Research Paper

Neurobiological correlates of EMDR therapy effect in PTSD

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ABSTRACT

Objective. – Posttraumatic stress disorder (PTSD) is a trouble that arises in the aftermath of a traumatic event. The overwhelming resulting stressful memory can be desensitized by a brief therapy, Eye Movement Desensitization and Reprocessing (EMDR). The aim of the present study is to explore the functional brain correlate of such an effective treatment (EMDR) in PTSD.

Method. – Sixteen PTSD patients underwent fMRI during negative emotional face recognition task, before and after EMDR treatment. Brain activity changes at test and retest (P < 0.005) were compared to those of 16 healthy controls matched for age, gender, and education.

Results. – In PTSD patients, EMDR therapy elicited significant functional decreases in deep gray matter (including the amygdala, thalamus, and caudate nucleus) and cortical activities (including notably the precuneus, and the ventromedial and dorsolateral prefrontal cortex), as compared to healthy controls (P < 0.005). The right thalamic activity decrease was positively correlated with PTSD symptom reduction (r = 0.62, n = 16, P < 0.01).

Conclusions. – The healing process of traumatic memory desensitization by EMDR would act through a functional decrease in brain regions shown to be disrupted in PTSD. Given the role of these structures in memory, self-perception, fear extinction, REM sleep, reward, and attention, we discuss possible explanations of EMDR mechanisms of action in PTSD that may help further improve this therapy.

1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by a panoply of symptoms in the aftermath of a traumatic event including re-experiencing of the aversive event, avoidance of its reminders and hypervigilance (American Psychiatric Association, 2013).

Although the pathophysiology of PTSD remains largely unknown, the most prevailing hypothesis in PTSD is that of a deficient fear-processing pathway (Milad et al., 2009; Orr, Metzger, & Pitman, 2002; Wurtz et al., 2016). This pathway mainly relies on the amygdala and prefrontal cortex (Åhs, Kragel, Zielinski, Brady, & LaBar, 2015; Fullana et al., 2018), and these structures are known to be altered in PTSD. Extensive animal and human research points to the orchestrating role of the amygdala in the acquisition of associative fear learning in classical conditioning tasks (LaBar & LeDoux, 1996; Milad et al., 2007; Milad & Quirk, 2012; Orr et al., 2002; Pitman et al., 2012). Amygdala volume (Kuo, Kaloupek, & Woodward, 2012; Morey et al., 2012) and functional overactivation might account for exaggerated fear responses and persistence of traumatic memories as well as altered emotional regulation (Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013; Feng, Zheng, & Feng, 2016; Milad et al., 2009). According to this literature, increased bilateral amygdala activation remains the most consistent finding in PTSD while processing emotional cues.

While the amygdala is a central part of the neural circuitry of emotion, it does not operate in isolation (Stein et al., 2007). Anatomically, the amygdala is highly interconnected with the ventral portion of the PFC, including the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) (Bracht et al., 2009; Johansen-Berg et al., 2008). These three frontal areas have often shown decreased activation or volumetric changes in PTSD (Carroll, Weems, Richert, Hoffman, & Reiss, 2010; Karl & Werner, 2010; Kasai et al., 2008; Kim et al., 2006; Kitayama, Quinn, & Bremner, 2006; Nardo et al., 2010; Schuff et al., 2008; Sekiguchi et al., 2013). Its implication in fear extinction in animal and human studies has led to the elaboration of its role in top-down regulation...
of the amygdala (Garcia, Vouimba, Baudry, & Thompson, 1999; Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004). Deficits in its ability to modulate the activity of the amygdala have been hypothesized to be instrumental in PTSD development (Hariri, Bookheimer, & Mazzotta, 2000).

