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Original article

Increased BDNF levels after a trauma A pilot study on clinical and non-clinical samples, exposed or non-exposed to an earthquake

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SUMMARY

Background

Brain-Derived Neurotrophic Factor (BDNF) modulates synaptic modifications that can constitute part of brain adaptive processes in the aftermath of trauma exposure. Thus, BDNF increase could be determined either in psychiatric patients or healthy subjects who, despite exposed to stressful events, did not develop stress-related symptoms.

Methods

BDNF plasma levels were evaluated in a clinical and a non-clinical populations exposed to the 2009 L'Aquila earthquake and in a comparable population not exposed to such event or other trauma.

Results

Statistically significant differences emerged according to diagnosis (clinical samples vs. controls), while a trend toward significance was found according to exposure (exposed vs. not-exposed subjects). The exposed clinical sample showed statistically significant higher BDNF levels than the not-exposed one.

Conclusions

Lack of statistical difference between exposed and not exposed subjects suggests that no BDNF modification intervened after the stressful event. Exposed samples however showed the highest BDNF levels with a trend toward significance. A ceiling effect that impede the possibility of exceeding a possible maximum level in the control sample can be hypothesized. Clinical sample shows instead room for stress related BDNF increase. If so, such a BDNF increase could have a neuroprotective adaptive role after stress.

Key words: Brain-Derived Neurotrophic Factor (BDNF), stress event, ceiling effect, stress adaptation, earthquake

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Conflict of interest
The Authors declare no conflict of interest

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Introduction

Brain-Derived Neurotrophic Factor (BDNF) is one of the most important neurotrophin involved in cerebral synaptic plasticity and cognitive functions regulation. It is highly sensitive to environmental factors and its increase enhances neurogenesis, neurite sprouting, electrophysiological activity with beneficial effects on cognitive functions such as learning and memory [1-3]. Alterations in the BDNF expression and functioning has been widely linked with stress both in animal and clinical studies suggesting a possible resilience correlate [4-13].

Synaptic modifications can constitute an adaptive process to stress events and BDNF is a relevant modulator of such modifications [14]. In the aftermath of stressful events exposure, a relevant information processing is needed in order to identify opportunities and possibilities to overcome the encountered difficulties. Serum BDNF levels have been reported to be involved in decision-making processes [15].

If the process is successful, the rapid BDNF capacity of performing cerebral modifications could avoid unwanted stress consequences and pathologies [16,17]. On the other hand, if no such neurotrophin and synaptic plasticity modifications append, pathological stress consequences could result [18].

In this study, we aimed to study BDNF changes in subjects who did not show psychiatric symptoms or worsening of symptoms despite having experienced a relevant stress event such as an earthquake.

We hypothesized that if no stress-related symptom or relapse/worsening of ongoing psychopathology appeared in subjects who suffered relevant stress, BDNF variation could be due to stress exposure. Thus, we enrolled a sample of subjects exposed to the same stress event, i.e. a clinical and non-clinical populations exposed to a natural catastrophe (i.e. the 2009 L'Aquila earthquake), and compared it to a similar population not exposed to such trauma. Because natural disasters are random events that expose unselected populations to the same trauma, they offer the opportunity to explore the effects 'triggered' by a unique trauma, disentangling confounding issues of pre-existing risk for exposure to traumatic events.

Methods

Study participants

In the framework of a study on clinical and neurobiological factors related to post-traumatic stress spectrum symptomatology in the aftermath of an earthquake exposure [12], we considered a sample of healthy control subjects and depressed/anxious patients exposed to such trauma compared to a sample of healthy control subjects and depressed/anxious patients not exposed to this event or to other relevant trauma.

The total sample included: 1) fifteen healthy control subjects with no current or lifetime DSM-IV-TR disorder or use of psychotropic medication exposed to the L'Aquila 2009 earthquake (10 women and 5 men; mean age ± SD: 46.3 ± 10.6 years); 2) a consecutive sample of 11 outpatients (5 women and 6 men; mean age ± SD - 42.2 ± 10.2 years), 8 with major depression (MDD) and 3 with panic disorder (PD). These subjects were diagnosed before the earthquake and did not show worsening or relapse of the symptoms after the event. The healthy subjects were recruited from among those accompanying the outpatients. The recruitment was performed about two years after the traumatic event (July-December 2011) at the National Mental Health Care Service facilities in L'Aquila; 3) a consecutive sample of 10 outpatients (5 women and 5 men; mean age ± SD 52.3 ± 12.3 years) with a diagnosis of MDD or PD were recruited at the Clinic of Psychiatry of the Department of Clinical and Experimental Medicine of the University of Pisa (Italy); 4) thirty-seven healthy control subjects were enrolled from Pisa (23 women and 14 men; mean age ± SD 33.1 ± 7.4 years) by the same recruitment method used in L'Aquila. These two latter samples were not exposed to the L'Aquila 2009 earthquake or to other relevant trauma in their lifetime.

At the time of BDNF evaluation all patients were treated with low doses of benzodiazepines and / or antidepressants, as the Ethical Committee did not allow any drug free period. No patients were treated with antipsychotics or mood stabilizers.

The Ethics Committees of the Azienda Sanitaria Locale of L'Aquila and of the Azienda Ospedaliero - Universitaria of Pisa 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.

Procedures

All subjects were assessed by means of the: Structured Clinical Interview for DSM-IV Axis-I disorders Patient Version (SCID-I/P) [19] for psychiatric diagnoses; Clinical Global Impression (CGI), for the severity of illness.

