LIVELLI SIERICI DI BDNF NEL TRAUMA

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NEUROTROFINE

Le neurotrofine sono molecole che intervengono nel trofismo e nella plasticità neuronale.

La prima neurotrofina, il Fattore di Crescita Neuronale o Nerve Growth Factor o NGF, fu scoperta da Rita Levi Montalcini nel 1951.

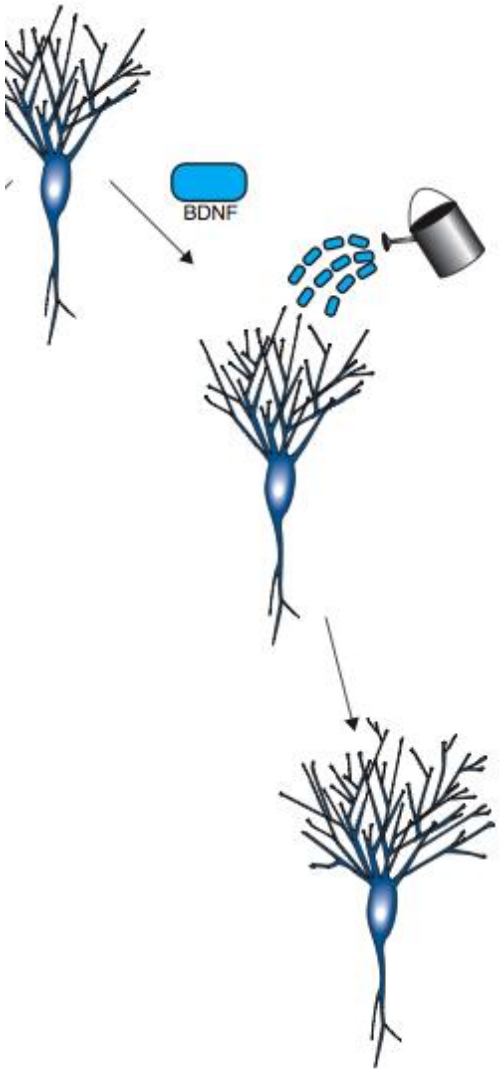
NEUROTROFINE: IL BDNF

Il Fattore Neutrofico Cerebrale (Brain-Derive Neurotrophic Factor – BDNF) è una proteina codificata dal *gene BDNF*.

Negli esseri umani, il BDNF è prevalente a livello cerebrale, ed in periferia si può rilevare tanto nel siero quanto nel plasma.

E’ noto che il BDNF attraversa la barriera ematoencefalica in entrambe le direzioni, essendo il BDNF circolante sia di origine neuronale che gliale.

IL BDNF SOSTIENE LA NEUROGENESI E LA PLASTICITÀ SINAPTICA



Promuove crescita e sviluppo di neuroni immaturi (inclusi quelli monoaminergici).

Accresce la sopravvivenza e la funzionalità di neuroni adulti.

Aiuta il mantenimento delle connessioni sinaptiche.

Stahl S. M. Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Application. Cambridge University Press, New York, 2013

BDNF: FUNZIONI

Il BDNF regola funzioni fondamentali all'interno del Sistema Nervoso Centrale (SNC), quali:

1. Differenziazione delle cellule staminali neuronali;
2. Accrescimento e differenziazione neuronale e sinaptica;
3. Interventi favorenti per la sopravvivenza dei neuroni già esistenti
4. Azioni su fenomeni plastici quali:

    - Il rimodellamento sinaptico
    - L'aumento delle connessioni sinaptiche
    - La differenziazione e l'accrescimento neurale.

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BDNF: STATI DI RIDUZIONE

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS

Vol. 26, no. 3, 347-356 (2012)

EDITORIAL

NERVE GROWTH FACTOR AND BRAIN-DERIVED NEUROTROPHIC FACTOR CONCENTRATIONS IN SCHIZOPHRENIA: A REVIEW

G. MARTINOTTI, G. DI IORIO, S. MARINI, V. RICCI, D. DE BERARDIS and M. DI GIANNANTONIO

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Received January 31, 2012 – Accepted July 30, 2012

Original Paper

Further evidence supporting the influence of brain-derived neurotrophic factor on the outcome of bipolar depression: independent effect of brain-derived neurotrophic factor and harm avoidance

Laura Mandelli[1], Marianna Mazza[2], Giovanni Martinotti[2], Daniela Tavian[3], Elisa Colombo[3], Sara Missaglia[3], Marco Di Nicola[2], Diana De Ronchi[1], Gloria Negri[3], Roberto Colombo[3,4], Luigi Janiri[2] and Alessandro Serretti[1]

Psychopharm

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BDNF E SCHIZOFRENIA

J Biol Regul Homeost Agents. 2012 Jul-Sep;26(3):347-56.

Nerve growth factor and brain-derived neurotrophic factor concentrations in schizophrenia: a review.

Martinotti G, Di Iorio G, Marini S, Ricci V, De Berardis D, Di Giannantonio M.

Abstract

There is growing interest in the role of neurotrophins in the pathophysiology of schizophrenia. Neurotrophins are a large family of dimeric polypeptides that promote the growth and the differentiation of developing neurons in the central and peripheral nervous systems as well as the survival of neuronal cells in response to stress. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) concentrations are here reviewed in relation to medication-naive early psychotic patients and in medicated chronic schizophrenic patients. Most data point to decreased plasma and serum NGF and BDNF concentrations in naive drug and in medicated schizophrenic patients compared to healthy controls. Higher BDNF levels were observed in patients with the paranoid subtype of schizophrenia. Low serum BDNF levels were associated with reduction in hippocampal volume (HV) at the onset of schizophrenia. Evidence on the correlation between BDNF levels and positive and negative schizophrenic symptoms were ambiguous. There are contrasting results on a possible correlation between increase in BDNF concentrations and treatment with antipsychotics. Antipsychotic treatment can elevate NGF values, specifically atypical. Growth factors might be good candidates as prognostically and diagnostically useful markers in schizophrenia.

BDNF E DISTURBO BIPOLARE

J Affect Disord. 2014 Jun;162:67-72. doi: 10.1016/j.jad.2014.02.038. Epub 2014 Mar 24.

Serum level of brain derived neurotrophic factor (BDNF) among patients with bipolar disorder.

Rabie MA[1], Mohsen M[2], Ibrahim M[3], El-Sawy Mahmoud R[2].