However, despite the consistent finding of ACC and of bilateral amygdala involvement in PTSD (Hayes, Hayes, & Mikkedis, 2012), a broader range of dysfunctions further contributes to PTSD development. Additional brain regions were found to be functionally or anatomically altered in this pathology as the hippocampus (Bremner et al., 1995; Gurvits et al., 1996; Pavic et al., 2007; Smith, 2005; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Thomas et al., 2008; Woon, Sood, & Hedges, 2010), the dorsolateral prefrontal cortex (dPFC), the basal ganglia, the insula, the precuneus, and the thalamus (Aupperle et al., 2012; Herringa, Phillips, Almeida, Insana, & Germain, 2012; Lanius et al., 2003; Simmons et al., 2008; Strigo et al., 2010; Yan et al., 2013).

The APA (American Psychiatric Association, 2004) recommends two psychotherapies for the treatment of PTSD. Cognitive Behavioral Therapy and Eye Movement Desensitization and Reprocessing (EMDR) come as first line therapy before other treatments (Bisson et al., 2007), including pharmacological interventions. EMDR is a brief therapy directly focusing on the desensitization of the emotion associated with the traumatic event ( Shapiro & Maxfield, 2002).

Only a few studies have explored the neurobiological correlates of this psychotherapy. These studies were diverse in the tools used (morphometry, SPECT, fMRI, NIRS, EEG). However, the cerebral structures that have been identified as targets of EMDR seem to parallel those known to be disrupted in PTSD. Results showed morphometric changes in limbic structures such as the hippocampus (Bossini et al., 2012; Letizia, Andrea, & Paolo, 2007; Smith, 2005), right insula and posterior cingulate cortex (Nardo et al., 2010), amygdala (El Khoury-Malhame et al., 2011; Laughrane et al., 2016; Nardo et al., 2010) and prefrontal structures (Boukezzi et al., 2017) following EMDR therapy. Changes in brain activity have been shown with an increase in brain activity in the frontal regions (dPFC, OFC, left inferior frontal gyrus and the ACC) (Lansing, Amen, Hanks, & Rudy, 2005; Levin, Lazrove, & van der Kolk, 1999; Oh & Choi, 2007; Pagani et al., 2012, 2007) and a decrease in the limbic regions (temporal association cortex, left parietal, right precentral frontal lobe) (Lansing et al., 2005; Oh & Choi, 2007) after treatment. In all these studies, the sample size was small, which limits the impact of the results. Still, the few studies investigating EMDR mechanisms of action in PTSD have recurrently shown PFC involvement. This is in line with the previously described PFC abnormalities in PTSD patients (Hughes & Shin, 2011).

The aim of the present experiment was therefore to explore the effect of EMDR therapy on brain activity during an emotional task in PTSD patients. To further investigate the neurobiological correlates of this major healing process of emotion desensitization in PTSD, we measured BOLD activity in 16 patients before and after successful EMDR treatment, during a negative face recognition task, using fMRI, and compared them to healthy controls.

Facial expressions have been especially effective in probing increased amygdala response and brain emotional circuitry in healthy controls (Hariri et al., 2000; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002), but more so in anxiety disorders such as social phobia (Blair et al., 2010), generalized anxiety disorder (Monk, 2008), and PTSD (Cisler, Olatunji, & Lohr, 2009). The fMRI task exploring the brain mechanism in PTSD was chosen to activate the amygdala and PFC. If EMDR therapy acts through modifications of the emotional brain structures altered in PTSD, we expect the functional activity to be restored in the amygdala, PFC, and hippocampus. We hypothesized that other structures evidenced to be involved in PTSD may also intervene (thalamus, PCC, precuneus, basal ganglia, and insula).

2. Materials and methods

2.1. Subjects

We included 16 healthy controls matched for age, gender, and education level with 16 PTSD patients (see Table 1) after exclusion of 4 subjects in each group because of technical reasons (they moved too much during fMRI acquisitions) or because they did not understand the instructions for the task or they did not come back for the second sessions.

