODS

Ethics Statement

The study was approved by the Bioethics Committee at the Faculty of Medicine and Health Sciences in Kielce and all patients signed an informed consent and agreed to participate in the study.

Participants

The study included 37 GBM patients and their 37 caregivers, coming from Warsaw in Poland. All patients were outpatients and had received at baseline steroid therapy. Once included in the study all patients were additionally treated with radio- and chemotherapy. None of the patients fulfilled indication for a surgical intervention. The time between diagnosis of GBM and study entry was in all cases between 2 and 3 months. None of them had received psychological or supportive therapy before. None of the patients received psychopharmacotherapy before or during the study. Caregivers, indicated by patients as those who provided them with direct care, were also included in the study and were evaluated as a further objective source of possible psychological changes. The study participants were receiving medical care at the Oncology Centre in Warsaw and gave their consent to take part in the study. For ethical reasons, due to the high mortality of the cancer type, this study was designed as a non-randomized, controlled trial. Patient consent to receive the EMDR therapy was the condition for being assigned to a specific group The EMDR group consisted of persons who, after being diagnosed with cancer, expressed their consent to use EMDR therapy (18 patients) whereas the control group did not consent to a psychotherapeutic intervention but did to evaluations (19 patients). Both groups, however, were comparable in demographic variables such as gender, age and socio-economic status (see **Table 1**).

The following in- and exclusion criteria were applied:

(1) diagnosis of a GBM brain tumor; (2) did not qualify for surgical intervention; (3) was diagnosed no earlier than 3 months prior to start of the study; (4) outpatient; (5) was not receiving individual or group psychological or psychotherapeutic therapy; (6) no psychopharmacotherapy; (7) had a level of communication allowing to perform a psychotherapy, and (8) consented to participate in the study.

Measurements

As primary outcome criteria we explored anxiety and anger symptoms of the patients using the self-rating Hospital

TABLE 1 | Baseline demographic and clinical characteristics.

Characteristics	Experimental group (*N* = 18)	Control group (*N* = 19)	Statistics
Gender		All female	
Age (min – max)	63.00 (52–5 7)	65.50 (53–79)	$t = 0.841$ $P = 0.406$ (n.s.)
Children			
Yes	18	19	$x^2 = 0.094$ $p = 1.000$ (n.s.)
Education level			
Elementary	1	0	$x^2 = 0.000$
Secondary	10	11	$p = 1.000$ (n.s)
Higher	7	8	
Employment at the time of diagnosis			
Yes	13	12	$x^2 = 0.056$ $p = 0.728$ (n.s.)
Being in a relationship at the time of diagnosis			
Yes	14	14	$x^2 = 0.000$ $p = 1.000$ (n.s.)

Anxiety and Depression Scale (HADS-M) questionnaire (Zigmond and Snaith, 1983, validated in Polish by Majkowicz, 2000). The following thresholds are defined for both depression and anxiety: 0–7 (no disorder); 8–10 (boundary state); 11–21 (confirmed disorder). The original version consists of 14 items which was expanded to 16 items in the validated version (from 0–3). Two items evaluate anger, proposing the higher the result obtained by the examined person, the higher the level of anger currently experienced by the patient. The α-Cronbach's α coefficient for the modified questionnaire was 0.887 (Majkowicz, 2000). Of note, this scale is an evaluation of symptoms but not a diagnostic interview.

Furthermore, caregivers were assessed with respect to possible affective changes. The caregivers' assessments were analyzed based on results obtained from the Patient Caregiver Questionnaire. This questionnaire was developed based on a pilot study of 100 randomly selected persons, who had cared for GBM patients for at least 5 years (publication in process). They provided information on the most characteristic psychopathological changes with a focus on the expression of anger or anxiety. The results obtained were ordered from the most to the least frequent in the descriptions provided, and the six most common for each group were selected. Consequently, the Patient Caregiver Questionnaire was developed by the authors of the present study, consisting of 12 questions divided into two groups: questions concerning behavior described by caregivers as anxiety-related, and questions concerning behavior described as expressing anger. Each question is assigned four possible answers, referring to the potential frequency of a given behavior's occurrence. For each answer, the examined person is given a certain number of points from 1–4. The sum of points for each category constitutes the result, which determines the frequency of anxiety-related or anger-related behavior.

The secondary outcome criterion was the evaluation of the general psychological and emotional state of the patients, including their sense of the quality and meaningfulness of life. As mentioned before, this construct was developed by Antonovsky in 1979 and named "sense of coherence" (Antonovsky, 1979; validated in Polish, Mroziak, 1996). The self-rating Sense of Coherence Scale (SOC-29) questionnaire measures the intensity of the sense of coherence and its three components: Scom (comprehensibility); Sman (manageability) and Smf (meaningfulness). The SOC-29 questionnaire consists of 29 questions. Each question is equipped with a seven-point semantic scale, on which the examined person marks his/her answer. Evaluations of individual questions are summed up to obtain the result. The higher the result obtained on the scale, the higher is the sense of coherence. Cronbach's α for the internal consistency of the SOC-29 questionnaire ranges from 0.84 to 0.93.

Examination Procedure

At baseline, all participants in the study were interviewed regarding their sociodemographic data (using a questionnaire developed by the authors of the present study) and were asked to complete the before mentioned questionnaires, the HADS-M and the SOC 29. Then, patients in the experimental group started with EMDR therapy with an average length of the therapy of around 14 weeks, 12–14 therapeutic weekly sessions lasting 60–90 minutes. The standard eight-phase EMDR therapy protocol was employed by an experienced psychologist and accredited EMDR Practitioner, with a 5-year experience as an EMDR therapist. As patients were outpatients but somatically affected, EMDR therapy was performed in their homes. Fourteen weeks after baseline, patients from both groups were asked to complete the same questionnaires again. Caregivers in both groups completed also the Patient Caregiver Questionnaire both at baseline and again 14 weeks later.

Statistical Analysis

Calculations were performed using the advanced statistical package STATISTICA 10 PL. Differences in quantitative data were demonstrated using the Student's *t*-test for dependent samples and a Wilcoxon test. Correlation relationships between the initial and final measurements were observed using the method of series course (short series, small samples) and additionally with the Spearman's method, due to the common ambiguity of the solutions for small samples with the use of Pearson's method. Cohen's *d* effect size was used for the final control of the influence of therapy on the level of anxiety symptoms in the examined patients. Correlation analyses were conducted independently for the questions asked. Qualitative observations constituted supplementary procedures. In that sense, a triangulation procedure was employed: quantitative tests were supplemented with qualitative tests of the study subject.

RESULTS

As regards the primary outcome, symptoms of anxiety, depression and anger decreased in a statistically significant way after EMDR therapy, when compared to the control group. Conversely, in the control group a statistically significant increase

of anxiety and depressive symptoms was observed. At baseline (T0), the number of affective symptoms in the HADS-M scale in all patients examined in the experimental group indicated a confirmed disorder. After therapy, almost 25% of the patients entered in clinical remission (no disorder), while half showed a reduction of symptoms toward a boundary state, and slightly over 25% remained in the range of a disorder. In the control group, two-thirds of the sample fulfilled symptoms of a disorder and one third exhibited a boundary state. At T1 all except one patient in the control group fulfilled symptoms indicative of a disorder; only one patient had a decrease of anxiety symptoms with a sum score indicative of an absent disorder.

With respect to depressive symptoms in the HADS-M scale, at T0 almost all subjects in the experimental group exhibited symptoms indicating the possibility of a disorder. Following the application of EMDR therapy (T1), the number and intensity of depressive symptoms decreased in over 50% of the participants to the level where a disorder was absent, while almost a third remained in the boundary state and only two persons continued within the range of a possible disorder. In the control group at baseline over two thirds of the participants showed a boundary state or the absence of a disorder. At T1, the symptoms had intensified to the level of a disorder in almost all participants.

With regard to anger symptoms of the HADS-M scale, the results of the present study also indicate a significant change in the experimental group, since the intensity of the symptoms dropped by almost a half in all patients. However, in the control group a similar tendency occurred: patients in the control group demonstrated a slight decrease in the frequency of anger symptoms (**Table 2**). Baseline levels of anxiety, depression and anger differed in both groups with a statistical significant difference. Statistics can be gathered from **Tables 2**, **3**.

The value of Cohen's *d* indicated a strong relationship between the use of EMDR therapy in the experimental group and the decrease in the level of anxiety, depression, and anger symptoms (see **Table 4**).

The positive result of the HADS-M scale was confirmed by the external evaluation of the caregivers of GBM patients receiving EMDR therapy. In the experimental group, a decrease in anxiety-related behavior from T0 ($\mu = 6.89$) to T1 ($\mu = 3.34$) ($p = 0.021$) and in anger-related behavior in T0 ($\mu = 5.06$) to T1 ($\mu = 2.90$) ($p = 0.057$). In change, in the control group caregivers described an increase in anxiety-related behavior from T0 ($\mu = 4.05$) to T1 ($\mu = 6.31$) ($p = 0.461$), as well as a slight increase in anger-related behavior T0 ($\mu = 4.42$) to T1 ($\mu = 4.80$) ($p = 0.001$).

The secondary outcome, sense of coherence, showed also positive results in the EMDR group. At baseline (T0) the mean sense of coherence level was lower in the experimental group (103.278; $SD = 28.219$) than in the control group (125.579; $SD = 28.545$) which resulted statistically significant ($t = -2.388$; $DF = 35$; $p < 0.022$). The same effect could be observed with regards to symptoms of depression, anxiety and anger resulting from HADS-M (**Table 3**). In T1 the mean sense of coherence in the experimental group increased (140.389; $SD = 27.641$) while it decreased in the control group (118.789; $SD = 23.950$). The difference between both was again statistically significant ($t = 2.544$; $DF = 35$; $p < 0.016$).

TABLE 3 | Differences in levels of anxiety, depression, anger, and sense of coherence in T0 and T1.

	Experimental group (EMDR) (*N* = 18)	Control group (*N* = 19)	Student's *t*	*P*
Anxiety – T0	17,5	13,16	4.306	0.000
Anxiety – T1	9,89	14,89	−4.324	0.000
Depression – T0	16,44	10,79	4.086	0.000
Depression – T1	7,56	13,68	−5.337	0.000
Anger – T0	3,39	2,58	1.867	0.07 (n.s.)
Anger – T1	1,72	2,36	−1.34	0.068 (n.s.)
Coherence – T0	103,278	125,579	−2.388	0.022
Coherence – T1	140,389	118,789	2.544	0.016

EMDR, eye movement desensitization and reprocessing; T0, first measurement; T1, second measurement, after therapy (in experimental group) or after 14 weeks (in control group); n.s., not significant.

TABLE 4 | Influence of therapy on the level of anxiety, depression, and anger of examined patients.

	Experimental group (EMDR)		Control	Group
	P	Cohen's *d*	*P*	Cohen's *d*
Anxiety	0.000	2.11	0.055 (n.s.)	0.47
Depression	0.000	2.25	0.013	0.63
Anger	0.001	0.97	0.385 (n.s.)	0.20

EMDR, eye movement desensitization and reprocessing; n.s., not significant.

TABLE 2 | Characteristics of anxiety, depression, and anger symptoms according to the HADS-M questionnaire in the present study, with evaluation of the variability significance.

	Experimental group (EMDR)					Control group				
	T0 (mean ± SD)	T1 (mean ± SD)	Student's *t*	*P*	Wilcoxon test	T0 (mean ± SD)	T1 (mean ± SD)	Student's *t*	*P*	Wilcoxon test
Anxiety	17.50 ± 2.36	9.89 ± 3.79	8.971	0.000	$p < 0.000$	13.16 ± 3.61	14.89 ± 3.25	−2.049	0.055 (n.s.)	$p < 0.048$
Depression	16.44 ± 4.03	7.56 ± 3.78	9.574	0.000	$p < 0.000$	10.79 ± 4.37	13.68 ± 3.19	−2.740	0.013	$p < 0.016$
Anger	3.39 ± 1.46	1.72 ± 0.96	4.123	0.001	$p < 0.004$	2.58 ± 1.17	2.36 ± 1.11	0.889	0.385 (n.s.)	$p < 0.417$ (n.s.)

EMDR, eye movement desensitization and reprocessing; T0, first measurement; T1, second measurement, after therapy (in experimental group) or after 14 weeks (in control group); n.s., not significant.

The increase in the sense of coherence in the experimental group and the decrease in the sense of coherence in the control group was also statistically significant, respectively ($t = -10.769$; $DF = 17$; $p < 0.000$; $t = 2.465$; $DF = 18$; $p < 0.024$). Changes in the general sense of coherence are presented in **Figure 1**.

We also found a highly significant correlation of the general sense of coherence between T0 and T1 for the experimental group ($r = 0.885$; $p = 0.000$).

The statistics of the influence of EMDR therapy on the individual components comprehensibility (Scom), manageability (Sman), and meaningfulness (Smf) is presented in **Table 5**. The value of Cohen's *d* demonstrates the strong influence of the EMDR therapy on all components in the experimental group. In a subsequent analysis, relationships between anxiety symptoms and the sense of coherence indicated a negative correlation, both in T0 ($r = -0.124$; $p < 0.624$) and T1 ($r = -0.548$, $p < 0.019$).

DISCUSSION

To the best of the authors' knowledge, this is the first controlled study using a structured psychotherapy, in this case the standard 8 phase EMDR protocol, in a homogenous group of patients with a specific cancer, GBM, to test whether this intervention improves psychological aspects of the disease. Overall, we found first positive evidence of EMDR on affective symptoms and sense of coherence, specifically an improvement in comprehensibility, manageability and meaningfulness, in a sample of female GBM patients. The HADS-M questionnaire was used to determine the levels of anxiety, depression, and anger and showed approximately a 50% score decrease in all patients of the experimental group after EMDR therapy.

The presence and intensification of anxiety symptoms following cancer diagnosis, as detected in all participants at baseline in our work, has been reported in previous studies. Stark and House (2000) demonstrated for instance that about 48% of 178 patients diagnosed with various cancers fulfilled the diagnosis anxiety disorders following ICD10 classification. Similar data were found in patients with breast cancer proposing a high prevalence of PTSD (Vin-Raviv et al., 2013). Of importance, EMDR reduced anxiety symptoms in our sample of GBM patients. These results are in line with three further EMDR studies conducted in subjects diagnosed from various other types of cancer which also reduced anxiety symptoms. Capezzani et al. (2013) measured for instance anxiety symptoms with the State-Trait Anxiety Inventory and the State-Trait Anxiety Inventory which decreased following EMDR therapy including patients with various types of cancers during the active phase of medical treatment. Two further studies obtained also positive results with EMDR therapy in anxiety and PTSD symptoms, respectively, in patients diagnosed also with different cancer types (Faretta et al., 2014; Jarero et al., 2015). Both Faretta et al. (2014) and Capezzani et al. (2013) studies observed also a decrease in depressive symptoms among participants following the use of EMDR therapy, measured by Back Depression Inventory (BDI) questionnaire. This positive effect of EMDR was also detected in our trial and is of importance as not only anxiety but also depressive symptoms increase over time in this population, especially if no psychotherapeutic assistance is offered (Wellisch et al., 2002; Pinquart and Duberstein, 2010).

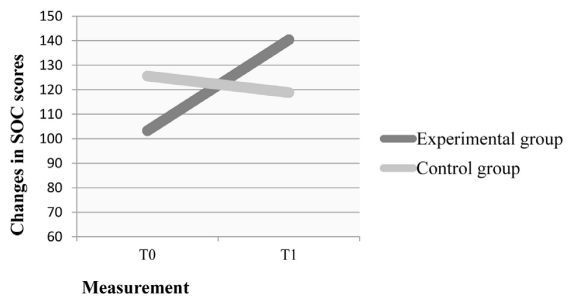

FIGURE 1 | T0 - first measurement; T1 - second measurement, after therapy (in experimental group) or after 14 weeks (in control group). SOC: Sense of Coherence Scale.

Anger as an affective reaction to a diagnosis of cancer is understandable but understudied so far. A review by Thomas et al. (2000) concluded low levels of anger in cancer patients which were interpreted as a strong suppression and restraint of emotions considered inappropriate and reprehensible. Interestingly, at baseline (T0) we found a mean score of 3.39 in the experimental group and a mean score of 2.58 in the control group. Both can be considered as clinically relevant as scores are intermediate with the greatest intensity of 6 scores in this scale. As stated, scores in anger in our GBM sample decreased in the EMDR group but this was not statistically significant as the control group decreased as well in anger symptoms.

The positive effect on affective symptoms, especially anxiety and depression using the HADS-M, was confirmed by the Patient Caregiver Questionnaire. The differences in anger- and anxiety-related behavior in the experimental group after EMDR therapy were statistically significant. Of note, the second measurement after EMDR therapy showed that the caregivers' assessments in relation to an improvement of anxiety and anger-related behaviors was in accordance with the subjective assessments performed by the patients themselves via the HADS-M questionnaire. The same was true for the control group where caregivers and patients both declared an intensification of anxiety-related behaviors and symptoms; however, it is interesting that anger symptoms slightly decreased as per both caregivers and patients questionnaires. These results seem relevant to us as studies of anger in cancer populations are scarce so far, especially comparing the subjective assessment of cancer patients with any kind of external assessment. Our results indicated, as stated, that in both groups the caregivers' assessments did not differ from the assessments of the patients themselves. It cannot be excluded, though, that the caregivers' assessment regarding anger perceived by their patients might have been in part countertransference by the caregivers via their own stress, sense of responsibility or guilt.

The present study employed also the SOC-29 questionnaire to determine the general state of patients with GBM-type

TABLE 5 | Influence of EMDR therapy on the level of Scom, Sman, and Smf in examined patients.

	Experimental group (EMDR)					Control group				
	T0 (mean ± sd)	T1 (mean ± sd)	Student's *t*	*P*	Cohen's *d*	T0 (mean ± sd)	T1 (mean ± sd)	Student's *t*	*P*	Cohen's *d*
Scorn	37.94 ± 9.45	49.56 ± 10.01	−7.953	0.000	1.87	47.32 ± 7.88	40.58 ± 6.50	4.989	0.000	1.14
Sman	34.17 ± 11.67	46.00 ± 10.67	−7.008	0.000	1.65	42.47 ± 11.51	40.89 ± 9.89	1.452	0.164 (n.s.)	0.33
Smf	31.17 ± 9.45	44.83 ± 8.00	−9.555	0.000	2.25	35.79 ± 10.57	37.32 ± 9.88	−1.454	0.163 (n.s.)	0.33

EMDR, eye movement desensitization and reprocessing; T0, first measurement; T1, second measurement, after therapy (in experimental group) or after 14 weeks (in control group; Scom, sens of comprehensibility; Sman, sens of manageability; Smf, sens of meaningfulness; n.s., not significant.

cancer. This measured their level of well-being or quality of life, including their emotional state and "sense of coherence," such as the ability to cope with situations. Numerous tools exist allowing medical practitioners to determine the well-being of cancer patients. However, as emphasized by Cheng et al. (2010), the poor physical prognosis limits typical tools for patients with cancer, including brain tumors. Analyses of the results in the present study indicate that the SOC-29 might be a useful tool as the sense of coherence increased in patients in the experimental group, both in general, and in its individual components. This finding is supported by the Cohen's *d* value, suggesting that EMDR therapy had a strong influence on the increased levels of comprehensibility, manageability, and meaningfulness in the experimental group. At the same time, a statistically significant decrease in the sense of coherence was noted in the control group which might be due to the physical and psychological deterioration within the follow-up period.

Various other forms of psychotherapeutic assistance in the case of cancer patients (Hagerty et al., 2005; Strong et al., 2007; Espie et al., 2008; Hoffman et al., 2012) have been performed but not in a pure GBM sample. Furthermore, the majority of studies are limited solely to the determination of psychological consequences of the disease (Burgess et al., 2005; Gil et al., 2005; Linden et al., 2012). Some studies, however, focused also on the outcome of psychotherapeutic interventions and found little evidence for an improvement in affective symptoms. Breitbart et al. (2012) investigated, for example, Individual Meaning-Centered Psychotherapy in 120 patients with advanced cancer (III and IV stage), a therapy directed at methods of coping with difficult situations. They could not detect any effect of this intervention on the levels of anxiety and depressive symptoms. A similar negative result with regards to depressive symptoms was observed by de Vries et al. (1997) in an earlier study, which used individual experimental-existential counseling. A further study has been performed by Arnold et al. (2008) which evaluated the efficacy of psychopharmacological drugs in persons with brain tumors and corresponding psychopathological symptoms. Results were non-significant for psychopharmacological drugs, leading the authors to emphasize the significance and need to study psychoeducation and/or psychotherapy for this group of patients. Another study found that high drop our rates limit often psychotherapeutic interventions (Applebaum et al., 2012). In this study, more than half of the 153 patients dropped out due to a deterioration of their physical state and/or difficulties in attending the 8 programmed sessions. In light of these findings, the appropriate selection of the type of intervention gains considerable importance, particularly in patients with such a specific tumor type as GBM. In our EMDR group no patient dropped out, but our study was much smaller than the before mentioned work and candidates were well defined and in a comparable physical state at baseline.

Various limitations of our study have to be taken into account before translating our results into clinical practice. First of all, the relatively small number of included patients which limits the statistical analysis. Then, we did not randomize patients in a methodologically sound way. As stated before, this was not done due to ethical considerations, as subjects were diagnosed with a diagnosis with a high and rapid mortality. Instead, a "natural" randomization process of patients either consenting or not consenting to a psychotherapeutic intervention was chosen. The principles of random selection would indicate the use of a waiting list option. However, such an option was in our opinion not acceptable in our GBM patients, as the development of severe neurological symptoms and deterioration in communication during the study duration would have meant control group patients would afterwards have been unable to participate in a compensatory EMDR therapy. For those reasons, it was also difficult to carry out an adequate follow-up to confirm our results at mid- and long-term. Both patient groups were similar in demographic variables but a further limitation due to the lack of a randomization process is that the experimental group showed more psychopathological symptoms at baseline. This fact may suggest that the patients who granted their consent to receive the EMDR therapy were also different from the no-consent patients in terms of other psychological variables, such as sense of control, helplessness, optimism/pessimism, etc. in ways that contributed to positive outcomes in the EMDR group. Future studies could clarify this issue better by providing an alternative type of active treatment (e.g., cognitive-behavioral therapy) for the control group rather than applying no treatment at all. We also included female patients only, meaning we cannot generalize results to male patients. Finally, it is also important to emphasize that scales were self-rating evaluations which possibly created a bias in the patients' perception of their psychological symptoms. However, the inclusion of a caregiver questionnaire added valuable and more objective information. Fidelity checks have not been performed in this study.

Strengths of the study include the pure GBM sample in a severely somatic ill population, the comparable samples in demographic variables in both groups, the use of a standardized EMDR protocol, and, as stated, patients and additional objective caregivers' ratings. Furthermore, subjects did not receive psychopharmacological drugs as potential confounders. Finally, studies so far in this population are scarce and it is of merit and an important clinical need to include patients with a disease of a rapid and high mortality.

This study is, in our mind, an important and clinically relevant work, with the possibility that EMDR might be incorporated in oncological consultation liaison services, with the aim of improving the psychological situation of a complex population with a high somatic and psychological vulnerability. Future psychotherapeutic replication studies in GBM patients should include a larger number of patients, randomize patients possibly to a comparable psychotherapeutic intervention and scales should be hetero-applied by blind to treatment raters.

AUTHOR CONTRIBUTIONS

MS and MO both contributed equally to the design of the work. MO conducted the studies and collected results for the work. MS was responsible for methodical input regarding data analysis and data interpretation. MS and MO prepared the paper and approved the final version for publication. BA revised and edited the final version.

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The Effectiveness of Eye Movement Desensitization and Reprocessing Integrative Group Protocol with Adolescent Survivors of the Central Italy Earthquake

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Earthquakes, which can cause widespread territorial and socio-economic destruction, are life-threatening, unexpected, unpredictable, and uncontrollable events caused by the shaking of the surface of the earth. The psychological consequences, such as PTSD, anxiety, depression, and suicidal ideation, are well-known to clinicians and researchers. This study was conducted with the aim of evaluating the use of the Eye Movement Desensitization and Reprocessing (EMDR) Integrative Group Treatment Protocol on a sample of adolescents, after the earthquake in Central Italy on 24 August 2016. The objective of the EMDR intervention was to reduce PTSD symptoms. Before and after EMDR, specific assessment to find changes in PTSD symptoms was made using the Impact of Event Scale-Revised and through the analyses of the Subjective Units of Disturbance. The EMDR treatment was given in three sessions (T1, T2, and T3), each lasting 90 min, and the results at follow-up phase (T4) were also monitored. The results are very encouraging, showing significantly reduced PTSD symptoms in the majority of the subjects. The clinical implications and limitations will be discussed.

Keywords: earthquake, EMDR, PTSD, disaster response, adolescents

BACKGROUND

Earthquakes have always characterized human history as they are among the most common and devastating natural disasters. Today, despite scientific progress in increasing the predictability of seismic phenomena, earthquakes continue to cause devastating damage, and major destruction all over the world.