⊕ Author information

Abstract

BACKGROUND: There is a growing body of evidence that serum brain derived neurotrophic factor (BDNF) is altered during the episodes of bipolar disorder. The aim of this study was to investigate serum BDNF levels in bipolar disorder patients during manic and depressive episodes and its clinical utility in bipolar disorder compared to other psychiatric disorders.

METHODS: The study was conducted on 80 Egyptian patients, who were classified into 4 groups: group Ia (25 patients with depressive episodes), group Ib (25 patients with manic episodes), group II (15 patients having Schizophrenia) as pathological controls and group III (15 healthy subjects) as controls. All subjects were diagnosed according to DSM-IV, assessed using the Hamilton Rating Scale for depression (HAM-D), and the Young Mania Rating Scale (YMRS). sBDNF concentrations were measured using the quantitative sandwich enzyme immunoassay technique.

RESULTS: sBDNF showed significantly lower levels in patients with depressive episodes or manic episodes. The best cut-off for sBDNF in discriminating depressed patient from healthy control was ≤33,000pg/ml (AUC=0.891, sensitivity of 84%, and specificity of 80%). Moreover, the best cut-off for sBDNF in discriminating mania patients' group from healthy control was ≤29,500pg/ml, (AUC=0.984, asensitivity of 96%, and specificity of 86.7%).

LIMITATIONS: Only a small sample size was considered which included only drug free patients. BDNF was measured in serum not in CSF or brain tissue.

CONCLUSIONS: Low sBDNF levels are strongly associated with active phases of bipolar disorder, in depressive and manic episodes.

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BDNF E DEPRESSIONE

E’ stato osservato che i livelli di BDNF sono influenzati dalle situazioni stressanti, ed i livelli della neurotrofina che si rilevano in soggetti depressi sono inferiori rispetto a quelli dei controlli sani, ma possono aumentare in corso di trattamento con farmaci antidepressivi.

Consistentemente con la variazione dei livelli di BDNF in relazione ai sintomi depressivi, si è dimostrato che gli eventi stressanti riducono l’espressione del BDNF a livello delle regioni limbiche cerebrali che controllano le espressioni affettive.

BDNF E DEPRESSIONE

In modelli sperimentali di depressione, **i farmaci antidepressivi hanno dimostrato di poter prevenire la down regulation del BDNF**. Le concentrazioni diminuiscono in risposta a stress e depressione.

La carenza di molecole trofiche funge da trigger per l'attivazione di processi apoptotici e di spopolamento neuronale.

Tuttavia, in primo luogo, non ci sono evidenze che la riduzione del BDNF causi direttamente la depressione, e, secondariamente, il meccanismo attraverso il quale la depressione e i farmaci antidepressivi influenzano i livelli di BDNF sono ancora poco chiari, e sono attualmente oggetto di studio.

BDNF E ANTIDEPRESSIVI

La terapia antidepressiva potrebbe ripristinare la cascata di trasduzione del segnale legata al sistema monoaminergico

aumentare i livelli di BDNF ed altri fattori neurotrofici

ripristinare la sinaptogenesi e la neurogenesi

The early non-increase of serum BDNF predicts failure of antidepressant treatment in patients with major depression: A pilot study

André Tadić [a,*,1], Stefanie Wagner [a,1], Konrad Friedrich Schlicht [a], Dirk Peetz [b], Liudmyla Borysenko [a], Nadine Dreimüller [a], Christoph Hiemke [a], Klaus Lieb [a]

[a] Department of Psychiatry and Psychotherapy, University Medical Centre Mainz, Germany
[b] Institute for Clinical Chemistry and Laboratory Medicine, University Medical Centre Mainz, Germany

Secondo il presente studio, modificazioni o mancate modificazioni precoci nei livelli di BDNF sierico possono essere predittivi della risposta o della non-risposta alla terapia nei pazienti con DDM.

STUDIO SPERIMENTALE:

- 41 pz con Disturbo Depressivo Maggiore
- Studio naturalistico
- I sintomi depressivi e i livelli di BDNF sono stati valutati settimanalmente per sei settimane

RISULTATO
Il mancato incremento del BDNF e il mancato miglioramento alla scala HAM-D nella seconda settimana sono risultati predittivi di non-risposta alla terapia.

BDNF E ANTIDEPRESSIVI

Pharmacopsychiatry. 2013 Mar;46(2):54-8. doi: 10.1055/s-0032-1321908. Epub 2012 Sep 7.

Thieme eJournals

Changes of serum concentrations of brain-derived neurotrophic factor (BDNF) during treatment with venlafaxine and mirtazapine: role of medication and response to treatment.

Deuschle M[1], Gilles M, Scharnholz B, Lederbogen F, Lang UE, Hellweg R.

Author information

Abstract

INTRODUCTION: Depression, stress and antidepressant treatment have been found to modulate the expression of brain-derived neurotrophic factor (BDNF). Recent research suggests that serum BDNF concentration is reduced in depression and that antidepressant treatment leads to an increase in serum BDNF concentration.

METHODS: We studied depressed patients receiving a randomized antidepressant treatment with either mirtazapine (n=29) or venlafaxine (n=27) for 28 days in a prospective design. Changes in the concentrations of serum neurotrophins in response to antidepressant treatment were assessed.

RESULTS: There was a significant "treatment" by "medication" interaction effect on BDNF serum concentrations that indicated a decline of BDNF in venlafaxine-treated patients (7.82±3.75-7.18±5.64 ng/mL), while there was an increase in mirtazapine-treated patients (7.64±6.23-8.50±5.37 ng/mL). There was a trend for a "treatment" by "remission" interaction with a favourable clinical course being related to increasing serum BDNF.

DISCUSSION: Changes in BDNF serum concentrations as a result of antidepressant therapy depend on the antidepressant and potentially on the clinical course.

