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Eye movement desensitization and reprocessing therapy in subsyndromal bipolar patients with a history of traumatic events: A randomized, controlled pilot-study

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ABSTRACT

Traumatic events are frequent in bipolar patients and can worsen the course of the disease. Psychotherapeutic interventions for these events have not been studied so far. Twenty DSM-IV bipolar I and II patients with subsyndromal mood symptoms and a history of traumatic events were randomly assigned to Eye Movement Desensitization and Reprocessing therapy ($n=10$) or treatment as usual ($n=10$). The treatment group received between 14 and 18 Eye Movement Desensitization and Reprocessing sessions during 12 weeks. Evaluations of affective symptoms, symptoms of trauma and trauma impact were carried out by a blind rater at baseline, 2 weeks, 5 weeks, 8 weeks, 12 weeks and at 24 weeks follow-up. Patients in the treatment group showed a statistically significant improvement in depressive and hypomanic symptoms, symptoms of trauma and trauma impact compared to the treatment as usual group after intervention. This effect was only partly maintained in trauma impact at the 24 weeks follow-up visit. One patient dropped from Eye Movement Desensitization and Reprocessing group whereas four from the treatment as usual group. This pilot study suggests that Eye Movement Desensitization and Reprocessing therapy may be an effective and safe intervention to treat subsyndromal mood and trauma symptoms in traumatized bipolar patients.

1. Introduction

Traumatic events include early childhood adversities and negative life events during the later life, both of which are experienced frequently by patients with bipolar disorder (Johnson et al., 2008; Post et al., 2013). Not surprisingly, traumatic events often lead to the diagnosis of post-traumatic stress disorder (PTSD) with symptoms, such as flashbacks, feeling emotionally numb, loss of interests, being easily startled or sleeping problems. PTSD is highly comorbid in adult bipolar disorder as suggested by findings from the STEP-BD study of 3158 bipolar patients with an overall prevalence rate of 20% for lifetime PTSD, a rate that is roughly three times its lifetime prevalence in the general population (Hernandez et al., 2013). This comorbidity is associated with a poorer outcome with more rapid-cycling, more (hypo)manic and depressive symptoms, more suicide attempts and substance abuse and a lower quality of life, when compared to bipolar patients without PTSD (Goodman et al., 2001; Quarantini et al., 2010). Same clinical consequences have also been found in populations with bipolar disorder and a history of traumatic events, not meeting necessarily criteria for PTSD (Goodman et al., 1997; Mueser et al., 1998; Etain et al., 2013). The comorbidity of traumatic events/PTSD and bipolar disorder may also negatively impact on response to treatment as trauma related avoidance with further social isolation, anxiety and depressive symptoms worsen affective symptoms (Cresswell et al., 1992; McElroy, 2004).

The evidence of negative effects of traumatic events or PTSD on the course of bipolar disorder is robust but no treatment trials have been directed so far to this comorbidity. One form of treatment which is increasingly used in PTSD is Eye Movement Desensitization and

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Reprocessing (EMDR) therapy (Shapiro, 2001). This form of psychotherapy uses a standardized eight phase protocol which involves making side-to-side eye movements while simultaneously focusing on symptoms and experiences related to the traumatic event; the approach also incorporates elements of cognitive behavioral, interpersonal, and body-centered therapies (Shapiro, 1999, 2001). Three independent meta-analyses have found Eye Movement Desensitization and Reprocessing therapy to be effective in PTSD, with benefits similar to trauma-focused cognitive behavioral therapy (Seidler and Wagner, 2006; Bisson et al., 2013; Watts et al., 2013).

The usefulness of Eye Movement Desensitization and Reprocessing therapy has not so far been investigated in bipolar disorder. The aim of this pilot trial was to evaluate whether Eye Movement Desensitization and Reprocessing therapy can have mood stabilizing effects in bipolar patients with mild depressive and/or hypomanic symptoms, called subsyndromal symptoms (Tohen et al., 2009). We chose subsyndromal symptoms as they are clinically relevant by causing more affective relapses and poor functioning (Altshuler et al., 2006; Judd et al., 2008). Furthermore, bipolar patients would be also more likely to be able to tolerate and benefit from Eye Movement Desensitization and Reprocessing therapy than those who were currently experiencing a moderate to full-blown depressive or manic/mixed episode. We hypothesized a mood-stabilizing effect of Eye Movement Desensitization and Reprocessing therapy via processing the trauma as (1) bipolar patients with trauma –as stated above- suffer from more affective symptoms than bipolar patients without trauma (e.g. Leverich and Post, 2006; Quarantini et al., 2010), and (2) preliminary results suggest that Eye Movement Desensitization and Reprocessing therapy develops mood-stabilizing properties via the modulation of the Default Mode Network which is dysfunctional in both PTSD and bipolar disorder (Landin-Romero et al., 2013).