The patients were recruited by psychiatrist among traumatized patients at the Conception hospital in Marseille, France. They all met the DSM-IV criteria for PTSD following a single traumatic event with no previous history of neurologic or psychiatric disorders. The traumatic events included motor vehicle accidents (4), work related accidents (1), aggressions (9), and griefs (2). The average duration of symptom progression since the traumatic event was 3.75 ± 5.2 years. One patient took an association of antidepressants and anxiolytics, 4 patients took only antidepressants, and the remaining 11 were not on medication.

The healthy adult controls had no history of neurologic or psychiatric disorders and were recruited via screening lists at the clinical investigation center at the Timone Hospital in Marseille, France.

2.2. Psychological assessment

All participants were assessed by a psychiatrist using the structured Mini-Internal Neuropsychiatric Interview for DSM-IV (Lecrubier, Weiller, Hergueta, Bonora, & Lepine, 2018), to check for the absence of psychiatric disorders (prior to the trauma for patients) and to screen for PTSD and potential comorbid psychiatric disorders in patients. Accordingly, 2 patients had social phobia, 6 Generalized Anxiety Disorder, 3 Panic Disorder, 6 Agoraphobia, 4 had high suicidal risks, 1 had alcohol abuse, and 9 Major Depressive Disorder. Participants responded to demographic questionnaires and patients completed the PTSD Check List Scale (PCL-S) (Ventureyra, Yao, Cottraux, Note, & De Mey-Guillard, 2002). All patients had a PCL-S score above the pathological threshold of 44 (Table 1).

2.3. EMDR therapy

All PTSD patients underwent EMDR therapy (American Psychiatric Association, 2004). EMDR consists of an eight-step standardized protocol based on an adaptive information-process-

| Table 1  |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Subjects numbers | Age (mean ± SD) in years | Sex ratio (m/f) | Education level (mean ± SD) in years | PCL-S scores session 1 (mean ± SD) | PCL-S scores session 2 (mean ± SD) |
| PTSD patients | 16 | 35.4 ± 8.4 | 9/7 | 9.3 ± 1.6 | 59.7 ± 10.9 | 26.3 ± 4.9 |
| Controls | 16 | 33.6 ± 2.4 | 7/9 | 7.7 ± 2.3 | – | – |
Patients were treated by one of four therapists, all certified by the European Institute of EMDR. There was no fixed number of sessions. When possible, sessions were planned every 7 to 15 days according to the availabilities of patients and therapists. However, due to vacations, delays between EMDR sessions could be greater. The treatment was considered successful and complete when patients reported no more feelings of distress when thinking about their trauma. They were again interviewed by a psychiatrist using the MINI. They were subsequently retested when they no longer met PTSD classification according to DSM-IV criteria. Patients required an average of 2.5 sessions to no longer meet PTSD classification according to DSM-IV criteria. Patients were treated by one of four therapists, all certified by the European Institute of EMDR. There was no fixed number of sessions. When possible, sessions were planned every 7 to 15 days according to the availabilities of patients and therapists. However, due to vacations, delays between EMDR sessions could be greater. The treatment was considered successful and complete when patients reported no more feelings of distress when thinking about their trauma. They were again interviewed by a psychiatrist using the MINI. They were subsequently retested when they no longer met PTSD classification according to DSM-IV criteria.

2.4. Central activity: emotional face Matching task

The matching task used was the one validated by Hariri et al. (Hariri et al., 2000). In the emotional condition, subjects viewed a target face and selected which of two faces presented below it on the same screen expressed the same emotion (fear or anger). In the control condition, they viewed a target shape and chose which of two shapes presented below it on the same screen matched the target (round or oval). The paradigm consisted of 12 experimental blocks of 44.5 s duration each, alternating emotional and control blocks. Each block contained 10 stimuli presented for 4 s with an inter-stimulus interval of 0.5 s. The inter-block interval was 2 s, giving a total scan length of 9 min. We used 4 different sets of geometric forms for the control blocks, and for the emotional blocks we used 60 different images, 10 per block, 5 of each gender, all derived from the Karolinska database (Lundqvist, Flykt, & Öhman, 1998).