BDNF E ANTIDEPRESSIVI

Molecular Psychiatry (2011) 16, 1088–1095
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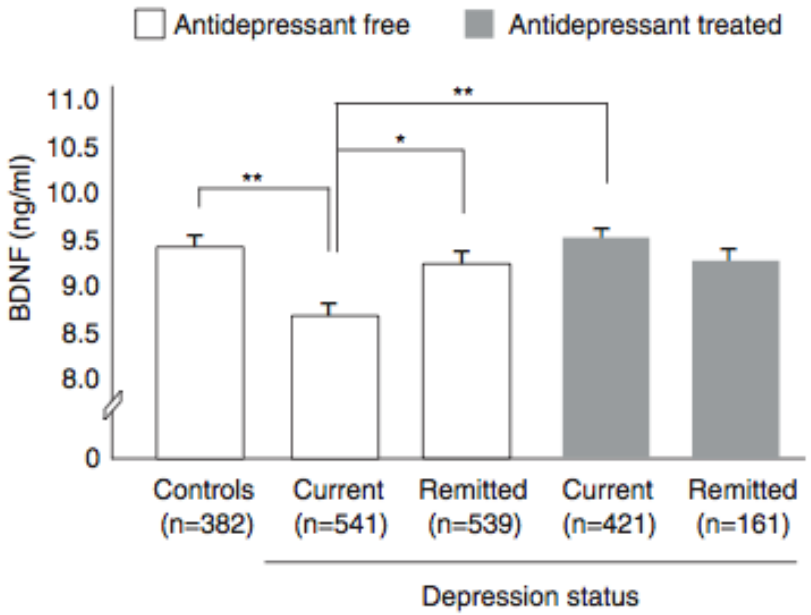
ORIGINAL ARTICLE

Serum levels of brain-derived neurotrophic factor in major depressive disorder: state–trait issues, clinical features and pharmacological treatment

ML Molendijk[1,2], BAA Bus[3], Ph Spinhoven[1,2,4], BWJH Penninx[4,5,6], G Kenis[7], J Prickaerts[7], RC Oude Voshaar[3,6] and BM Elzinga[1,2]



Livelli di BDNF:

- minori in depressi non trattati rispetto ai controlli sani;
- minori in pz depressi non in trattamento rispetto a quelli non in trattamento dopo remissione;
- minori nei depressi non trattati rispetto a quelli in trattamento.

BDNF E ANTIDEPRESSIVI

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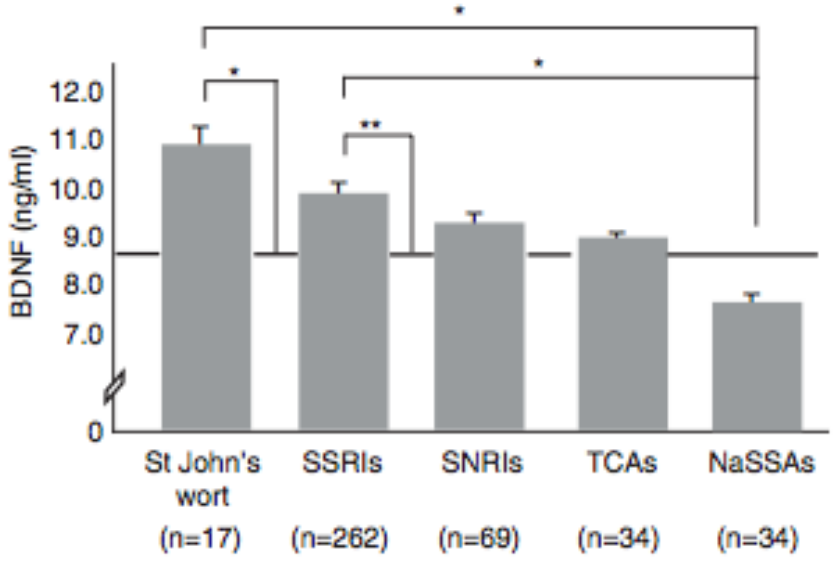

I livelli di BDNF sembrano aumentare in modo molto differente in base alla terapia farmacologica assunta.

Sembrano subire incrementi sensibilmente maggiori assumendo agenti con spiccata azione serotoninergica

BDNF E ANTIDEPRESSIVI

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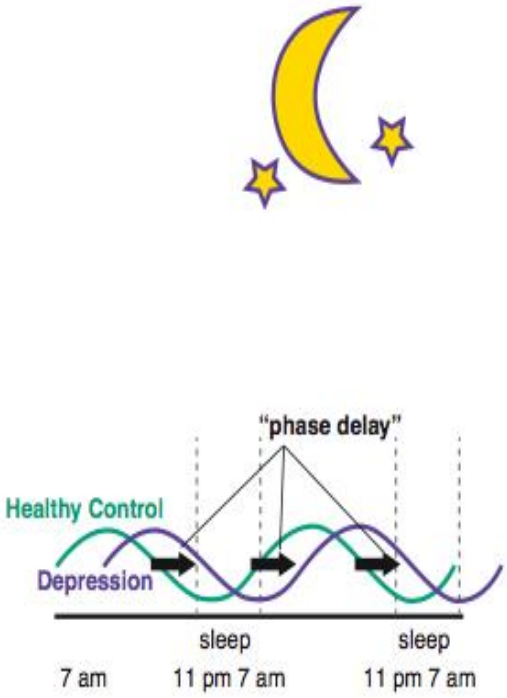
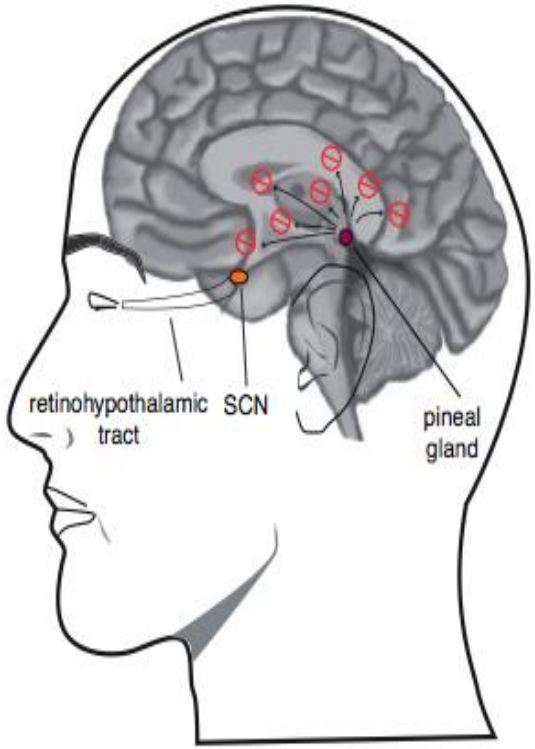
Bassi livelli sierici di BDNF potrebbero essere caratteristica di stato della depressione, anormalità evidente in stato clinico attivo e nelle fasi iniziali di remissione ma non durante la piena remissione

Alcune caratteristiche cliniche core della depressione potrebbero non essere correlate ai livelli sierici di BDNF

L' aumento dei livelli sierici di BDNF sembra essere un effetto farmacologico specifico della tp antidepressiva