2. Methods

2.1. Study design

The study was designed as a single-blind, randomized, controlled trial to evaluate the efficacy of Eye Movement Desensitization and Reprocessing therapy as an adjunctive treatment in bipolar patients with subsyndromal symptoms and a history of traumatic events. Participants were randomly assigned to 12 weeks of treatment with Eye Movement Desensitization and Reprocessing therapy or treatment as usual. The participants were re-assessed at the end of this period and also after a further 12 weeks of follow-up which was considered sufficient to test whether possible effects of Eye Movement Desensitization and Reprocessing therapy were maintained or not. The primary outcome measures were depression and mania ratings. Secondary outcome criteria included changes in trauma scales and safety aspects of Eye Movement Desensitization and Reprocessing therapy. A priori participants were considered as drop-outs if they withdrew their informed consent or developed a full blown affective episode.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was reviewed by the ethical committee "Comité Ético de Investigación Clínica de las Hermanas Hospitalarias" (Barcelona, Spain) and written informed consent of the participants was obtained after the nature of the procedures had been fully explained. All participants were also informed in case of their non participation that this has no direct or indirect influence or consequence on their usual treatment.

The trail was registered in ClinicalTrials.gov (NCT01620866).

2.2. Subjects

Participants were recruited from September 2010 through July 2011 from the outpatient unit of a psychiatric hospital (Benito Menni CASM, Sant Boi de Llobregat, Spain). Last follow-up ended accordingly in December 2011. To be included, all participants were required to have a diagnosis of bipolar disorder I or II according to DSM-IV criteria. They were also required to show subsyndromal affective symptoms, defined following the International Society for Bipolar Disorder criteria (Tohen et al., 2009) as scores of $>8<14$ on the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), or $>8<14$ on the Young Mania Rating Scale (YMRS; Young et al., 1978). The participants were also required to be on stable doses of mood-stabilizers for at least 3 months. Furthermore, all participants had to have experienced at least three documentable traumatic events over their lifetime, which were still causing a clinically relevant distress. This was defined as a score of at least five or more Subjective Units of Disturbance, known as SUD, usually used in the Eye Movement Desensitization and Reprocessing standard protocol (scores from 0 to 10, with 10 being of maximum disturbance). The traumatic events and their current impact were determined using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) and the Impact of Event Scale (IES; Weiss and Marmar, 1997) (see details below).

Participants were excluded if they had a history of neurological disease or abuse/dependency on alcohol or drugs. Suicidality, an affective episode in the last 3 months, previous Eye Movement Desensitization and Reprocessing treatment and a score higher than 25 in the Dissociative Experiences Scale (DES; Bernstein and Putnam, 1986) were further exclusion criteria. The rationale for this last exclusion was that a more extensive Eye Movement Desensitization and Reprocessing protocol (beyond the standard eight phase Eye Movement Desensitization and Reprocessing protocol) is recommended when dissociative symptoms are present.

2.3. Procedure

Participants were allocated by the senior author (BLA) to Eye Movement Desensitization and Reprocessing therapy or treatment as usual by alternation. They were evaluated at 6 time-points, baseline, 2 weeks, 5 weeks, 8 weeks, 12 weeks, and then again at 24 weeks.

The participants who were assigned to Eye Movement Desensitization and Reprocessing therapy were allocated to one of nine Eye Movement Desensitization and Reprocessing therapists. All therapists had more than 10 years experience with Eye Movement Desensitization and Reprocessing therapy. Each of them discussed their patient with all the other therapists and they jointly defined the main targets for the trauma therapy. Eye Movement Desensitization and Reprocessing treatment followed the standard protocol of eight phases developed by Shapiro (Shapiro, 1999, 2001). All participants received between 14 and 18 individual sessions, lasting 90 min over a period of 12 weeks. The criterion for completion of Eye Movement Desensitization and Reprocessing therapy was attendance at all therapy sessions during 12 weeks.