2.5. Procedure

Participants performed the protocol twice; for the EMDR group before and after therapy, and for healthy controls they were also tested twice to mimic PTSD patients’ procedure at durations between test and retest similar to that of patients.

2.6. Ethics

The study was reviewed and approved by the local ethics committee (CPP South Mediterranean 2), and all participants provided written informed consent.

2.7. fMRI specification

All data acquisition was performed on a 3-T MEDSPEC 30/80 AVANCE imager (Bruker, Ettlingen, Germany) at the fMRI center of Marseille, France. All stimuli were back-projected onto a screen that subjects viewed though a mirror positioned above their eyes. After an initial localizing scan to place image slices, fMRI scans were acquired using a T2*-weighted GE-EPI sequence (TR/TE = 2533/30 ms; FOV = 19.2 × 19.2 cm, 64 × 64 matrix; flip angle = 82.4°). Thirty-eight interleaved axial slices, tilted -30° to the inter-commissural plane in order to reduce artifacts in prefrontal regions, were obtained with a contiguous slice thickness of 3 mm without gap to cover all the brain. Following the fMRI scans, a set of high-resolution T1-weighted images were acquired for the purpose of anatomical identification (sagittal MPRAGE sequence, TE/TR = 4/10 ms, TI = 800 ms, flip angle = 30°, matrix = 256 × 256 × 128).

2.8. Data and statistical analyses

2.8.1. Behavioral data analysis on the Matching task

We routinely checked all subjects’ reaction times to fit the 4 sec image time-frame. Differences in task performance (accuracy score and reaction time) were then compared using a two-way ANOVA, with Group (control and patient) as a between factor and Session (test and retest) as a within factor.

2.8.2. fMRI data analysis of the Matching task

2.8.2.1. Preprocessing. Data were processed using SPM5 software (Wellcome Department of Cognitive Neurology, University College London). The first four scans, corresponding to a period of signal stabilization, were discarded. The remaining scans were corrected for differences in slice acquisition time. To remove the effects of head movement during scanning, the 234 scans of each session were realigned to the first scan of the session. Functional volumes were normalized into a standardized coordinate system corresponding to the Montreal Neurological Institute (MNI) space. Next, these images were then spatially smoothed with an isotropic Gaussian kernel (full width at half maximum of 8 mm). The T1-weighted structural images were co-registered to the EPI mean images and segmented into with matter, grey matter and cerebrospinal fluid and next normalized into the MNI space.

2.8.2.1.1. First level. Individual statistical maps were calculated for each subject to evaluate differences between the emotional versus control conditions. Each condition was modeled and convolved with a canonical hemodynamic response function to form regressors.

The six movement parameters were included in the analysis regressors of no interest to model residual effect due to head motion. A 128 s high-pass filter was applied to the data to remove low-frequency noise.

2.8.2.1.2. Second level. The individual contrast images were then entered into a second-level model to compare between the two groups (PTSD and control) the evolution after vs. before treatment for the contrast visage vs. form. fMRI brain activity data were analyzed by a flexible factorial design in SPM which used three factors: Subjects, Group (PTSD or Control) and Time (before or after treatment). We created the main interaction between the factors Group and Time to analyze the results. A gray matter mask selected using the WFU PickAtlas (Version 2.4) was applied to avoid analyzing white matter. We performed whole brain analysis for each contrast. All effects were thresholded at P < 0.005 (uncorrected at the voxel level) with a cluster size k > 33 (expected k = 32).

2.8.3. Correlation analysis on the Matching task

We wanted to assess the relationship between cerebral changes in patients after treatment and their symptoms’ disappearance. Pearson correlation was performed between the PCL-S scores changes after EMDR and BOLD changes in patients’ brain structures that were significantly modified by the symptoms disappearance and for which we had hypothesized involvement in the therapy. These areas are the amygdala, thalamus, vmPFC, and dlPFC. We consequently applied a Bonferroni correction (k = 5, P < 0.01).
3. Results

3.1. Clinical data

Groups did not differ in terms of age, gender, and education level. In accordance with the clinical evaluations, PTSD patients scored higher than the cut-off for pathology on the PCL-S scale. After treatment, PCL-S scores were significantly decreased (t = 13.4, n = 16, P < 0.001), below the cut-off for pathology (44) (Table 1) and the reliable change index (equal to 7.5) indicates a very significant symptoms scores reduction.

