Acta Neuropsychiatrica
An International Journal of Translational Neuropsychiatry

Acta Neuropsychiatrica 2012: 24: 384–386

DOI: 10.1111/j.1601-5215.2011.00623.x

ACTA NEUROPSYCHIATRICA

Debate paper

Letter to the editor

Plasma brain-derived neurotrophic factor level may contribute to the therapeutic response to eye movement desensitisation and reprocessing in complex post-traumatic stress disorder: a pilot study

DOI: 10.1111/j.1601-5215.2011.00623.x

We investigated the relationship between plasma levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) and responses to eye movement desensitisation and reprocessing (EMDR) in complex post-traumatic stress disorder (complex PTSD). Before and after EMDR, plasma levels of neurotrophic factors and scores in the indices of self-questionnaires were obtained for eight men with complex PTSD. Baseline plasma levels of BDNF and NGF of responders and of non-responders were compared. The plasma BDNF levels of responders were higher than those of non-responders. However, plasma NGF levels did not differ in two groups. Plasma BDNF level might contribute to the therapeutic response to EMDR in trauma-related psychiatric disorders, such as complex PTSD.

Complex PTSD is a proposed diagnosis that describes the psychological sequelae of survivors with prolonged, repeated, and interpersonal trauma, including childhood physical abuse, incest, and other forms of family violence. The diagnostic criteria for complex PTSD consist of the functional alterations in six areas: (1) regulation of affect and impulses; (2) attention or consciousness; (3) self-perception; (4) relations with others; (5) somatisation; and (6) system of meaning. Changes in the neural substrates of patients with complex PTSD may reflect the relationship, established in critical developmental phases, between traumatic experiences and neurobiological factors. Recently, a morphometric study showed that patients with childhood abuse-related complex PTSD had more extensive involvements of neural substrates (reduced anterior cingulate and orbitofrontal volumes) than those with classical PTSD (1). Therefore, the deficits in emotional/self-awareness, emotion regulation, social emotional processing and self-referential processing should be emphasised in the assessment of patients with complex PTSD.

EMDR is an integrative and comprehensive psychotherapy originally developed to resolve symptoms of psychic trauma. It has been also proposed as a rapid and effective application for treating the core symptoms of complex PTSD (2). In the present study, we assess the potential of levels of neurotrophic factors as biological predictors of EMDR responses in complex PTSD.

The diagnoses were confirmed by two psychiatrists using the Structured Interview for Disorders of Extreme Stress (SIDES), which was designed to measure the presence of complex PTSD. Before and after eight-session EMDR, plasma levels of BDNF and NGF were obtained for eight men with complex PTSD. No psychotropic medication was given during the subsequent period of EMDR treatment. However, either 2-mg lorazepam or 10-mg diazepam was allowed for sleep management. The amounts of BDNF and NGF in plasma were measured with enzyme-linked immunosorbent assay (ELISA) kits (Quantikine, R & D Systems, Minneapolis, MN, USA) following the manufacturer's instructions. The Symptom Checklist-90-Revision (SCL-90-R) was employed to assess the participants' symptomatic status, because all the symptomatic dimensions of complex PTSD could not be assessed using the

Clinician-Administered PTSD Scale (CAPS) which is the standard method in classical PTSD assessment. Changes of BDNF and NGF levels and symptomatic status after the eight-session EMDR were assessed using Wilcoxon test. The estimated response (ER) of a given symptomatic dimension to EMDR was calculated as $X_{ER} = (X_{preEMDR} - X_{postEMDR})/X_{preEMDR}$. Correlations between baseline BDNF and NGF plasma levels and ERs to EMDR were assessed by the Kendall's tau test. Because SIDES was not validated as a measuring tool of treatment outcome, the patients' responses to EMDR were assessed using the Clinical Global Impression-Change Scale (CGI-C). Patients whose scores on the CGI-C scores were above the 'much improved' level after EMDR were classified as responders. Baseline plasma levels of BDNF and NGF and baseline symptomatic indices were compared in responders and non-responders, using the Mann–Whitney U test.

Levels of anxiety (Wilcoxon test; $S = -2.243$, $p = 0.025$), phobia ($S = -2.207$, $p = 0.027$) and dissociation ($S = -2.251$, $p = 0.012$) were significantly lowered after EMDR. However, there were no significant changes in plasma levels of BDNF ($S = -0.140$, $p = 0.889$) and NGF ($S = -0.700$, $p = 0.484$). Baseline plasma BDNF levels were positively correlated with the ERs of depression (Kendall's tau test; $b = 0.643$, $p = 0.026$) and anxiety ($b = 0.571$, $p = 0.048$) (Table 1). On the other hand, baseline plasma NGF levels were negatively correlated with the ER of depression ($b = -0.643$, $p = 0.026$) (Table 1). Responders had higher plasma BDNF levels than non-responders. However, there two groups did not differ in plasma NGF levels or symptomatic indices (Table 2).