All sessions were video-taped and a fidelity check was made by an external Eye Movement Desensitization and Reprocessing therapist (IF) who randomly selected 10 sessions and evaluated if therapists followed the procedure and the targets of the Eye Movement Desensitization and Reprocessing standard protocol. All selected videos were positively rated as such. Participants in the treatment as usual group continued to receive standard outpatient care from their treating psychiatrists.

2.4. Assessments

All participants were evaluated by a single assessor (VV), a psychiatrist who was not otherwise involved in the study. He was not trained in Eye Movement Desensitization and Reprocessing and had no allegiance to this form of psychotherapy. The assessor was unaware of treatment allocation and the participants were instructed not to reveal their treatment group to him.

To assess affective symptoms, the HDRS and the YMRS were used, plus the Clinical Global Impression-Bipolar Disorder (CGI-BP; Spearing et al., 1997). The CGI-BP is divided into subscales for manic (CGI-BP-m) and depressive symptoms (CGI-BP-d) and general symptoms (CGI-BP-g). Participants were evaluated on these scales at baseline, 2 weeks, 5 weeks, 8 weeks, 12 weeks and 24 weeks.

The two trauma scales, the IES-R (Weiss and Marmar, 1997) and the CAPS (Blake et al., 1995), were administered at baseline, after 12 weeks and 24 weeks. The CAPS is a 30-item structured interview that assesses the seventeen symptoms for PTSD outlined in the DSM-IV, along with five associated features. It can be used to make a current (past month) or lifetime diagnosis of PTSD or to assess symptoms over the past week. Additionally, questions target on improvement in symptoms since the previous CAPS administration, overall PTSD severity and frequency. Severity scores can be also calculated by summing the frequency and intensity ratings for each symptom. The IES-R is a 22-item self-report measure that assesses subjective distress caused by traumatic events. Patients are asked to identify a specific stressful life event and then indicate how much they were distressed or bothered by it during the past seven days. Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The IES-R yields a total score (ranging from 0 to 88) and scores can also be calculated on Intrusion, Avoidance, and Hyperarousal subscales. Subscale scores can be weighted on a component score to calculate the likelihood of a PTSD diagnosis. The closer to 0, the more likely is the diagnosis of PTSD. As participants had to present with at least three disturbing traumatic events in the history, we evaluated the trauma impact of each of them separately: IES 1, IES 2 and IES 3.

Premorbid IQ was estimated using the Word Accentuation Test [Test de Acentuación de Palabras, TAP (Del Ser et al., 1997; Gomar et al., 2011)], a word reading test which requires pronunciation of low-frequency Spanish words whose accents have been removed. Current IQ was measured using four subtests of the Spanish version of the Wechsler Adult Intelligence Scale III (WAIS-III), Vocabulary, Similarities, Matrix Reasoning, and Block Design. Raw scores were converted into scaled scores for the relevant age group, and then prorated to calculate full-scale IQ.

2.5. Statistical analysis

This study was designed as a pilot trial and thus it did not include formal sample size estimation. A total number of 20 participants was considered as

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sufficient to get a signal whether Eye Movement Desensitization and Reprocessing therapy exerts beneficial effects or not in traumatized bipolar patients. All analyses were carried out by intention-to-treat, using the last-observation-carried-forward (LOCF) technique.

The effects of treatment in the evolution of each scale (e.g. YMRS score) from baseline to the 12 weeks visit and from baseline to the 24 weeks visit were assessed using repeated-measures analysis of variance (RMANOVA) tests, with group (treatment vs. control), visit (pre vs. post) and their interaction as fixed effects, and the participant id as random effect. This model was also conducted with covariation by baseline scores. *p*-Values were corrected for multiple comparisons (10 scores) using the false discovery rate (FDR). Clinical scores at baseline were compared with independent sample *t*-tests (numeric data) or Fisher's tests (nominal data). The significance level was set at $p < 0.05$ two-tailed in all analyses.

3. Results

3.1. Patient recruitment and baseline assessments

Demographic and related clinical baseline data is shown in Table 1. Twenty-six bipolar patients were screened, of whom 20 fulfilled the inclusion criteria (16 bipolar I, 4 bipolar II). There were no statistically significant differences between the Eye Movement Desensitization and Reprocessing and treatment as usual groups on most demographic variables, other than the previous number of affective episodes and employment status. The medication was also comparable in both groups. During the study a change in medication was made in 3 participants from each group.