The consequences of earthquakes are not limited to the dangerousness of physical damage, indeed their traumatic repercussions have always been a subject of study in psychology. Post-traumatic stress disorder (PTSD) is the most-studied psychopathology resulting from earthquakes and natural disasters, due to the very high correlation ratios between earthquakes and this psychopathology, as documented in various studies (e.g., Pynoos et al., 1993; Bödvarsdóttir and Elklit, 2004). In recent years, among the various treatments and therapies for PTSD within emergency situation, various studies have indicated that EMDR (Eye Movement Desensitization

and Reprocessing) therapy is particularly suitable for treating PTSD thanks to its applicability in emergency situations and its rapidity in achieving appreciable and lasting results (Konuk et al., 2006; Fernandez, 2007). EMDR is a structured psychotherapeutic method widely used to treat various psychopathologies and problems relating to traumatic events and emotionally stressful experiences, and adopts as a theoretical base the AIP model (Adaptive Information Processing), which works on insufficiently worked-through memories.

The project came into being following the intervention by the *Associazione EMDR Italia* between September and October 2016 when the receivers were students of the *Istituto di Istruzione Superiore di Amandola* (Fermo Province) who had survived the earthquake, and the aim was to treat PTSD through administration of the EMDR-IGTP (Integrative Group Treatment Protocol).

THE SEISMIC EVENTS OF 2016 IN CENTRAL ITALY

Due to its particular geodynamic position where the African and Eurasian plates converge, Italy has frequently been subjected to very strong seismic events sadly noted for the great damage they cause, above all in the zones of the center and south affected by the tectonics of the Apennines. One of the most recent seismic event in Italy, defined "Amatrice-Norcia-Visso seismic sequence" by the National Institute of Geophysics and Vulcanology, made itself felt from the end of summer 2016 to January 2017 with various tremors of magnitudes between 5.5 and 6.5 on the Richter scale.

On 24 August 2016, an earthquake with a magnitude of 6.0, with the epicenter along the Valle del Tronto between the communes of Accumoli (Rieti Province) and Arquata del Tronto (Ascoli Piceno Province) struck the regions of Abruzzo, Lazio, Marche, and Umbria in Central Italy (INGV, 2016).

The Civil Protection Department reported 299 dead, numerous injured, and serious damage throughout the area (Ricci Bitti, 2016).

Two months later, on 26 October 2016, two more tremors, with the epicenter on the Umbria-Marche boundary and magnitudes of 5.4 and 5.9, were recorded in the Macerata province communes of Castelsantangelo sul Nera and Ussita, respectively, and followed by a series of tremors with magnitudes of between 3.0 and 4.5. On 30 October 2016, a devastating 6.5-magnitude tremor, with the epicenter between the towns of Norcia, Preci, and Castelsantangelo sul Nera in the Province of Perugia, caused numerous collapses and serious damage but no victims.

On 18 January 2017, four tremors with magnitudes of 5.1, 5.5, 5.4, and 5.0 hit the previously stricken areas, with the epicenters in the Aquila Province communes of Montereale, Capitignano, and Pizzoli, and the Rieti Province commune of Cagnano Amiterno, respectively. The emergency situation was further worsened by the bad weather: an intense cold snap and heavy snowfalls with snowdrifts over a meter and a half high hampered rescue operations to the stricken populations (INGV, 2016).

The Intervention of the Associazione EMDR Italia

After the 24 August 2016 earthquake, the *Associazione EMDR Italia* carried out a post-emergency intervention in the commune of Amandola (Fermo Province) to provide the population with specialist psychological support through a team specialized in psychotraumatology in emergency situations. The intervention started officially on 13 September with an informative meeting in the Council Room of the Amandola commune, and the various sessions were held mainly in the communal library, although specialist interventions were also held in private homes. Thanks to the collaboration of the Amandola commune, group interventions according to the EMDR-IGTP protocol were carried out in local primary and secondary schools (Cronache Fermane, 2016). The intervention in the commune of Amandola was part of a wider intervention, carried out from 26 August to 17 December 2016 in support of those struck by the earthquake in the areas of Amatrice, Norcia, Val Norcina, and the Province of Perugia, by the *Associazione EMDR Italia* together with institutional representatives, the Civil Protection, the Order of Psychologists of Umbria, and heads of the area mental health service. It involved 145 psychotherapists, all certified by the recognized accrediting association in Italy (*Associazione EMDR Italia*) to practice EMDR in emergency contexts. The intervention continued via further humanitarian missions even after the new tremors in January, at the same time as the emergencies caused by the weather (EMDR Italia, 2016; Fernandez, 2017).

The EMDR-IGTP Protocol

The EMDR Integrative Group Protocol (EMDR-IGTP, Jarero et al., 2006, in the readapted version by Maslovaric and Fernandez, 2016) was used for the intervention.

The EMDR-IGTP was developed by members of the Mexican association AMAMECRISIS (Mexican Association for Crisis Therapy), as a result of the high need for mental health services occurring as a result of the destruction of Mexico's Pacific coastline in 1997 by Hurricane Pauline. The team of doctors had initially designed a traditional, individually applied EMDR intervention aimed only at a limited number of children, adolescents, and adults who had lost family members or become homeless. However, on the first day in the field, those in need of treatment numbered more than 200. The AMAMECRISIS team were faced with the challenge of developing a suitable methodology to give so many needing support simultaneously an efficacious and specific treatment for trauma, such as the EMDR, initially developed to be applied to one person at a time (Jarero et al., 2006).

The EMDR-IGTP protocol combines the EMDR therapy of eight standard phases (Shapiro, 1995, 2001) with a group therapy model (Jarero et al., 1999; Artigas et al., 2000) and uses a particular form of bilateral stimulation called the Butterfly Hug, which is why the IGTP protocol is also known as the Group

Butterfly Hug Protocol, together with the use of drawing tasks (Maxfield, 2008). The initial hypotheses behind the development of this protocol aimed at developing a methodology which could offer greater coverage than the individual EMDR approach and more efficacious results than traditional group therapies (Jarero et al., 2008). Originally developed for use with children, the EMDR-IGTP has shown that it can be applied also to group interventions with adolescents and adults: the protocol is structured as a form of play therapy, but has been successfully applied to disaster survivors with ages ranging from 7 to over 50 (Jarero and Artigas, 2010).

The advantages of the application of this protocol, apart from its simultaneous applicability to several subjects, are connected with the non-specificity of the setting, which must no longer necessarily be "private" and thus difficult to find in emergency situations. In addition, the IGTP protocol does not ask the subjects in the group to verbalize information regarding the trauma, the therapy can be applied over several consecutive days, there are no particular tasks to carry out between sessions, and treating several subjects makes it possible to rapidly involve many sections of the affected community. A further advantage offered by application of the IGTP protocol is that the clinical specialists can be assisted by paraprofessionals, teachers, and family members, and this makes wider application of the treatment protocol possible in particular emergency situations where the availability of professionals is limited (Luber, 2013).

The protocol modified by Maslovaric and Fernandez (2016) was designed to adapt the EMDR-IGTP protocol to the context of emergency situations in Italy. It takes about 90 min and foresees three sessions of intervention. The main differences with the original EMDR-IGTP protocol lie in the phases of Installation (phase 5), Body scan (phase 6), and Reevaluation (phase 8) (for further details, refer to Maslovaric and Fernandez, 2016).

The efficacy of the EMDR-IGPT approach has been documented in the literature by pilot studies in the field (Jarero et al., 1999, 2006; Artigas et al., 2000) and various case reports (Wilson et al., 2000; Korkmazlar-Oral and Pamuk, 2002; Fernandez et al., 2004; Birnbaum, 2007; Gelbach and Davis, 2007; Errebo et al., 2008; Zaghrout-Hodali et al., 2008).

In the specific field of earthquakes, there are as yet few studies and these present some methodological limitations, despite pointing out that EMDR seems a suitable methodology also for dealing with natural calamities (Konuk et al., 2006; Farrell et al., 2011). A study in 2006 by Konuk et al. (2006) analyzed the use of EMDR techniques in an experimental situation on more than 1500 trauma victims of the 1999 earthquake in Marmara, Turkey, (which had a magnitude of 7.6 and caused over 25,000 deaths), who were diagnosed with PTSD and treated with EMDR through a field study aimed at assessing a sample of 41 participants. The study indicated that EMDR treatment carried out with an average of five 90-min sessions was enough to eliminate PTSD symptoms in 92.7% of subjects and significantly reduce them in the others. It pointed out the advantages of EMDR in the emergency context typical of earthquake-affected populations who receive treatment in tent cities, compared to other strategies such as exposure-based cognitive behavioral therapies, or the techniques of "belief-restructuring" and "stress inoculation," strategies which are considered inappropriate and difficult to apply given the emergency situation and chaotic conditions of tent cities. Furthermore, the techniques based on exposure which center on the stressful details of the event are generally considered unsuitable for a population exposed to high levels of anxiety, suffering many bereavements and under constant threat from the risks of further tremors (Bryant and Harvey, 2000). The study underlined that for such situations the EMDR-based approach was one of the most reccomended (American Psychiatric Association [APA], 2004), also in terms of the reduced number of sessions (from three to five, for a trauma based on a specific single event) compared to other treatments commonly used in similar situations (Van Etten and Taylor, 1998; Maxfield and Hyer, 2002). Moreover, the fact that it does not ask the subjects for an excessive amount of detail in their description of the traumatic event or for particular work to be carried out between sessions, makes it the specific treatment of choice for large-scale post-traumatic earthquake situations (Konuk et al., 2006). The EMDR approach was also evaluated as efficacious in similar conditions in a 2011 study by Farrell and colleagues, after EMDR techniques had been used in a humanitarian assistance training program following the 7.6-magnitude earthquake which struck northern Pakistan in 2005, killing more than 73,000, including over 35,000 children, and injuring over 135,000 (Farrell et al., 2008, 2011).

THE STUDY

Method

Given the mode of operation of the health care providers and the humanitarian aim of the intervention, it was not possible to implement a randomized, delayed treatment condition. Here it is necessary to focus attention on certain ethical concerns (such as limited research funding versus the need for an expert research team, or the importance of a prompt intervention versus a rigorous and well-planned research design) in the context of humanitarian emergencies, based on the indications of the R2HC program (Research for Health in Humanitarian Crises, O'mathúna, 2015). There are various ethical concerns to consider in each research phase, from planning the research design to applying the protocols and reviewing the results. In each phase, it is necessary to try and bear in mind the individual needs of the receivers of the intervention, of the various groups and of all the affected population, as well as those of the rescuers, researchers, and all the staff involved.

It is essential to balance costs and benefits, to continually reassess the value of the aim of the research, which must answer concrete questions about the scientific validity of the research plan which must be appropriate to the demand, and ensure that the times of research take into account the timings and needs dictated by the humanitarian interventions and the allocation of resources. Informed consent and voluntary participation, which must in no way be a prerequisite for receiving adequate treatment or humanitarian support, are of fundamental importance in each phase of the research, as are respect for participants and the implementation of instruments

which are properly structured for, and adapted to, the receivers of the intervention.

This study was conducted in accordance with the Declaration of Helsinki (2001), under the approval of the research guidelines of the *Centro di Ricerca e Studi in Psicotraumatologia* (C.R.S.P.) of Bovisio Masciago (Monza and Brianza province, Italy) and Article 10 of the "National Board of Italian Psychologists Code of Ethics for the Psychologist." Moreover, regarding the ethical issues, the study was implemented following the request for intervention by the City of Amandola and upon the approval of the ethic panel of the EMDR Italian Association (Prot. EMDR_Amatrice, 1.0, 08-09-2016).

Prior to data collection, all subjects (and, because underage adolescents, their parents) received complete information concerning the rationale and effectiveness of EMDR and the study procedures, and gave written informed consent for their participation in the study.

Participants

In choosing the sample, it was decided to exclude all participants who, in the view of the care providers, had in the assessment phase shown symptoms of psychosis or dissociative disorders, or presented a clear risk of harming themselves or others, but no participant fulfilled any of these conditions. All 119 students of the *Istituto di Istruzione Superiore di Amandola* (Fermo Province) agreed to take part in the study. Of the 119, 116 gave valid answers when filling out the socio-demographic form regarding age and sex. The initial sample was thus composed of 65 males (average age 16.34; std dev 1.482) and 51 females (average age 16.22; std dev 1.604) for a total of 116 subjects aged 13–20 (average 16.28; std dev 1.531).

In a clinical and preventive perspective, support with the EMDR-IGTP protocol was made available to all participants, but here analysis will be of the data of the 45 out of 104 subjects (56.7% of the whole sample) who at T1 scored more than 24 points (possible diagnosis of PTSD). Of these, 17 (16.3%) scored from 24 to 32 points (partial PTSD), 7 (6.7%) scored from 33 to 36 points (full PTSD), and 21 (20.2%) scored more than 37 points (severe PTSD).

At T1, valid answers were given to all the items on the socio-demographic form except for the one concerning previous trauma, where a single answer was missing. All the subjects said that they were at home during the earthquake, except for one who was away from home; 42 (93.3%) said they lived at home, 3 (6.7%) away from home. None had been physically injured, only one reported injured family members, and 8 out of 45 (17.8%) reported damage to property due to the earthquake. 13 (28.9%) reported previous therapeutic treatment; 11 (25%), previous exposure to traumatic events (**Table 1**).

Procedure and Instruments

In the first treatment session (T1), a socio-demographic form was administered to collect data on sex, year at school, current living status, location during the earthquake, injuries received during the earthquake, injured family members, damage to property, previous therapeutic treatment, and previous exposure to potential traumatic events.

In the first and last treatment sessions (T1 and T3) and in the follow-up (T4), the adult version of the self-report IES-R (Impact of Event Scale Revised) questionnaire was administered, in order to assess PTSD (Weiss, 2007).

The IES-R, the updated version of the IES questionnaire (Horowitz et al., 1979), assesses the subjective distress perceived in relation to a potentially traumatic event. Each item is assessed according to a scale from 0 to 4 points, where 0 represents absence of relevance to the item and 4 extreme relevance. Of the 22 items assessed, eight relate to the Intrusion scale (items 1, 2, 3, 6, 9, 14, 16, 19, and 20), eight to the Avoidance scale (items 5, 7, 8, 11, 12, 13, 17, and 22), and six to the Hyperarousal scale (items 4, 10, 15, 18, 19, and 21). The reference scales are based on the PTSD symptoms as classified in the relative symptomatic clusters in the DSM-IV. The total score on the scale can range from a minimum of 0 to a maximum of 88 points, with a score over 24 considered indicative of possible PTSD. A score from 24 to 32 indicates a situation of "clinical concern" for PTSD and a possible diagnosis of partial PTSD, or in any case the presence of certain symptoms. A score from 33 to 36 represents the cutoff for a probable diagnosis of full PTSD, while a score over 37 indicates a possible diagnosis of severe PTSD (EMDRHAP, 2014).

For the data analysis, questionnaires with at most two omitted answers were considered valid. When one or two answers were missing, a substitute value (the average of the column) was inserted. At T1, 104 questionnaires were considered valid, of which 9 had one missing item and only 1 had two missing items.

TABLE 1 | Results of socio-demographic form, subjects with post-traumatic stress disorder (PTSD) at T1 ($N = 45$).

	N	%
Sex		
Male	19	42.2
Female	26	57.8
Location during earthquake		
At home	44	97.8
Away from home	1	2.2
Current habitation		
At home	42	93.3
Away from home	3	6.7
Physical injuries reported		
No	45	100.0
Yes	–	–
Family members injured		
No	44	97.8
Yes	1	2.2
Damage to property		
No	37	82.2
Yes	8	17.8
Previous therapeutic treatment		
No	32	71.1
Yes	13	28.9
Previous trauma		
No	33	75.0
Yes	11	25.0

TABLE 2 | Impact of Event Scale-Revised (IES-R) scores.

T	Total		Intrusion		Avoidance		Hyperarousal	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
T1 (*N* = 45)	38.27	11.42	13.28	6.23	14.71	3.92	10.29	4.08
T3 (*N* = 36)	23.59*	12.57	7.69*	4.8	9.89*	5.3	6.01*	4.26
T4 (*N* = 35)	29.66*	15.82	9.43*	6.18	11.86*	6.32	8.37	5.15

*, *Significant statistical difference between the averages, with* $p < 0.01$.

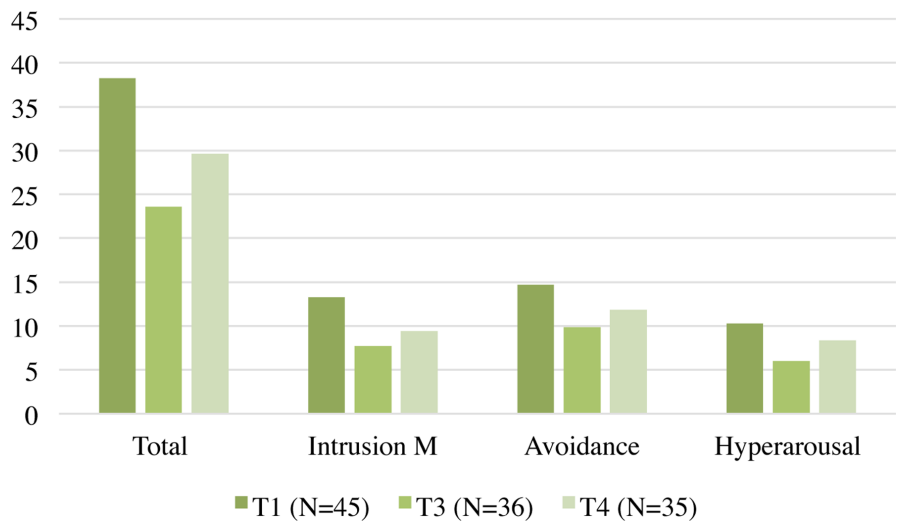

FIGURE 1 | Impact of Event Scale-Revised (IES-R) scores.

The relative scores on the Subjective Units of Disturbance (SUD) scale at T1 and T3 were also taken into consideration. At each EMDR-IGTP session, the subjects were asked to make a drawing connected to the earthquake, to assign a score from 0 to 10 to represent the negative emotions associated with the drawing (SUD score) and to carry out bilateral stimulation four times. EMDR-IGTP treatment aims to reduce the SUD score associated with negative emotions regarding the event from the first drawing in a session to the last, and from the first session to the last. In the EMDR protocol, the reduction of the SUD score acts as an indicator for what is represented in the mind of the subject and for the negative emotions which the drawing arouses in the subject.

The results of the IES-R questionnaire of the 45 subjects with scores over 24 at T1 were monitored up to the third EMDR-IGTP administration (T3), where 36 questionnaires were considered valid, and at the follow-up (T4), where 35 were considered valid.

Analysis of the PTSD level of subjects at T1 showed 17 with partial PTSD (37.8%), 7 with full PTSD (15.6%), and 21 with severe PTSD (46.7%). The IES-R questionnaire scores went from a minimum of 24 to a maximum of 65 (average: 38.27 and std dev: 11.42).

During assessment of the follow-up at T4, the IES-R questionnaire showed 13 subjects without PTSD (37.1%), 8 with partial PTSD (22.9%), 3 with full PTSD (8.6%), and 11 with severe PTSD (31.4%), as well as 10 missing cases.

The results of the total scores and of the IES-R subscales are shown in **Table 2** and **Figure 1**.

To compare the results of the IES-R and subscales at T1, T3, and T4, an ANOVA for repeated measures and a *post hoc* Bonferroni-corrected analysis were performed to determine the significance and direction of the differences of the IES-R scores relating to the first and third administrations (T1 and T3) and the measures performed at follow-up (T4).

The analysis of the total scores on the IES-R scale with $F(2.58) = 17.195$, $p < 0.001$, $\eta^2 = 0.37$ showed statistically significant differences between T1 and T3, and between T1 and T4, but not between T3 and T4.

Analysis of the subscales showed a significant statistical difference only between T1 and T3 for the hyperarousal subscale with $F(2.58) = 10.802$, $p < 0.001$, $\eta^2 = 0.27$; a significant difference between T1 and T3 and between T1 and T4, but not between T3 and T4 for the avoidance subscale with $F(2.58) = 12.961$, $p < 0.001$, $\eta^2 = 0.31$; and the same for the intrusion subscale with $F(2.58) = 14.648$, $p < 0.001$, $\eta^2 = 0.34$ (**Table 3**).

Results SUD Scores

To analyze the scores on the SUD scale, an ANOVA for repeated measures and a *t*-test for paired samples were performed to verify the reduction of the SUD score at the ends of the first (SUD A, SUD B, SUD C, and SUD D at T1) and third sessions (SUD A,

TABLE 3 | Impact of Event Scale-Revised score comparisons.

	(I) IES-R total	(J) IES-R total	Mean difference (I-J)	Std. error	Sig. b	95% confidence interval for difference	
						Lower bound	Upper bound
Total score	T1	T3	16.05*	2.88	0.00	8.72	23.38
		T4	9.99*	2.63	0.00	3.32	16.67
Avoidance	T1	T3	5.03*	0.95	0.00	2.62	7.44
		T4	3.53*	1.04	0.00	0.88	6.18
Intrusion	T1	T3	6.64*	1.30	0.00	3.34	9.95
		T4	4.43*	1.31	0.00	1.10	7.77
Hyperarousal	T1	T3	6.64*	1.30	0.00	3.34	9.95
		T4	4.43*	1.31	0.00	1.10	7.77

*Comparison of pairs, correction for multiple comparison: Bonferroni, *$p < 0.05$.*

SUD B, SUD C, and SUD D at T3), as well as of the first and the last scores on the SUD scale from the first session to the last (SUD A and SUD D at T1 and T3).

The results of the analysis showed a significant reduction of the SUD score during the first administration between the first score (SUD A) and the third and fourth scores (SUD C and SUD D) (**Table 4**).

As well as the average decrease recorded in each phase of the administration, it is interesting to note, as evidence of the progressive working-through of the trauma, that also the initial levels of SUD (A) progressively diminish over time, in the same way that there is a significant reduction of the SUD linked to the final reading (D) between T1 and T3 ($p < 0.05$) (**Figure 2**).

TABLE 4 | Subjective Units of Disturbance (SUD) scores at T1 and T3.

T		Total	
		M	*SD*
T1 ($N = 40$)	SUD A*	6.93	2.06
	SUD B	6.09	2.36
	SUD C*	5.55	2.76
	SUD D*	4.93	3.11
T3 ($N = 30$)	SUD A*	2.93	2.377
	SUD B	2.63	2.428
	SUD C*	2.27	2.149
	SUD D*	1.43	1.357

$p < 0.05$.

Discussion

The analysis of the scores reported on the IES-R and SUD scales by subjects who in the first administration had scored a total over 24 on the IES-R scale (possible diagnosis of PTSD) made it possible to hypothesize the efficacy of the EMDR-IGPT treatment in reducing in the subjects, in every phase of the intervention, both the PSTD symptoms and the negative emotiveness connected with the representations of the traumatic event.

The results of this research obtained positive confirmation with regard to the EMDR-IGTP protocol for the treatment of PTSD in a sample of adolescent survivors of an earthquake, for both the results of the IES-R scale and those of the analysis of the SUD scales.

The analysis of the IES-R scale and relative subscales makes it possible to hypothesize the efficacy of the treatment in reducing the number of subjects with probable PTSD, as seen in the comparisons between the first and final sessions of the treatment, between the first session and administration of the

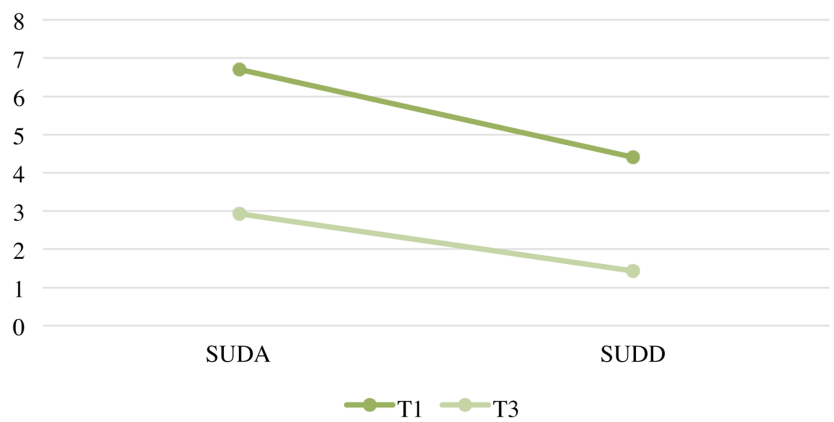

FIGURE 2 | Graphic Subjective Units of Disturbance (SUD) A and SUD D at T1 and T3.

IES-R questionnaire in the follow-up more than 3 months later, in the total scores and in the scores on the avoidance and intrusion subscales. The analysis thus seems to confirm the efficacy of the treatment and the lasting nature of the results of application of the EMDR-IGPT protocol, as already documented in various studies and despite possible retraumatization caused by successive tremors. With regard to the hyperarousal subscale, the only significant result was the reduction between the first and last administration, and not the reduction concerning the results which emerged in the follow-up. This latter fact can be explained by the clinical significance of the hyperarousal scale, which highlights a state of alarm and continued perception of a state of possible danger. Yet considering the living conditions of the population studied (temporary housing in the stricken areas) and their exposure to a second earthquake, this does not come as a surprise. Indeed, it acknowledges the importance of a structured intervention with the dual aim of managing PTSD symptoms and preventing the worsening of the post-traumatic condition in vulnerable subjects. The fluctuating scores of the results of the IES-R questionnaire were found, although much less markedly, in other studies on the efficacy of the EMDR treatment, in particular in the reference study by Konuk et al. (2006) on the 1999 earthquake in Marmara, Turkey, which showed a substantial reduction of PTSD symptoms between the pre- and post-treatment phases, and an increase in the symptomatology, although slight, between the post-treatment and the follow-up. The differences in extent of this phenomenon between the reference study and our results may have two explanations. The first is methodological and organizational: in the study by Konuk et al. (2006), five sessions of traditional EMDR treatment were held, two more than in the EMDR-IGPT treatment applied in this research. The second concerns the continuing strong seismic activity between the various phases of the treatment of this research. While causing no victims, as there was no post-traumatic period of safety, it added to a perception of continuing danger which could both prevent consolidation in the subjects' memory of the critical event of the first unexpected tremor and elicit negative feelings and emotions similar to those of the original event (Fernandez, 2017).

