INTRODUCTION

Eye Movement Desensitization and Reprocessing (EMDR) is a psychotherapy that has been found to effectively resolve the effects of traumatic experiences and following numerous randomized clinical trials in patients with post-traumatic stress disorder (PTSD) it has been recognized as a first-line treatment for PTSD.
Morphovolumetric changes after EMDR treatment in drug-naïve PTSD patients

PTSD is characterized by dysfunction and structural alteration of several discrete brain regions. Neurobiological investigations of PTSD have shown that it may be characterized by lower density in limbic and paralimbic cortices, with changes in gray and white matter volume and concentration (GMV and GMC, respectively) in hippocampus, parahippocampal gyrus and cingulum. However possibly due to the high heterogeneity of traumatic events causing PTSD and of patients symptoms (i.e. hyperarousal vs dissociation) as well as of cohort sizes a surprisingly large variance across studies has been reported.

Most Magnetic Resonance Imaging (MRI) studies on PTSD have measured volumetric changes in discrete brain regions or small brain structures. Karl et al. in a meta-analysis of structural brain MRI in PTSD concluded that the disorder is associated with abnormalities in multiple frontal-limbic system structures, notably in hippocampus, amygdala, and anterior cingulate cortex. Similarly, a recent meta-analysis by Woon et al on 39 hippocampal volumetric studies identified significant hippocampal volume reduction in individuals with PTSD.

Furthermore, investigating the changes in GMC in patients with and without PTSD, Zhang et al. found those with PTSD showing significantly decreased GMC in left anterior hippocampus and left parahippocampal gyrus and Nardo et al. showed a lower grey matter density in limbic and paralimbic cortices to be associated with PTSD diagnosis.

Studies investigating the effect of Cognitive Behavioural therapy (CBT) on hippocampal volume in PTSD patients have reported conflicting results. Recently functional studies have reported EMDR-related neurobiological changes and our group has investigated the structural changes after successful treatment of PTSD with EMDR showing an average increase of 6% in hippocampal volume following remission of diagnosis after three months of EMDR therapy.

The aim of the present study was to extend such investigation beyond the regional assessment computing in PTSD patients and healthy controls a voxel-wise analysis on the whole brain assessing the anatomical changes occurring following EMDR therapy.

**METHOD**

**Participants**

Thirty-eight participants were studied: 19 drug-naïve patients with PTSD (10 men and 9 female) and 19 age matched healthy controls (15 men and 4 women). The patient group was recruited at the Center for the Diagnosis and Treatment of Post-Traumatic Stress Disorder, Department of Psychiatry, University of Siena, between September 2010 to May 2012 and largely overlapped the cohort recruited for a previous study. Patient inclusion criteria were: age between 18 and 65 years and the drug-naïve status. Exclusion criteria were: a history of current and/or lifetime comorbid psychiatric diagnoses as determined by the SCID; previous or current use of any psychotropic medications; history of head trauma; presence of neurological, endocrine, or degenerative disorders. Healthy controls were recruited at the hospital “Le Scotte” in Siena, Italy, and matched for age, education, handedness, weight and height. Exclusion criteria for controls were: a history of meningitis, traumatic brain injury, presence of neurological, en-
RESULTS

Patients and controls did not statistically differ for demographic data, as reported in Table 1. Patients’ diagnoses of PTSD at baseline (T1) were confirmed by clinical evaluation and by the fulfillment of all the criteria at CAPS. All patients had experienced a one-time adult trauma: natural disaster (n=3), sudden death of a family member (n=5), car accident (n=2), assault/robbery (n=6), and terrorist attack (n=4). One patient dropped out because of a depressive episode onset and consequently we removed a matched healthy control participant.

Baseline comparisons between patients and controls: Grey Matter Volume

The GMV comparison between patients and healthy participants at baseline showed significant differences (F1,35=3.674; p=.008; η2=.298). Analyses revealed a region of significantly decreased GMV in patients’ left parahippocam-
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Pal region, supplementary motor area, lingual gyrus, and both left and right superior frontal gyrus. Patients with PTSD also showed a significant increase in GMV corresponding to right angular gyrus, inferior parietal lobule and left inferior temporal gyrus. MNI coordinates of each significant cluster, F-values and clusters dimension are reported in Table 2.

Baseline comparisons between patients and controls: Grey Matter Concentration

The GMC comparison between patients and healthy participants at baseline did not show any significant differences (F 1,35=0.984; p=.332).

Longitudinal comparisons for patients’ clinical PTSD symptom scales pre and post EMDR

During the baseline assessment, patients showed a moderate to severe PTSD symptom severity, as highlighted by the DTS values: DTS total score was 99 +/- 9 with mean scores for each subscale of Intrusion 32 +/- 9, Avoidance 40 +/- 14 and Hypervigilance 27 +/- 9. At pre-treatment, the mean CAPS total score was 75.8 ( +/- 21.8), with mean score for re-experiencing subscale of 17.0 +/- 8, avoidance 20.5 +/- 9.0; and hyperarousal 18.5 +/- 9.8. After 12 sessions of EMDR (Time 2), there was a significant pre-post decrease on the mean CAPS total score (19.3 +/- 15.5) (t (35)=2.132, p<.004) and hyperarousal subscale (4.1 +/- 9.8; p<.001) (t (35)=1.347, p<.008), and a non-significant trend to decrease on the re-experiencing (6.8 +/- 8.0) and avoidance (9.8 +/- 9.0) subscales. All 19 patients completed EMDR therapy and reported improvements in their PTSD symptoms, with 16 patients no longer satisfying necessary criteria for PTSD diagnosis.