Results from the baseline clinical scores – affective and trauma symptoms – are shown in table 2. There were no significant differences at baseline in manic, depressive or general affective symptoms and functioning between the Eye Movement Desensitization and Reprocessing and treatment as usual groups. As shown in Table 2, both groups were also comparable with respect to trauma symptoms and impact of trauma. Traumas reported by the participants included kidnaping, robbery, witness of violence, accidents, sudden death of a family member, sexual abuse, physical aggression, psychological abuse, parental neglect, traumatic divorce, first affective episode and admission to a psychiatric hospital with mechanical restraint.

Table 1
Socio-demographic and clinical baseline scores of the EMDR and TAU groups.

Variable	EMDR ($n=10$)	TAU ($n=10$)	Statistic, *p*
Age, mean (S.D.)	43.90 (6.87)	44.80 (6.86)	$t=-0.29$, $p=0.773$
Gender, *n* (%)			
Female	7 (70)	5 (50)	Fisher test, $p=0.650$
Male	3 (30)	5 (50)	
Estimated pre-morbid IQ (TAP)	25.40 (2.83)	26.44 (2.006)	$t=-0.1916$, $p=0.372$
Estimated current IQ (WAIS III)	100.6 (10.90)	102 (15.70)	$t=-0.228$, $p=0.823$
Marital status, *n* (%)			
Single/divorced	3 (30)	3 (30)	Fisher test, $p=0.443$
Married	7 (70)	7 (70)	
Working status, *n* (%)			
Active	2 (20)	0 (0)	Fisher test, $p=0.033$[b]
Unemployed	1 (10)	0 (0)	
Sick leave/disability	7 (70)	10 (1 0 0)	
Duration of illness (months), mean (S.D.)	18 (10.28)	23.3 (7.86)	$t=-1.29$, $p=0.212$
Affective episodes, mean (S.D.)	12.80 (12.22)	27.85 (6.71)	$t=-3.32$, $p=0.004$[b]
Hospital admissions, mean (S.D.)	0.9 (0.87)	6.10 (8.02)	$t=-2.03$, $p=0.056$
Previous psychotherapy, *n* (%)			
None	5 (50)	7 (70)	Fisher test, $p=0.350$
CBT[a]	5 (50)	2 (20)	
Psychodynamic	0 (0)	1 (10)	
Seasonal affective cycle, *n* (%)			
Yes	7 (70)	9 (90)	Fisher test, $p=0.582$
No	3 (30)	1 (10)	
Psychotic symptoms, *n* (%)			
Yes	5 (50)	6 (60)	Fisher test, $p=0.656$
No	5 (50)	4 (40)	
Substance abuse, *n* (%)			
Yes	3 (50)	6 (60)	Fisher test, $p=0.370$
No	7 (50)	4 (40)	
Mood stabilizer, *n* (%)			
None	1 (10)	0 (0)	Fisher test, $p=0.217$
One	7 (70)	1 (10)	
Two	2 (20)	0 (0)	
Antipsychotics, *n* (%)			
None	4 (40)	2 (20)	Fisher test, $p=0.104$
One	6 (60)	4 (40)	
Two	0 (0)	4 (40)	
Antidepresants, *n* (%)			
None	6 (60)	5 (50)	Fisher test, $p=1$
One	4 (40)	4 (40)	
Two	0 (0)	1 (10)	
Anxiolytics, *n* (%)			
None	7 (70)	3 (30)	Fisher test, $p=0.241$
One	2 (20)	6 (60)	
Two	1 (10)	1 (10)	

EMDR: Eye Movement Desensitization Reprocessing; TAU: Treatment As Usual; TAP: Test de Acentuación de Palabras (Word Accentuation Test); WAIS III: Wechsler Adult Intelligence Scale III.

[a] Cognitive Behavioral Therapy.
[b] Statistical significance between groups.

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Table 2
Affective symptoms, trauma symptoms and functioning at baseline and change mean scores from baseline to the 12 week and 24 week visit of the EMDR and TAU groups.