BDNF E RITMI CIRCADIANI

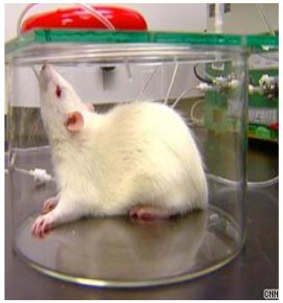




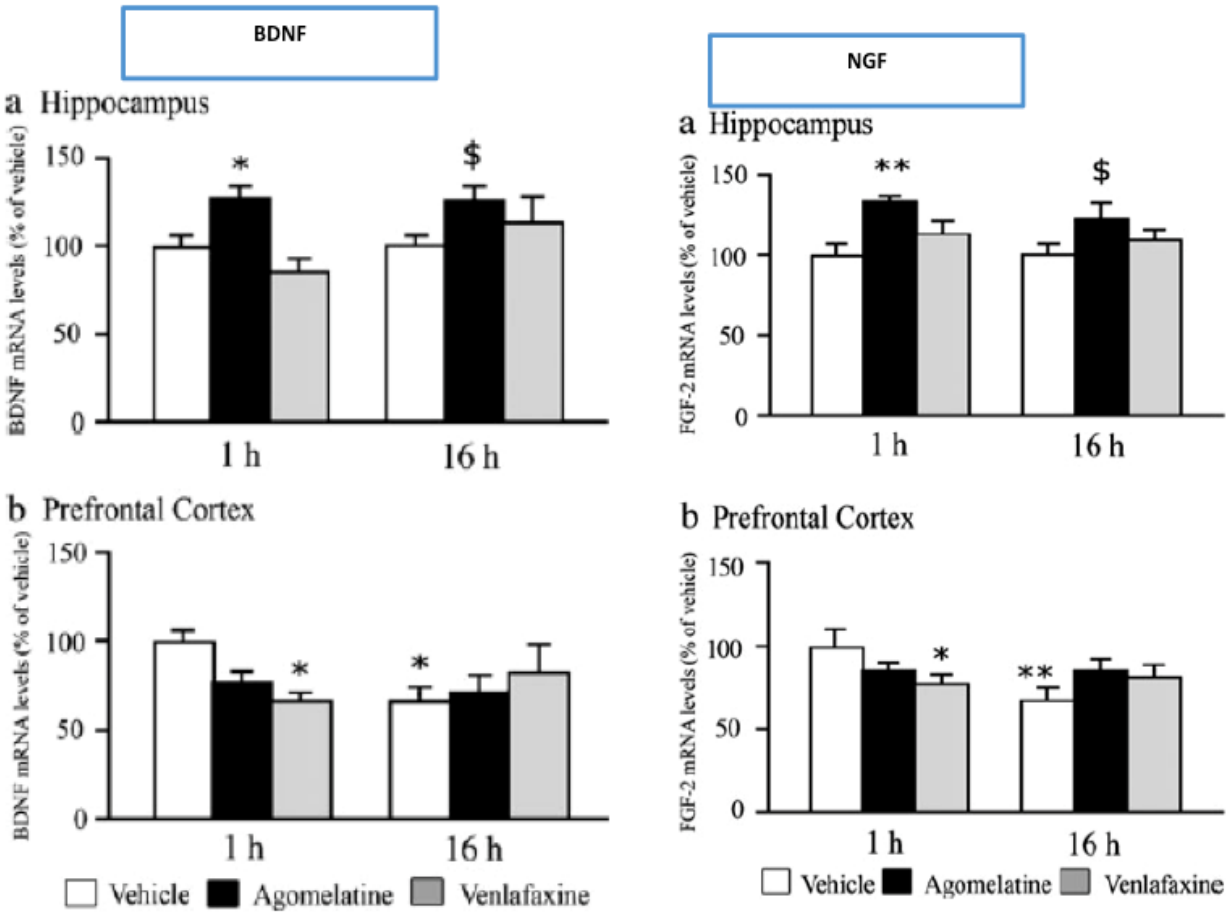
L' alterazione dei ritmi circadiani, una delle caratteristiche core della depressione, potrebbe influire sui livelli di BNDF e sulla neurogenesi che trova il suo picco nella fase notturna in un normale ciclo sonno-veglia.

Stahl S. M. Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Application. Cambridge University Press, New York, 2013

AUMENTO DEI FATTORI DI TRASCRIZIONE IN SEGUITO AD ESPOSIZIONE AD AGOMELATINA



STIMOLATION OF NEURONAL GROWTH FACTORS



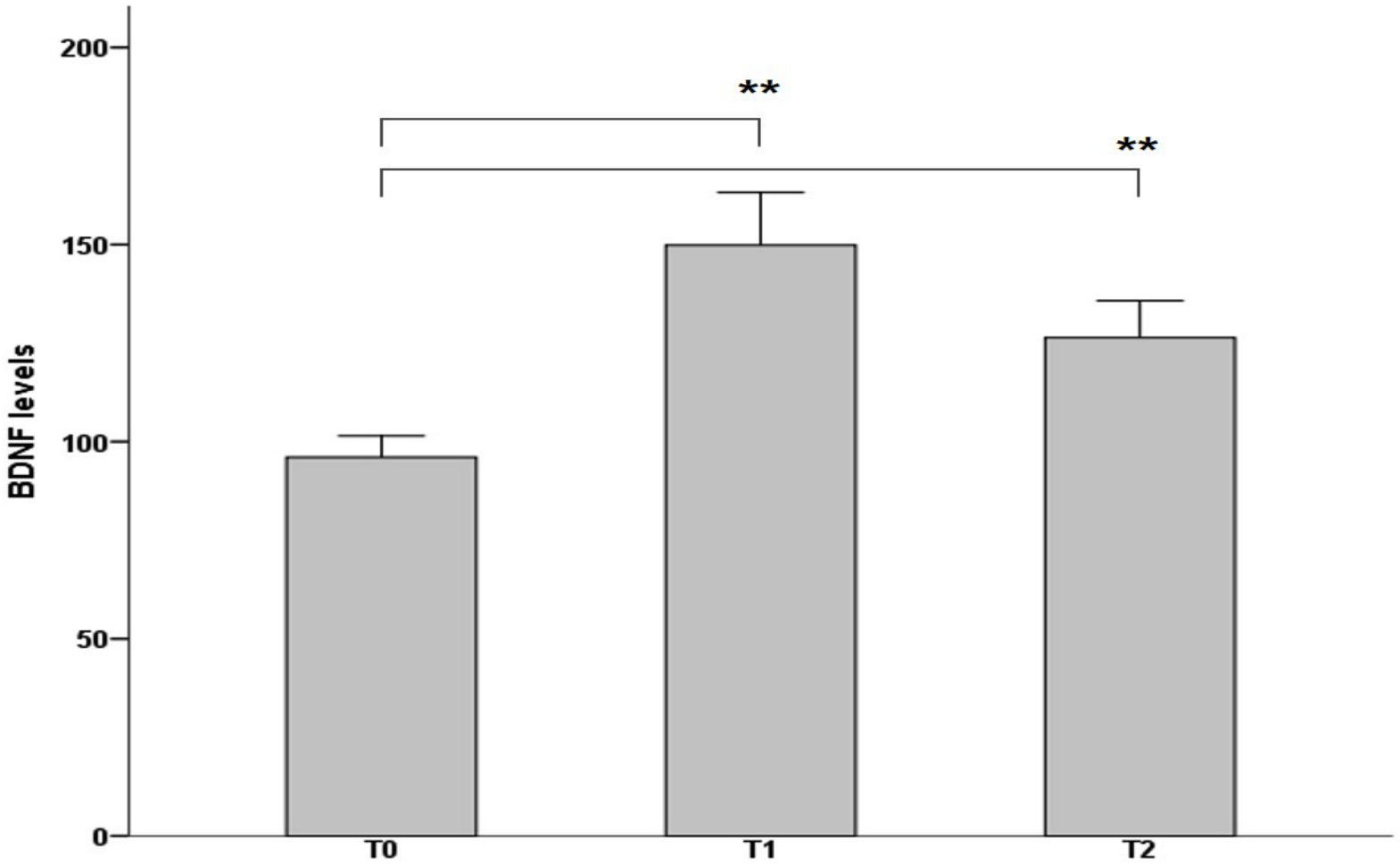
Calabrese F et al Psychopharmacology 2011