3.2. Results on the behavioral performance in the Matching task

There were no significant Group X Session interactions in terms of accuracy and reaction time for the emotional matching and control conditions.

3.3. Results on the fMRI BOLD data for the Matching task

There was a significant Group X Session effect. Fifteen clusters of BOLD differences between emotional and neutral conditions were found to be significantly decreased at session 2 as compared to session 1 in patients relative to controls (see Table 2 and Fig. 1a–f). These clusters correspond to the right (R) thalamus, and left (L) caudate nucleus, L amygdala, L anterior temporal cortex (AntTC) including a part of the L hippocampus (hipp) and the insula, R inferior temporal cortex (R InfTC), middle and posterior cingulum (mCC and postCC) including BA31, R parieto-central cortex (PCentralC) including BA3, R central cortex (CentralC) including BA4, R middle, and L Precuneus (BA7), ventromedial prefrontal cortex (vmPFC) (BA10), and L dlPFC including BA9.

3.4. Correlation analysis

There was one significant positive correlation between the R thalamus BOLD signal decrease after EMDR therapy and PCL-S score decrease, as displayed in Fig. 2 (r = 0.62, n = 16, P < 0.01).

4. Discussion

Neurofunctional test-retest analysis clearly differentiated patients from controls, although patient groups showed no behavioral differences in terms of reaction times and error numbers in the matching task.

Our results evidenced decreased activity in several brain structures in PTSD after EMDR treatment as compared to controls in the negative face-matching task. These structures are known to be activated during the matching task in healthy controls (Fakra, Salgado-Pineda, Delaveau, Hariri, & Blin, 2008) and are the same ones reported to be frequently over-activated in PTSD (amygdala, dl PFC, ACC). We replicate some of the ones previously observed in imaging study before and after EMDR (Lansing et al., 2005; Levin et al., 1999; Nardo et al., 2010; Oh & Choi, 2007) or during EMDR (Pagani et al., 2015; Pagani et al., 2012; Richardson et al., 2009). To the best of our knowledge, this is the first report showing an association between modification of thalamus activity and remission of PTSD symptoms after EMDR. Our result is therefore in agreement with Bergmann’s meta-analysis, which showed a steady decrease in thalamus activity in PTSD compared to healthy subjects (Bergmann, 2008). Post-treatment changes in brain activation support some hypotheses regarding the mechanisms of EMDR action.

4.1. The memory and self-based hypotheses

Inasmuch as memory dysfunction is involved in PTSD, alteration of the hippocampus seems central. In fact, the decreased activity of the left anterior temporal cortex (including the hippocampus) in PTSD after treatment agrees with experiments showing smaller hippocampus volumes especially of the left one (Ahmed-Leitao, Spies, van den Heuvel, & Seedat, 2016; Bossini et al., 2008; van Rooij et al., 2015), and, decreased activity of the hippocampus (Milad et al., 2009; Rauch, Shin, & Phelps, 2006; Thomae et al., 2009).

Moreover, the middle and posterior parts of the cingulate cortex are involved in retrieving memories from autobiographical episodic memory (Maddock, Garrett, & Buonocore, 2001). Verbal retrieval is done in connection with the left hippocampus (Heun et al., 2006). Another structure relating to memory is the precuneus (Bonni et al., 2015). It is less activated in war veterans with PTSD than controls during word encoding and rest (Geuze et al., 2008; Yan et al., 2013). This structure regulates self-consciousness; the anterior region would participate in self-centered mental imagery strategies, and a posterior region would subserve episodic memory retrieval (Cavanna & Trimble, 2006). EMDR therapy may allow an adapted storage of the traumatic event with an integration of the intense negative emotions.