Venous blood samples were taken in the morning (between 8:00 and 9:00 am), to avoid diurnal variations of BDNF levels [20]. Blood samples were processed using enzyme-linked immunosorbent assay (ELISA) protocol on plasma to determine BDNF values that are expressed as pg/ml.

Statistical analyses

The descriptive statistics on the BDNF levels showed high skewness (1.33) and kurtosis (2.75). In order to control the gaussian distribution, BDNF values were log transformed reaching satisfactorily distribution indexes (skewness - 0.31 and kurtosis - 0.24). One-way analysis of variance (ANOVA) and two-way analysis of covariance (ANCOVA) were utilized. Main effects were further analyzed with post hoc planned t-test analysis. Chi square and Pearson's r correlation were also used. All analyses yielding a p-value less than.05 were considered significant.

Results

Among the four sub-samples, statistically significant age differences emerged (1-way ANOVA F = 14.9, d.f.

TABLE I. *Comparison of BDNF plasmatic levels (pg/ml, mean ± SD) and age between depressed/anxiety (dep/anx) patients and healthy subjects, exposed or not exposed to the earthquake.*

Subjects	Plasma BDNF	Age
Dep/anx exposed (n = 11)	3650.6 ± 1648.2	42.2 ± 10.2
Dep/anx not exposed (n = 10)	2495.0 ± 1335.9	52.3 ± 12.3
Controls exposed (n = 15)	6004.8 ± 4100.2	46.3 ± 10.6
Controls not exposed (n = 37)	5526.2 ± 2659.4	33.1 ± 7.4

Two-way ANCOVA for plasmatic BDNF, after natural logarithm transformation, with exposition and diagnosis as factors and age as covariate. Exposure factor $F = 2.7$; $p < 0.10$. Diagnosis factor $F = 14.3$; $p < 0.0005$. Exposure by diagnosis interaction $F = 1.6$; $p = 0.20$.

3, $p < 0.0005$), but not in gender distribution ($X^2 = 5.7$, d.f. 3, NS) or in the correlation with BDNF. No significant difference in CGI severity of illness scores between exposed and not exposed clinical samples (L'Aquila *vs* Pisa) was found.

BDNF plasma levels in the four sub-samples are reported in Table I. Two-way ANCOVA was used considering diagnosis, i.e. clinical sample *vs* controls. and exposure, i.e. earthquake exposed *vs* not exposed subjects, as factors; age was considered as covariate. Statistically significant difference was observed according to diagnosis ($F = 14.3$; $p < 0.0005$), but not to exposure ($F = 2.7$; $p < 0.10$), or exposure by diagnosis interaction ($F = 1.6$; NS). Post-hoc planned t-tests showed statistically significant difference between exposed and not-exposed clinical samples ($t = 2.1$, d.f. 19, $p < 0.05$).

Discussion

The lack of global statistically significant difference between earthquake exposed and not-exposed subjects would corroborate the null hypothesis that no BDNF modification intervened after the stressful event.

Some considerations however have to be made: although the difference did not reach statistical significance, exposed subjects showed the absolute highest BDNF levels, and a trend toward significance emerged with respect to not-exposed subjects ($p = 0.09$). Further, a statistically significant difference emerged in BDNF levels between the two clinical samples with exposed patients showing significantly higher levels.

The possibility of a ceiling effect cannot be excluded, in particular among healthy control subjects where it could not be possible to exceed a certain level. However, if a ceiling effect could explain findings in healthy control subjects, this could not be the case of clinical samples where a significant difference between exposed and not-exposed patients was found with almost twice as much of the neurotrophin levels in the former. Although BDNF decrease in subjects with affective disorders as well as panic disorder is a well reported finding [21–27], the possibility for a stress related increase seems to be possible. As BDNF peripheral levels may parallel changes occurring in the brain, the trend of plasma BDNF increase in L'Aquila clinical and healthy control samples, with respect to not-exposed subjects, could be interpreted as a residual 'signal', two years after the trauma, related to a neuroprotective reaction to the stress.

Our results are in line with several studies from both animal and human models eventually.

Increase in BDNF expression has been observed after stress in rats hypothesized as part of a coping compensatory response to stressful stimuli [28,29].

In humans, subjects with trauma but not showing Post Traumatic Stress Disorder (PTSD) symptoms evidenced higher BDNF serum levels compared to patients affected by PTSD [30]. Elevated serum BDNF levels were found in imprisoned women, likely suffering from prison-related stress without PTSD [31]. Peripheral levels elevation has been observed in worker exposed to occupational stress [32]. BDNF increased levels have been interpreted as further evidence of BDNF involvement in stress response, as contribution to neuron protection under stress reducing behavioral sequelae of PTSD [33].

Some important limitations should be taken into account while interpreting these results. First of all, the sample size that, despite not large, should be sufficient for a pilot study of heuristic value. Second, healthy control subjects samples required the exclusion of any kind of symptom. Third is the selection of comparison groups in a quasi-experimental design where the samples are not equated prior to manipulation of the independent variable (i.e. earthquake exposure). Fourth, the time from exposure: BDNF levels were assessed two years after the earthquake occurred and thus we cannot exclude that a putative early BDNF increase, well superior to that we observed, may have occurred in the aftermath of the event followed by a trend toward the normalization over time. Fifth, the lack of assessment of post-traumatic stress symptomatology at the time of the earthquake. Although a PTSD diagnosis has been excluded at the SCID interview, the possibility of some trauma symp-

toms could have been emerged in the aftermath of the event that could be related to BDNF modifications, cannot be excluded.

Globally, our results shed more light on the mechanisms regulating BDNF levels in response to stress, delineating a landscape somewhat more complex than what could be expected from the somewhat inconsistent literature on PTSD alone [5,12,13,34,35].

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