CORRELAZIONI TRA USO DI AGOMELATINA E LIVELLI DI BDNF NEL TRATTAMENTO DEI DISTURBI DEPRESSIVI

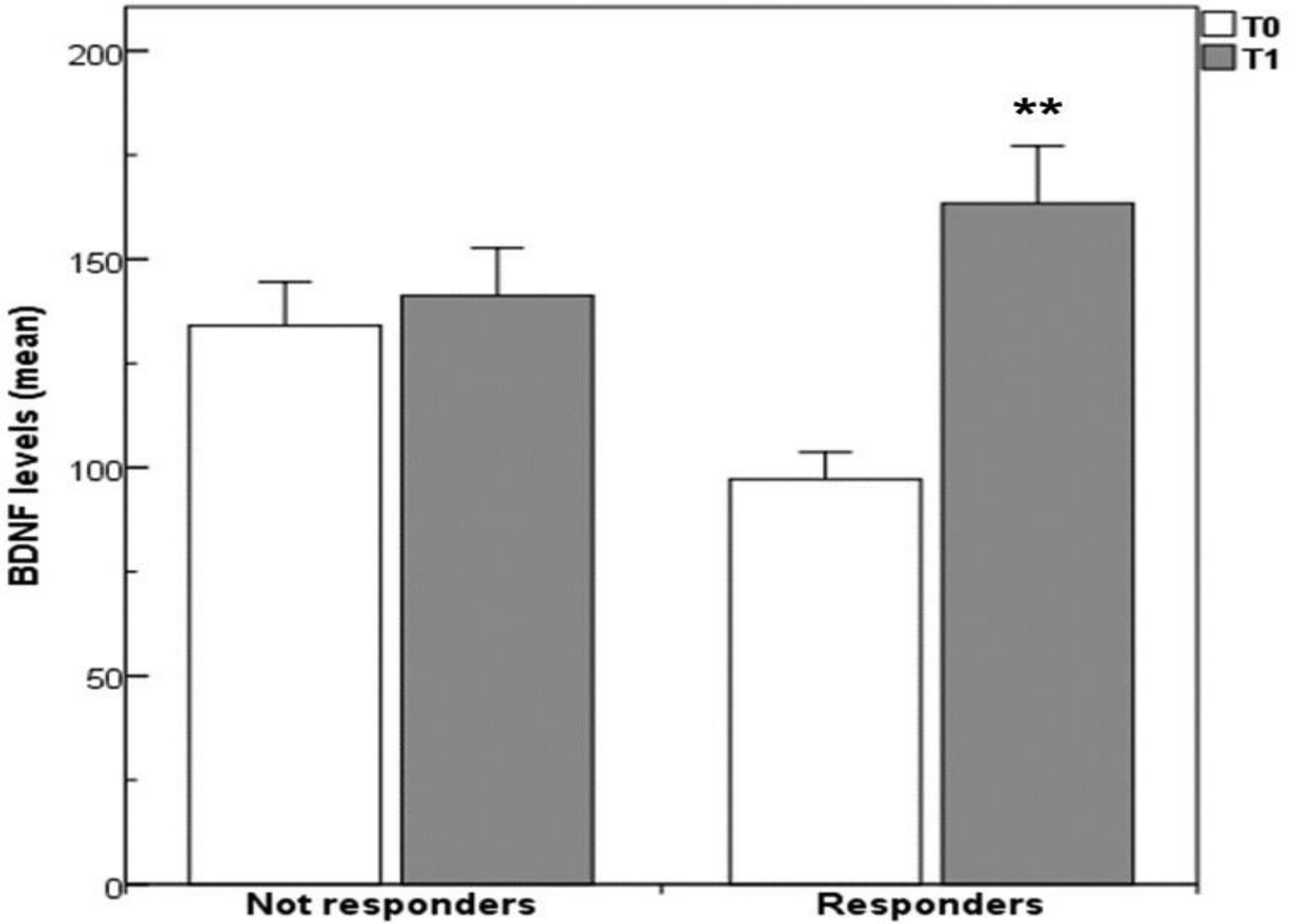
Metodologia:

- 27 pazienti e 29 controlli sani
- Diagnosi di Disturbo Depressivo Maggiore, Disturbo Depressivo Minore o Distimia, corrispondenti all'area dei Disturbi Depressivi del DSM-5
- Tre valutazioni: al baseline, dopo 2 settimane, e dopo 8 settimane di trattamento con agomelatina (dose iniziale 25 mg, incrementabili a 50 mg in caso di mancata risposta clinica dopo 2 settimane)
- Valutazione clinica: SCID-I/P, SHAPS, Hamilton Depression e Hamilton Anxiety Inventory, CGI
- Valutazione biologica: concentrazioni di BDNF e NGF nel siero

VALUTAZIONE DELL'EFFETTO DI AGOMELATINA SUI LIVELLI DI BDNF IN SOGGETTI DEPRESSI



VALUTAZIONE DELL'EFFETTO DI AGOMELATINA SUI LIVELLI DI BDNF IN SOGGETTI DEPRESSI



BDNF: STATI DI INCREMENTO

Livelli elevati di BDNF sono legati a una iperattività del sistema immunitario sia a livello centrale che periferico.