Note that the modulation of conscious processes by the precuneus is shared by two other structures modified after treatment: the PCC and the medial PFC. These structures also allow the evaluation of one’s own and others’ emotional experiences. Since these three structures were less active after

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Table 2: Brain structures significantly desactivated post-treatment versus pre-treatment in PTSD patients as compared to Controls.

<table>
<thead>
<tr>
<th>Structures</th>
<th>MNI coordinates (xyz)</th>
<th>Voxels number</th>
<th>t-values</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Thalamus</td>
<td>20 -8 8</td>
<td>50</td>
<td>3.14</td>
<td>0.001</td>
</tr>
<tr>
<td>R Caudate Nucleus (head)</td>
<td>12 20 14</td>
<td>94</td>
<td>3.41</td>
<td>0.001</td>
</tr>
<tr>
<td>R Caudate Nucleus (body)</td>
<td>8 6 20</td>
<td>54</td>
<td>3.27</td>
<td>0.001</td>
</tr>
<tr>
<td>L Caudate Nucleus (body)</td>
<td>-8 6 10</td>
<td>39</td>
<td>2.87</td>
<td>0.003</td>
</tr>
<tr>
<td>L Amygdala</td>
<td>-20 0 -18</td>
<td>42</td>
<td>3.09</td>
<td>0.02</td>
</tr>
<tr>
<td>L anterior temporal cortex (including the hippocampus)</td>
<td>-38 -10 -12</td>
<td>55</td>
<td>3.29</td>
<td>0.001</td>
</tr>
<tr>
<td>R Inferior Temporal Cortex</td>
<td>60 -22 -22</td>
<td>40</td>
<td>3.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Middle and posterior cingulum</td>
<td>-2 -36 40</td>
<td>42</td>
<td>3.36</td>
<td>0.01</td>
</tr>
<tr>
<td>R parieto-central cortex</td>
<td>38 -36 64</td>
<td>53</td>
<td>3.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R central cortex</td>
<td>40 -22 44</td>
<td>50</td>
<td>3.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R Precuneus</td>
<td>20 -56 42</td>
<td>223</td>
<td>5.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M Precuneus</td>
<td>-8 -56 52</td>
<td>258</td>
<td>4.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L Precuneus</td>
<td>-20 -50 52</td>
<td>105</td>
<td>4.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>vm PFC (BA 10)</td>
<td>-4 54 42</td>
<td>42</td>
<td>3.01</td>
<td>0.002</td>
</tr>
<tr>
<td>L dl PFC (BA9)</td>
<td>-24 30 34</td>
<td>53</td>
<td>3.34</td>
<td>0.001</td>
</tr>
</tbody>
</table>
EMDR in PTSD patients, EMDR might participate in modifying traumatic memory perception by changing patients’ view of their own and other protagonists’ experiences. This modification of self-perception in PTSD by the treatment is crucial because negative cognitions regarding the self were prospectively associated with an increase in PTSD symptoms in 156 Israeli trauma victims (Shahar, Noyman, Schnidel-Allon, & Gilboa-Schechtman, 2013).

4.2. The emotion regulation hypothesis or extinction hypothesis

The altered fear circuitry in PTSD, encompassing the amygdala, PFC (medial and dorsolateral), and hippocampus, is modified post-EMDR with a decreased activity after the therapy. These three main structures are largely interconnected (Price & Drevets, 2010) with the structures we have studied, i.e., the temporal cortex, caudate nucleus, and thalamus. The responsiveness of the mPFC has been positively correlated to symptom severity in PTSD (Scott L. Rauch et al., 2006). The mPFC is often described as being hypoactive in PTSD, notably during trauma recall. It has been hypothesized that this decreased frontal activity favors enhanced amygdala activity and subsequently elevated PTSD symptoms (Francati, Vermetten, & Bremner, 2007; Hayes et al., 2012). However, this prevailing hypothesis behind PTSD dysfunction is challenged by studies showing both amygdala and mPFC hyper-activation in PTSD during non-conscious processing of fear (Bryant et al., 2008).