The results of analysis of the SUD scores can be used as general indicators of the therapeutic process and of the working-through of the traumatic event, in that they provide a relative indication of the negative emotional load associated with the subjects' representations of the event (Kim et al., 2008). These results highlighted a significant reduction in the emotional disturbance of the subjects in every phase of administration, and a reduction over time of both the initial SUD levels and the final SUD scores, as evidence of the progressive working-through of the traumatic event. From a clinical point of view, because part of the IGPT protocol is to identify subjects who are not responding to the group process, it was provided additional individual EMDR work with those individuals.

Limits of the Research

It is necessary to underline certain limits of this research determined by the humanitarian nature of the intervention, such as the relatively limited sample number, the absence of randomization procedures and the impossibility of setting up a control group, a forced choice due to the priority of guaranteeing to all receivers of the intervention treatment aimed at preventing medium- and long-term psychological disturbances arising and treatment of the acute and chronic symptoms due to post-traumatic stress.

CONCLUSION

This study allows us to hypothesize the efficacy of the EMDR-IGPT intervention in a group of adolescent earthquake survivors. Today, EMDR continues to be the subject of scientific research in the field of PTSD therapy and its efficacy continues to be confirmed by many studies. However, especially in the field of emergencies, which are characterized by a series of challenges due to the event's implicit characteristics, such as non-predictability and the ethical implications which oblige sudden intervention, there is an important difficulty in monitoring the results of the intervention.

Further studies and scientific evidence are auspicable and, as underlined by Shapiro herself, the need continues for studies concerning this issue, especially to reach a more profound understanding of the underlying mechanisms and neurobiological correlates of the treatment (Shapiro and Laliotis, 2011).

AUTHOR CONTRIBUTIONS

GM, MZ, and CC planned the research design and wrote the article; CM and SP contributed to the manuscript; DT and VL contributed to the statistical analyses under CC's supervision.

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The Progressive Approach to EMDR Group Therapy for Complex Trauma and Dissociation: A Case-Control Study

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Eye Movement Desensitization and Reprocessing is a psychotherapeutic approach with recognized efficiency in treating post-traumatic stress disorder (PTSD), which is being used and studied in other psychiatric diagnoses partially based on adverse and traumatic life experiences. Nevertheless, there is not enough empirical evidence at the moment to support its usefulness in a diagnosis other than PTSD. It is commonly accepted that the use of EMDR in severely traumatized patients requires an extended stabilization phase. Some authors have proposed integrating both the theory of structural dissociation of the personality and the adaptive information processing model guiding EMDR therapy. One of these proposals is the Progressive Approach. Some of these EMDR procedures will be evaluated in a group therapy format, integrating them along with emotional regulation, dissociation, and trauma-oriented psychoeducational interventions. Patients presenting a history of severe traumatization, mostly early severe and interpersonal trauma, combined with additional significant traumatizing events in adulthood were included. In order to discriminate the specific effect of EMDR procedures, two types of groups were compared: TAU (treatment as usual: psychoeducational intervention only) vs. TAU+EMDR (the same psychoeducational intervention plus EMDR specific procedures). In pre-post comparison, more variables presented positive changes in the group including EMDR procedures. In the TAU+EMDR group, 4 of the 5 measured variables presented significant and positive changes: general health (GHQ), general satisfaction (Schwartz), subjective well-being, and therapy session usefulness assessment. On the contrary, only 2 of the 5 variables in the TAU group showed statistically significant changes: general health (GHQ), and general satisfaction (Schwartz). Regarding post-test inter-group comparison, improvement in subjective well-being was related to belonging to the group that included EMDR procedures, with differences between TAU and TAU+EMDR groups being statistically significant [$\chi^2(1) = 14.226$; $p < 0.0001$]. In the TAU+EMDR group there was not one patient who got worse or did not improve; 100% experienced some improvement. In the TAU group, 70.6% referred some improvement, and 29.4% said to have gotten worse or not improved.

Keywords: EMDR, complex trauma, dissociation, group therapy, progressive approach

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INTRODUCTION

Nowadays, EMDR therapy (Shapiro, 1989, 2001) is one of the main treatments of choice for post-traumatic stress disorder (PTSD), as recent meta-analysis have demonstrated (Bisson et al., 2013). Bilateral stimulation (BLS)–characterized by saccadic eye movements, tactile (tapping), or auditory BLS–is a specific component of this type of psychotherapy, and an active contributor to its therapeutic effectiveness (Lee and Cuijpers, 2013).

EMDR is a therapeutic approach structured into eight phases. Phase 1 includes case conceptualization and development of a therapeutic treatment plan. Phase 2 consists of patient stabilization and preparation for further trauma work. Phases 3 to 8 focus on accessing and processing the traumatic memories that are at the core of the presenting problems. Treatment covers past events, present triggers, and future templates.

The use of EMDR in severely traumatized patients with complex trauma and dissociative disorders requires a specific evaluation in Phase 1 and an extended stabilization phase. Different international groups support this phase-oriented model (International Society for the Study of Trauma, and Dissociation [ISSTD], 2011; Cloitre et al., 2012), but a strong debate is taking place in the scientific community regarding the need for specific procedures such as Resource Development and Installation, emotional regulation training, or working with the internal system of dissociative parts (Jongh et al., 2016).

Different authors have proposed adapting the standard EMDR procedure for the treatment of those severely traumatized patients who are included in the complex trauma and dissociation categories (Forgash and Copeley, 2008; Paulsen, 2009; Gonzalez and Mosquera, 2012). A recent review of these adaptations based on the theory of structural dissociation of the personality has been proposed by Van der Hart et al. (2010, 2014a,b). Nevertheless, this area of study lacks systematic research on the use of these EMDR protocols. One of the proposals is the Progressive Approach (Gonzalez and Mosquera, 2012), characterized by gradually approaching traumatic contents. Specifically in Phase 2, psychoeducational work on understanding the general impact of early attachment and trauma, self-care patterns, emotional regulation, and personality fragmentation, is combined with protocols that include BLS. In these protocols, the target to be processed is not a memory; instead, the work focus on dissociative phobias, difficulties in healthy self-care, blockages, and small fragments of traumatic issues. In these interventions, the patient focuses on a self-care image or a dissociative part, noticing the disturbance related to this. BLS is used to desensitize the negative emotions elicited by the target. BLS is also used to reinforce adaptive elements such as resources, adequate self-care, or co-consciousness. In this case, the target is a positive element, and shorter sets of BLS are applied, that usually promotes connection with that resource and reinforces it. The Progressive Approach hypothesis is that this work will promote emotional regulation and dual attention, which are essential for accessing and processing traumatic memories in Phases 3 to 8 of the standard EMDR protocol.

EMDR group therapy is a proposal by Jarero et al. (2006) and Jarero and Artigas (2010). Initially developed for childhood populations, it has also been used successfully with adults, mainly in the context of catastrophes (Jarero and Artigas, 2010; Jarero et al., 2011). In these studies, the patients had been through the same event, thus sharing a common processing target.

In this article, EMDR procedures from the Progressive Approach proposal (Gonzalez and Mosquera, 2012) were tested in a group format on patients with complex trauma and a history of different kinds of intrafamilial childhood trauma and/or gender abuse. Patients had different clinical diagnosis, frequent comorbidity and, many of them, relevant levels of dissociative symptomatology. The main objective was working on stabilization, so treatment was considered as a part of Phase 2. Trauma work was intentionally avoided and would be approached individually. Two types of groups were analyzed, and in one of them specific EMDR protocols were included, such as resource development and installation (RDI; Korn and Leeds, 2002), self-care pattern procedures, and processing of dissociative phobias and blockages (Gonzalez and Mosquera, 2012).

MATERIALS AND METHODS

The study was conducted on patients referred to the Trauma and Dissociation Program of A Coruña University Hospital due to an identified history of severe trauma or relevant dissociative symptomatology. The Trauma and Dissociation Program provides a multi-modal approach, including individual therapy (EMDR), family therapy, and trauma-oriented group therapy.

In its initial phase, group therapy focused predominantly on psychoeducation, including information about trauma, attachment, and structural dissociation; emotional regulation; and interpersonal difficulties derived from adverse experiences.

This study attempted to assess whether certain procedures - including BLS- could be introduced in a group setting. Due to the fact that patients in this sample did not share a common event, but did share common difficulties, targets included the latter. Patients in the Trauma and Dissociation Program usually suffer from severe emotional dysregulation and show low functioning levels; thus, procedures were very controlled and directive, but adapted for each patient's particular characteristics.

The hypotheses to be tested were:

(1) EMDR procedures proposed in the Progressive Approach (Gonzalez and Mosquera, 2012), including BLS, can be used during Phase 2 stabilization in patients with complex trauma and dissociation.
(2) These procedures can be included in a group therapy format.
(3) Specific procedures, such as resource installation, self-care techniques, and processing of dissociative phobias (phobia of dissociative parts, mental contents, change) and blockages can be safe and helpful for this type of patients.
(4) When these procedures are included, the group will experience more benefits than when they are not included.

Bilateral stimulation was performed using tactile stimulation (tapping) instead of eye movements for practical reasons. Self-administered BLS was the predominant modality used due to the difficulty of using eye movements in this setting. The therapists guided the timing, the modality, and the duration of the BLS sets. Patients were provided with minimal information about BLS effects, the therapist explained them some elements of EMDR therapy will be used at some specific moments, and that the effect could be different in different people. This vague description tried intentionally to not suggest any beneficial effect of BLS.

The group was presented as oriented to the consequences of trauma, but not the traumatic memories itself. When these memories emerged, the therapist oriented the patients to the present time and help them to focus on the general topic of the session.

Sample

Among the different group formats in the Program of Trauma and Dissociation, psychoeducational groups were selected for the study, due to the fact that they share a common structure. This psychoeducational work was considered the TAU condition. All the patients included in the groups were informed about the study, and they consent to participate in it. The content of the sessions was related to the main issues observed in complex traumatization and dissociative disorders (Boon et al., 2011; Gonzalez and Mosquera, 2012; Gonzalez, 2013; Mosquera, 2013). Group work covered the aftermath of trauma related to core beliefs, emotional regulation, and personality fragmentation. Group sessions were structured based on the following topics:

(a) General difficulties to engage in therapy and general rules for the group, emphasizing behavioral activation, and personal commitment to the therapeutic process.
(b) Phobia of future and healthy change, and lack of positive expectations as common consequences of trauma.
(c) Defense mechanisms stuck in trauma time, which become automatisms in the face of non-dangerous triggers.
(d) Understanding personal symptoms and problems, as well as their origins.
(e) Identifying dysfunctional emotional regulation strategies and attachment styles.
(f) Self-care patterns.
(g) Dissociative parts of the personality and core beliefs.
(h) Learning assertiveness and setting boundaries.

EMDR procedures were introduced when therapists considered that the reinforcement of adaptive elements was relevant or when specific dissociative phobias were activated. Working on early traumatic events was intentionally avoided, allowing these memories to be individually processed in EMDR therapy Phases 3–8. Patients had the option of stopping BLS or not using it at any given time. Short sets of tapping were used, and the therapist was in charge of establishing the beginning and the end of each set.

EMDR procedures including BLS were introduced after session 3, gradually increasing the amount of sets per session. The total duration of BLS sets per session did not exceed 10 min. After each set, consisting of 6–8 movements, therapists checked the effect of BLS on every participant, helping with cognitive interweaves as needed.

Patients in both groups (group TAU and group TAU + EMDR) attended additional individual therapy with their psychiatrist and psychologist. Group sessions lasted 90 min, usually on a weekly basis.

Psychometric Instruments

Instruments covering a wide range of symptomatic areas were used, given that patients presented a variety of clinical diagnoses (depressive, anxiety, bipolar, psychotic, personality, and dissociative disorders) with very different symptomatic profiles. Dissociative symptomatology was specifically evaluated given the recommended precautions when using EMDR with these populations (Fine et al., 1995).

Dissociative Experiences Scale (DES)

A 28-item self-administered instrument, developed by Bernstein and Putnam (1986), designed to measure dissociative symptomatology. Items are scored, depending on the frequency of each dissociative experience, in a range from 0 to 100, where 0 represents "never" and 100 "always." Central points represent 50% of the time. The global score is the sum of the score given to every item, divided by 28. The higher the global score, the more severe the dissociative symptomatology, so improvement is indicated by a decrease in the DES score. The DES has good psychometric properties, with a Cronbach's α of 0.91 in its Spanish validation (Icarán et al., 1996). Cronbach's α in our sample was 0.9.

General Health Questionnaire (GHQ-28)

Developed by Goldberg and Hillier (1979), this 28-item self-administered questionnaire is designed to evaluate mental health in a broad sense. Answers are to be given in reference to the last few weeks. Items are divided in four sub-scales: A (somatic symptoms), B (anxiety and insomnia), C (social dysfunction), and D (severe depression). Items are scored using values of 0, 0, 1, 1 for the answers. A decrease in the general sub-scales scores represents improvement. In this study, the Spanish version by Muñoz et al. (1979) is used. It was validated by Lobo et al. (1986), showing good psychometric properties, with 84.6% of sensitivity and 90.2% of specificity. Cronbach's α in our sample was 0.94.

Schwartz Outcome Scale (SOS-10)

Developed by Blais et al. (1999), this brief self-report tool measures mental health treatment outcomes (Blais et al., 2011). The Spanish version was developed by Rivas-Vazquez et al. (2001). It has shown to be a reliable measurement of mental health and well-being sensitive to change with treatment. The SOS-10 is a 10-item scale using scores that range from 0 to 6. Improvement is reflected in the increase of the global score. The instrument shows good psychometric properties, with a Cronbach's α of 0.84–0.96, and good construct validity and applicability in different samples (Young et al.,

2003; Haggerty et al., 2010). Cronbach's α in our sample was 0.89.

Analog Scale of Inter-sessions Well-being

Patients evaluate their general well-being in an analog scale, ranging from 0 to 10, in which 0 represents "very bad" and 10 "very good."

Analog Scale of Therapy Session Usefulness

Patients evaluate the general subjective usefulness of therapy sessions in an analog scale ranging from 0 to 10, in which 0 represents "not useful at all" and 10 "very useful."

Procedure

Two groups of patients were analyzed (TAU = psychoeducational only, and TAU+EMDR = the same educational work plus EMDR procedures), each one of them composed of several sub-groups. By clinical reasons, each therapeutic group cannot include more than eight patients. BLS was introduced in two of the groups, along with the previously described procedures. In three of the groups, the psychoeducational content was the same, but BLS was not included. These groups were recruited once there were seven patients in the Trauma and Dissociation Program who met the inclusion criteria and accepted to participate in the study. Inclusion was random; it depended only on when each patient arrived to the program and did the initial evaluation. Groups with and without BLS were created alternatively (TAU/TAU+BLS/TAU/TAU+BLS/TAU). Assigning patients to each group was not based on clinical, personal, or sociodemographic characteristics. It was considered that, since the patient's arrival to the program was entirely random, inter-group homogeneity was guaranteed. Any other kind of randomization would force many patients to have to wait for months to be treated, so it was disregarded for ethical reasons. The Ethics Committee of Galicia approved the study (resolution 2016/279), and all participants signed an informed consent.

The total sample consisted of 31 patients [$M = 28$ (90.3%), $H = 3$ (9.7%)] distributed in a control group (group therapy without EMDR: TAU) and an experimental group (group therapy and EMDR: TAU+ EBL). Group TAU+ EMDR included 14 patients (12 women and 2 men) and group G, 17 patients (16 women and 1 man). Ages ranged from 20 to 59 years.

The inclusion criteria was accepting to participate in a group therapy (some patients with prominent social phobia preferred only individual therapy), having a history of severe traumatization, understanding by this the presence of early severe and interpersonal trauma. Most patients had suffered early intrafamilial abuse (emotional, physical or sexual) and attachment disruptions with their main caregivers. In some cases, there were additional significant traumatizing events in adulthood, such as intimate partner violence, sexual assault, or severe accidents. Early severe traumatization has multiple psychopathological consequences, and clinical diagnoses were diverse. The sample included depressive disorders ($N = 12$), anxiety disorders ($N = 2$), dissociative disorders ($N = 7$), schizoaffective disorder ($N = 2$), substance abuse ($N = 2$), OCD ($N = 1$), conversion disorder ($N = 2$), and PTSD ($N = 3$). Comorbidity was common, and 16 patients met criteria for personality disorder.

Eight patients who met inclusion criteria and participated in some group sessions were not included in the analysis, because they did not attend more than 50% of the sessions. Thus, the amount of treatment was considered insufficient for evaluation. Two other patients did not complete the post-treatment evaluation. From these 10 patients, 6 have been included in the TAU group, and 4 in the TAU+EMDR group.

Mann–Whitney test was used for pre-test and post-test comparison. Wilcoxon signed rank test was used for pre-post intra-group comparisons. Finally, a Chi-square test was performed after recoded variables as improvement/no improvement categories, to analyze post-test results from a clinical perspective.

RESULTS

Pre-test Comparison

Patients included in both groups presented a general symptomatology mean of 27.67 (measured with GHQ) and a dissociation mean of 27.64 (measured with DES), indicating significant dissociative symptomatology.

There were no statistically significant differences at pre-test between TAU and TAU+EMDR in dissociative symptoms (DES), general satisfaction (Schwartz), and general well-being using the Mann–Whitney test. Nevertheless, general symptomatology levels -measured using GHQ scores- offered statistically significant differences at pre-test between the TAU and TAU+EMDR groups ($p = 0.001$). The TAU group, as it may be noted, presented more dispersion in GHQ scores, being a less homogeneous group in regards to symptom severity. Statistics are presented in **Table 1**.

Pre-post Differences in the TAU+EMDR Group

In the TAU+EMDR group (see **Table 2**), 4 of the 5 measured variables presented significant changes: GHQ general health decreased symptomatology from $M = 22.428$ ($SD = 4.586$) to $M = 18.642$ ($SD = 6.628$); Schwartz general satisfaction increased from $M = 26.214$ ($SD = 9.56$) to $M = 32.785$ ($SD = 11.053$); subjective well-being increased from $M = 3.357$ ($SD = 2.179$) in the first half of the sessions to $M = 5.578$ ($SD = 2.08$) in the second half (effect size: 0.45); and therapy session usefulness assessment changed from $M = 3.9256$ ($SD = 1.402$) in the first half of the sessions to $M = 5.091$ ($SD = 1.746$) in the second half. General health and general satisfaction showed a medium effect size (>5) and subjective well-being and session perceived usefulness a large effect size (>7).

Pre-post Differences in Group TAU

Only 2 of the 5 variables in the G group (see **Table 2**) showed statistically significant changes: GHQ general health ($Z = -2.479$; $p = 0.013$) scores decreased from $M = 32$

TABLE 1 | Main pre-test statistics in TAU and TAU+EMDR groups.

	TAU+EMDR				TAU			
	M	*SD*	Median	IQR	*M*	*SD*	Median	IQR
General satisfaction (Schwartz)	26.21	9.56	25.0	12.25	21.53	9.76	18.0	14.5
Dissociative symptoms (DES)	25.56	13.37	23.75	22.76	29.35	19.49	25.36	27.85
General health (GHQ)	22.43	4.58	18.5	12.25	32.0	10.23	27.0	18.5

TABLE 2 | Wilcoxon signed rank test intragroup pre-post differences.

	TAU+EMDR			TAU		
	Z	*p*-Value	Effect size	*Z*	*p*-Value	Effect size
General health (GHQ)	−2.50	0.001	**0.66**	−2.48	0.013	**0.60**
General satisfaction (Schwartz)	−2.48	0.013	**0.66**	−2.29	0.022	**0.55**
Dissociative symptoms (DES)	−0.94	0.345	0.25	−1.28	32.0	0.31
Subjective well-being	−3.30	0.001	**0.88**	−1.28	0.201	0.28
Session usefulness assesment	−2.95	0.003	**0.78**	−1.16	0.246	0.22

Bold values represent significant values or medium-large effect size.

($SD = 10.228$) to $M = 29$ ($SD = 12.267$), and Schwartz general satisfaction ($Z = -2.294$; $p = 0.022$) increased from $M = 21.529$ ($SD = 9.760$) to $M = 29.058$ ($SD = 13.413$). Both variables presented a medium effect size.

Differences in Compliance with Sessions

The TAU+EMDR group showed less compliance rates. In this group, only 7 out of 14 (50%) attended more than 80% of the sessions. The percentage patients attending more than 80% of the sessions in group TAU was 88.2%: 15 out of 17. These differences are statistically significant [$\chi^2(1) = 5.452$; $p = 0.020$].

Nevertheless, attending a higher number of sessions does not appear to be related to increase in improvement. Between patients attending more than 80% of the sessions in both groups, 22.7% of them ($N = 5$) stated feeling worse or the same, and 77.3% ($N = 17$) referred feeling better [$\chi^2(1) = 14.226$; $p < 0.0001$]. All patients attending less than 80% of the sessions (100%, $N = 9$) referred improved well-being.

As discussed below, this result may be related to the lower attendance in the TAU+EMDR group, which on the other hand, presents better results in a higher number of variables. The group using BLS procedures showed less therapeutic compliance (over 50%), but this did not affect clinical improvement. We do not know whether better compliance would have improved results in the TAU+EMDR group.

Post-test Inter-group Comparison

Pre-post comparisons determined the statistical significance reached by inter-group differences. Patients were classified into two categories depending on whether symptoms worsened/not improved or improved. TAU and TAU+EMDR groups were compared. The following results were observed:

Improvement in subjective well-being (**Figure 1**) was related to belonging to the group that included EMDR procedures, with differences between TAU and TAU+EMDR groups being statistically significant [$\chi^2(1) = 14.226$; $p < 0.0001$]. In the TAU+EMDR group there was not one patient who got worse or did not improve; 100% experienced some improvement. In the TAU group, 70.6% referred some improvement, and 29.4% said to have gotten worse or not improved.

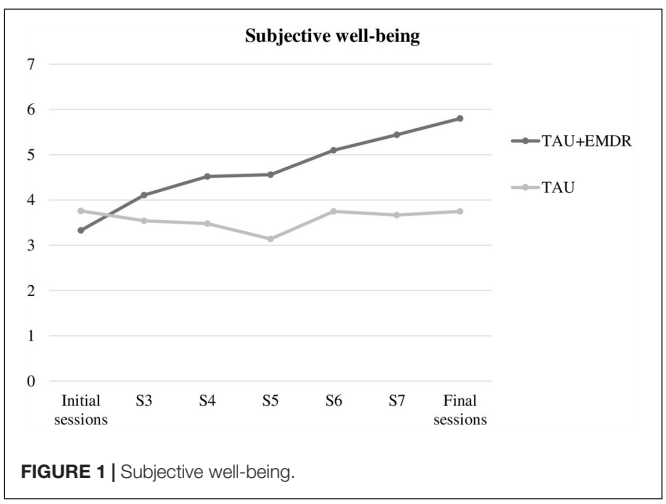

FIGURE 1 | Subjective well-being.

In addition, a statistically significant association was found between session subjective usefulness (**Figure 2**) both in the first and second half of the therapy, and belonging either to TAU or TAU+EMDR [$\chi^2(1) = 0.9323$; $p = 0.002$], with a higher tendency in TAU+EMDR (85.7% vs. 70.6% in TAU) to evaluate sessions in the second part of therapy -which included more EMDR interventions- as more useful. Interestingly, the mean assessment of session usefulness was more irregular in the TAU+EMDR group, with many sessions presenting a lower evaluation, which could be related to the BLS effect of increasing connection with unpleasant emotions.

When comparing other variables presenting pre-post intra-group differences (GHQ and Schwartz) (**Figures 3**, **4**),

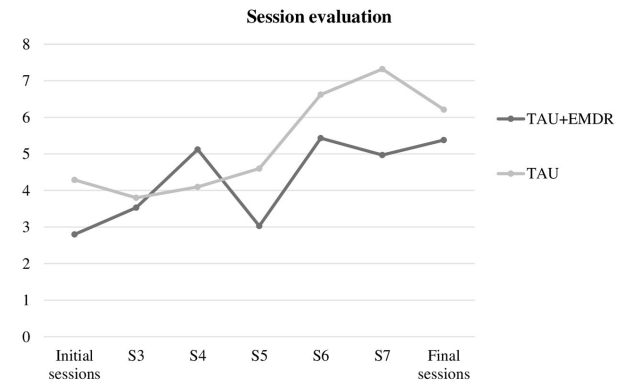

FIGURE 2 | Session evaluation.

