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Clinical correlates of plasma brain-derived neurotrophic factor in post-traumatic stress disorder spectrum after a natural disaster

Paolo Stratta [a,*], Patrizia Sanità [b], Roberto L. Bonanni [a], Stefano de Cataldo [a], Adriano Angelucci [b], Rodolfo Rossi [d], Nicola Origlia [c], Luciano Domenici [c,d], Claudia Carmassi [e], Armando Piccinni [e], Liliana Dell'Osso [e], Alessandro Rossi [d]

[a] Department of Mental Health, ASL 1, L'Aquila, Italy
[b] General Pathology and Immunology Laboratory, Department Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy
[c] Neuroscience Institute, CNR, Pisa, Italy
[d] Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy
[e] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

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ABSTRACT

Clinical correlates of plasma Brain-Derived Neurotrophic Factor (BDNF) have been investigated in a clinical population with Post Traumatic Stress Disorder (PTSD) symptoms and healthy control subjects who survived to the L'Aquila 2009 earthquake. Twenty-six outpatients and 14 control subjects were recruited. Assessments included: Structured Clinical Interview for DSM-IV Axis-I disorders Patient Version, Trauma and Loss Spectrum-Self Report (TALS-SR) for post-traumatic spectrum symptoms. Thirteen patients were diagnosed as Full PTSD and 13 as Partial PTSD. The subjects with full-blown PTSD showed lower BDNF level than subjects with partial PTSD and controls. Different relationship patterns of BDNF with post-traumatic stress spectrum symptoms have been reported in the three samples. Our findings add more insight on the mechanisms regulating BDNF levels in response to stress and further proofs of the utility of the distinction of PTSD into full and partial categories.

1. Introduction

Stress-related alterations of Brain-Derived Neurotrophic Factor (BDNF) expression and functioning have been reported both in animal and human studies (Duman and Monteggia, 2006; Machado-Vieira et al., 2007; Savitz et al., 2007; Andero and Ressler, 2012; Rakofsky et al., 2012). Post-Traumatic Stress Disorder (PTSD) represents the prototypical form of stress-induced mental disorder, but only recently BDNF studies in patients with such a diagnosis have been performed with inconsistent observations of lower BDNF plasma (Dell'Osso et al., 2009b) and serum levels (Angelucci et al., 2014), negative results in cerebrospinal fluid (Bonne et al., 2011) and higher levels in serum (Hauck et al., 2010; Matsuoka et al., 2013) and plasma (Zhang et al., 2012).

In previous report on L'Aquila (Italy) earthquake survivors, using a sample categorization based on a dimensional approach of the disorder symptomatology, we found reduced BDNF level in subjects with full blown PTSD but not in those with partial PTSD (Stratta et al., 2013).

Recent efforts have been oriented to explore the prevalence rates and impact of not only full blown PTSD in individuals exposed to a traumatic event but also of partial or subthreshold forms. The concept of partial PTSD was introduced for those subjects who fulfill only a subset of the DSM-IV criteria (B, C or D) for PTSD (Weiss et al., 1992; Stein et al., 1997; Marshall et al., 2001; Breslau et al., 2004; Mylle and Maes, 2004; Hepp et al., 2005). More recently, dimensional approaches to PTSD have also been developed conceptualizing post-traumatic stress reactions as three main dimensions: the nature of the stressor, the possible responses to trauma, including atypical, subthreshold symptoms, and the symptom severity (Dell'Osso et al., 2008, 2009a).

The spectrum approach represents an important challenge to the PTSD construct, allowing to identify relevant subclinical comorbidities that may contribute either to the "complex" presentation of PTSD or to the frequent behavioral outcomes and complications, such as self-harm behavior and suicidality. Studies on partial PTSD agree in reporting significantly less symptoms severity and functional impairment than in patients with full-blown disorder, but significantly more than in no-PTSD subjects, with an associated need for treatment (Stein et al., 1997; Dell'Osso et al., 2011).

* Correspondence to: Department of Mental Health, ASL 1, Via Capo Croce, 67100 L'Aquila, Italy.
E-mail address: psystr@tin.it (P. Stratta).

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The aim of this controlled study is to investigate the clinical correlates of plasma BDNF levels in a clinical population showing PTSD symptomatology, along with the post-traumatic spectrum that considers not only full expression of PTSD but also sub-threshold manifestations, such as partial PTSD, by means of a dimensional assessment.

2. Methods

2.1. Subjects

A consecutive sample of 26 outpatients (19 women and 7 men; mean age ± SD: 47.15±12.12 years), L'Aquila (Italy) 2009 earthquake survivors, referring for post-traumatic stress symptoms, were recruited at the National Mental Health Care Service (NMHCS) facilities in L'Aquila. Fourteen healthy subjects recruited from among those accompanying the outpatients, also survived to the same earthquake, and who were matched for age and gender (F/M 12/2; mean age 44.5±10.47 years) were enrolled. The recruitment was performed about two years after the traumatic event (July–December 2011). Time interval between trauma exposure and blood sampling was therefore 27–32 months with no differences among the groups.