L’esercizio fisico aumenta la disponibilità di BDNF.

Il livello può aumentare in caso di morte cellulare per uso di sostanze.

Può aumentare in seguito ad un trauma grave.

BDNF e sostanze d'abuso

ORIGINAL ARTICLE

doi:10.1111/j.1369-1600.2010.00221.x

Ecstasy (MDMA)-addicted subjects show increased serum levels of brain-derived neurotrophic factor, independently from a rise of drug-induced psychotic symptoms

Francesco Angelucci[1], Valerio Ricci[1,2], Giovanni Martinotti[2], Ilaria Palladino[1], Gianfranco Spalletta[1,3], Carlo Caltagirone[1,3] & Pietro Bria[2]

Department of Clinical and Behavioural Neurology, IRCCS Santa Lucia Foundation, Italy[1], Institute of Psychiatry, Catholic University, Italy[2] and Department of Neuroscience, Tor Vergata University, Italy[3]

ABSTRACT

The recreational drug 'ecstasy' [3,4-methylenedioxymethamphetamine (MDMA)] exerts a potent action on central serotonergic and dopaminergic neurons. These neurons utilize neurotrophins for their survival and function. In order to explore MDMA effects on neurotrophins, we measured by enzyme-linked immunosorbent assay the serum levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor in 'ecstasy-addicted', 'ecstasy-addicted with signs of psychosis' and 'healthy' subjects. We found that BDNF serum levels were significantly increased in both groups of 'ecstasy-addicted' as compared with 'healthy subjects', supporting the hypothesis that BDNF is involved in MDMA action.

Keywords Addiction, BDNF, ecstasy, MDMA, NGF, psychosis..

BDNF e sostanze d'abuso

Table 1 Clinical characteristics of ecstasy-addicted subjects, ecstasy-addicted subjects with psychotic symptoms and controls.

	Ecstasy users (n = 23)	*Ecstasy users with psychotic symptoms (n = 21)*	*Healthy subjects (n = 19)*
Age (years)	20.56 ± 2.98	20.90 ± 2.07	20.63 ± 2.03
Sex (male/female)	13M/10F	11M/10F	10M/9F
Years of education	12.17 ± 3.25	11.85 ± 2.53	12.05 ± 2.5
Age at first ecstasy use	16.65 ± 1.99	16.76 ± 1.94	—
Duration of ecstasy use (years)	3.08 ± 1.37	3.14 ± 1.27	—
Frequency of ecstasy use (tablets per week)	1.91 ± 0.90	1.95 ± 0.97	—
Frequency of ecstasy use (days per month)	4.04 ± 1.29	4.09 ± 1.33	—
DAST	18.82 ± 4.48	18.66 ± 5.41	—

Data are the mean ± standard deviation. DAST = Drug Abuse Screening Test; F = female; M = male; *n* = number of subjects included in the study.

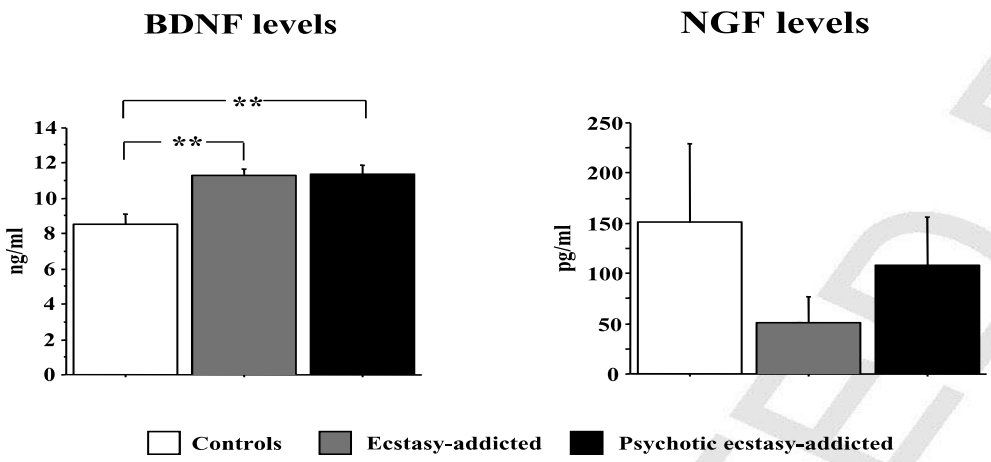
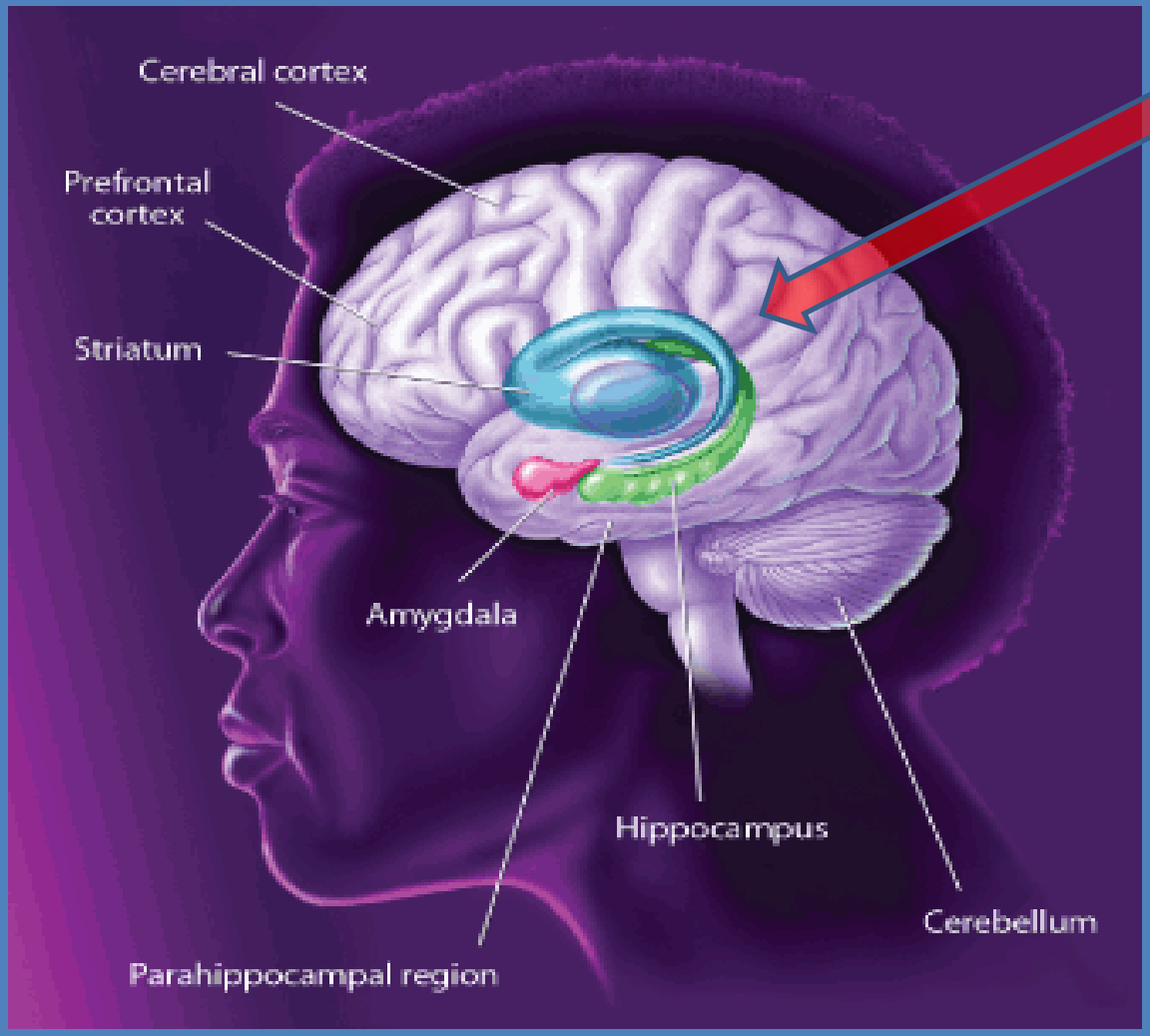