Longitudinal comparisons between patients and controls: Grey Matter Volume

Group-time interactions for GMV maps were significant (F (1,35)=4.324; p=.006; $\eta^2=.398$), indicating a larger increase in GMV in patients as compared to healthy controls, specifically for left parahippocampal gyrus (F (1, 35)=11.237; p=.001, MNI x=-24, y=-21, z=-29; voxels=246), where patients had showed a significantly smaller GMV compared to controls before the EMDR treatment (Figure 1). Additionally, in comparison to healthy controls, a cluster of decreased GMV was found in patients’ left thalamus region after EMDR treatment (F (1, 35)=9.432; p=.002, MNI x=-9, y=-24, z=6; voxels=168) (Figure 2). No differences between first and second MRI acquisition were highlighted for healthy control participants (F 1,35=0.134; p=.389).

DISCUSSION

In this study brain MRI measurements with Optimized Voxel-Based Morphometry was used to investigate the neurobiological effects of EMDR treatment in drug-naïve PTSD without comorbidity. Consistent with other volumetric findings, when we compared patients with PTSD to healthy

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### Table 2. Significant GMV Differences at Baseline between patients with PTSD and healthy controls.

<table>
<thead>
<tr>
<th>Clusters</th>
<th>Voxels</th>
<th>MNI Coordinates</th>
<th>Peak $F_{(1,35)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &gt; Healthy controls at baseline*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>cluster 1</strong></td>
<td>89</td>
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<tr>
<td>Right angular gyrus</td>
<td>42</td>
<td>-73</td>
<td>40</td>
</tr>
<tr>
<td><strong>cluster 2</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior temporal gyrus</td>
<td>-45</td>
<td>-54</td>
<td>-8</td>
</tr>
<tr>
<td>Right inferior Parietal lobule</td>
<td>51</td>
<td>-54</td>
<td>48</td>
</tr>
<tr>
<td>Patients &lt; Healthy controls at baseline*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cluster 1</strong></td>
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<tr>
<td>Left parahippocampal gyrus</td>
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<td>-22</td>
<td>-20</td>
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<tr>
<td><strong>Cluster 2</strong></td>
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<td>Left supplementary motor area (SMA)</td>
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<td><strong>Cluster 3</strong></td>
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<td>Right superior frontal gyrus</td>
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<td><strong>Cluster 4</strong></td>
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<td>Left lingual gyrus</td>
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<tr>
<td>Left superior frontal gyrus</td>
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<td>26</td>
<td>55</td>
</tr>
</tbody>
</table>

*Patients=19; Healthy controls = 18.
controls at baseline, we found significantly smaller GMV in the patients’ parahippocampal, parietal and frontal regions, and significantly larger GMV in temporal and parietal areas (Table 2) all regions involved in processing and storing mechanism of traumatic events. Furthermore, after treatment completion comparisons with baseline showed in patients a significant increase in GMV in left parahippocampal gyrus and a significant GMV decrease in left thalamus. The implementation of VBM has allowed to extend the structural analysis to the entire brain overcoming the limitation of our previous investigations restricting the assessment of the effect of EMDR to the hippocampal region. Structural evaluation provides understanding of a disorder’s neurobiological substrate and allows to anatomically identify and measure changes which have clinical implications. Although to date we are still far from matching symptoms and single alterations, several works investigating PTSD suggested that many symptoms and/or psychopathological characterizations appear to be closely related to some specific neurobiological alterations. In the present study hippocampus, the main site for short-term memory processing, was found at baseline significantly smaller than in healthy controls and its volume increased following successful EMDR therapy. Hippocampus is involved in encoding, consolidating and retrieving declarative memories and receives extensive inputs from several regions of the neocortex. Hippocampal dysfunction has been claimed to play a key role in the memory disturbances considered to be the core component in PTSD and it is known by long that PTSD is associated with abnormalities in activity and volume of the hippocampus, as is it true in the symptomatic phase for our patients. It has been speculated that in PTSD emotional information is retained in amygdala and hippocampus and this pathological condition might be related to hippocampal volume reduction, possibly due to the effect of chronic release of cortisol, affecting specifically this brain region. Moreover, a failure in the func-
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Riv Psichiatr 2017; 52(1): 24-31

LIMITATIONS AND RECOMMENDATIONS

One limitations of this study is the small sample size possibly overestimating the number of foci showing significant differences. On the other hand the relative high costs of the methodology, makes the recruitment of an inadequate number of subjects to be investigated a common limitation in neuroimaging studies. For this reason in our study as in other ones in the past patients recruitment and characterization suffer of the presence of different trauma types and of discrepancies about the number of previous traumas, both issues potentially biasing the results. We also acknowledge that the recruitment of PTSD patients without comorbidity and of non-traumatized control subjects might render the results of the present investigation not directly comparable to other studies in the same field. However, the with-in subject analysis strengthened, along with the objective decrease of PTSD clinical scores, the reliability of the pre- to post-therapy changes and in the most of the control subjects mix lifetime traumas, even if not causing symptoms have certainly happened. Furthermore, the absence of follow-up to evaluate the maintenance of symptomatic improvement and the volumetric changes does not allow to draw conclusion on the long-term effectiveness of EMDR therapy. Future research might benefit of optimized voxel based morphometry and by the use of diffusion weighted images acquisition aimed at white matter fiber tracts changes detection, to examine the possible impact of psychotherapies on brain structural connectivity.

Acknowledgements: Louise Maxfield, Ph.D. professionally edited this paper. She is a Psychologist in London Ontario Canada, affiliated with London Health Sciences Centre, the Departments of Psy-
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Conflicts of interest: the authors declare that no source of funding was received to prepare this article.

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