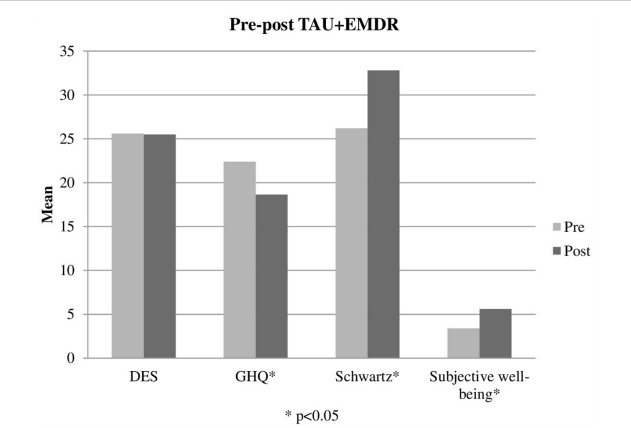

FIGURE 3 | Pre-post TAU+EMDR.

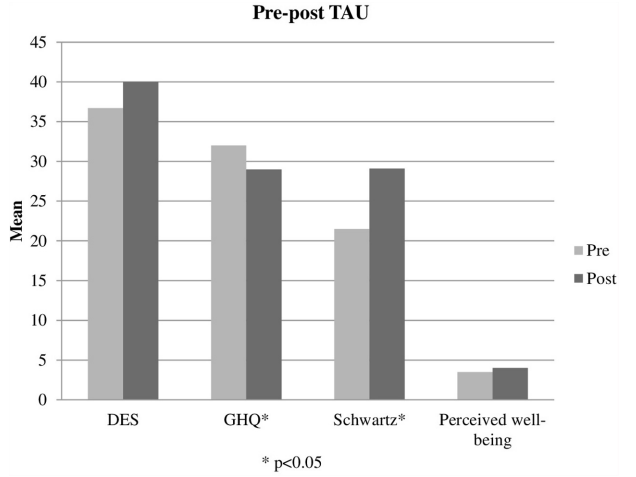

FIGURE 4 | Pre-post TAU.

differences between TAU and TAU+EMDR groups did not reach statistical significance. In the Schwartz scale, there was a larger tendency of improvement for TAU+EMDR (71.4% improved their scores) compared to TAU (58.8% improved). Similarly, dissociative symptomatology (using DES scores) decreased 57% in TAU+EMDR and 35.3% in TAU.

An additional post-test inter-group comparison was done analyzing quantitative variables using a Mann–Whitney test. All the variables showed a more positive tendency in the TAU+EMDR, but only general well-being was close to statistical significance ($p = 0.07$) with an effect size (0.32). Effect size for general satisfaction was low (0.19) and also for dissociative symptoms (0.09). General health variable also reached statistical significance ($p = 0.017$) but this variable presented pre-test significant differences. Perceived session usefulness presented an effect size of 0.26.

Interestingly, there was a discrepancy between session usefulness subjective evaluation and changes in well-being. When comparing the first half of the sessions and the second half, the evaluation was higher in the TAU+EMDR group than in the TAU group. But when analyzing each session's graphics, there is a tendency in TAU+EMDR to evaluate the part of the session including a higher number of BLS procedures as less useful. This tendency changed for the final sessions, in which both groups presented more similarities.

In regards to well-being, the graphic appears completely different. The TAU+EMDR group showed a gradual increase in subjective well-being mean, while the TAU group barely changed throughout the eight therapy sessions.

The analysis of these outcomes supports the clinical impressions from the therapists. Groups including EMDR procedures seemed to evolve more positively, but given that patients suffer from complex trauma and high levels of dissociative symptomatology, BLS sometimes has the effect of increasing the connection with unpleasant emotions and sensations. These patients used to disconnect from those emotions, or showed a tendency to avoid or suppress them.

DISCUSSION

Results should be analyzed with caution due to the following limitations of the study: groups did not run in parallel, but consecutively, due the characteristics of the Trauma and Dissociation Program. The study was performed in a clinical setting, so it is not a pure research design. Diagnosis was heterogeneous, and a limited number of subjects were included. Contrary to Jarero et al. (2011) proposal, patients did not share an identical traumatic event, but common consequences of different types of severe trauma.

Nevertheless, this study may offer relevant information. Firstly, in a group of severely traumatized people, the application of EMDR procedures that included BLS was safe when used in a very limited and controlled way. The group in which EMDR procedures were applied showed a more positive tendency, with improvement in a higher number of intra-group variables and significant positive differences in inter-group well-being at follow up. General satisfaction showed a positive tendency in this group, though statistical significance was not reached. On the contrary,

dissociation remained at similar levels in TAU+EMDR, while increased in TAU, without reaching statistical significance.

Results are modest but relevant, keeping in mind that BLS was used very tentatively, in short sets, only after session 3, and only for a few minutes -a maximum of 10 min-, including preparation for the procedure, patients' feedback and therapist interventions to contain disturbing material. Eight sessions of group therapy are only a small portion of the therapeutic process required for this kind of patients, so small changes should be valuable.

At the same time -and along with the observations referred by the therapists-, the fact that some of the sessions that included EMDR procedures in the second period were valued as less useful, make us think that patients in this clinical population would show difficulty tolerating longer sets of BLS. Connection with emotions and self-regulation of disturbance is not easy for severely traumatized individuals. EMDR with adapted protocols could be used to promote improvement in this clinical group, but the amount of time allotted for these interventions should be carefully calculated.

Another interesting result was that these specific EMDR procedures, with limited BLS use, were safe for patients with relevant levels of dissociative symptomatology, resulting in a discrete decreasing tendency in DES scores in the group that included EMDR, and some increase in TAU groups.

During group sessions, EMDR therapy was intentionally not described in depth, explaining only that BLS was meant to unblock emotions and sensations. The reason for giving so little information was to avoid the suggestive component in the application of BLS. But at the same time, it could influence the fact that patients in the TAU+EMDR group valued some sessions as less useful. These results favor the need of giving more information in order to prepare the patients for understanding the effects of BLS and manage their emotions and sensations.

Based on the outcomes of this pilot study, a second stage of group therapy will be developed, which will include: specific EMDR preparation, more occasional specific material to promote reflective thinking, and improving patient's understanding of relevant concepts, such as self-care and personality fragmentation.

CONCLUSION

Introducing certain specific EMDR procedures in a group therapy setting for severely traumatized patients appears to be safe and positive. These procedures seem to offer additional benefits to the psychoeducational work oriented toward post-traumatic consequences, when they are included progressively in a very directive and controlled manner. This allows the patient to tolerate connection with disturbing material and assimilate the changes that he or she is experiencing.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of Galicia with written informed consent from all subjects in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Galicia.

AUTHOR CONTRIBUTIONS

All authors contributed to the final version of the manuscript. Study design and intervention: AG-V, IF, FG-G, and LR-L; method: MS-P and MS-G; data analysis: AG-V, MS-P and MS-G.

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Dealing With the Aftermath of Mass Disasters: A Field Study on the Application of EMDR Integrative Group Treatment Protocol With Child Survivors of the 2016 Italy Earthquakes

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This study explored the effects of the EMDR Integrative Group Treatment Protocol (EMDR-IGTP) on child survivors of the earthquakes that struck Umbria, a region of central Italy, on August 24th and on October 26th 2016. Three hundred and thirty-two children from the town of Norcia and nearby severely disrupted villages received 3 cycles of EMDR-IGTP. The Emotion Thermometers (ET-5) and the Children's Revised Impact of Event Scale (CRIES-13) were administered before (T0) and about 1 week after the conclusion of the third cycle (T3) of EMDR-IGTP. At T3, older children showed a reduction of distress and anger, whereas younger children reported an increase on these domains; moreover, older children reported a greater reduction of anxiety than younger ones. A greater reduction of distress, anxiety, and need for help was evidenced in females, whereas a greater improvement in depressive symptoms was evidenced in males. The effects of the EMDR-IGTP treatment on post-traumatic symptoms were particularly evident in older children, compared to younger ones, and marginally greater in females than in males; moreover, a greater improvement was found in children who had received a timelier intervention, than in those who received delayed treatment. These results provide further evidence for the utility of EMDR-IGTP in dealing with the extensive need for mental health services in mass disaster contexts. Also, these data highlight the importance of providing EMDR-IGTP in the immediate aftermath of a natural disaster, to contribute significantly in restoring adaptive psychological functioning in children, especially in older ones.

Keywords: EMDR-IGTP, earthquake, mass disaster, children, emotional problems, post-traumatic reactions

INTRODUCTION

Scientific literature has provided large evidence for the detrimental psychopathological *sequelae* of natural disasters among children and adolescent survivors. Even though some individuals may show resilience after facing such traumatic experiences and manifest temporary sub-clinical stress responses (Bonanno, 2004), a wide range of psychopathological outcomes has been documented in the exposed population. The prevalence of psychopathological symptoms among child survivors after natural disasters vary largely across studies, according to differences in the implemented methodologies, disaster type and magnitude, as well as in the diagnostic criteria (for a systematic review, see Wang et al., 2013). Nevertheless, severe psychopathological outcomes, such as anxiety, depression, and post-traumatic stress disorder (PTSD) are commonly observed in individuals who are exposed to natural disaster (Liu et al., 2011; Zhang et al., 2011), along with other forms of emotional distress (Toyabe et al., 2006; Oyama et al., 2012), difficulties in regulating anger (Durkin, 1993; Kar and Bastia, 2006; Becker-Blease et al., 2010), and poorer quality of life (Tsai et al., 2007; Jia et al., 2010).

The prompt availability of psychological interventions in the aftermath of a natural disaster has become essential to prevent the onset, as well as the worsening of psychopathological symptoms in exposed individuals (National Institute of Mental Health, 2002; Te Brake et al., 2009), especially in children, who are more vulnerable to the dramatic effects of critical events, compared to adults (Norris et al., 2002b). Indeed, children's psychopathological responses may be enduring (Ularntinon et al., 2008; Piyasil et al., 2011) and persist until adulthood (Honig et al., 1993; Green et al., 1994), with a significant impairment of their individual functioning throughout their lifespan.

The use of relatively brief trauma-focused treatments has relevant implications in the field of mass disaster contexts, where crisis interventions meet the urgent need "to first stabilize and then reduce symptoms of distress or dysfunction, so as to achieve a state of adaptive functioning, or to facilitate access to a continuum of care when necessary" (Everly and Mitchell, 2008, p. 8). The practice guidelines of the World Health Organization (2013) recommend trauma-focused cognitive behavioral therapy (CBT) and Eye Movement Desensitization and Reprocessing (EMDR; Shapiro, 1989) for children, adolescents, and adults manifesting PTSD symptomatology. However, although both treatments have been proven effective in mitigating the effects of PTSD, in a randomized controlled trial study, EMDR resulted in a faster recovery compared with a more gradual improvement provided by CBT (Nijdam et al., 2012). This is due to the fact that, unlike CBT, EMDR does not require extended exposure, does not ask the traumatized individuals to provide detailed descriptions of the event, and does not include direct challenging of beliefs or homework (World Health Organization, 2013). Therefore, these factors make EMDR therapy particularly suitable to rapidly deal with the psychological *sequelae* of a natural disaster.

EMDR has been recommended as a first-line trauma treatment in the international practice guidelines of several organizations, including the American Psychiatric Association (2004) and the Department of Defense Department of Veterans Affairs (2017). The clinical effectiveness of EMDR for treatment of trauma in adults has been broadly documented in about 30 randomized controlled studies, as reported by the EMDR International Association (EMDRIA, retrieved from http://emdria.site-ym.com/?page=Randomized) and an incremental effect of EMDR has been observed in children and adolescents when EMDR was used along with CBT (Rodenburg et al., 2009). Furthermore, in the field of mass disaster contexts, several studies have examined the role of EMDR in alleviating trauma-related symptoms following natural disasters (Grainger et al., 1997; Chemtob et al., 2002; de Roos et al., 2011; Tang et al., 2015). In this domain, research has documented that, although EMDR and CBT are equally able to induce a long-term amelioration of children's disaster-related post-traumatic symptoms, treatment gains of EMDR are reached in fewer sessions (de Roos et al., 2011).

The theoretical model of the Adaptive Information Processing, which guides the EMDR procedures (AIP; Shapiro, 2001), posits that the intense disturbing affect that accompanies trauma causes the information processing system to fail in adequately processing and storing the information (e.g., images, thoughts, emotions, and sensations associated to the traumatic event) into functional memory networks. The eight-phased EMDR protocol aims at accessing these dysfunctionally stored information and facilitates the integration of traumatic memories, leading to their adaptive resolution (Shapiro, 2012). Throughout the 8 EMDR phases, the person is asked to focus on his/her traumatic memories (*target*), while simultaneously being exposed to alternating bilateral stimulation (i.e., eye movements, tactile taps, or auditory tones).

In the last years, several theoretical models have been proposed to account for the mechanisms of action involved in EMDR: among them, the *working memory theories* and the *orienting response theory* appear particularly interesting. According to the *working memory theories* of EMDR, eye movements and visual imagery both draw upon the same limited capacity working memory resources (Baddeley, 2000). The competition created by the dual task performance impairs imagery, causing it to become less vivid and less emotionally intense (Gunter and Bodner, 2008; Maxfield et al., 2008; van den Hout and Engelhard, 2012): as a result, this can facilitate the accessing and processing of the traumatic memory from a more observational or detached perspective, since the person experiences it as less distressing (Maxfield et al., 2008). According to the *orienting response theory* of EMDR, eye movements activate an "investigatory reflex," which at first induces a state of heightened alertness, and subsequently a reflexive pause, leading to de-arousal in the absence of threat, allowing cognitive processes to become more flexible and efficient (Armstrong and Vaughan, 1996; Kuiken et al., 2001; Lee and Cuijpers, 2013). In addition to these theoretical perspectives, more recent outcomes from electroencephalographic (Pagani et al., 2011, 2012; Trentini et al., 2015) and neurobiological findings (Pagani et al., 2017) have proposed that bilateral stimulation might reproduce the neurophysiological conditions favorable for memory consolidation, weakening the perception of the

traumatic memory, reducing its vividness, and inducing a sense of relaxation and safety.

Several modified EMDR protocols have been developed to tailor EMDR procedures to the processing of traumatic experiences in individuals who reported acute traumatic stress. Among these adjusted protocols, the EMDR Integrative Group Treatment Protocol (EMDR-IGTP) results particularly useful to quickly restore psychological functioning in large groups of survivors of natural disaster. EMDR-IGTP was developed by the members of the Asociación Mexicana para Ayuda Mental en Crisis (AMAMECRISIS) to respond rapidly to the need for mental health interventions, after the 1997 hurricane Pauline that struck the Western coast of Mexico. The EMDR-IGTP takes the wisdom of the Standard EMDR Protocol and applies it in an adapted form, together with a group therapy model, an art therapy format, and the use of the Butterfly Hug (BH), which is a form of self-administered bilateral stimulation (Boel, 1999; Artigas et al., 2000; Artigas and Jarero, 2009; Jarero et al., 2012). This protocol was originally designed within a play therapy format with children and was modified later for its application with adults. The EMDR-IGTP has been largely used in its original format or with some adjustments according to different cultural circumstances, to fulfill the need of post-disaster psychological interventions of survivors of natural or man-made disasters, in numerous places around the world (Jarero et al., 2012; for an extensive review, see http://emdrresearchfoundation.org/toolkit/igtp-children.pdf).

On August 24th and on October 30th 2016, two earthquakes (of 6.0 and 6.5 Richter scale magnitude; retrieved from http://cnt.rm.ingv.it/events?starttime=2016-08-24%2B00%253A00%253A00&endtime=2016-10-31%2B23%253A59%253A59&last_nd=-1&minmag=4&maxmag=10&mindepth=-10&maxdepth=1000&minlat=35&maxlat=49&minlon=5&maxlon=20&minversion=100&limit=30&orderby=ot-desc&tdmt_flag=-1&lat=0&lon=0&maxradiuskm=-1&wheretype=area&box_search=Italia&page=1) struck Umbria, a central region of Italy, causing heavy disruption in the town of Norcia, as well as in many surrounding villages. The day after the first earthquake, the Psychologists Order of Umbria, supported by the Civil Protection of Umbria, established a psychological support network for the population, in collaboration with emergency psychologists and the Italian EMDR National Association. A network of EMDR therapists working *pro bono* immediately delivered an EMDR early intervention, as well as ongoing treatment to survivors. An EMDR-IGTP treatment plan was immediately implemented within an extensive on-site emergency psychology program, 1 day following the first earthquake, with an outreach program based on the principles of emergency psychology: (a) reaching out to the affected community and exposure groups; (b) carrying out an initial psychological triage, to assess the severity of psychological problems and emotional disturbances in the population; (c) providing information in written and verbal form about the typical posttraumatic stress reactions; (d) providing written information to the affected community about the availability of on-site psychological support and EMDR therapists; (e) developing an outreach program and linking with the local municipalities, schools and institutions, police forces, as well as health and social services, in order to provide consistent information among the population. Furthermore, professionals were debriefed about the provision of emergency post-disaster services during the acute phase to the affected population (firefighters, policemen, Carabinieri, members of the Red Cross and forest rangers). Special attention was given to schools, delivering timely psychological support to parents, teachers and students, and planning EMDR-ITGP interventions in accordance with the Ministry of Education, Universities and Research (MIUR).

This intervention was a clear example of a successful collaboration among the Italian EMDR National Association, all institutions and local services that contributed in dealing with the emergency in the aftermath. This preliminary study investigated the effects of EMDR-ITGP on emotional problems and post-traumatic symptoms in children who had been exposed to both earthquakes that struck central Italy on August 24th and on October 26th 2016.

MATERIALS AND METHODS

Participants

Initially, a total of 701 children were recruited at the schools of Norcia and from the nearby severely damaged villages. The schools provided an opportunity to rapidly recruit children, since many people had been displaced from their homes and were living in container homes and makeshift camps. According to the guidelines of emergency psychology, which strongly recommend to provide all individuals (both, those presenting PTSD symptomatology, as well as those presenting subclinical conditions) with prompt intervention, all recruited children were treated with EMDR-IGTP.

Children received EMDR-IGTP once a week for 3 weeks (that is, 3 EMDR-IGTP cycles) and were tested before (T0) and about 1 week after the conclusion of the third treatment cycle (T3). As agreed with the school administrators, and in order to restore normal school routine as quickly as possible, children received only 3 cycles of EMDR-IGTP.

Children who did not complete all EMDR-IGTP cycles ($N = 369$) were excluded from the statistical analyses; thus, the final sample included 332 children, aged between 5 and 13 (Mean = 9.15, Standard Deviation = 2.31).

This study has been carried out in accordance with the recommendations of the Ethics Committee of the Institute of Cognitive Sciences and Technologies of the Italian National Research Council (ISTC-CNR) of Rome. Prior to data collection, children's parents received complete information concerning the rationale and effectiveness of EMDR-IGTP, the study procedures, and handed over their written informed consent to allow their child to participate to the research study, as stated in the Declaration of Helsinki.

EMDR-IGTP Procedure

EMDR Therapists administered the EMDR-IGTP to 22 groups, including 7–24 children (Mean = 10.57, Standard Deviation = 7.01), in the schools of Norcia and of other nearby villages. Each group (hereafter referred to as "EMDR-ITGP Group") had two co-therapists: having two partnered therapists facilitates the management of particularly intense post-traumatic

reactions in some children, who might have blocking beliefs, previous traumatic experiences, and/or might require additional time for processing. Each child completed EMDR-ITGP cycles within the same EMDR-ITGP Group.

The intervention was conducted according to the recommendations of Shapiro (2001) on EMDR treatment, and following the procedures of a partially modified version of the EMDR-IGTP (Fernandez and Maslovaric, 2016) (**Table 1**, **Figures 1**, **2**). The therapists used a symptom-focused approach, to identify the most disturbing aspect of the traumatic event, as well as current triggers and related future anxiety. EMDR-IGTP session duration varied from 60 to 90 min, based on the children's development stage, as well as on how they responded.

Clinical Scales

The Emotion Thermometers [ET-5; Mitchell et al., 2010; Italian translation, retrieved from http://www.psycho-oncology.info/ET.htm] is a widely used tool for the detection and monitoring of emotional disorders. ET-5 includes single-item five scales, providing rapid and reliable measures of four emotional domains (distress, anxiety, depression, anger) and one non-emotion domain (need for help). Each scale is a graphic thermometer chart, which includes the Distress Thermometer, the Anxiety Thermometer, the Depression Thermometer, the Anger Thermometer, and the Need Help Thermometer (**Figure 3**). Each domain is rated on an 11-point Likert scale, ranging from 0 (None) to 10 (Extreme), based on the level of emotional distress experienced during the past week. This is an easy to use tool in a post disaster and field study context, with a simple scoring system. The Children's Revised Impact of Event Scale (CRIES-13; Perrin et al., 2005) is a 13-item scale adapted from the Impact of Event Scale (IES; Horowitz et al., 1979), widely used to screen children at high risk for PTSD. Items are rated on a 4-point Likert scale (None = 0, Rarely = 1, Sometimes = 3, and A lot = 5), according to the frequency of recurrence of post-traumatic stress reactions during the past week, as well as in relation to a specific traumatic event noted at the top of the scale. The total score ranges from 0 to 65 and

TABLE 1 | Overview of the EMDR-IGTP for children.

EMDR-IGTP Phases	Description
Phase 1: Client History	It involves history taking, client evaluation, identification of traumatic memories to be targeted, and treatment planning. In this phase, information collected from parents, caregivers and teachers are an essential aspect of the intervention, since they allow to better evaluate the children's "*ability to deal with the high levels of disturbance potentially precipitated by the processing of dysfunctional information. Evaluation therefore involves an assessment of personal stability and current life constrains"* (Shapiro, 2001, p. 70).
Phase 2: Preparation	Children are prepared for treatment, through stabilization procedures and by increasing access to positive affects. This phase is very important for establishing rapport and trust, as well as for facilitating group formation. Children are repeatedly validated regarding their feelings and other post-traumatic symptoms. Subsequently, the team leader instructs children to perform the BH (Artigas et al., 2000) by crossing their arms and alternating tappings on their chest. Children are asked to close their eyes and think of a place where they feel safe or calm, by using their imagination, visualizing the colors and sounds of this "safe place." At the end of this phase, children are given crayons and paper and are instructed to divide a sheet of the paper in four, marking each square with either A, B, C, and D.
Phase 3: Assessment	Instead of being asked to access the perceptual, cognitive, affective, and somatic components of a specific disturbing memory (as in the standard EMDR protocol), children are asked to think about the most disturbing part of the event (that is, the aspect that made them feel most frightened, angry, or sad), and then draw the image on the paper (see **Figure 1**, drawing A). Therefore, the critical event (and its associated negative emotions) is not visualized mentally (as in traditional EMDR): it is concretely represented in the children's drawing. Children are asked to rate the level of emotional disturbance elicited of their drawing, referring to a scale from 0 to 10 (where 0 is no disturbance and 10 is worst disturbance), and write the number on the upper right hand corner of the drawing. This provides the team with the children's measures of the Subjective Units of Disturbance (SUD).
Phase 4: Desensitization	Children are asked to focus on the first drawing and on its associated emotions, thoughts and bodily sensations, while simultaneously using the BH (for about 30–60 s, depending on the development stage and the level of affect tolerance). After 3 or 4 BH sets, children are asked to draw a second picture related to the event (in square B), and rate it according to its level of distress. Next, children focus on the second drawing and use the BH. This process is repeated until four drawings are done (**Figure 1**).
Phase 5: Installation*	Children are asked to focus on the positive memories or bodily sensations they have experienced throughout the BH sets, and then to draw the image on the back of the paper. Children who can't find any positive memory or sensation are asked to draw the place they feel safe in, along with a written word or a written sentence that describes the picture (see **Figure 2**). The drawing and the word (or sentence) are paired with the BH bilateral stimulation (for about 15–20 s).
Phase 6: Body Scan*	Any residual physical disturbance associated with the memories are processed until children report that the body is clear and free of any disturbance.
Phase 7: Closure*	Children's stability at the end of an EMDR session and between sessions is ensured.
Phase 8: Reevaluation*	At the beginning of the following sessions, therapists assess whether results are maintained or if further reprocessing is needed. In addition to targeting past traumatic experience, EMDR also targets current triggers and related future anxieties.

*BH, Butterfly Hug; *phases in which adjustments to the original EMDR-IGTP (Jarero et al., 2012) were introduced by Fernandez and Maslovaric (2016).*

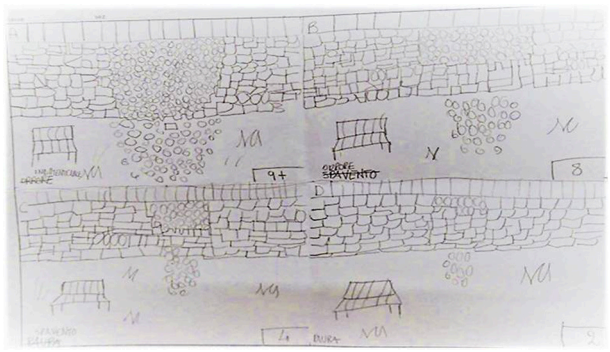

FIGURE 1 | Example of a child's drawings completed during the Assessment and the Desensitization phase of EMDR-IGTP. These drawings have been reproduced with permission from parents.