The amygdala is connected with the mPFC, but also with other memory or emotional structures (Anggleton, 2000). It is an alarm center and is essential for fear learning (Pitman et al., 2012). It may act as a link between stimuli that predict future reward or punishment (Hampton, Adolphs, Tyszka, & O’Doherty, 2007) to ensure appropriate responses to danger. After EMDR therapy, amygdala activity diminishes, similarly to vmPFC and hippocampus activity. When the BOLD signal is restored, the organism is no longer in an alert state. A study on animals suggests that such fear extinction is underlain by these three structures as a consequence of extinction memory formation (Moustafa et al., 2013).

The dlPFC is also involved in selective attention processes in PTSD in combination with the ventrolateral PFC, ACC, and amygdala (Bremner et al., 2004; El Khoury-Malhame et al., 2011; Felmingham et al., 2009). In PTSD, greater dlPFC activation is associated with lower symptoms in an emotional anticipation task (Aupperle et al., 2012), and smaller dlPFC activation was found in response to threat cue trials (Fani et al., 2012). Aupperle et al. (Aupperle et al., 2012) made the assumption that the mPFC and amygdala would process emotions whereas the dlPFC would more generally relate to inhibitory control, regardless of whether the context is emotional or cognitive. However, these structures should influence each other. Post-EMDR dlPFC modification may be the consequence of the amygdala activity decrease following symptom remission in PTSD, reflecting the safety increase during emotion processing of the faces.

In addition to the involvement of many modified structures for emotion regulation it also seems that EMDR therapy may act through its action on reward mechanisms.
4.3. The reward hypothesis

Basal ganglia activity including the caudate nucleus also appears disrupted in PTSD (Looi et al., 2009; Mickleborough et al., 2011). These two subcortical structures are functionally interconnected and both connect with the prefrontal lobe. This gives them a major role in attention, learning, motor control (Herrera, Barcia, & Navarro, 2002), and reward mechanisms (Haber & Knutson, 2010). The caudate nucleus is largely understudied in PTSD, although it was shown to have decreased volume and functional modification in PTSD (Herriga et al., 2012; Lucey et al., 1997; Nardo et al., 2011; Sachinvala, Kling, Suffin, Lake, & Cohen, 2000). Reward function impairment was also described in PTSD (Hopper et al., 2008), with symptoms such as emotional numbing through deficient expression of positive emotions associated with appetitive motivation (Litz & Gray, 2002). Such impairment seems to involve mPFC and amygdala activity (Haber & Knutson, 2010; Rushworth, 2008). As such, EMDR might be restoring patients’ reward mechanisms and positive outcome information (Sailer et al., 2008) by reducing the activity of the amygdala, mPFC, thalamic, and caudate. The reprocessing phase in EMDR that aims at increasing the validity of one’s positive self-cognition may particularly enhance positive reinforcement by restoring the reward-related processes (Hopper et al., 2008). If the reward mechanisms are correctly activated by restoring the caudate nucleus activity post-treatment, one would observe improved encoding instructed motivational contexts for goal-directed action (Kimura, Yamada, & Matsumoto, 2003) as well emotion regulation (Hare, Tottenham, Davidson, Glover, & Casey, 2005). The caudate nucleus is highly active when one avoids positive information (Hare et al., 2005); its decreased activity following EMDR may enhance positive emotions and cognitions and counterbalance the negative emotions and beliefs activated by the trauma memory.