Figure 1 Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) serum levels in ecstasy-addicted subjects, ecstasy-addicted subjects with psychotic symptoms and controls. Data are the mean ± standard error of the mean. Values are expressed in ng/ml (BDNF) and pg/ml (NGF). Asterisk (*) indicates significant difference between groups; $^{**}P < 0.001$

ED PROOF

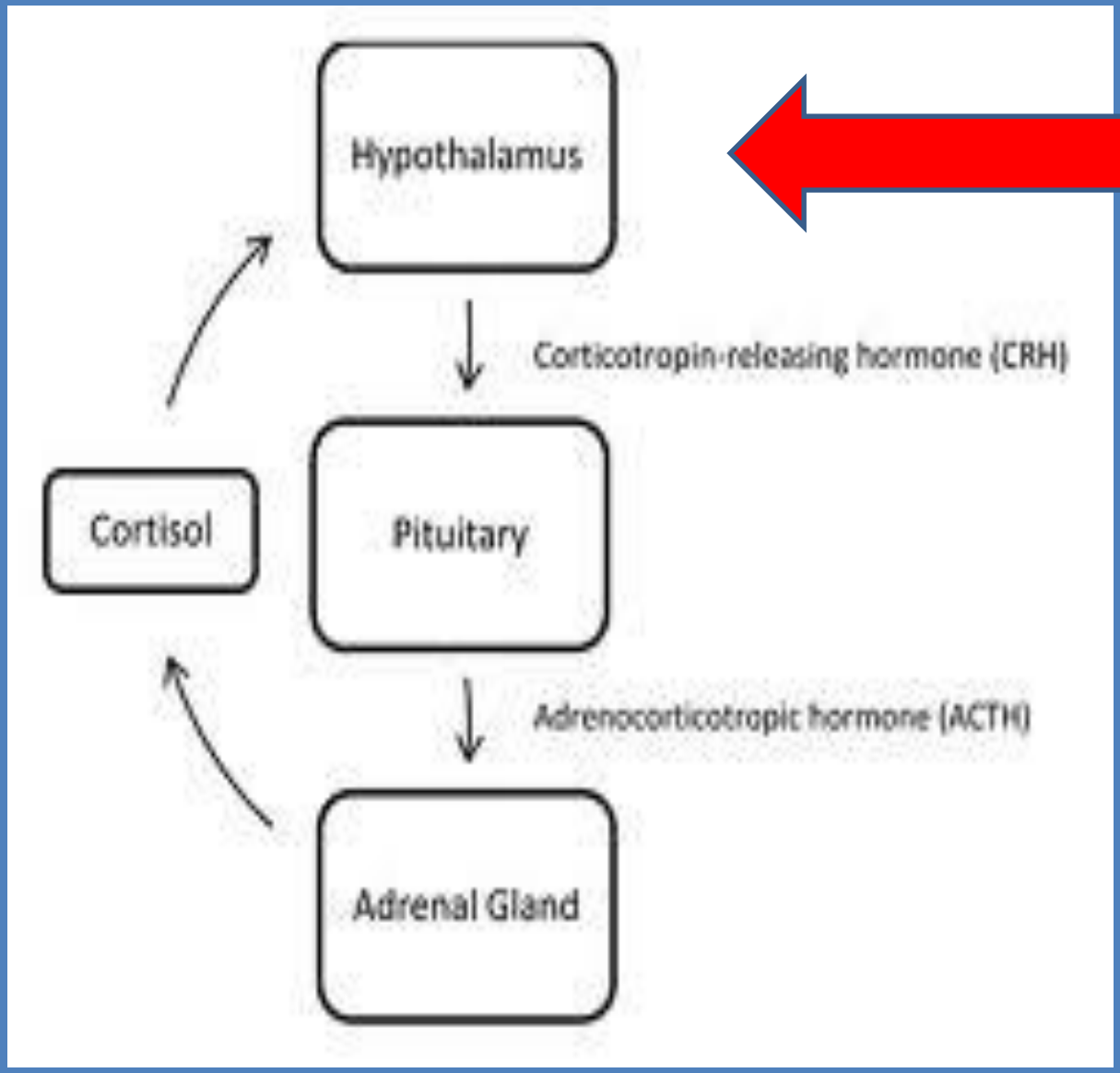
BDNF ed eventi traumatici



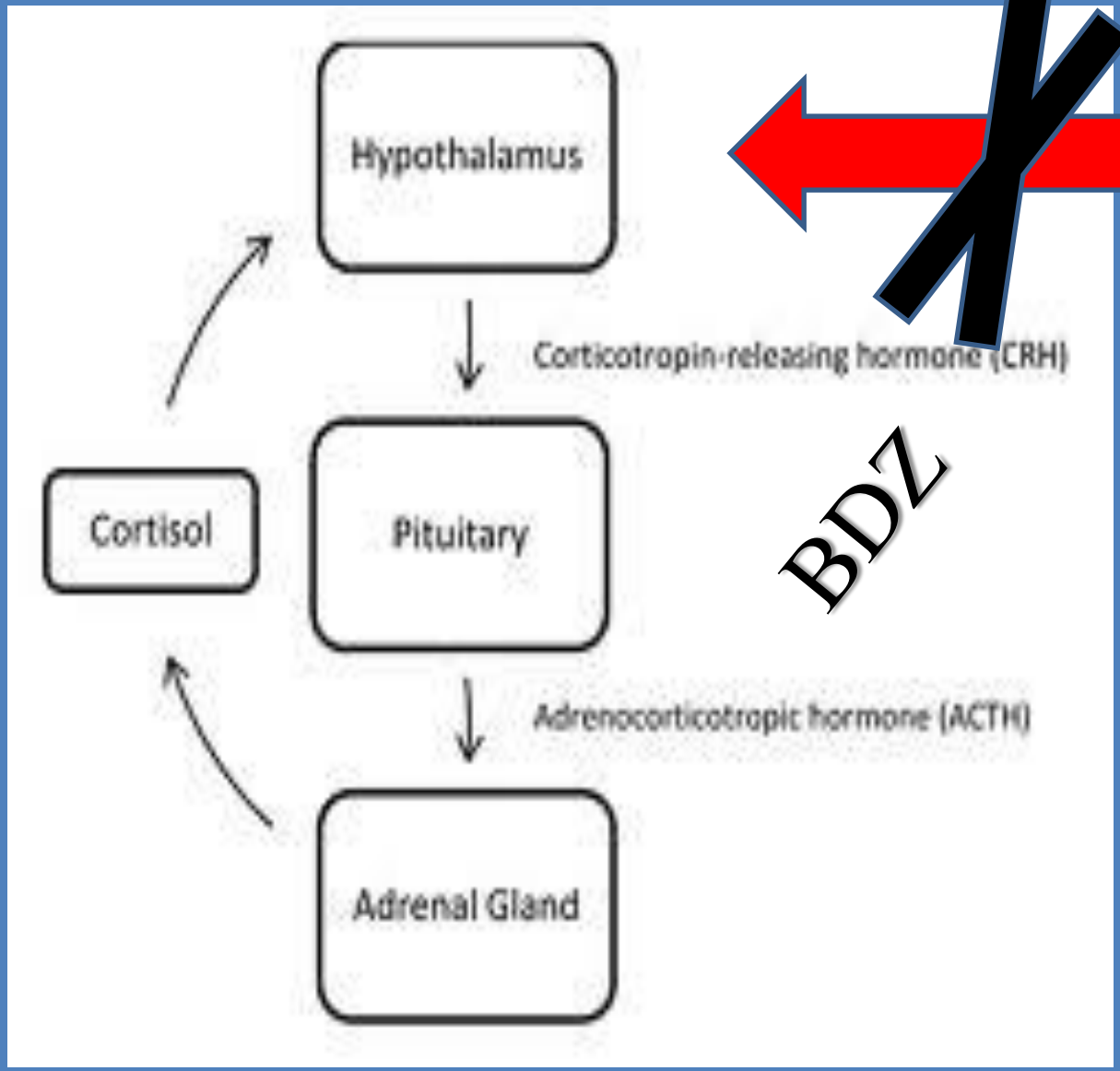
BDNF

Cortisolo

TRAUMA


Hypothalamus
Corticotropin-releasing hormone (CRH)
Pituitary
Cortisol
Adrenocorticotropic hormone (ACTH)
Adrenal Gland

TRAUMA


Hypothalamus
Corticotropin-releasing hormone (CRH)
Pituitary
Cortisol
Adrenocorticotropic hormone (ACTH)
Adrenal Gland

TRAUMA

BDZ

BDNF, trauma e PTSD

Brain and Cognition 84 (2014) 118–122

Contents lists available at ScienceDirect

Brain and Cognition

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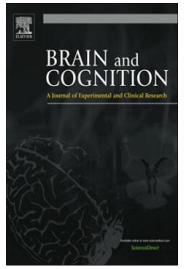

BDNF serum levels in subjects developing or not post-traumatic stress disorder after trauma exposure

Francesco Angelucci [a,*], Valerio Ricci [a], Francesca Gelfo [a], Giovanni Martinotti [b], Marcella Brunetti [b], Gianna Sepede [b], Maria Signorelli [c], Eugenio Aguglia [c], Mauro Pettorruso [d], Federica Vellante [b], Massimo Di Giannantonio [b], Carlo Caltagirone [a]

[a] *IRCCS Santa Lucia Foundation, Department of Clinical and Behavioural Neurology, 00179 Rome, Italy*
[b] *Department of Neuroscience and Imaging, University "G.d'Annunzio", Chieti, Italy*
[c] *Department of Psychiatry, University of Catania, Italy*