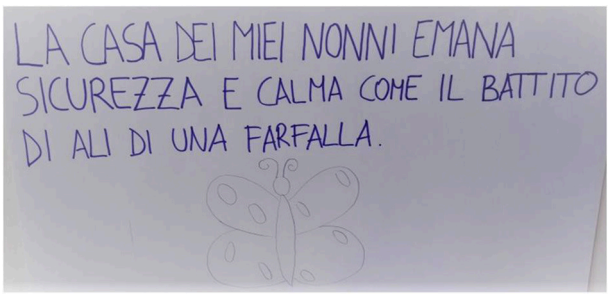

FIGURE 2 | Example of a child's drawing completed during the Installation phase of EMDR-IGTP (translated from Italian to English: "My grandparents' house makes me feel safe and calm, just like the flutter of the wings of a butterfly"). This drawing has been reproduced with permission from parents.

is obtained from the scores on three subscales: Intrusion (four items), Avoidance (four items) and Arousal Symptoms (five items). In this study, only Total score was used in the analyses. Cronbach's α for CRIES-13 score in this study was $\alpha = 0.79$.

Data Analysis

Linear Mixed-Model Repeated Measures were conducted to assess reduction in the severity of emotional problems and post-traumatic symptoms in children over time, assuming pre- and post-EMDR-IGTP as a *Within-Subject* factor (T0 and T3, respectively). Time elapsed from the second earthquake and the administration of EMDR-IGTP (hereafter referred to as "Time elapsed"), Age and Gender were entered as covariates in the analyses to check for their modulation of a *Within-Subject fixed effect* of treatment as well as for identifying systematic *Between-Subjects fixed effects*. EMDR-ITGP Group was a covariate to control for the possible *random effect* of the clustering of the subjects (that is, the inclusion of children within the respective EMDR-ITGP Groups). *Effect sizes* for Total Model (Cohen's f^2) and *specific effects* (η^2_p) were assessed according to Selya et al. (2012) and Olejnik and Algina (2003), respectively.

The analyses were carried out using SPSS 24.0.

RESULTS

The mean and the standard deviations scores of the dependent variables at T0 and T3 are reported in **Table 2**.

As regards the Distress Thermometer, analyses revealed a marginally significant main effect of Time and significant interactions of Time*Age and Time*Gender (**Table 3** and **Figure 4**). These results indicated a relevant reduction of distress in older children and a mild increase on this domain in younger ones over time. Moreover, reduction of distress was greater in females than in males.

Significant interactions of Time*Age and Time*Gender were also observed on Anxiety Thermometer scores (**Table 4** and **Figure 5**). These results evidenced that the decrease of anxiety from T0 to T3 was greater in older children than in younger ones and greater in females than in males.

As regards the Depression Thermometer scores, analyses showed significant Time*Gender interaction, indicating an improvement in depressive symptoms, which was more evident in males than in females (**Table 5** and **Figure 6**).

As regards the Anger Thermometer scores, analyses evidenced a significant main effect of Time and a significant interaction effect of Time*Age (**Table 6** and **Figure 7**). These results evidenced that, at T3, older children showed a reduction of anger, whereas younger children showed an increase on this domain.

A significant interaction effect of Time*Gender was observed on Need Help Thermometer: these results indicated that the decrease of need for help was more relevant in females than in males (**Table 7** and **Figure 8**).

As regards the CRIES scores, analyses evidenced a reduction of post-traumatic reactions in children from T0 to T3, that resulted to be significantly associated with the time that had elapsed since the second earthquake and since the administration of EMDR-IGTP treatment (Time*Time elapsed), with children's age, and with children's gender (**Table 8** and **Figure 9**). These results evidenced that the reduction of post-traumatic symptoms increased in children who had received treatment earlier. Moreover, such improvement was greater in older children than in younger ones and marginally greater in females than in males.

Analyses revealed no significant *random effect* of EMDR-ITGP Group, for both ET-5 Thermometers and CRIES scores. Model *effect size* (Cohen's f^2) approached the very large threshold for CRIES, the large threshold for Anxiety Thermometer, the small-medium threshold for Distress and Need Help Thermometers, and the small threshold for Depression and Anger (Cohen, 1988) (**Tables 3–8**).

DISCUSSION

Research has largely documented the dramatic effects of natural disasters among children and adolescent survivors. Even though the reported prevalence rates of symptoms significantly vary across studies (Wang et al., 2013), PTSD, anxiety, and depression are commonly observed in the exposed population (Liu et al., 2011; Zhang et al., 2011), in conjunction with other forms of

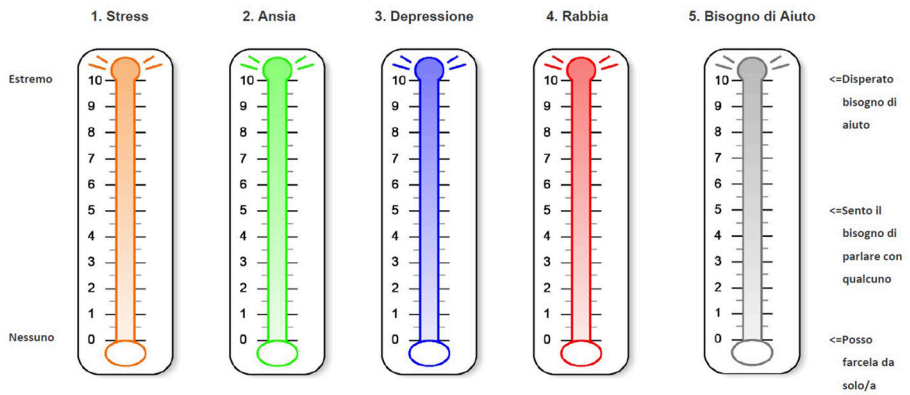

FIGURE 3 | The Emotion Thermometers. Translation from Italian to English: "Istruzioni: Le chiediamo di indicare, nelle prime quattro colonne, il numero che da 1 a 10 meglio descrive lo stato d'animo vissuto nella scorsa settimana, includendo anche la giornata odierna. Nell'ultima colonna Le chiediamo di indicare il bisogno di aiuto desiderato per gestire queste emozioni = Instructions: In the first four columns, please mark the number (0–10) that best describes how much emotional upset you have been experiencing in the past week, including today. In the last column please indicate how much you need help for these concerns." "Distress," "Distress;" "Ansia," "Anxiety;" "Depressione," "Depression;" "Rabbia," "Anger;" "Bisogno di aiuto," "Need Help;" "Disperato bisogno di aiuto," "Desperately;" "Sento il bisogno di parlare con qualcuno," "Need to talk with someone;" "Posso farcela da solo/a," "Can manage by myself".

TABLE 2 | Mean (M) and Standard Deviation (*SD*) scores on ET-5 and CRIES-13 at pre and post EMDR-IGTP in children.

Clinical measures	T0		T3	
	n	M (*SD*)	*n*	M (*SD*)
Distress Thermometer	332	3.84 (3.72)	265	3.01 (3.41)
Anxiety Thermometer	332	5.11 (3.92)	264	1.39 (1.95)
Depression Thermometer	332	3.62 (3.65)	266	2.70 (3.33)
Anger Thermometer	332	4.33 (4.02)	263	4.33 (4.10)
Need Help Thermometer	332	3.92 (3.72)	265	3.28 (3.71)
CRIES-13	332	20.21 (17.63)	323	9.88 (13.71)

TABLE 3 | Pre vs. post EMDR-IGTP treatment: statistically significant differences on Distress Thermometer scores in children.

Source of variation	*F*	*p*	η_p^2	Cohen's f^2
				0.07
Time	3.845	0.051	0.01	
Time*Time elapsed	0.645	n.s	0.01	
Time*Age	5.604	0.004	0.04	
Time*Gender	10.572	0.001	0.08	

emotional distress (Toyabe et al., 2006; Oyama et al., 2012) and severe difficulties in regulating anger (Durkin, 1993; Kar and Bastia, 2006; Becker-Blease et al., 2010; Forbes et al., 2015).

Coherently with such premises, in this preliminary study the ET-5 and the CRIES-13 was used to investigate the effects of EMDR-ITGP on emotional disorders and post-traumatic symptoms in children who experienced both earthquakes that hit central Italy in 2016. The ET-5 and the CRIES-13 have been implemented in this study to obtain valid measures of psychopathological symptoms in children, with the aim of providing them with immediate help and support, and to restore rapidly their psychological adaptive functioning. The ET-5 is a simple rapid modular screening tool that is widely used for the detection and the monitoring of emotional disorders, both in clinical and research practice. The simple visual-analog thermometer format on which the 5 scales (distress, anxiety, depression, anger, and need for help) are presented is particularly easy to understand for children, quick to administer and simple to score (Mitchell et al., 2010). The CRIES-13 is an easy to understand self-report instrument, which has been specifically designed to identify children with PTSD using the minimum number of items necessary to accurately detect this disorder. The CRIES-13 utility in the screening of post-traumatic distress has been largely documented in tens of thousands of children around the world, in the aftermath of natural disasters (Perrin et al., 2005).

After the conclusion of the intervention, older children showed a reduction of distress and anger, whereas younger children reported an increase on these domains; moreover, older children reported a greater reduction of anxiety than younger ones. A greater reduction of distress, anxiety, and need for help was evidenced in females, whereas a greater improvement in depressive symptoms was evidenced in males. The effects of the EMDR-IGTP treatment on post-traumatic symptoms were

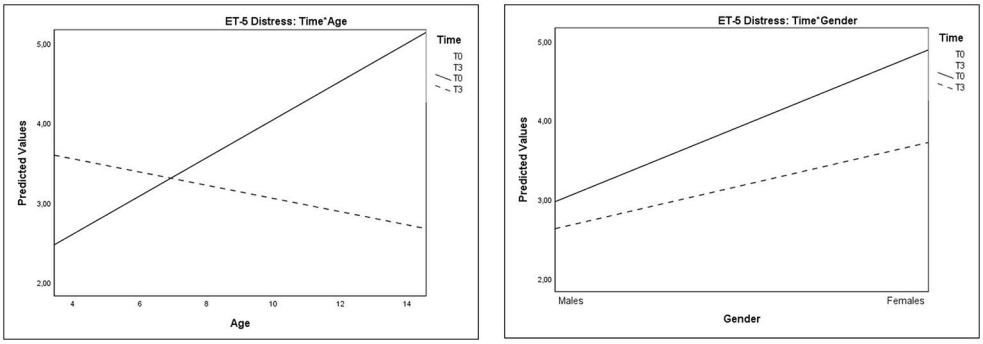

FIGURE 4 | Plots showing significant interactions of Time*Age and Time*Gender for Distress Thermometer scores.

TABLE 4 | Pre vs. post EMDR-IGTP treatment: statistically significant differences in Anxiety Thermometer scores in children.

Source of variation	*F*	*p*	η_p^2	Cohen's f^2
				0.47
Time	1.100	n.s.	0.00	
Time*Time elapsed	0.936	n.s	0.01	
Time*Age	3.544	0.030	0.03	
Time*Gender	17.708	0.001	0.12	

particularly evident in older children, compared to younger ones, and marginally greater in females than in males; moreover, a greater improvement was found in children who had received a timelier intervention, than in those who received delayed treatment.

The results of this study provide further evidence for the contribution of EMDR procedures in restoring psychological functioning in child survivors of natural disasters (Grainger et al., 1997; Chemtob et al., 2002; de Roos et al., 2011; Tang et al., 2015).

It may be assumed that children coping strategies are more vulnerable to the overwhelming effects of a disaster compared to adults (Norris et al., 2002b), which makes children particularly sensitive to early psychological support. On the other hand, research in clinical settings has documented, that stress reactions in children are not only very different from those manifested by adults, but also vary according to their age (Şalcioğlu and Başoğlu, 2008). In preschoolers, the severity and manifestation of post-traumatic stress is strictly linked to the emotional reactions of their primary caregiving system, to their parent's ability to face trauma, as well as to the latter's ability transmit to their child a sense of safety and security (Green et al., 1991). Young children show less emotional numbing (Eth and Pynoos, 1985), and tend to manifest persistent reactivity toward a variety of stimuli which may not be directly associated with the original trauma, as they lack the capacities to recognize and regulate strong emotions (Schwarz and Perry, 1994). As a result, young children who experience trauma are consistently unable to adequately monitor their behaviors (Dodge, 1995), experience more anger, and display more overt aggression with parents and peers (Perrin et al., 2000; Vigil-Colet and Codorniu-Raga, 2004; Cohen et al., 2010). Traumatic events are commonly re-experienced through repetitive and compulsive play, in which trauma is reenacted, and/or through drawings that realistically depict some specific aspects of the traumatic experience(s) (Scheeringa et al., 1995). Moreover, young children's ability to put into words avoidance reactions is significantly hampered by their limited capacity for complex cognitive introspection. As a result, it is very difficult to accurately diagnose PTSD in young children according to the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). On the contrary, older children are more likely to manifest post-traumatic responses similar to those seen in adults (Cohen et al., 2010), because of their higher cognitive ability in understanding traumatic events, as well as the consequences from a long-term perspective (Dyregrov and Yule, 2006). In our study, the observed increase of distress and anger in young children at T3 may be ascribed to the contribution of EMDR-ITGP in increasing their ability to correctly identify negative emotions, compared to the pre-treatment phase.

Studies in the field of trauma have documented that, as among adults, gender tends to predict risk for the development of symptomatic distress also during childhood. In fact, female children tend to show higher rates of mood or anxiety symptoms following traumatic stress (Bokszczanin, 2007; Lazaratou et al., 2008), whereas male survivors may show higher rates of behavior symptoms (Shaw et al., 1996). Mechanisms that have been proposed to account for such differences include that female survivors may exhibit more extreme acute reactions to traumatic events and are more likely to use rumination (Hampel and Petermann, 2005): it has been proposed that these reactions may account for an increased risk of developing trauma-related symptoms in females (Udwin et al., 2000; Pine and Cohen, 2002).

The present study provides a clear picture of gender differences in children's response to EMDR-ITGP after a natural disaster. At the end of the treatment, females showed a greater reduction in the severity of emotional problems (that is, distress, anxiety, and need for help) and post-traumatic symptoms compared to males: these findings may be ascribed to the contribution of EMDR-ITGP in restoring psychological functioning in females, by increasing their ability to control

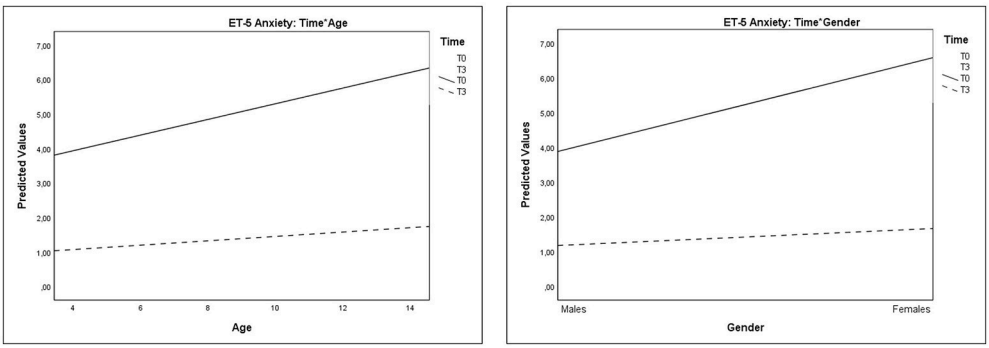

FIGURE 5 | Plots showing significant interactions of Time*Age and Time*Gender for Anxiety Thermometer scores.

TABLE 5 | Pre vs. post EMDR-IGTP treatment: statistically significant differences in Depression Thermometer scores in children.

Source of variation	*F*	*p*	η_p^2	Cohen's f^2
				0.05
Time	0.697	n.s	0.00	
Time*Time elapsed	0.729	n.s	0.01	
Time*Age	2.338	n.s	0.02	
Time*Gender	7.218	0.001	0.05	

acute reactions to traumatic events. On the contrary, females showed a lower improvement in depression compared to males: these results are coherent with those of previous studies, which indicate a greater vulnerability for depressive symptomatology in female children following traumatic stress (Bokszczanin, 2007; Lazaratou et al., 2008). These aspects may be congruent with the *social-cognitive approach*, according to which male and older children tend to report better control of their feelings, compared to females and younger children (Chen et al., 2002; Norris et al., 2002a; Bokszczanin, 2007).

Given this, it might be assumed that, as in the case of post-traumatic stress expression, both age and gender may influence child's treatment responses, especially in the context of a natural disaster, where the environmental disruption can be very challenging to cope with. We believe that these assumptions need to be largely explored by further researches.

The main results of this study highlight the fact that the promptness of treatment may be a key component in restoring a child's post-traumatic reactions.

A very recently published study (Saltini et al., 2017) has explored the effects of EMDR Recent Traumatic Episode Protocol (EMDR R-TEP; Shapiro and Laub, 2008, 2009, 2014; Shapiro, 2012) on post-traumatic distress of acutely traumatized adults, who were exposed to the earthquake that hit Emilia Romagna (a Northern region of Italy) in 2012. The restored psychological adaptive functioning in these subjects was modulated by the treatment provided, not by the time that had elapsed since the traumatic event. These results are coherent with the findings reported by Konuk et al. (2006), who evaluated the effects of EMDR on PTSD symptoms in adult survivors of the 1999 Marmara, Turkey, earthquake.

The above-mentioned findings are very different from those of the present investigation, in which promptness of treatment contributed to post-traumatic symptom reduction in children. There is a large consensus about the importance of early interventions for dealing with the traumatic child responses to natural disaster (Wang et al., 2013; Pfefferbaum et al., 2017). Treatment promptness is fundamental to prevent the worsening of post-traumatic symptoms (Norris et al., 2002b), as well as their persistence across time in children (Honig et al., 1993; Green et al., 1994; Ularntinon et al., 2008; Piyasil et al., 2011).

Psychological interventions are defined as "early" when they are delivered within three months from the traumatic event (Bisson and Cohen, 2006; Bisson and Andrew, 2007; Gibson et al., 2007; Roberts et al., 2009, 2010; Berkowitz et al., 2011). Early psychological interventions are strongly fostered by the American Academy of Child and Adolescent Psychiatry (AACAP) disaster parameter (Pfefferbaum et al., 2013), as well as by the Council of Europe, which established that all European citizens have an equal right to receive psychological support during emergencies.

In a very recent publication, Pfefferbaum et al. (2017) have reported a review of the empirical evidence of early child disaster interventions. This extensive study was done to respond to the "urgent need," stressed by the National Institute of Mental Health (2002), to establish an evidence base for research on early psychological interventions delivered to exposed children. Only 11 empirical studies (examining 16 early interventions) were identified as eligible for this review, while no empirical investigation of psychological first aid delivered early in the post-disaster phase was found. Among the included studies, only four randomized controlled trials reported improvement on several outcomes, including PTSD, post-traumatic stress symptoms, depression, anxiety, and psychological functioning. Although these results document the effectiveness of the identified interventions, nonetheless, they indicate a lack of evidence of acute interventions in the field of mass disaster contexts.

We believe that these findings should be carefully considered, since they underline the difficulty in promptly planning and carrying out research in the aftermath of a mass disaster, as

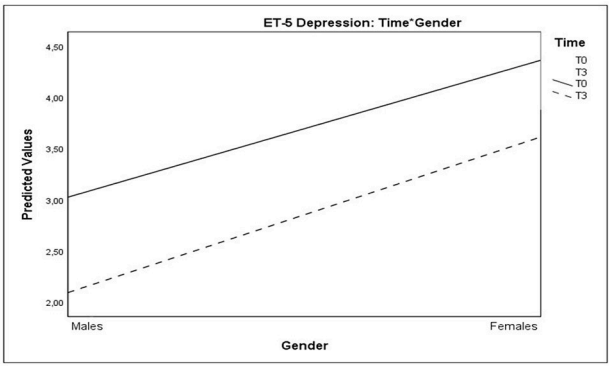

FIGURE 6 | Plots showing significant interactions of Time*Gender for Depression Thermometer scores.

TABLE 6 | Pre vs. post EMDR-IGTP treatment: statistically significant differences in Anger Thermometer scores in children.

Source of variation	*F*	*P*	η_p^2	Cohen's f^2
				0.04
Time	9.738	0.002	0.04	
Time*Time elapsed	1.188	n.s.	0.01	
Time*Age	9.581	0.001	0.07	
Time*Gender	0.374	n.s.	0.00	

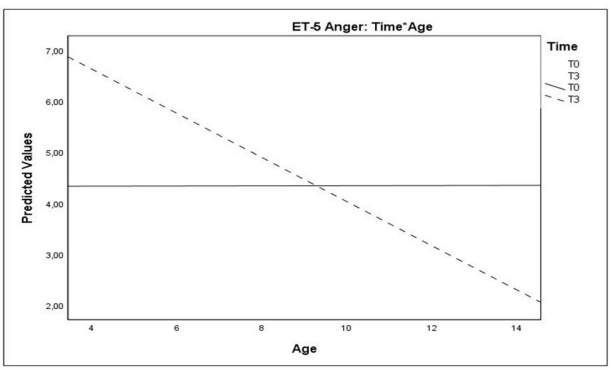

FIGURE 7 | Plots showing significant interactions of Time*Age for Anger Thermometer scores.

well as the difficulty in guaranteeing a systematic evaluation of the effectiveness of post-crisis interventions, through canonical research methods. As Wang et al. (2013) posited, "Disaster research is different from most other fields in that much of the work is motivated by a sense of urgency and concern; further, most of the research is theoretical, and little of it is programmatic" (p. 1714). In mass disaster contexts, the priority is to provide help and support, in order to restore rapidly the individual's psychological adaptive functioning. Furthermore, the implementation of systematically designed research is often limited by more urgent needs, such as planning and establishing services for the population.

TABLE 7 | Pre vs. post EMDR-IGTP treatment: statistically significant differences in Need Help Thermometer scores in children.

Source of variation	*F*	*p*	η_p^2	Cohen's f^2
				0.08
Time	1.373	n.s.	0.01	
Time*Time elapsed	0.194	n.s.	0.00	
Time*Age	2.507	n.s.	0.02	
Time*Gender	15.479	0.001	0.11	

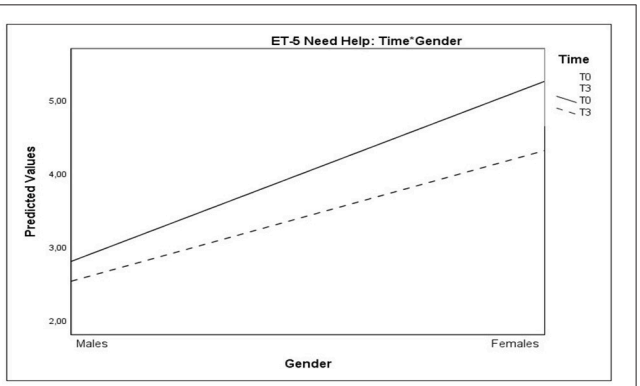

FIGURE 8 | Plots showing significant interactions of Time*Gender for Need Help Thermometer scores.

TABLE 8 | Pre vs. post EMDR-IGTP treatment: statistically significant differences in CRIES-13 scores in children.

Source of variation	*F*	*P*	η_p^2	Cohen's f^2
				1.19
Time	2.287	n.s.	0.01	
Time*Time elapsed	17.331	0.001	0.12	
Time*Age	72.186	0.001	0.36	
Time*Gender	5.693	0.004	0.04	

In this study, the dramatic circumstances of the aftermath, along with the urgent need to provide children with treatment on an equitable basis, precluded the possibility to include a control group. Undoubtedly, this aspect (which is the major constraint of this investigation) raises the question whether the positive changes in children might have been the result of spontaneous recovery, rather than of the EMDR-ITGP treatment. To partially correct this limitation, we also controlled the effect of the elapsed time between the second earthquake and the intervention provision, thus providing a comparison between subjects similar to a wait-list control group. The statistically significant effect of the "Time elapsed" parameter that we found on post-traumatic symptoms may be considered as a *proxy* of a dose-effect relation of EMDR: if an early treatment can be discriminated against a "late" one, it follows that EMDR has an action of its own and that the observed amelioration cannot be ascribed to the pure effect of time.

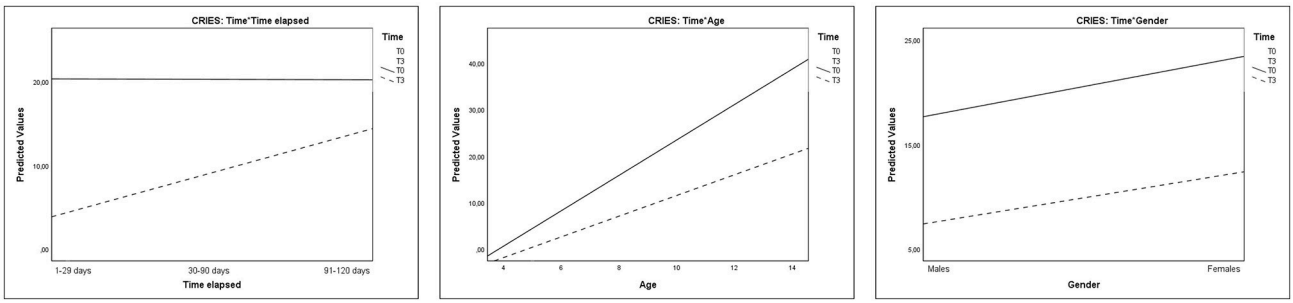

FIGURE 9 | Plots showing significant interactions of Time*Time elapsed, Time*Age, and Time*Gender for CRIES scores.