Table 1. Correlations between baseline plasma levels of neurotrophic factors and the ERs* of symptomatic indices to EMDR

	BDNF		NGF	
	B‡	p	B‡	p
Somatisation	0.429	0.138	0.286	0.322
Obsessive-compulsive	0.500	0.083	−0.357	0.216
Interpersonal sensitivity	0.500	0.083	0.214	0.458
Depression	0.643	0.026†	−0.643	0.026†
Anxiety	0.571	0.048†	0.000	1.000
Hostility	0.000	1.000	0.143	0.621
Phobia	0.327	0.262	0.036	0.901
Paranoid ideation	0.071	0.805	−0.071	0.805
Psychoticism	0.071	0.805	−0.214	0.458
GSI§	0.286	0.322	−0.429	0.138
PSDI¶	0.429	0.138	−0.429	0.138
PST‖	0.071	0.805	0.357	0.216

*$X_{ER} = (X_{preEMDR} - X_{postEMDR})/X_{preEMDR}$.
†$p < 0.05$.
‡By Kendall's tau test.
§Global severity index.
¶Positive symptom distress index.
‖Positive symptom total.

Table 2. Comparison of EMDR responders and non-responder

	Total ($N = 8$)	Responders ($N = 3$)	Non-responders ($N = 5$)	U*	p
Age (years)	20.1 (1.4)	21.0 (2.0)	19.6 (0.5)	4.000	0.273
Somatisation	59.5 (9.8)	59.6 (11.0)	59.4 (10.4)	7.000	0.879
Obsessive-compulsive	70.4 (10.9)	76.7 (12.3)	66.6 (9.2)	3.500	0.227
Interpersonal sensitivity	74.9 (12.6)	85.7 (5.9)	68.4 (10.9)	1.000	0.053
Depression	70.0 (15.0)	78.0 (10.1)	65.2 (16.3)	3.500	0.230
Anxiety	70.8 (9.3)	72.0 (4.6)	70.0 (11.8)	7.000	0.881
Hostility	68.8 (11.7)	63.0 (11.8)	72.0 (11.4)	4.500	0.368
Phobia	68.3 (16.3)	74.0 (16.5)	64.8 (17.0)	4.000	0.288
Paranoid ideation	77.0 (12.3)	86.3 (11.5)	71.4 (9.6)	1.500	0.070
Psychoticism	70.1 (13.6)	76.3 (16.5)	66.4 (11.8)	5.000	0.453
GSI	72.3 (11.2)	77.7 (11.7)	69.0 (10.9)	4.000	0.297
PSDI	72.6 (8.3)	75.0 (7.5)	71.2 (9.3)	5.000	0.453
PST	62.1 (7.5)	65.0 (5.3)	60.4 (8.7)	5.000	0.456
BDNF (pg/ml)	3406.9 (1193.8)	4435.6 (1273.4)	2789.7 (643.2)	<0.001	0.025†
NGF (pg/ml)	1447.2 (387.8)	1223.9 (267.0)	1581.2 (409.4)	3.000	0.180

*By Mann–Whitney U test.
†$p < 0.05$.

The associations between high plasma BDNF levels, low NGF levels, and favuorable responses to EMDR are in accord with a prior animal study. A study in the mouse revealed that high levels of hypothalamic BDNF and low levels of NGF are believed to be long-term effects of social and physical enrichment on neurobehavioural markers of brain plasticity and of the ability to cope with social challenges. At the same time, it has been suggested that exposure to chronic stress contributes to the sequential activation of NGF and BDNF. After exposure to chronic stress, increased NGF levels in the periphery may lead to decreased BDNF levels in limbic structures, so reducing brain plasticity and increasing vulnerability to depression and anxiety disorders (3).

Our conclusion is in accord with that of a previous clinical study. A study of panic disorder and cognitive-behavioural therapy (CBT) demonstrated that the serum BDNF levels of patients giving good responses were higher than those of patients giving poor responses (4). A morphometric study found that better EMDR outcomes in PTSD were associated with high grey matter densities in the limbic and paralimbic cortices, which are implicated in memory and emotion processing, and are thought to represent a potential neural basis for PTSD symptoms (5). Members of the NGF superfamily including BDNF are strongly expressed in the hippocampus, and may mediate stress-induced atrophy of the hippocampus. Moreover, there is evidence that low serum BDNF levels may be reflective of the biological

https://doi.org/10.1111/j.1601-5215.2011.00623.x Published online by Cambridge University Press

vulnerability to depression. A morphometric study revealed that the reduced hippocampal volume in women with major depression is associated with a history of childhood abuse. It can be inferred that a history of prolonged and severe childhood trauma may lead to the vulnerability to depressive symptoms by lowering levels of BDNF. Thus our results suggest that plasma BDNF levels, which are implicated in vulnerability to depression, may contribute to the therapeutic response to EMDR. One concludes that plasma BDNF level might contribute to the therapeutic responsiveness to eye movement desensitisation and reprocessing in complex PTSD.

The present study has some limitations. First, the sample was small, and the findings need to be confirmed in larger studies. However, to our knowledge, the association between the application of EMDR and neurotrophic factors has not previously been addressed in the literatures. Our pioneering investigation provides initial support for the idea that the response to EMDR is related to the basal plasma level of BDNF, although the sample size was small. Second, complex PTSD is described in the associated features of PTSD, since complex PTSD is not an identified diagnosis in DSM-IV. Due to the conceptually arbitrary nature of complex PSTD, we cannot draw any definite conclusions from the results of this study. Finally, the complex PTSD symptomatology was based on self-questionnaires.

In spite of these limitations, this pilot study has the virtue of pioneering the investigations of EMDR responses associated with neurogenesis.

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https://doi.org/10.1111/j.1601-5215.2011.00623.x Published online by Cambridge University Press