	EMDR ($n=10$)			TAU ($n=10$)			Comparison between EMDR and TAU		
	Baseline mean (S.D.)	12 weeks difference (S.D.)	24 weeks difference (S.D.)	Baseline mean (S.D.)	12 weeks difference (S.D.)	24 weeks difference (S.D.)	Baseline 2-sample *t*-test[a]	12 weeks time X group interaction[a]	24 weeks time X group interaction[a]
YMRS	6.20 (4.10)	−5.20 (4.39)	−4.00 (3.97)	8.30 (3.33)	1.40 (3.30)	−1.60 (4.19)	$t=-1.25$, $p=0.637$	$F=14.41$, $p=0.004$**	$F=1.73$, $p=0.411$
HDRS	10.90 (3.07)	−5.60 (2.31)	−4.60 (2.79)	10.00 (2.94)	−0.20 (2.61)	−2.60 (5.01)	$t=0.66$, $p=0.731$	$F=23.86$, $p=0.001$**	$F=1.21$, $p=0.463$
CGI-m	2.20 (0.91)	−1.20 (0.91)	−0.50 (1.08)	2.50 (0.97)	0.00 (0.94)	−0.50 (1.35)	$t=-0.70$, $p=0.731$	$F=9.22$, $p=0.018$*	$F=0.31$, $p=0.601$
CGI-d	3.40 (0.51)	−1.20 (0.91)	−0.90 (1.19)	3.30 (0.94)	−0.10 (0.73)	−0.50 (1.35)	$t=0.29$, $p=0.785$	$F=5.32$, $p=0.047$*	$F=0.77$, $p=0.491$
CGI-g	3.60 (1.07)	−0.50 (1.26)	−0.60 (1.17)	4.00 (0.00)	−0.20 (0.63)	−0.40 (0.69)	$t=-1.17$, $p=0.637$	$F=0.45$, $p=0.552$	$F=1.03$, $p=0.463$
CAPS	23.00 (31.06)	−18.90 (24.57)	−17.20 (22.91)	33.00 (28.01)	−1.30 (5.18)	−0.70 (5.29)	$t=-0.52$, $p=0.750$	$F=6.26$, $p=0.037$*	$F=5.03$, $p=0.126$
IES1	−0.39 (1.95)	−3.02 (1.54)	−3.22 (1.38)	−1.65 (2.22)	0.37 (1.87)	−0.08 (1.61)	$t=1.34$, $p=0.637$	$F=20.36$, $p=0.001$**	$F=20.32$, $p=0.003$**
IES2	−1.27 (1.95)	−2.15 (2.09)	−2.14 (1.75)	−1.07 (2.40)	−0.39 (1.65)	−0.50 (1.89)	$t=-0.27$, $p=0.785$	$F=4.34$, $p=0.065$†	$F=3.98$, $p=0.153$
IES3	−0.77 (1.83)	−2.78 (1.96)	−2.66 (1.98)	−1.70 (2.65)	−0.47 (1.93)	−0.05 (2.75)	$t=0.90$, $p=0.731$	$F=7.046$, $p=0.032$*	$F=5.92$, $p=0.126$
FAST	31.60 (18.49)	−2.10 (11.57)	−0.10 (13.92)	42.10 (9.02)	2.60 (7.21)	4.30 (6.51)	$t=-1.61$, $p=0.637$	$F=0.37$, $p=0.552$	$F=0.28$, $p=0.601$

EMDR: Eye Movement Desensitization Reprocessing; TAU: Treatment as Usual; w- weeks; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; CGI-m: Clinical Global Impression-mania; CGI-d: Clinical Global Impression-depression; CGI-g: Clinical Global Impression-general; CAPS: Clinician Administered PTSD Scale; IES1: Impact of Event Scale 1; IES2: Impact of Event Scale 2; IES3: Impact of Event Scale 3; FAST: Functioning Assessment Short Test.

† Trend level statistical significance.
* $p \leq 0.05$.
** $p \leq 0.01$.
[a] False discovery rate (FDR)-corrected for multiple comparisons.