Exclusion criteria were the following: current or lifetime diagnosis of organic mental disorder, schizophrenia, schizophreniform or other psychotic disorders, substance-related disorders, uncontrolled or severe medical conditions. In addition to the patient exclusion criteria, controls were also screened for any psychiatric condition and they were clinically evaluated for PTSD symptoms with Trauma and Loss Spectrum-Self Report (TALS-SR).

At the time of BDNF evaluation all patients were treated with low doses of benzodiazepines and/or Selective Serotonin Reuptake Inhibitors (SSRI) antidepressants, as the Ethical Committee did not allow any drug free period. No patients were treated with antipsychotics or mood stabilizers. Benzodiazepine low doses are considered $\leq$ 10 mg of diazepam dose equivalents (van der Hooft et al., 2008); antidepressants low dose was calculated on the basis of fluoxetine equivalents SSRI medications conversion (Bollini et al., 1999).

2.2. Clinical assessment

The assessment included: the Structured Clinical Interview for DSM-IV Axis-I disorders Patient Version (SCID-I/P) (First et al., 1995); the Trauma and Loss Spectrum-Self Report (TALS-SR) for assessing post-traumatic stress spectrum symptoms related to the April 2009 earthquake (Dell'Osso et al., 2009a; Dell'Osso. et al., 2013; Carmassi et al., 2013, 2014).

The SCID-I/P was administered to patients by a psychiatrist (PS) trained and certified in the use of the instrument. The training included observing live administrations, and conducting practice interviews with other experienced psychiatrists. During the training process all trainees received feedback until they demonstrated high level of reliability.

On the basis of the SCID interview Full and Partial PTSD distinction has been made. A diagnosis of partial PTSD was assessed when criteria B and or C or D for DSM-IV were satisfied (Stein et al., 1997), while full-blown PTSD subjects meet all the disorder criteria.

Subjects were also asked to complete the symptomatological domains of the TALS-SR, referring to the last week condition. The TALS-SR explores a range of post-traumatic spectrum symptoms comprising emotional, physical and cognitive responses to the trauma, including re-experiencing it, avoidance and numbing, and arousal symptoms. According to the aims of the present study, subjects were asked to fulfill domains IV and over, referring to symptoms that occurred after the earthquake exposure. Domain IV (Items 59–76) includes a range of emotional, physical and cognitive responses to this event. Domain V (Items 77–85), Domain VI (Items 86–97) and Domain VIII (Items 106–110) include re-experiencing, avoidance and numbing, and arousal symptoms respectively, Domain VII (Items 98–105) targets maladaptive coping.

The Ethics Committee of the Azienda Sanitaria Locale of L' Aquila approved all recruitment and assessment procedures. All subjects included provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

2.3. BDNF evaluation procedure

Venous blood samples were taken in the morning (between 8:00 and 9:00 am) to avoid diurnal variations of BDNF levels (Dell'Osso et al., 2009b). Blood was drawn into EDTA-coated tubes that were kept on ice, centrifugated at 2000 × *g* for 10 min for separating plasma from cells and supernatant was stored at −80 °C until the analysis. To measure the amount of total BDNF, acidification and subsequent neutralization of the samples were followed before proceeding with the enzyme-linked immunosorbent assay (ELISA) protocol, according to manufacturer's instruction (Promega, Wallisellen, Switzerland). The well plates were coated with anti-BDNF monoclonal antibody and incubated at 4 °C for 18 h. The plates were then incubated in a blocking buffer for 1 h at room temperature, then samples were added. The samples and BDNF standards were maintained at room temperature under shaking for 2 h, followed by washing with the appropriate buffer. The plates were successively incubated with anti-human BDNF polyclonal antibody at room temperature for 2 h, washed and incubated with anti-IgG antibody conjugated to horseradish peroxidase for 1 h at room temperature. The plates were incubated in peroxidase substrate and tetramethylbenzidine solution to produce a colour reaction. The reaction was stopped with 1 M HCl. The absorbance at 450 nm was measured with a microplate reader (iMark, Microplate reader, Bio Rad Laboratories) to determine BDNF values that are expressed as pg/ml.

2.4. Statistical analyses

Due to the small size of the sample and no gaussianity of BDNF distribution (skewness 1.9 and kurtosis 3.9), non-parametric statistic was chosen. Kruskal Wallis Test and Chi Square were used. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons.

Spearman's rho for correlation analysis and Fisher r-to-z transformation for comparison between correlations were also used. One way parametric analysis of variance was used for between group age comparison. All analyses yielding a $p < 0.05$ were considered significant.

3. Results

By means of SCID interview, 13 patients were diagnosed as showing Full PTSD and 13 patients as showing Partial PTSD (age 44.9±10.2, 10 women and 3 men and age 44.4±13.6; 9 women and 4 men respectively). No differences in sex distribution ($X^2 = 1.05$, df = 2, NS) or age (F = .89, df = 2,32, NS) among the three samples were observed. No differences in distribution of benzodiazepines / antidepressants assumption were seen.

Non parametric comparisons (Kruskal Wallis Test) showed significant differences among the groups for BDNF and TALS domains (Table 1). All the comparisons for TALS-SR domains between