While scientific literature on the natural course of child PTSD after natural disaster is limited, findings from several researches support the assumption, premised in the present study, that reduced emotional disturbances and post-traumatic symptoms in children, may be the effect of EMDR-ITGP, rather than of spontaneous remission. Several investigations have provided evidence for the PTSD persistence in exposed individuals across time. A long-term follow-up of survivors of the Aberfan disaster in Wales, documented that the levels of PTSD symptoms were still very high 33 years after the critical event (Morgan et al., 2003). In a randomized control trial study, Chemtob et al. (2002) evaluated EMDR effectiveness in child survivors of Hurricane Iniki, Hawaii, who had been previously treated using a school-based, counselor-administered, and brief psychosocial intervention. At a one-year follow-up of the previous intervention, children were still exhibiting significant trauma-related symptoms. In a longitudinal study on the natural course of PTSD in 125 adolescents and young adults, Perkonigg et al. (2005) documented that, 34–50 months after the critical event, nearly half of the subjects reported no significant remission of symptoms. Goenjian et al. (1995) found that 1.5 years after the 1988 Armenian earthquake, 95 percent of children who survived from a severely hit city and 26 percent of others who suffered a less strong earthquake, were still experiencing severe levels of PTSD. Finally, in a study by Carr et al. (1997), the prevalence of PTSD in survivors of the 1989 earthquake in Newcastle, Australia, had only decreased by about 50 percent in the first 2 years after the event (Carr et al., 1997). In line with these empirical evidences, it seems reasonable to state that EMDR-IGTP contributed substantially to the reduction of post-traumatic symptoms in children included in this study. Such results appear particularly relevant, if we consider that EMDR-IGTP was administered to children who had experimented both earthquakes (including ongoing seismic oscillations and aftershocks).

EMDR's effectiveness in the treatment of trauma is now largely documented; its efficacy has received empirical evidence in the field of natural disasters, where the emergency circumstances are a real obstacle for the implementation of experimental designs (Grainger et al., 1997; Chemtob et al., 2002; de Roos et al., 2011; Tang et al., 2015). In this preliminary study, the use of EMDR-ITGP provided a great opportunity to deliver psychological interventions to a great number of exposed children, maximizing the possibility to rapidly deal with the emergency crisis.

CONCLUSIONS

The field of mass disaster psychology has rapidly developed in the past years given the dramatic *sequelae* of natural disasters that have occurred in several places of the world, causing death, disruption, and terror. There is now universal consensus about the importance of early psychological interventions to prevent both the worsening and persistence of trauma-related symptoms in post-disaster survivors, especially in children who are less equipped to cope with the effects of critical events.

Results of this preliminary field study show that EMDR-ITGP contributed significantly in reducing emotional disturbances and post-traumatic symptoms in exposed children, principally (regarding the post-traumatic symptomatology) in those who had received treatment earlier. As we have stated above, the need to respond to the emergency precluded, mainly for ethical reasons, the possibility to include a control group. We believe that this aspect is the major "scientific" limitation of this study (when considering only the compliance factor to the experimental design criteria), yet also its major strength, since the urgent need to treat children on an equitable basis is the main priority of any experimental design.

In the future, more rigorous studies may shed further light on the role of children's age, gender, and other relevant dimensions (e.g., parent's ability to instill a sense of security) in modulating the response to EMDR-ITGP in child survivors of natural disaster.

AUTHOR CONTRIBUTIONS

CT analyzed data and wrote this paper. As first author, she is primarily accountable for all aspects of the work. ML analyzed data, revised the paper for intellectual content, and approved its final version to be published. AG contributed substantially to data analysis, revised the paper for intellectual content, and approved its final version to be published. GM contributed substantially to the recruitment of subjects, administered EMDR therapy, and acquired psychological data. She revised the paper

for intellectual content and approved its final version to be published. RT revised the paper for intellectual content and approved its final version to be published. IF conceived the work, supervised substantially to the recruitment of subjects, provided a substantial contribution to the interpretation of data, and counseled in essential questions about EMDR-ITGP therapy. She revised the paper for intellectual content and approved its final version to be published. MP monitored data acquisition and provided a substantial contribution to the interpretation of data. He revised the paper for intellectual content and approved its final version to be published. ML, AG, GM, RT, IF, and MP agreed to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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An Eye Movement Desensitization and Reprocessing (EMDR) Group Intervention for Syrian Refugees With Post-traumatic Stress Symptoms: Results of a Randomized Controlled Trial

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The number of refugees has increased significantly over the past few years. PTSD and depression are among the most common mental health problems among refugees. Eye Movement Desensitization and Reprocessing (EMDR), an effective treatment for PTSD, is usually administered individually. The availability of mental health resources would be greatly enhanced when EMDR can be delivered to groups. The EMDR G-TEP is a group protocol based on Early EMDR intervention protocols. There is clinical evidence and one field study published on the effect of EMDR G-TEP and there is only one RCT published on the treatment of PTSD and depression in a refugee camp. The aim of our study was to investigate the efficacy of EMDR G-TEP in treating post-trauma symptoms and depression and preventing the development of chronic PTSD among refugees living in a refugee camp. 47 adult participants with PTSD symptoms were randomly allocated to experimental ($n = 18$) and control ($n = 29$) groups. We measured Impact of Event Scale (IES-R), Beck Depression Inventory-II (BDI-II) and International Neuropsychiatric Interview (MINI) at pre-, post- and 4-week follow-up. Analysis of the results showed that the EMDR G-TEP group had significantly lower PTSD and depression symptoms after intervention. The percentage of PTSD diagnosis decreased from 100 to 38.9% in the EMDR G-TEP group and was unchanged in the control group. Following the EMDR G-TEP intervention 61.1% of the experimental group no longer had a PTSD diagnosis; this decrease was maintained at 4 weeks follow-up. In the control group the percentage of people who no longer met the diagnostic criteria for PTSD was 10.3% post-test and 6.9% at 4 weeks follow-up. A significant decrease in depression symptoms from pre-test levels was found in EMDR group but not in the control group follow up-test. This

study indicated that EMDR G-TEP effectively reduced PTSD symptoms among refugees living in a camp, after two treatment sessions conducted over a period of 3 days. Further studies need to be performed using a larger number of participants, followed for a longer period of time and given more treatment sessions to strengthen our findings.

Keywords: EMDR, G-TEP, group therapy, refugee, PTSD, war, trauma

INTRODUCTION

Over the last few years there has been a dramatic increase in the number of forcibly displaced people all around the world. The total number of refugees has increased significantly and consistently over the past 4 years. According to the UNHCR Mid-Year Trends 2015 Report, this number reached 59.5 million by the end of 2014 due to persecution, conflict, generalized violence, and human rights violations. This Report (2015) indicates that the number of refugees at the end of 2011 was 10.4 million and it had reached an estimated 15.1 million by mid-2015, its highest level in 20 years. The war in Syria has been the main contributor to this trend. Countries surrounding Syria have been heavily affected by this crisis. As one of these countries, Turkey hosts more than 2.6 million Syrian refugees (mid-February 2016, The UN Refugee Agency, 2016). By April, 2018 the total registered Syrian refugees number is 5,636,302 and 3,572,565 of which is in Turkey according to UNHCR. Given the large unregistered refugee population, the true figure may be even larger. The UNHCR Report also indicates that Turkey has the highest Syrian refugee number in the world.

Refugees have had to leave their homes because of various traumatic life experiences such as rape, torture, starvation, injury, and the threat of being murdered and the disappearance of family members. Research reveals that there is a strong relationship between mental health problems and the traumatic experiences in this population (Rousseau et al., 2001; Trautman et al., 2002). A study of refugees in camps on the Thailand-Cambodia border revealed that 55% of the population was diagnosed with depression while 15% of them had post-traumatic stress disorder (PTSD) (Mollica et al., 1993). EMDR has been used in cases of mass disaster (e.g. Jarero et al., 2006, 2008; Maxfield, 2008; Natha and Daiches, 2014; Allon, 2015; Maslovaric et al., 2017).

Moreover, it has been suggested that even in the absence of clinically significant symptoms, up to 68% of those who are exposed to traumatic life events are more likely to develop delayed onset PTSD (Andrews et al., 2007). North (2007) states that after a trauma people have various psychological problems including depressive reactions, phobias, alcohol and substance abuse, psychotic reactions and conversion symptoms. Likewise, Brady et al.'s study (Brady et al., 2000) conducted among assault victims demonstrated that following an adverse life event, victims might develop not only PTSD but also major depressive disorder (60%) and substance abuse (25%).

Mass traumas such as war, tsunami, and earthquake affect a significant number of people. The victims of trauma may have to face repeated exposure to stressors after the main event. They may face many difficulties including loss, migration and poverty, which they have to cope with as part of their daily life. These accumulated traumas can decrease their resilience and quality of life while increase the risk of health problems.

It is proposed that early intervention is important to prevent the development of more serious mental problems including PTSD, depression, anxiety, as well as to increase resilience and even to prevent conflict in community (Slobodin and de Jong, 2015). Since traumatic stress is a risk factor for PTSD and other trauma related disorders the need for an effective early intervention to treat distress and prevent the development of pathology is paramount.

The Cochrane reviews of controlled studies (Bisson and Andrew, 2007; Roberts et al., 2010) revealed that there are effective psychological interventions for people who are exposed to traumatic events. Many international clinical guidelines recommend Focused Cognitive Behavioral Therapy (CBT) and Eye Movement Desensitization and Reprocessing (EMDR Therapy) as treatments of choice for PTSD (e.g., Bisson and Andrew, 2007; World Health Organization, 2013; National Institute for Clinical Excellence, 2016).

EMDR as a brief, effective approach for processing traumatic memories is very suited for Early Intervention. EMDR Therapy is based on the Adaptive Information Processing (AIP) Model. Shapiro (2001), Shapiro and Solomon (1995), and Shapiro et al. (2007) states that "In terms of AIP current symptoms are viewed as resulting from disturbing experiences that have not been adequately processed and have been encoded in state-specific, dysfunctional form." The heart of EMDR involves the transmutation of these dysfunctionally stored experiences into an adaptive resolution that promotes psychological health (Solomon and Shapiro, 2008).

Trauma can be conceptualized as an impairment of integrative functions. The intrusive fragmented elements of the traumatic memory cannot be assimilated and metabolized by the mind (Tofani and Wheeler, 2011). After the earthquake in the San Francisco Bay area in 1989, Francine Shapiro discovered that working with recent traumas required a different approach, since at some level of information processing the memory cannot have sufficient time to consolidate into an integrated whole. She proposed the Recent Event Protocol as an application of the standard EMDR protocol, conceptualizing the recent traumatic event as a fragmented experience that has not yet been consolidated and also reintroduced her original EMD Protocol for use in emergency situations (Shapiro, 2001). Based on these protocols, E. Shapiro and Laub developed the Recent Traumatic Episode Protocol (R-TEP) in 2008 (Shapiro and Laub, 2008). The EMDR R-TEP is an integrative recent trauma-focused protocol for Early EMDR Intervention (EEI). It includes procedures and measures for containment and safety. The intervention can be on consecutive days because no homework is required, The EMDR

R-TEP protocol introduced a focus on the trauma *episode* rather than on only the initial trauma *event*. The original traumatic event, together with the traumatic aftermath, is seen as an ongoing *traumatic episode* continuum because the experiences are not yet consolidated, integrated or adaptively processed (see Jarero and Artigas, 2018). E. Shapiro later introduced a group application, the Group Traumatic Episode Protocol (G-TEP) in 2013 (Shapiro, 2013). It is adapted from EMDR Recent Traumatic Episode Protocol (R-TEP) for using with different age groups and populations who have experienced recent traumatic experiences or adverse events with ongoing impact not necessarily recent. The main goal is to use a group framework to process a Trauma Episode to reduce traumatic stress, promote adaptive processing, strengthen resilience and prevent post-trauma complications (Shapiro, 2015).

Considering the limited number of resources such as health care professionals, money, accommodation, time and the high number of refugees under the risk of post-traumatic stress, it is crucial to provide cost and time effective, easily learned and applied interventions. Therefore, we planned a study with Syrian refugees utilizing EMDR G-TEP. The aim of the study was to investigate the effectiveness of EMDR G-TEP Group Protocol to reduce trauma and depression symptoms and prevent the development of PTSD, among Syrian refugees living in a refugee camp. This was the third of a series of studies. The first was a pilot study that made minor changes to the EMDR Standard Protocol (Acarturk et al., 2015). The project included training and giving supervision to local therapists, working for the Ministry of Family and Social Policies and municipalities, in EMDR Level 1. We wanted to evaluate the effectiveness of our treatment of the refugees. A second pilot study utilizing the EMDR Recent Traumatic Episode Protocol (R-TEP) showed positive results, indicating that the implementation of the protocol significantly reduced PTSD and depression (Acarturk et al., 2016). As the pilot study appeared to be effective, the present study was conducted with a larger population.

MATERIALS AND METHODS

Design

This study was a single blind research comparing an experimental group, who received two sessions of EMDR G-TEP intervention, to a control group at three time points (pre-, post- and 4 weeks follow up test). Participants provided their written informed consent to participate in the study.

Participants and Procedure

This study took place at the Kilis Refugee camp in southeast Turkey on the Syrian border. Five therapists at the camp gave seminars about "war and trauma" at schools and leisure centers of the camp. The study and the therapy program was announced at several locations at the camp by the school and leisure center personnel in early September. Between September and October 2014 clinical staff at the Psychosocial Support Center within the camp identified potential participants who met the study inclusion criteria. Participants escaping from Syria due to war and taking refuge in Turkey, residing at the refugee camp, aged 18 and older and who had PTSD symptoms according to the IES-R ($\geq$33) were invited to participate in the study. Ninety seven people intended to join the study. Participants who were pregnant, had mental retardation, psychotic, used psychiatric medication or were receiving any psychotherapy and refused to join the study were excluded. The number of participants who enrolled in the study was 67 (**Figure 1**), but four participants had to be excluded because they could not manage self—containment during the screening part of EMDR G-TEP. Participants who had an IES-R score of equal or above 33 were randomly assigned by a computer program to the experimental group (EMDR G-TEP = 31) and the EMDR control group (control group = 32). Ten people from the experimental group were unable to attend two sessions of G-TEP and so were also excluded from the study ($n = 21$). The demographic and pre-test characterisitcs of these ten subjects was similar to those who completed the two sessions. MINI test was applied to participants. The result showed that three participants in both experimental and control group were not diagnosed with PTSD so they were excluded from the study. The remaining 47 participants were randomly assigned to groups (experimental group = 18 and control group = 29, see **Figure 1**). As there was a common prejudice about getting psychological help, especially among men, the number of male participants were small ($n = 12$; 19%). It is recognized that conducting quality research in emergency situations has inherent difficulties and is likely to require some compromises with gold standard guidelines (Yehuda et al., 2015; Shapiro et al. submitted 2018).

Measurements

There were three instruments used in this research:

Beck Depression Inventory-II (BDI-II): A 21-question self-report inventory, for depression (Beck et al., 1996). The Arabic version of BDI-II was developed by Ghareeb (2000) using 17 different Arabic speaking populations including Syrians. The total BDI score varies between 0 and 63, and a score of 11–16 indicates: Depressive Mood, 17–20: Mild Clinical Depression, 21–30: Moderate Depression 31–40: Severe Depression and 40 and above: Very Severe Depression.

Impact of Events Scale (IES-R): The Impact of Event Scale—Revised (IES-R), has 22 questions, 5 of which were added to the original IES to better capture the DSM-IV criteria for PTSD (Weiss and Marmar, 1997). The validity of IES-R has been tested in different populations (Panahi et al., 2011). Based on previous studies, we used a cutoff score of $\geq$33 as indicating the presence of PTSD (Weiss and Marmar, 1997). The scale was translated to Arabic by two independent translators. After back translation the scale yielded a Cronbach's alpha of $\alpha = 0.93$ (Zaghrout, unpublished manuscript). Moreover, previous research with Syrian refugees indicated good psychometric properties of the scale (Acarturk et al., 2015).

MINI International Neuropsychiatric Interview (MINI): The Mini International Neuropsychiatric Interview (MINI) is a short diagnostic structured interview, developed in clinician (MINI-CR) and patient-rated (MINI-PR) formats, with 17 Diagnostic

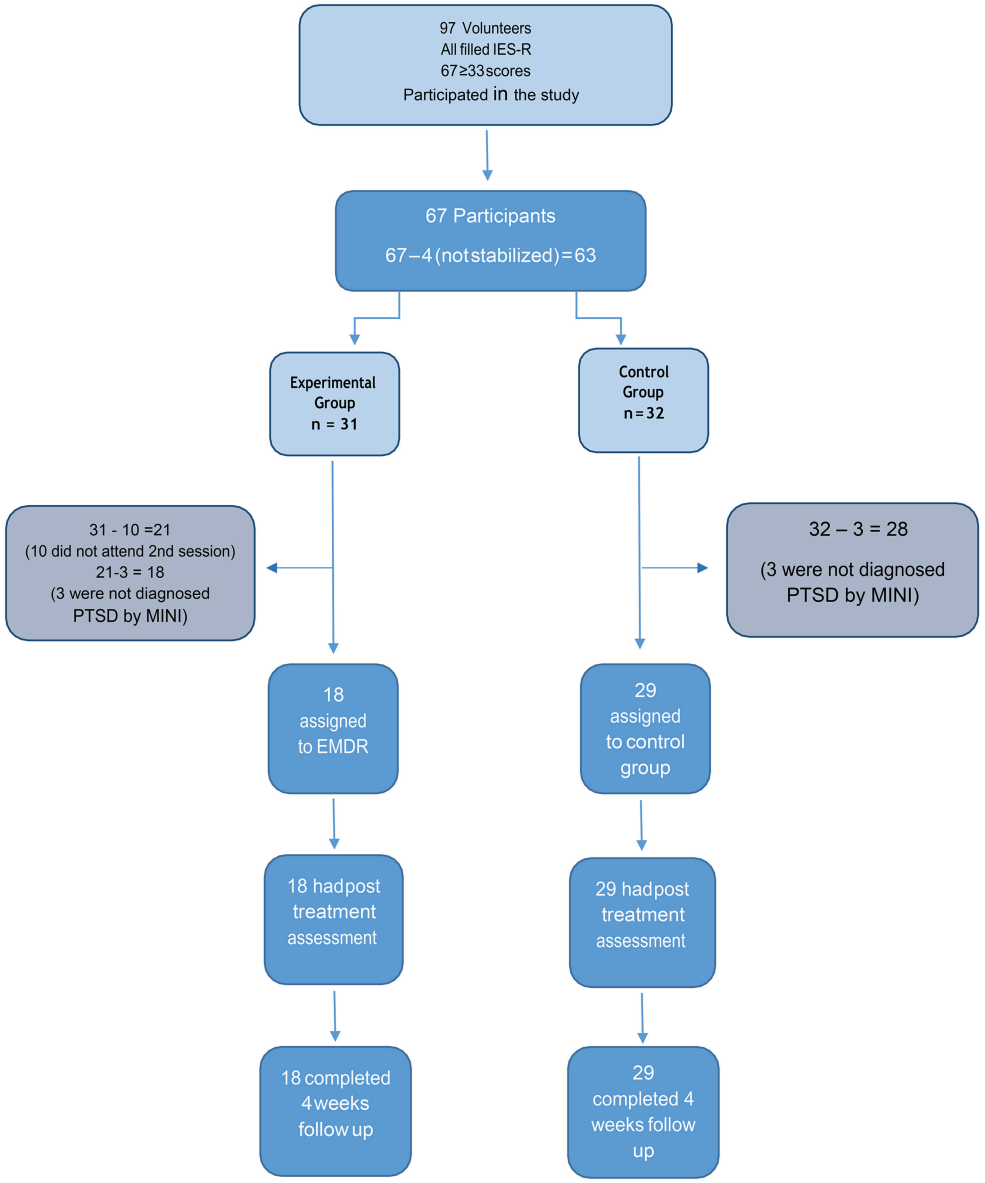

FIGURE 1 | Study design and flow of patients throughout the trial.

and Statistical Manual (DSM)-III-R Axis I psychiatric disorders (Sheehan et al., 1998). The Arabic version was developed by Kadri et al., in Moroccan Arabic in (Kadri et al., 2005).

The camp residents who were interested in participating in this study were screened based on the eligibility criteria mentioned above. The testers who spoke Arabic and Turkish fluently applied the instruments to the volunteers. Then, a final list was formed among applicants over 18 years old who had PTSD measured with the MINI and an IES-R score with the cutoff point ≥33 (Creamer and Falilla, 2002). The experimental and control groups were frequency matched for gender, age, marital status and education.

EMDR G-TEP GROUP INTERVENTION

The experimental group participants received two sessions of EMDR G-TEP in total, on three consecutive days. The group sessions took approximately 4 hours because the translation during the session doubled the time. Moreover, the participants needed breaks. The psychometric measures were applied to both experimental and control groups before the EMDR G-TEP group therapy started, a week after treatment and then a month later. None of the therapists who ran the groups took a role in conducting the surveys of the participants or saw the results. The EMDR G-TEP team consisted of four professionals who had EMDR Level 1 and Level 2 training and experience in EMDR of

3–15 years. The team received the EMDR G-TEP training from Elan Shapiro, the originator of the protocol, in 2013 and used it with different populations in order to prepare for the study.

Statistical Methods

In order to test whether there were statistically significant differences between the experimental and control groups in the categorical sociodemographic characteristics, chi-square or Fisher's exact test where appropriate were performed. Independent sample *t*-test was used to test whether there was a difference in age, IES-R and BDI-II between the two groups. In order to determine whether there were group differences in IES-R and BDI-II, a two factor Repeated measures ANOVA was used for pre-, post- and follow up tests. One way Repeated measures ANOVA was also used for pre-, post- and follow up tests. Bonferroni *post-hoc* testing was used to analyze the differences between the experimental and control group post and follow-up scores. In order to test whether there were differences in the percentage of participants with PTSD between groups, chi-square tests were conducted at each time point. In order to test whether there was a reduction in the percentage of PTSD among the participants over time, chi- square tests were conducted within each group. Significance was considered to be $p < 0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows 19.0.

Results

There was no statistically significant difference between the experimental and control group in sociodemographic variables (see **Table 1**). In addition, there was no statistically significant difference in age [experimental group: 39.89, control group: 35.93, $t_{(45)} = 1.196$; $p > 0.05$].

In this study a 2 (groups) × 3 (time) factor RM Anova was used to evaluate the IES-R and BDI measures (see **Table 3**). The procedure was run on 47 patients representing experimental and control groups.

Pre-treatment mean IES-R was 62.44 (see **Table 2**). Repeated measures analysis revealed no significant group effect [$F_{(1, 45)} = 3.07$; $p > 0.05$, effect size = 0.064]. In addition, there was a significant time effect [$F_{(2, 90)} = 6.46$; $p < 0.01$, effect size = 0.126]. Group by time interaction was not significant [$F_{(2, 90)} = 2.26$; $p > 0.05$, effect size = 0.048].

Bonferroni *Post-hoc* testing of the time effect revealed a statistically significant difference between the pre-test and post-test scores of IES-R (difference = 8.78, se = 2.77; $p < 0.01$) as well as a statistically significant difference between the pre-test and follow-up scores of IES-R (difference = 7.06, se = 2.19; $p < 0.01$). There was no significant difference between the mean post-test and follow-up scores of IES-R (difference = −1.72, s e= 2.77; $p > 0.05$).

As we were particularly interested in the treatment effect, a RM ANOVA was performed on the experimental group (**Table 3**). We found meaningful results (F $P < 0.05$). For this reason we used *post-hoc* tests. The same procedure was used for the control group.

Bonferroni *Post-hoc* testing of the time effect for the experimental group revealed a statistically significant difference between the pre-test and post-test scores of IES-R (difference = 14.22, se = 4.81; $p < 6.05$) as well as a statistically significant difference between the pre-test and follow- up scores of IES-R (difference = 10.5, se = 4.10; $p < 0.05$). There was no significant difference between the mean post-test and follow-up scores of IES-R (difference = −3.72, se = 3.76; $p > 0.05$).

There was no significant difference in the control group's pre-test and post-test (difference = −3.35, se = 3.18; $p > 0.05$), pre-test and the follow-up (difference = 3.62, se = 2.35; $p > 0.05$) and post- test and the follow-up IES- R mean scores (difference = −0.28, se = 3.67; $p > 0.05$).

Independent sample *t*-test of the two groups at each time point revealed that there was no statistically significant difference between the IES-R pre-test scores between the two groups ($t = -0.001$, $df = 45$; $p > 0.05$). At post-test, the experimental group had a significantly lower mean score as compared to the control group ($t = -2.09$, $df = 45$; $p < 0.05$). But at the follow-up test there was no statistically significant difference between the experimental group and the control group ($t = -1.439$, $df = 45$; $p > 0.05$).

Pre-treatment mean BDI was 31,85 indicative of severe depression. Repeated measures analysis revealed that there was no significant group effect [$F_{(1, 45)} = 1.28$; $p > 0.05$, effect size = 0.028]. However, there was a significant time effect [$F_{(2, 90)} = 9.86$; $p < 0.001$, effect size = 0.180]. In addition, there was no significant difference between Time × Group interaction [$F_{(2, 90)} = 1.49$; $p > 0.05$, effect size = 0.032].

Post-hoc testing revealed that there was a significant difference between the mean pre-test and follow-up scores of BDI-II (difference = 5.56, se = 1.78; $p < 0.01$). As well as a statistically significant difference between the pre-test and follow-up scores of IES-R (difference = 8.07, se = 1.96; $p < 0.001$). There was no significant difference between the mean post-test and follow-up scores of BDI-II (difference = 2.51, se = 1.84; p > 0.05).