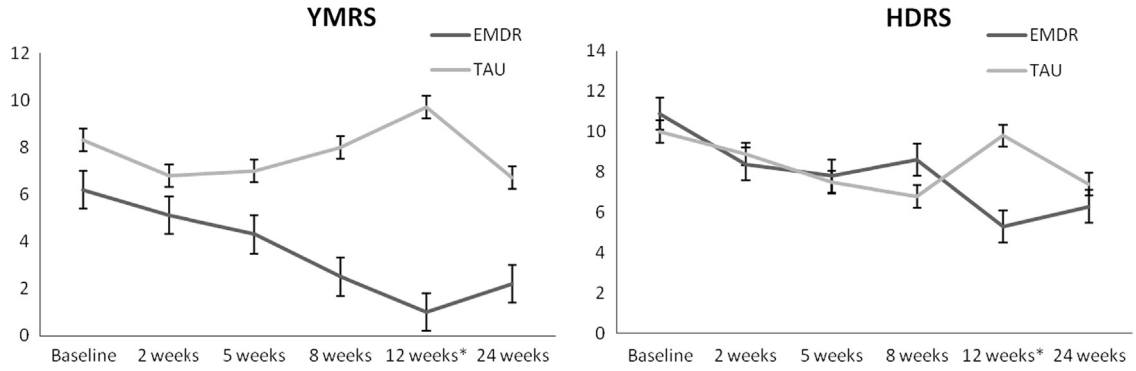

Fig. 1. Evolution of clinical scores with LOCF and intention-to-treat in the mood symptoms between the EMDR ($n=10$) and TAU ($n=10$) groups. LOCF: Last Observation Carried Forward; EMDR: Eye Movement Desensitization Reprocessing; TAU: Treatment as Usual; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; CGI-m: Clinical Global Impression-mania; CGI-d: Clinical Global Impression-depression; *Significant differences between groups

3.2. Drop-out analysis

Drop-out rate at 12 weeks was 0% for the EMDR and 30% ($n=3$) for the treatment as usual group (Fisher test $p=0.105$). The latter comprised two participants who withdrew consent shortly after the baseline visit and another one had to be excluded later on due to a high DES index score (high levels of dissociation, as noted above, require a more complex Eye Movement Desensitization and Reprocessing protocol).

Drop-out rate at 24 weeks was 10% ($n=1$) for the EMDR and 40% ($n=4$) for the treatment as usual group (Fisher test $p=0.152$). The former was a participant from the Eye Movement Desensitization and Reprocessing group who finished the treatment phase of 12 weeks but then suffered from a new traumatic event (sudden loss of a family member). It was decided for ethical reasons to continue with Eye Movement Desensitization and Reprocessing therapy beyond 12 weeks. The other from the treatment as usual group was a participant who was admitted to hospital with a relapse of mania and was considered as drop-out.

3.3. Group differences in mood symptoms after 12 and 24 weeks

Table 2 shows the results of the RMANOVAs used to assess differences between the groups in the change of mood symptoms from baseline to 12 weeks and from baseline to 24 weeks. There were significant differences in favor of the Eye Movement Desensitization and Reprocessing group in the change from baseline to 12 weeks of the YMRS, HDRS, CGI-m and CGI-d scales, i.e. Eye Movement Desensitization and Reprocessing therapy participants improved while treatment as usual group did not. Conversely, changes from baseline to 24 weeks did not reach statistical significance. Changes in CGI-g from baseline to either 12 or 24 weeks were neither statistically significantly different between the Eye Movement Desensitization and Reprocessing and treatment as usual groups. Results were identical or slightly more significant when baseline scores were included as covariate.

Fig. 1 shows a progressive decline in manic and depressive scores in favor of the Eye Movement Desensitization and Reprocessing group while the treatment as usual group's scores remained broadly stable up to 12 weeks of treatment. Reductions in depressive and manic scores in favor of the Eye Movement Desensitization and Reprocessing group resulted statistically significant at 12 weeks (YMRS, $p=0.004$; HDRS, $p=0.001$) but lost significance at 24 weeks (YMRS, $p=0.411$; HDRS, $p=0.463$).

3.4. Group differences in trauma symptoms and functioning after 12 and 24 weeks

Fig. 2 shows the evolution of the traumatic symptoms along the follow-up visits. At 12 weeks there was a sharp decline in the