4.4. The REM-sleep hypothesis

The neural network we found modified after EMDR therapy is known to be involved in REM sleep processes. Indeed, the precuneus and connected structures, i.e., PCC, dPFC, thalamus, hippocampus, and amygdala (Cavanna & Trimble, 2006; Zhang & Li, 2012) regulate REM sleep by either increasing (thalamus, amygdala, hippocampus, mPFC) or decreasing (precuneus, PCC, dPFC) their activities (Desseilles, Dang-Vu, Sterpenich, & Schwartz, 2011; Kussé et al., 2010; Maquet et al., 1996). The involvement of limbic and paralimbic structures in REM sleep seems to favor memory consolidation, particularly emotional memories (Desseilles et al., 2011; Miyachi, Misaki, Kan, Fukunaga, & Koike, 2009). REM sleep disturbance has been frequently reported in PTSD (Germain et al., 2013; Germain, Buysse, & Nozinger, 2008) and might amplify the altered amygdala and mPFC function (Germain et al., 2008). Given that bilateral eye-movements in EMDR resemble those induced in REM sleep, the recovery of patients’ symptoms and the restoration of their BOLD activity may be related to a REM sleep-like effect of EMDR on PTSD. This agrees with Stickgold’s hypothesis that EMDR acts as REM sleep to repair traumatic memories (Stickgold, 2002) by improving memory consolidation and by reducing the emotional tone of memories (van der Helm et al., 2011).

In addition, thalamocortical pathways are essential for the online monitoring of saccades (Tanaka & Kunimatsu, 2011). The generation of eye movements during EMDR may reinforce this circuitry and play a role in the restoration of the functional activity of the thalamus and its interconnected cortical structures. The thalamus seems to be at the core of EMDR therapy, because we found its activity modification positively correlated with symptom decrease. PTSD is indeed associated with functional and anatomical alterations of the thalamus (Bremner et al., 1999; Yin et al., 2011). In resting condition, thalamic activity is decreased (Yan et al., 2013) but in response to traumatic scenes it is increased (Bourne, Mackay, & Holmes, 2013). Our results showing thalamic activity decrease in PTSD with symptom disappearance thus agrees with thalamic hyperactivity in PTSD in response to traumatic scenes. It could be suggested that the decrease of sensory reactions of the thalamus after EMDR therapy may modify the inputs to its directly or indirectly connected areas such as amygdala, prefrontal structures and other neocortical structures whom functional activity is diminished.

One may wonder why eye movements in EMDR may be replaced by other BAS, i.e., auditory, kinetic, or somatosensory stimulations (Servan-Schreiber, Schooler, Dew, Carter, & Bartone, 2006), and thus, does the hypothesis involving REM-like mechanisms and thalamo-cortical stimulation still stand? Given that thalamo-cortical pathways are activated by sensory stimuli other than visual ones (Herrero et al., 2002), that may explain why BAS from different sensory modalities are efficient in EMDR therapy.

4.5. Limitations

Our study has many limitations that stem both from the patients recruited and the methodology employed. One limitation of our study is that some of the patients were on stable medical regimen for antidepressants and/or anxiolytics (5 of 16 patients) and had other comorbid anxiety and/or mood disorders (13 of 16 patients). None of the aforementioned factors (comorbidities and medication) significantly influenced our results, as indicated by covariate statistics. However, alteration of cognitive and neural processing cannot be totally ruled out. Another limitation is that the retest effect of the task (before and after therapy) was counterbalanced by the retest effect in healthy controls. Such a retest effect should ideally be monitored in trauma-exposed subjects without PTSD or in PTSD subjects without therapy (wait list group). From an ethical point of view, given the intensity of personal and professional dysfunction, it was impractical to consider a wait list group. Finally, the statistical thresholds used for the functional brain activity do not rule out that the structures identified are not activated by chance. Further experiments should be led to confirm our results.

5. Conclusion

The aim of this experiment was to explore the cerebral healing effect of EMDR therapy in PTSD. Brain structures involved in negative face processing that were hyperactivated in PTSD were modified after treatment and symptom remission. These structures have already been implicated in PTSD. Given the role of these structures in memory, self-perception, fear extinction, REM sleep, reward, and emotion, we discussed possible explanatory mechanisms of EMDR action in PTSD. To better address this issue, further experiments should also explore the healing mechanism of EMDR using on-line paradigms with fine temporal resolution.

Disclosure of interest

The authors declare that they have no competing interest.

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