RM of the experimental group revealed a significant difference between the mean pre-test and post-test scores of BDI-II (difference = 7.83, se = 2.84; $p < 0.05$) as well as a statistically significant difference between the pre-test and follow-up scores of BDI-II (difference = 11.17, se = 3.28; $p < 0.01$). There was no significant difference between the mean post-test and follow-up scores of BDI-II (difference = 3.33, se = 2.23; $p > 0.05$).

On the other hand, there was no significant difference in the control group's pre-test and post-test (difference = 3.28, se = 2.08; $p > 0.05$), pre-test and the follow-up (difference = 4.97, se = 2.32; $p > 0.05$) and post- test and the follow-up BDI-II mean scores (difference= 1.69, se = 2.53; $p > 0.05$).

The statistical analysis done for MINI scale (see **Table 4**) for each group separately revealed a time effect in the experimental group ($\chi 2 = 14.8$, $p < 0.001$) but not in the control group ($\chi 2 = 2.80$, $p > 0.05$). Time effect within the experimental group revealed a significant decline in the percentage of participants with PTSD between pre-test (100.0%) and both post- (44.4%; $p < 0.01$) and follow-up (38.9%, $p < 0.01$). There was no statistically significant difference in the percentage of PTSD between post and follow-up test times ($p > 0.05$).

There was no decrease in the trauma symptoms in the Control group. Following the EMDR G-TEP intervention post-test results

TABLE 1 | Demographic characteristics of groups at baseline.

Characteristic	Total ($n = 47$)	Experimental ($n = 18$)	Control ($n = 29$)	Analysis		
				χ^2	*df*	*p*
Gender				0.311	1	0.577
Male	11(23.4%)	5(27.8%)	6(20.7%)			
Female	36(76.6%)	13(72.2%)	23(79.3%)			
Marital status				0.038	2	0.981
Married	39(83.0%)	15(83.3%)	24(82.8%)			
Single	3(6.4%)	1(5.6%)	2(6.9%)			
Divorce	5(10.6%)	2(11.1%)	3(10.3%)			
Education				6.83	3	0.078
Not reading	6(12.8%)	3(16.7%)	3(10.3%)			
Primary School	25(53.2%)	6(33.3%)	19(65.5%)			
Middle School	6(12.8%)	2(11.1%)	4(13.8%)			
High School/University	10 (21.3%)	7(38.9%)	3(10.3%)			
Mean age	37.45(11.08)	39.89(10.96)	35.93(11.1)	$t = 1.196$	45	0.238
IES-R	62.45(11.04)	62.44(9.05)	62.45(12.2)	$t = -0.001$	45	0.999
BDI-II	31.85(10.99)	35.83(14.55)	29.38(7.3)	$t = 1.97$	45	0.051

EMDR, Eye movement desensitization and reprocessing; df, degrees of freedom; S.D., standard deviation; BDI- II, Beck Depression Inventory-II; IES-R, Impact of Event Scale—Revised.

TABLE 2 | Means (standard deviations) of the two measures over time.

	Pre		Post		Follow	
	EMDR	Control	EMDR	Control	EMDR	Control
MEASURE						
IES-R	62.44 (9.05)	62.45 (12.27)	48.22 (17.34)	59.10 (17.37)	51.94 (16.78)	58.83 (15.41)
BDI-II	35.83 (14.55)	29.38 (7.32)	28.00 (9.75)	26.10 (10.98)	24.67 (12.59)	24.41 (11.61)

TABLE 3 | 2 × 3 Repeated ANOVA results for IES-R and BD-II.

	Group			Time			Time × Group		
	df	*F*	η2	*df*	*F*	η2	*Df*	*F*	η2
MEASURE									
IES-R	1.45	3.06*	0.064	2.90	6.46***	0.126	2.90	2.26	0.048
BDI-II	1.45	1.278	0.028	2.90	9.86***	0.180	2.90	1.493	0.032

*$p < 0.05$; ***$p < 0.001$.

TABLE 4 | PTSD diagnosis according to the MINI assessment.

MINI		Pre		Post		Follow up		
Group	Yes	No	Yes	No	Yes	No	χ^2	*P*
Experimental	18 (100.0%)	0 (0.0%)	8 (44.4%)	10 (55.6%)	7 (38.9%)	11 (61.1%)	14.8	0.000**
Control	29 (100.0%)	0 (0.0%)	26 (89.7%)	3 (10.3%)	27 (93.1%)	2 (6.90%)	2.80	0.250
χ^2	0.000		11.35		16.32			
p	>0.05		<0.001		<0.001			

Data is N (%).
**$p < 0.01$*

demonstrated that 55.6% of the experimental group after 2 days of EMDR Therapy and 61.1% of the experimental group at the follow up no longer had a PTSD diagnosis.

DISCUSSION

To our knowledge this is the first study performed to evaluate the effectiveness of the EMDR G-TEP Group Protocol (a later study has subsequently been published (Lehnung et al., 2017) and the third RCT conducted in a refugee camp setting. (The first and second RCTs were conducted by Acarturk et al. (2015, 2016).

The aim of this study was to examine the effectiveness of the EMDR G-TEP Group Protocol as an early intervention to reduce the PTSD diagnosis compared to the control group, the trauma symptoms and depression and prevent the development of PTSD among refugees living in a camp. As expected, after the EMDR G-TEP 61% of the clients did not receive PTSD diagnosis at the follow up any more, whereas the control group remain the same.

As mentioned earlier, the total IES-R score of trauma symptoms in the EMDR G-TEP group decreased significantly and the effects were maintained a month later. The post-test mean score for IES-R post-trauma symptoms was significantly less than the control group mean score. At the follow-up test there was no statistically significant difference between the experimental group and the control group.

The same result applies for the BDI scores. In line with the reduction of trauma symptoms, the percentage of PTSD diagnosis in the EMDR G-TEP group decreased significantly. The depression scores of the EMDR G-TEP group decreased

significantly (diff = 7.83) and there was no significant difference in the control group's pre-test and post-test (diff = 3.23).

In this study we expected that the follow up test scores would be different too, but there was no difference between the experimental and control groups. We may explain this with the unusual circumstances and life going on in the refugee camps. After the treatment the experimental and the control groups continued their life at the camp Situations that the participants had to face each day in the camp, which is located close to the border, exposed them to ongoing stress as they were constantly triggered by re-traumatizing news about the war (e.g., violence; tortures, rapes, mass murders etc.,). They watched the TV channels where there were violent killings of their citizens, their husbands, wives and sons, who were fighting in Syria. That is their traumas continued being triggered, and may be new traumas have been developed. That is why we used G-TEP twice. It seems two sessions were not enough to reduce the scores more than the scores of the control group. If we regard this as a pilot study, in the future trials, we may do G-TEP three times or more.

The results of our study suggest that a group intervention with the EMDR G-TEP protocol can be used effectively with adults as an intervention during a period of significant on-going disruption and trauma, for screening and reducing symptoms of post-traumatic stress, self- reported distress and possibly for the reduction of depression.

Our study showed that EMDR G-TEP is an efficient group model, in terms of time, cost and resources, even in a situation of ongoing crisis, violence and war conditions with the effects maintained. A review of the literature showed that there are very few controlled studies on early interventions after large scale disasters. The research about refugees in a camp setting is even less studied. Therefore, this study stands out in this field. Further studies need to be done with different populations.

Limitations and Lessons

Due to practical and logistic difficulties we could only conduct the study with a relatively small number of participants over a limited time period. Also, the absence of a long term assessment of the control group is another limitation of the study.

It should be noted that for ethical considerations, after conducting EMDR G-TEP with the intervention group, we intended to complete EMDR G-TEP treatment with the control group as well (delayed treatment). However, due to unfortunate bureaucratic and security circumstances our request to continue and complete EMDR G-TEP with the control group was not possible. Therefore, EMDR therapists at the camp offered individual EMDR therapy to the control group and one third of them received EMDR Therapy.

Although the EMDR G-TEP can be conducted by a single therapist, considering the severity of the trauma in this population, with a possibility of intense abreactions and dissociation we decided to work with two therapists in each group. This gave us the opportunity to intervene one-on one if necessary. Finally, the worksheet format assumed the participants to be literate and to be able to follow the instructions. However, some of our participants were illiterate and they needed extra assistance. The option of using drawings as well as written expression here was helpful in this regard, but it should be taken into consideration in future studies. These aspects can be aided by employing paraprofessional support staff alongside the therapists.

ETHICS STATEMENT

EMDR Turkey Association Research Committee: The permission to get into the refugee camp was given for a short period and in an unexpected time so we were not able to get the ethical committee of the regional university. Therefore, the ethical approval was given by the EMDR Turkey Research Committee. The study was announced in the refugee camps by the leaders of the tribes in the camp. They explain the aim of the project to their members and were asked to be applied. Before the sessions begin, the team members gave a short information about the trauma and they were told that the aim of the study was to reduce the effect of the trauma that they were going through. Their names were written on a paper and they signed their confirmation to participate in the study. They were also told that if they feel the process is too difficult to carry on they can always leave the study. They were also assured that they will have an individual EMDR Therapy after the group work until they feel comfortable.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Eye Movement Desensitization and Reprocessing Integrative Group Treatment Protocol (EMDR-IGTP) Applied to Caregivers of Patients With Dementia

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Caregivers of patients with dementia experience high levels of stress and burden, with effects comparable to those of a traumatic event. Eye Movement Desensitization and Reprocessing (EMDR) appear to be effective in recovering post-traumatic stress disorder (PTSD). We aimed at investigating the effectiveness of the Eye Movement Desensitization and Reprocessing Integrative Group Treatment Protocol (EMDR-IGTP) on the "caregiver syndrome". Forty-four primary caregivers entered the study. They were randomly assigned to either the "immediate" branch, who received the treatment soon after recruitment, or to the "delayed" branch, who received it two months after recruitment. The treatment consisted of eight group sessions (one per week) spanning over two months. Emotional distress was measured before the treatment, immediately after the end of it, and two months later (follow-up), by means of several clinical scales (Impact of Event Scale-Revised, IES-R; Caregiver Needs Assessment, CNA; Caregiver Burden Inventory, CBI; Anxiety and Depression Scale-Reduced Form, AD-R). The "immediate" branch improved significantly more than the "delayed" (control) branch on The Impact of Event Scale-Revised, the Anxiety, and the Depression scales; however, after treatment such an improvement was maintained only in the first scale. The "delayed" branch took less advantage of the treatment, showing significant reduction only on the Depression scale, an effect which disappeared at follow-up. These preliminary results show for the first time that EMDR-IGTP reduces stress-related symptoms, anxiety, and depression in caregivers of patients with dementia. Interestingly, caregivers who were inserted in a waiting list after recruitment showed smaller treatment effects. Larger samples are needed to better interpret such differential clinical profiles.

Keywords: dementia, caregivers, EMDR Integrative Group Treatment Protocol, anxiety, depression, burden

INTRODUCTION

Dementia is a degenerative disease with a major impact on the whole family of the patient (Beinart et al., 2012), especially on primary caregivers. Prolonged care of patients with dementia is associated with somatic and psychological symptoms that characterize the "caregiver syndrome" (Gaugler et al., 2005). This syndrome together with wrong coping strategies may culminate in high risk of developing affective disorders, with high levels of stress, anxiety, depression (Cuijpers, 2005; Gaugler et al., 2005), and burden (Vitaliano et al., 2003; Passoni et al., 2010). The Behavioural and Psychological Symptoms of Dementia (BPSD), as well as the progressive disability in performing basic activities of daily life, have a negative impact on the immune system of the caregiver (Kiecolt-Glaser et al., 1991), inducing a decline in physical health with the rise of emotional and affective disorders (Dunkin and Anderson-Hanley, 1998; Burns, 2000).

Caregivers of patients with dementia experience such symptoms soon after diagnosis. Several studies show that caregivers have higher levels of psychiatric and physical morbidity and use psychotropic drugs more frequently than other family members who are not directly involved in the assistance (Dunkin and Anderson-Hanley, 1998; Burns, 2000). In a nutshell, the caregiver becomes a "secondary victim" of the disease, a problem that in turn reduces his/her competence in caring.

For all these reasons, being involved in the assistance of a patient with dementia can well be considered as a traumatic event. Worse still, taking care of a patient with dementia exposes the caregiver to multiple traumatic events – the daily contact with the patient exposes him/her to repeated and prolonged stress triggers, similar to the acute trauma of the initial diagnosis in their effects (Freedman et al., 1999; Jarero and Uribe, 2011, 2012). This multi-traumatic sequence makes caregivers more likely to show symptoms of post-traumatic stress disorder (PTSD) than individuals who experienced a single stressful event (McFarlane, 1989; Uddo et al., 1996).

Canonical strategies for reducing caregivers' distress include pharmacotherapy and psychosocial interventions such as psychotherapy (cognitive-behavioral in focus, e.g., Passoni et al., 2014) and psycho-educational programs (Pinquart and Sorensen, 2006; Cooper et al., 2007; Gallagher-Thompson and Coon, 2007; Elvish et al., 2012). These interventions mainly focus on practical issues concerning disease managing (Gallagher-Thompson et al., 2010; Elvish et al., 2012) and neglect the traumatic event experienced by the caregiver. We wished to take into account this aspect by treating caregivers with the Eye Movement Desensitization and Reprocessing (EMDR) technique.

EMDR was developed by Shapiro (2001) and Shapiro and Maxfield (2002) and is often used to treat PTSD. The World Health Organization [WHO] (2013) and several international guidelines (e.g., Cochrane Review) recommend EMDR for treating PTSD in children, adolescents and adults (Bisson and Andrew, 2007). The alternation of eye movement or tactile/auditory stimulation represents the core of this therapy, which is held to favor the elaboration of the trauma on which patients are focusing.

Because of its effectiveness with PTSD, the use of EMDR has been extended to sexual and physical abuse, bereavement, or abortion, with apparently reduction of the emotional distress. As a consequence of the flood caused by the Pauline Hurricane in Mexico (1997), a huge demand of urgent psychotherapeutic intervention occurred that overwhelmed the mental health services. Psychotherapists of the Mexican Association for Mental Health Support in Crisis (AMAMECRISIS; Jarero et al., 2008; Jarero and Artigas, 2009) decided to administer EMDR to large groups of children, thus developing the EMDR Integrative Group Treatment Protocol (EMDR-IGTP) for early intervention.

This protocol, originally designed for children (Artigas et al., 2014) was later adapted for adults (Jarero and Artigas, 2014) and used with appropriate modifications in different circumstances around the world (Maxfield, 2008; Jarero and Artigas, 2012). EMDR appears to be effective when compared to other group treatments in terms of time, resources and outcome (Adúriz et al., 2009).

Two broad categories of application contexts are considered. The first concerns large groups of people who experienced the same critical event, such as natural and man-made disasters (Jarero et al., 2006, 2008; Errebo et al., 2008; Jarero and Uribe, 2012) or traumatic events with an impact on small communities (suicide of a boy, murders, etc.). The second concerns people experiencing the same type of trauma, although in separate critical events (e.g., rescuers, parents of disabled children, patients with cancer, etc.; Jarero et al., 2014).

A recent pilot study showed that EMDR-IGTP was effective in 24 women with cancer diagnosed with PTSD (Jarero et al., 2014).

However, overall, evidence on the effectiveness of EMDR-IGTP is still scanty.

To our knowledge, EMDR has never been used in caregivers of patients with dementia, and this would be a suitable population given the frequency of PTSD symptoms within it. Hence, the aim of the present work was to test whether EMDR-IGTP is effective in reducing post-traumatic and emotional symptoms (anxiety, burden, depression, needs related to care) in dementia patients' caregivers.

MATERIALS AND METHODS

Participants

Caregivers of patients with dementia were recruited at the Memory Clinic of the Cognitive Neuropsychology Centre of the Niguarda Hospital, in Milan. Potential caregivers were informed on the opportunity to attend the study by the neurologist during the clinical evaluation of the patient. A caregiver entered the trial only if s/he met the inclusion/exclusion criteria listed below and if s/he gave written informed consent to the participation after having been informed about the objectives of the study. If a caregiver gave informed consent, a set of further, relevant clinical variables regarding the patient (MMSE, ADL, IADL), were collected by the physician during the neurological evaluation.

The study was approved by the Local Ethics Committee of the Niguarda Hospital (September 18th, 2015, approval number

443-092015) and was conducted following the principles for standards of Good Clinical Practice.

Inclusion Criteria

- Being a caregiver of a patient with a diagnosis of dementia on grounds of the DSM-IV (American Psychiatric Association [APA], 1994) criteria.
- Being the *primary* caregiver (the one most involved in the care in terms of time).
- Being a relative of the patient.
- Having assisted the patient for at least six consecutive months, at home (in this way we could guarantee safer AD diagnoses and stability of the stressful caregiver–patient relationship).
- Showing evidence of one or more traumatic events causing trauma related symptoms (IES-R > 0, and Subjective Units of Distress, SUD > 5).
- Being fluent in Italian and with at least three years of education.

Exclusion Criteria

- Evidence of severe psychiatric disorders.

Study Design

The study was monocentric, single-blind, and had two parallel branches (Schulz et al., 2010), thus conforming to an Individually Randomized Group Treatment Trial. The clinical effect of the EMDR-IGTP treatment in each branch was assessed at three time points (T0, T1, and T2) plus another time point, T3, for the second branch. Time points were two months apart (see **Figure 1**). Examiners who administered the clinical tests at each time point were blind to the branch of the evaluated caregiver.

In the first branch ("Immediate" EMDR-IGTP condition), therapy was administered between T0 and T1; in the second branch ("Delayed" EMDR-IGTP, or "Waiting List" condition) therapy was administered between T1 and T2. This branch did not undergo any intervention between T0 and T1, so it served as a control condition to be compared to the "Immediate" one. The direct effect of the EMDR treatment was thus quantified in terms of the differential improvement between T0 and T1 in the two branches.

After the initial assessment (T0) caregivers were randomly assigned to one of the two branches. Randomization was carried out by assigning one caregiver to one branch and the next to the other branch, on grounds of mere arrival order. This randomization technique (with the source of randomness being arrival order) was necessary in order to closely synchronize the two branches in their successive T1 and T2 assessments, thus matching every variable related to time-of-the-year between conditions (indeed, seasonal changes, like depression level, might be a source of confusion, Postolache et al., 1998).

The date when treatment sessions started was determined by practical constraints (e.g., the need to avoid interruptions because of holiday periods) and/or by the number of applicants assigned to the immediate condition reaching 10, that is, the maximum number of caregivers that were allowed to join in a single treatment group. Note that the term "group" will henceforth exclusively refer to a set of caregivers who attended the same treatment sessions. At the end of the study, six groups were formed, three per branch, with 7, 5, and 10 participants (Immediate branch) and 8, 4, and 10 participants (Delayed branch).

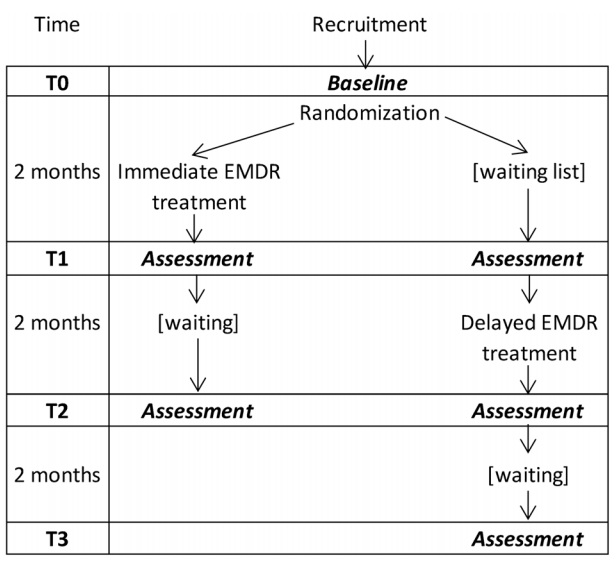

FIGURE 1 | Study design.

Measures

Caregiver Variables

The following questionnaires/tests were administered to the caregiver at each time point.

- A data form to collect clinical and socio-demographic features (age, gender, educational level, patient–caregiver kinship, caring time measure i.e., number of weekly and/or daily hours, duration of the caregiving role in months).
- *Visual Analog Scale: VAS*, a paper-and-pencil version of the Likert scale. Caregivers were asked to point to a graduated horizontal line (a 0–10 ruler) to rate their subjective perception of (i) the quality of the premorbid relationship with the patient, (ii) the severity of the patient's disease, and (iii) the relative speed of the evolution of the disease.
- *Impact of Event Scale-Revised: IES-R* (Horowitz et al., 1979; Weiss and Marmar, 1997). This 22-item self-report is useful for assessing subjective distress caused by traumatic events. Patients are asked to identify a specific stressful event and indicate how much they were distressed by it during the past 7 days. Items are rated on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). IES-R yields a 0–88 total score and specific subscale scores (Intrusion, Avoidance, Hyperarousal). IES-R is the most widespread self-administered measure of PTSD symptoms.
- *Caregiver Burden Inventory: CBI* (Novak and Guest, 1989). This scale quantifies burden and contains five

different sections: Time-dependence Burden (items 1–5), Developmental Burden (items 6–10), Physical Burden (items 11–14), Social Burden (items 15–19), and Emotional Burden (items 20–24). CBI's 24 items yield an overall 0–96 score.

- *Anxiety and Depression Scale-Reduced Form: AD-R* (Moroni et al., 2006). This tool was validated for patients in rehabilitation setting and consists of 25 items, 15 of which (range: 0–15) constitute the Depression Questionnaire Reduced Form (QD-R; Vidotto et al., 2010), and 10 of which (range: 10–40) constitute the State Anxiety Inventory – Reduced Form (STAI-X3; Spielberger et al., 1970; Vidotto and Bertolotti, 1991).
- *Caregiver Need Assessment: CNA* (Moroni et al., 2008) was used to assess the caregivers' needs related to care. This questionnaire consist of 17 items with 0–3 Likert responses (overall score: 0–51 the higher, the higher the level of need) and includes two subscales (which proved to be internally consistent) labeled "Needs of emotional and social support", CNA-1 (Cronbach $\alpha = 0.765$) and "Needs of information and communication", CNA-2 (Cronbach $\alpha = 0.742$).

Patient Variables

- *Mini Mental State Examination: MMSE* (Folstein et al., 1975; Measso et al., 1993), a widespread screening test, was administered to assess the patient's state of dementia; it samples various cognitive functions such as memory and orientation, and has a 0–30 range. Scores were adjusted for age and education (MMSE corr, Measso et al., 1993).
- *Instrumental Activities of Daily Living: IADL* (Lawton and Brody, 1969) with scores ranging 0–6, and *Activities of Daily Living: ADL* (Katz et al., 1963) with scores ranging 0–8, were used to estimate the patient's degree of autonomy in basic daily living activities and his/her ability to take care of his/her own person.

EMDR-IGTP Intervention

Two psychotherapists held the EMDR-IGTP sessions, an EMDR practitioner and an EMDR trainer.

All caregivers received eight group sessions of 120 min each, covering a 2-month period. The main protocol included the following steps.

(a) A first session delivered information as to the main characteristics of dementia and as to how to manage the behavioral and psychological symptoms of the disease. Caregivers were provided with suggestions concerning healthy behaviors for stress management and physical / psychosocial activities.

(b) A second session provided an assessment of dysfunctional cognitions in the context of the traumatic event of taking care of a person with dementia. In this session caregivers were trained by means of imagery exercises and stabilization techniques, such as "the safe place" (Shapiro, 2001), which can be practiced also at home as a strategy to reduce distress.

(c) The following sessions were dedicated to the re-processing of traumatic events through the EMDR-IGTP. This protocol combines the eight phases of the EMDR Individual Therapy treatment (Shapiro, 2001) in a group therapy model and an art therapy format. In EMDR-IGTP sessions, each caregiver is asked to focus upon the traumatic memory or highly stressful recollections related to the relative's disease. There is no verbalization of these contents: the caregiver is instructed to produce some drawings on a paper sheet that are related to the painful memories s/he is experiencing (after every image drawn, the level of distress is monitored by means of a "subjective units of discomfort" – SUD – rating scale). S/he is then required to focus upon the just-produced drawings, while simultaneously self-administering a form of bilateral self-stimulation known as the "butterfly hug" – with each self-stimulation lasting for approximately 45 s (Group Butterfly Hug Protocol, Artigas and Jarero, 2014). Towards the end of the group session, caregivers are asked whether they experienced some positive memories or feelings during the butterfly hug, and if so, they are asked to produce drawings relative to these, in order to close the session with a self-stimulation related to positive contents.

Statistical Analyses

The analyses were run in the R-studio (version: 1.0.143) environment using *ad hoc* created routines[1] based on the standard libraries available online. We started by exploring the relationship between clinical and socio-demographical variables by means of non-parametric Spearman's rank correlation test on the basis of specific *a priori* hypotheses.

As a second step, the clinical variables (namely IES-R, CBI, CNA, and Depression and Anxiety scales) were normalized according to the following formula:

$$\text{Normalized score } x = (x - \min_x)/(\text{MAX}_x - \min_x)$$

This normalization was carried out in order to make all the clinical variables fully comparable with one another (bounds all became 0–1).