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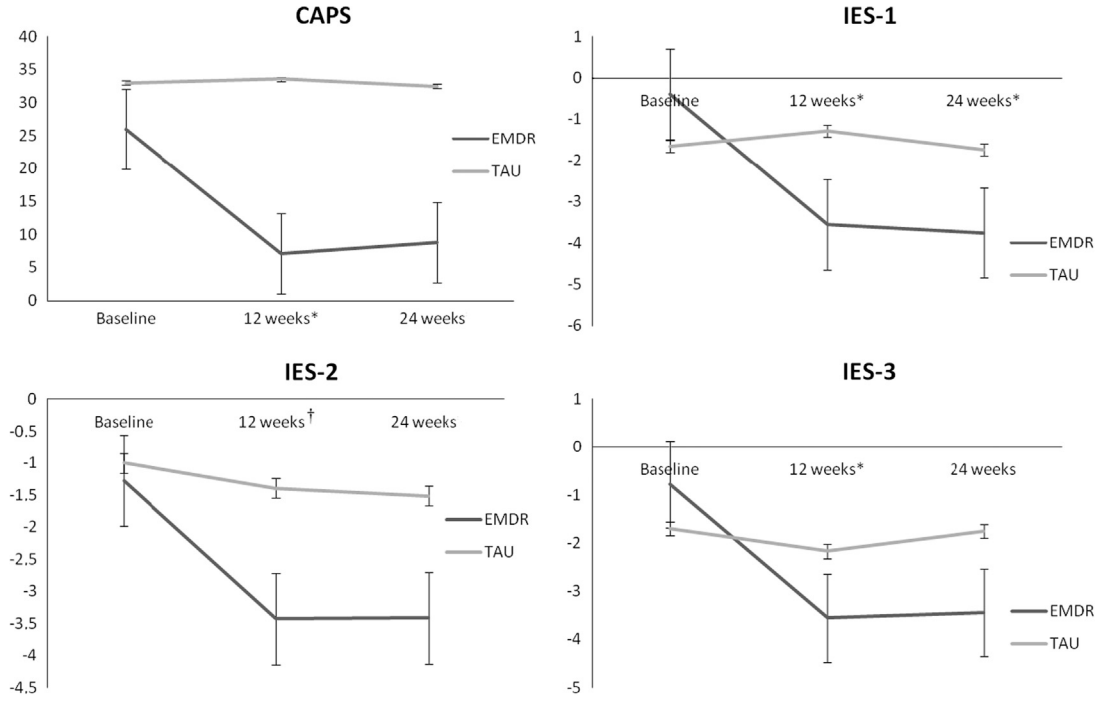

Fig. 2. Evolution of clinical scores with LOCF intention-to-treat in the trauma symptoms were significant differences were found between the EMDR ($n=10$) and TAU ($n=10$) groups. LOCF: Last Observation Carried Forward; EMDR: Eye Movement Desensitization Reprocessing; TAU: Treatment as Usual; CAPS: Clinician Administered PTSD Scale; IES-1: Impact of Event Scale 1; IES-2: Impact of Event Scale 2; IES-3: Impact of Event Scale 3; *Significant differences between groups, † Trend level statistical significance.

trauma symptoms from baseline in the Eye Movement Desensitization and Reprocessing therapy group that was maintained at 24 weeks of the trial. The scores of the treatment as usual group remained stable at 12 and 24 weeks.

As shown in Table 2, changes from baseline to 12 weeks were statistically significant in CAPS, IES-1, and IES-3 scores and trend-level significant in IES-2 scores in favor of the Eye Movement Desensitization and Reprocessing therapy treatment condition, i.e. participants in the latter improved while treatment as usual participants did not. The changes from baseline to 24 weeks in IES-1 scores remained statistically significant between groups, whereas we observed no significant differences in the in CAPS, IES-2 and IES-3 scores. There were neither significant differences between the Eye Movement Desensitization and Reprocessing therapy and treatment as usual groups in the changes of functioning from baseline to either 12 weeks or 24 weeks. Again, results were identical or slightly more significant when baseline scores were included as covariate.

4. Discussion

To the best of our knowledge this is the first trial of a trauma treatment intervention in patients with bipolar disorder. The primary outcome measure, of an improvement in subsyndromal mood symptoms in the Eye Movement Desensitization and Reprocessing group, was met: we found a statistically significant mood stabilizing effect for both depressive and (hypo)manic symptoms in instable bipolar patients at the end of the Eye Movement Desensitization and Reprocessing intervention. Documenting improvement in subsyndromal mood symptoms is of clinical relevance, since these are frequent in bipolar disorder and have been found to be associated with a higher risk of poor outcome on a variety of measures and are difficult to control with medication (Altshuler et al., 2006; Paykel et al., 2006; Judd et al., 2008; Marangell et al., 2009). Also, the study provides a 'proof-of-principle' that bipolar disorder is susceptible to treatment with a form of trauma-directed therapy.

We also found that bipolar patients with subsyndromal symptoms treated with Eye Movement Desensitization and Reprocessing improved significantly in terms of trauma-related symptomatology, as evaluated by the CAPS and the IES. This effect of Eye Movement Desensitization and Reprocessing therapy appeared to be partly enduring as at least the reduced impact of trauma was maintained at 24 weeks. These findings are in line with data from Eye Movement Desensitization and Reprocessing studies performed in patients with PTSD (Seidler and Wagner, 2006; Bisson et al., 2013; Watts et al., 2013) which suggest an acute efficacy that is at least as good as other psychotherapeutic interventions, in particular CBT, and a stable outcome up to 35 months (Hogberg et al., 2008). Clinical improvement in trauma scales was a secondary outcome of the study, and positive results were expected on the basis of what is known about the effects of Eye Movement Desensitization and Reprocessing therapy on patients with PTSD. Nevertheless, from a clinical point of view it is important to note that Eye Movement Desensitization and Reprocessing can be effective in reducing trauma symptoms and trauma load in traumatized bipolar patients without causing new affective episodes.

While it is intuitive that the treatment of comorbid trauma symptoms might produce a reduction in depressive symptoms in bipolar patients, the fact that hypomanic symptoms also improved is more difficult to explain. Possibly relevant here is a largely ignored finding of the National Comorbidity Survey in PTSD subjects that adults with PTSD are more prone to develop manic symptoms than unipolar depressive disorder (Kessler et al., 1995). More speculatively, a recent review by Rakofsky et al. (2012) has argued that there is a specific relationship between bipolar disorder and PTSD, which is mediated by the Brain Derived Neurotrophic Factor.

The question arises also of how Eye Movement Desensitization and Reprocessing therapy might exert mood-stabilizing effects in bipolar patients. Several different explanatory models have been proposed to explain its effectiveness in PTSD, including an

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increased inter-hemispheric connectivity, EEG changes, an overloading of working memory and the specific role of eye movements (Gunter and Bodner, 2008; Kapoula et al., 2010; Pagani et al., 2012; Jeffries and Davis, 2013). The findings in support of all these models are inconsistent, however. Neuroimaging studies so far have not established any firm conclusions either about effects of Eye Movement Desensitization and Reprocessing on neuromorphological or neurofunctional variables (e.g. Nardo et al., 2010). However, by chance, one subject in the present study underwent fMRI scanning during performance of the n-back task as part of another study before she started Eye Movement Desensitization and Reprocessing therapy and, after she improved, this was repeated after the end of the study. As described by Landin-Romero et al. (2013), after Eye Movement Desensitization and Reprocessing therapy the patient showed normalization in both activation abnormalities in the dorsolateral prefrontal cortex and other areas, and also in a pattern of failure of de-activation in the medial frontal cortex, which forms part of the default mode network. Noting the increasing evidence of default mode network abnormality in bipolar disorder (e.g. Fernandez-Corcuera et al., 2013), the authors speculated that Eye Movement Desensitization and Reprocessing might act as a mood stabilizer via an effect on this network.

Although preliminary, our findings support the utility of this treatment approach and suggest that Eye Movement Desensitization and Reprocessing therapy could be a promising and safe therapeutic strategy to reduce trauma symptoms and stabilize mood in traumatized bipolar patients with subsyndromal symptoms. Strengths of our trial include the randomized controlled design, a well matched sample and a moderate to strong positive effect of Eye Movement Desensitization and Reprocessing on trauma and mood. Limitations include that treatment allocation was performed by alternating allocation and not by an independent researcher which increases risk of bias. Furthermore, the trial was designed as a pilot study to find a signal but the small sample size has to be considered as a limitation that might have potentially influenced the results. Indeed, we suggest that all results should be replicated in larger studies, including a larger follow-up to clarify possible long-term effects of Eye Movement Desensitization and Reprocessing therapy on mood and trauma symptoms as both were not consistently significantly different to the treatment as usual group at the follow-up visit. A larger trial could also benefit from a further psychotherapeutic intervention of comparison such as supportive therapy or trauma focused cognitive behavior therapy.

Disclosure statement

F.S. is the originator of Eye Movement Desensitization and Reprocessing therapy and shareholder in one of the training organizations. F.G. is the president of the Spanish Eye Movement Desensitization and Reprocessing Association and I.F. the Vice-president of the European Eye Movement Desensitization and Reprocessing Association. B.L.A., P.N, R.L.R, J.Q., V.V., E.P.C., P.J.M. disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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