The normalized scores were then entered as dependent variables into a series of generalized linear mixed model with random intercept (grouped by subject) and with time (T0 vs. T1 vs. T2) and branch (Immediate vs. Delayed) as fixed effect predictors. Moreover, Intra-Class Correlations (ICC) were computed to ascertain whether the administration of treatment on separate groups produced critical violations of the assumption of statistical independence among observations (Searle, 1971; Thomas and Hultquist, 1978; Donner, 1979). **Table 1** reports the ICC values, which clearly indicate that the adoption of separate groups did not create any cluster of data. Hence, the random intercept was modeled only by subjects. In particular, these analyses were run using the lme4 package:

$$\textit{MODEL } X = \text{lmer(NORMALIZED SCORE X} \sim \text{BRANCH} * \text{TIME} + (1|\text{SUBJECT}), \text{data = mydata})$$

[1]The R script can be obtained by emailing MB.

TABLE 1 | ICC indices and 95% confidence intervals for the six "groups" of caregivers.

	ICC index	CI lower bound	CI upper bound
EMDR-efficacy			
IES-R	−0.025	−0.045	0.110
CNA	0.065	−0.008	0.411
CBI	0.078	−0.002	0.442
Anxiety	−0.041	−0.051	0.031
Depression	0.049	−0.014	0.372
FU-analyses			
IES-R	−0.006	−0.062	0.295
CNA	−0.024	−0.070	0.235
CBI	0.0362	−0.045	0.406
Anxiety	−0.064	−0.085	0.076
Depression	−0.009	−0.064	0.283

FU, Follow-Up.

The fixed effect marginal means were then extracted to plot the first and the second level effects; moreover, if significant, the BRANCH-by-TIME interaction effect was further explored by means of pairwise comparisons while adopting a FDR correction for multiple comparisons. In the case of the CNA, CBI, IES-R variables, if the BRANCH-by-TIME interaction effect was significant in the overall score, we further explored the same interaction within each subscale.

It is worth noting here that we were particularly interested in the BRANCH-by-TIME interaction as, according to our study design, that should genuinely reflect the effectiveness of the EMDR-IGTP treatment.

Finally, in order to explicitly evaluate the persistence of the EMDR-IGTP in the follow-up phase, we isolated the data collected at the end of the treatment in the two branches of caregivers (namely in the Immediate and Delayed branches) and the data collected after 2 months (i.e., the specific follow-up phase for each branch) and designed a new series of generalized linear mixed model with random intercept (grouped by subject) with time (post-treatment vs. follow up) and branch (immediate vs. delayed) as fixed effect predictors. These analyses were run using the lme4 package too. For all the *post hoc* comparisons, an FDR correction for multiple comparison was applied (R package "phia"; De Rosario-Martinez, 2013).

RESULTS

Socio-Demographical and Clinical Description of the Two Branches

We initially recruited 44 caregivers, 22 per branch; 11 of them dropped out of the study during the EMDR-IGTP intervention, eight from the Delayed condition, three from the Immediate condition (the difference between the two drop-out rates was not significant, $\chi^2 = 3.03$, $p = 0.082$). Apart from drop-outs, there were no missing data: all caregivers yielded a complete dataset in all sessions in which they participated. Given this lack of evidence of differential drop-out rates, we applied an *intention-to-treat* approach (Gupta, 2011), thus including dropped-out caregivers in the analyses (incidentally, this is the default choice of the mixed linear model approach). To test the appropriateness of such a choice, we also ran control *per-protocol* analyses (excluding drop-outs); given that per protocol-analyses yielded very similar results to those obtained by the intention-to-treat approach, we reported only the latter as they are based on slightly larger sample sizes.

Socio-Demographic Characteristics

Among the 44 caregivers, 34 were females and were most often the spouses ($N = 30$) of the patient. They had a mean age of 66.07 years ($SD = 11.32$), and an education level of 11.04 years ($SD = 4.09$).

Caregivers have been taking care of the patient for an average of 32.68 months ($SD = 22.84$). Thirty-two caregivers were living with the patient and most of them were involved in the care almost every day (mean = 6.2 days a week, $SD = 1.74$).

Half the caregivers did not receive help of any kind ($N = 22$), the others could count on some help from a third party (see **Table 2** for details).

Table 2 also reports demographics separately for the two conditions.

Caregivers included in our sample had generally homogeneous socio-demographic characteristics. The two branches did not differ on demographic variables, with the

TABLE 2 | Socio-demographic characteristics of caregivers.

	Immediate branch	Delayed branch
	Mean (*SD*)	**Mean (*SD*)**
Age (years)	64.9 (± 13.04)	67.22 (± 9.48)
Education (years)	12.45 (± 3.83)	9.63 (± 3.93)*
Caring time (number of days per week)	6.04 (± 1.86)	6.36 (± 1.64)
Caring duration (months since diagnosis)	34.41 (± 27.55)	30.95 (± 17.4)
	#	**#**
Sex of the caregivers		
• Female	16	18
• Male	6	4
Caregivers' Kinship status		
• Spouse	12	18
• Son/daughter	9	4
• Brother/sister	1	0
Caregivers' living status		
• With the patient	14	18
• Elsewhere	8	4
Type of help received		
• No help	8	14
• By a relative	9	4
• By a formal carer	3	3
• By a relative and a formal carer	1	1
• By a friend	1	0

**significant between-branches differences ($p < 0.05$). Between-branches comparisons were run using a Wilcoxon Mann–Whitney U-test as implemented in R.*

exception of educational level which was higher in the Immediate than in the Delayed branch ($t(42) = 2.405$, $p = 0.02$).

Correlations Between Clinical Variables at the Enrolment Phase

The relationships between the different clinical variables were explored on the scores obtained by the entire sample at enrolment (T0). We found a significant negative Spearman correlation between the level of burden of the caregiver (CBI) and the level of autonomy by the patient in daily activities (IADL; $\rho = -0.34$; S = 14390, p-value = 0.026) which suggests that the lower the patients' residual abilities of daily living, the higher the level of caregivers' burden. This correlation was particularly pronounced for the "Time" subscale ($\rho = -0.41$; S = 15074, p-value = 0.008).

Similarly, we found a significant negative correlation between the overall level of caregiver's burden and the perceived quality of the premorbid patient-caregiver relationship ($\rho = -0.34$; S = 19005, p-value = 0.024): the lower the quality of the relationship, the higher the level of burden. This correlation was particularly strong for the "Social" ($\rho = -0.35$; S = 19177, p-value = 0.019) and the "Physical" ($\rho = -0.42$; S = 20147, p-value = 0.004) subscales.

Effect of the EMDR-IGTP Intervention

As described in Section "Materials and Methods", we ran a series of linear mixed models with by-subject random intercept to test the BRANCH-by-TIME interaction effect.

In what follows, we report the main effect and the interaction effect for the overall scores of our clinical variables.

(a) **IES-R:** we could not find a main effect of BRANCH ($\chi^2 = 1.4$, $df = 1$, p-value = 0.23), but there was a significant main effect of TIME ($\chi^2 = 12.03$, $df = 2$, p-value = 0.002) and a significant BRANCH-by-TIME interaction effect ($\chi^2 = 8.72$, $df = 2$, p-value = 0.01). As shown in **Figure 2**, the interaction effect was due to a significant decrement of the IES-R score between T0 and T1 ($\chi^2 = 18.61$, $df = 1$, p-value < 0.001) and between T0 and T2 ($\chi^2 = 7.22$, $df = 1$ p-value = 0.02) in the Immediate condition only (FDR-corrected comparisons).

(b) **CNA:** we could not find a main effect of BRANCH ($\chi^2 = 2.66$, $df = 1$, p-value = 0.1); neither did we find a significant main effect of TIME ($\chi^2 = 4.05$, $df = 2$, p-value = 0.13), or a significant BRANCH-by-TIME interaction effect ($\chi^2 = 4.29$, $df = 2$, p-value = 0.11).

(c) **CBI:** in this analysis no significant main effect of BRANCH emerged ($\chi^2 = 0.5$, $df = 1$, p-value = 0.47); neither a significant main effect of TIME ($\chi^2 = 2.22$, $df = 2$, p-value = 0.33), nor a significant BRANCH-by-TIME interaction effect ($\chi^2 = 5.06$, $df = 2$, p-value = 0.08) could be found.

(d) **Anxiety:** albeit there was no significant main effect of BRANCH ($\chi^2 = 0$, $df = 1$, p-value = 0.99), a significant main effect of TIME emerged ($\chi^2 = 8.26$, $df = 2$,

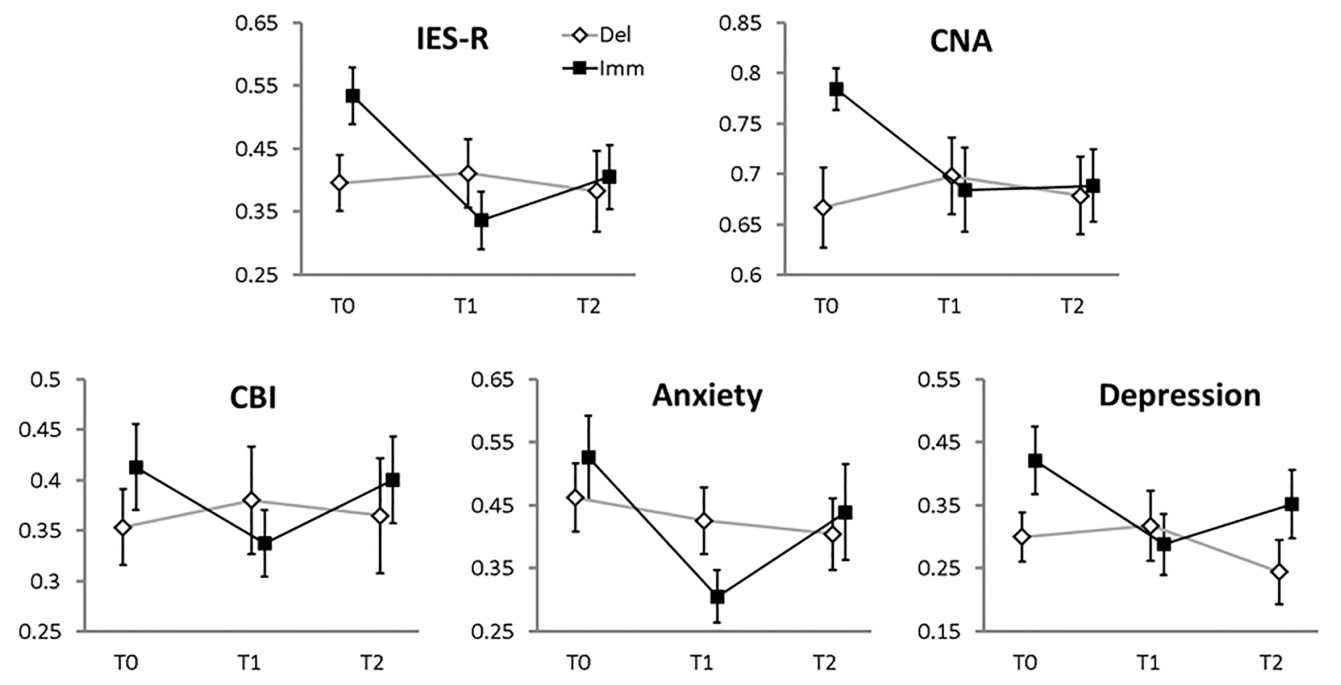

FIGURE 2 | Mean values (error bars: standard errors) of the main clinical variables (standardized to the 0–1 scale, 0 = minimum 1 = maximum score, reported on the *y*-axes). The *x*-axes report the time of assessment: T0, enrolment phase; T1, 2 months later (i.e., the end of the therapy for the Immediate branch, the end of the waiting-list period for the Delayed branch); T2, another 2 months later (the end of the therapy for the Delayed branch; follow-up visit for the Immediate branch). Filled squares, Immediate branch; open diamonds, Delayed branch.

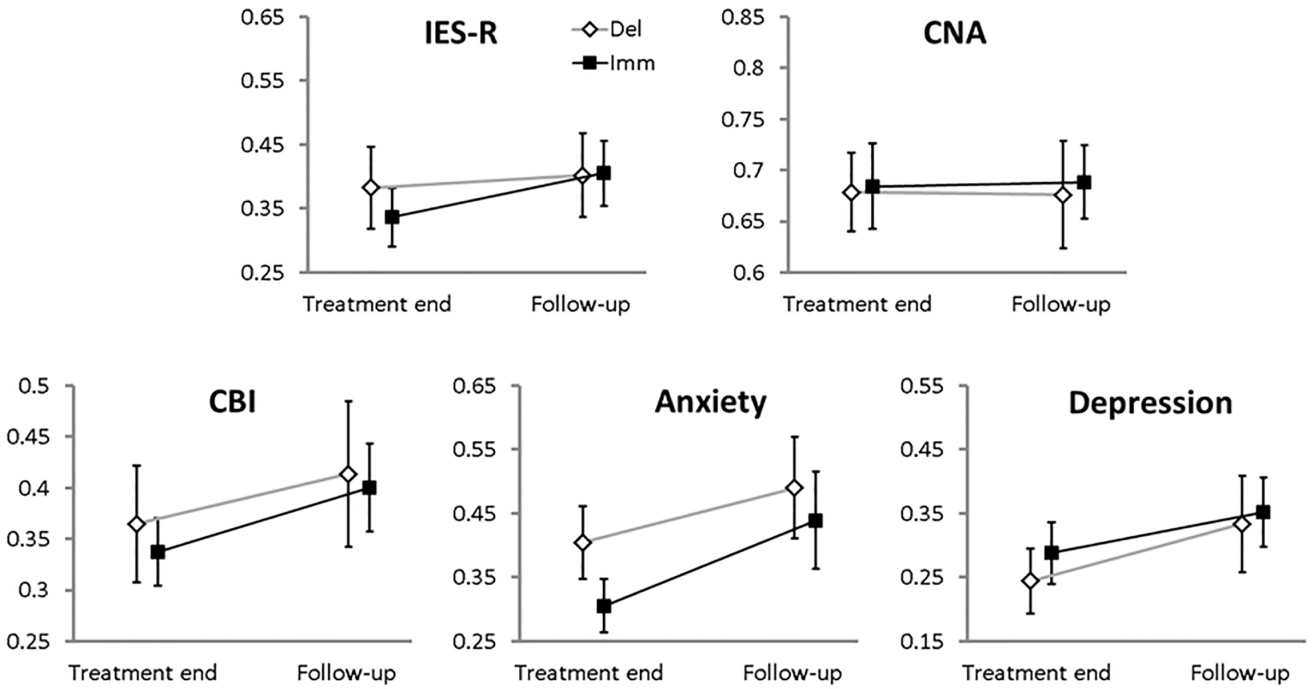

FIGURE 3 | Means (error bars: standard errors) for the 0–1 standardized main clinical variables collected at the end of the therapy and at the follow-up phase for each branch. Filled squares, Immediate branch; open diamonds, Delayed branch.

p-value = 0.01). The BRANCH-by-TIME interaction effect was not significant ($\chi^2 = 4.81$, $df = 2$, p-value = 0.09).

(e) **Depression:** we could not find a main effect of BRANCH ($\chi^2 = 1.8$, $df = 1$, p-value = 0.18), but there was a significant main effect of TIME ($\chi^2 = 7.36$, $df = 2$, p-value = 0.02) and a significant BRANCH-by-TIME interaction effect ($\chi^2 = 11.9$, $df = 2$, p-value = 0.002). As shown in **Figure 2**, the interaction effect was due to a significant decrement of the Depression score between T0 and T1 ($\chi^2 = 13.43$, $df = 1$, p-value = 0.001) in the Immediate condition, on the one hand, and between T1 and T2 ($\chi^2 = 5.55$, $df = 1$ p-value = 0.05) in the Delayed condition, on the other hand (FDR-corrected comparisons).

As described in Section "Materials and Methods", we further explored the BRANCH-by-TIME interaction effect in the subscales of the IES-R measure. In particular, for the "Avoidance" subscale a significant BRANCH-by-TIME interaction effect emerged ($\chi^2 = 6.4$, $df = 2$, p-value = 0.04) in the absence of significant main effects (BRANCH: $\chi^2 = 2.80$, $df = 1$, p-value = 0.09; TIME: $\chi^2 = 3.04$, $df = 2$, p-value = 0.21). The pairwise FDR-corrected comparisons showed that the BRANCH-by-TIME interaction effect in the "Avoidance" subscale was due to a significant difference between T0 and T1 ($\chi^2 = 7.36$, $df = 1$ p-value = 0.04) and T0 and T2 ($\chi^2 = 5.9$, $df = 1$ p-value = 0.04) in the Immediate condition only. In the "Intrusion" subscale we found a significant main effect of TIME ($\chi^2 = 15.32$, $df = 2$, p-value < 0.001) and a significant BRANCH-by-TIME interaction effect ($\chi^2 = 6.36$, $df = 2$, p-value = 0.04). The pairwise FDR-corrected comparisons showed that the BRANCH-by-TIME interaction effect in the "Intrusion" subscale was due to a significant difference between T0 and T1 ($\chi^2 = 19.71$, $df = 1$ p-value < 0.001) and T0 and T2 ($\chi^2 = 6.15$, $df = 1$ p-value = 0.04) in the Immediate condition only. A similar pattern of results emerged also for the "Hyperarousal" subscale: a main effect of TIME ($\chi^2 = 15.33$, $df = 2$, p-value < 0.001) and a significant BRANCH-by-TIME interaction effect ($\chi^2 = 13.09$, $df = 2$, p-value = 0.001) emerged. The pairwise FDR-corrected comparisons showed that the BRANCH-by-TIME interaction effect in the "Hyperarousal" subscale was due to a significant difference between T0 and T1 ($\chi^2 = 27.87$, $df = 1$ p-value < 0.001) and T0 and T2 ($\chi^2 = 7.9$, $df = 1$ p-value = 0.01) and T1 and T2 ($\chi^2 = 5.4$, $df = 1$ p-value = 0.04) in the Immediate condition only.

Stability of the EMDR-IGTP Intervention at the Follow-Up Phase

As a final step, we evaluated the persistence of the EMDR-IGTP effect in the follow-up phase, i.e., two months after the last treatment session (**Figure 3**). Also, in this case ICC were far from significance (they ranged from −0.065 to 0.036).

(a) **IES-R:** no effect was significant (BRANCH, $\chi 2 = 0.075$, $df = 1$, p-value = 0.78; TIME, $\chi 2 = 3.3$, $df = 1$, p-value = 0.07; BRANCH-by-TIME, $\chi 2 = 0.09$, $df = 1$, p-value = 0.76).

(b) **CNA:** we could find neither a main effect of BRANCH ($\chi^2 = 0.02$, $df = 1$, p-value = 0.89), nor of TIME

(χ^2 = 0.04, *df* = 1, *p*-value = 0.84), nor a BRANCH-by-TIME interaction effect (χ^2 = 0.02, *df* = 1, *p*-value = 0.87).

(c) **CBI:** we could not find a main effect of BRANCH (group, χ^2 = 0.07, *df* = 1, *p*-value = 0.78) but a significant main effect of TIME emerged (χ^2 = 8.01, *df* = 1, *p*-value = 0.004); the BRANCH-by-TIME interaction effect was not significant (χ^2 = 0.007, *df* = 1, *p*-value = 0.93).

(d) **Anxiety:** no main effect of BRANCH (χ^2 = 0.82, *df* = 1, *p*-value = 0.36) or BRANCH-by-TIME interaction effect emerged (χ^2 = 0.23, *df* = 1, *p*-value = 0.63); however a significant effect of TIME (χ^2 = 9.93, *df* = 1, *p*-value = 0.001) was found.

(e) **Depression:** we did not find a main effect of BRANCH (χ^2 = 0.29, *df* = 1, *p*-value = 0.58), but a significant main effect of TIME (χ^2 = 7.14, *df* = 1, *p*-value = 0.007) emerged. The interaction BRANCH-by-TIME was not significant (χ^2 = 0.24, *df* = 1, *p*-value = 0.62).

DISCUSSION

The purpose of the present study was to learn whether EMDR-IGTP could be proved effective in the treatment of the symptoms of emotional distress shown by primary caregivers of patients with dementia. We administered EMDR-IGTP to two randomized branches of caregivers, the former starting the treatment immediately after consent (Immediate), the latter inserted on a 2-month waiting list (Delayed).

We found two expected, negative correlations in the initial, enrolment phase: namely, the level of burden of the caregiver was inversely proportional to the level of autonomy of the patient in daily activities (IADL); moreover, caregivers describing a poor quality of the premorbid relationship with the patient had higher levels of social and physical burden.

The evaluation of the effectiveness of EMDR-IGTP in reducing post-traumatic distress symptoms in caregivers – the primary purpose of the present work – could be carried out by comparing the evolution of clinical scores in the Immediate vs. Delayed conditions. Indeed, between T0 (the time of baseline assessment) and T1 (2 months later) caregivers of the Immediate branch received the treatment, while those of the Delayed branch did not receive any treatment and remained in the waiting list. As expected, EMDR-IGTP treatment significantly reduced the level of subjective distress related to the traumatic event in the Immediate condition, while no detectable change was observed in the Delayed condition. This pattern was confirmed in all of the three IES-R subscales: treated caregivers showed a reduction of Intrusion, Avoidance, and Hyperarousal symptoms. Caregivers of the Immediate branch also showed a reduction in anxiety and an improvement of mood, with a decrease of the levels of depression. The reduction of distress (IES-R) was maintained after another 2 months (i.e., 2 months after interruption of the treatment), while anxiety, depression and burden (CBI) showed an increase in the same period.

The IES-R results mirror those of other studies focusing on EMDR and EMDR-IGTP on other populations, like patients with physical diseases (cancer or multiple sclerosis: Capezzani et al., 2013; Jarero et al., 2014; Carletto et al., 2016), albeit in the same studies depression and anxiety kept stable at follow-up.

In the Delayed condition, in which the caregivers received the EMDR-IGTP treatment later (between two and four months after initial enrolment and screening), a significant treatment effect was observed only on the depression scale. As for the follow-up, two months after the end of the treatment, the effects were virtually identical to those recorded from the Immediate branch, that is, a worsening of the anxiety and depression symptoms as well as an increase of burden (CBI).

In our experimental design caregivers of both branches received information on the EMDR treatment at the time of initial assessment; thus all caregivers probably developed positive expectations about the treatment – we have no reason to believe that the degree of such initial expectations was any different in the two branches, since caregivers were randomized into one of them after that initial assessment. We believe one explanation of this complex results profile is the following. During the 2 months in which caregivers of the Delayed branch had to wait before treatment began, a significant number of further stressful events related to caregiving occurred, against which they had no defense (yet). Indeed, it is well known that the severity of the patient's (often progressive) inability to perform basic activities of daily life, as well as his/her behavioral and psychological symptoms (BPSD) contribute to maintain high levels of stress, associated to emotional and affective disorders and burden (e.g., Dunkin and Anderson-Hanley, 1998; Burns, 2000; Vitaliano et al., 2003; Cuijpers, 2005; Gaugler et al., 2005; Passoni et al., 2010). Two more months without tools to stem the negative effects of the sequence of stressful events might have made the caregivers less responsive to the EMDR-IGTP treatment.

Finally, it is worth noting that although other studies explored the effectiveness of psychological treatments on caregivers, they typically compared the Immediate to the Delayed ("waiting list") condition, without exploring the effects of the therapy in the Delayed condition (Gallagher-Thompson et al., 2000; Akkerman and Ostwald, 2004). Our study also explored such effects.

Albeit preliminary, the present study is (to our knowledge) the first description of the effects of treatment timing. Further studies are needed to better understand the behavioral components characterizing caregivers in this different time frame.

Wrapping up, the issues raised in this discussion are relevant in the clinical setting: our study suggests that an *early* intervention is the best response to the difficulties experienced by caregivers of patients with dementia. Indeed, such an intervention would enable them to better cope with the unavoidable sequence of stressful events yielded by their relatives' condition. Without an early intervention, the steep progression of the patients' disease might worsen the emotional condition of caregivers so much as to make them less responsive to treatment.

Limits

The present results, albeit intriguing, need further investigation. In particular, we plan to extend the sample and to collect data from later follow-ups: indeed the suggestion that delaying the treatment might produce a loss of the positive treatment effects

needs further scrutiny. Another issue is the stabilization of the positive effects 2 months after the end of the treatment, which regarded distress symptoms but not depression and anxiety, which tended to increase again. Perhaps 2 months of treatment were enough for producing sizeable positive effects, but not enough for stabilizing them and/or generalizing them to all problematic sectors of the caregiver's mental status. Whether or not longer treatment periods, possibly covering various phases of the patients' degenerative disease, produce more stable effects is an empirical question.

CONCLUSION

The present study evaluates for the first time the efficacy of the EMDR-IGTP treatment in caregivers of patients with dementia.

Three of the five tested measures (Impact of Event Scale-Revised, Anxiety, and Depression) witnessed a clear and multifaceted improvement related to a therapy that lasted only 2 months. These preliminary data suggest that EMDR-IGTP might be considered as a valid tool to reduce distress symptoms in caregivers of patients with dementia.

AUTHOR CONTRIBUTIONS

SP and IF were responsible for the conception of the study. SP and AT designed the study. SP and TC conducted the study. MB and AT were responsible for data collection and statistical analyses. SP and MB wrote the article, which was critically revised by AT, TC, IF, and GB. All authors read and approved the final version of the manuscript, and guarantee the accuracy and integrity of this work in all its aspects.

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