[d] *Department of Neuroscience, Catholic University of Rome, Italy*

BDNF, trauma e PTSD

A B S T R A C T

Post-traumatic stress disorder (PTSD) is a syndrome resulting from exposure to a severe traumatic event that poses threatened death or injury and produces intense fear and helplessness. The neural structures implicated in PTSD development belong to the limbic system, an important region for emotional processing. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that serves as survival factor for selected populations of central nervous system (CNS) neurons and plays a role in the limbic system by regulating synaptic plasticity, memory processes and behavior. Impaired BDNF production in the brain can lead to a variety of CNS dysfunctions including symptoms associated with PTSD. However, so far fewer studies have investigated this neurotrophin in patients with PTSD. Furthermore, given the multiple role of BDNF in various CNS disorders, it cannot be excluded that traumatic events per se may influence neurotrophin levels, without a direct association to the PTSD syndrome.

To elucidate these issues, in this study we analyzed BDNF serum levels in two groups of subjects: patients with trauma exposure who developed PTSD, and subjects with trauma exposure who did not develop PTSD. We found that BDNF serum levels were lower in PTSD patients as compared to related control subjects. Thus, these data suggest that BDNF might be involved in pathophysiology of PTSD and consequently therapeutic approaches aimed at restoring BDNF serum levels may be beneficial to this pathology.

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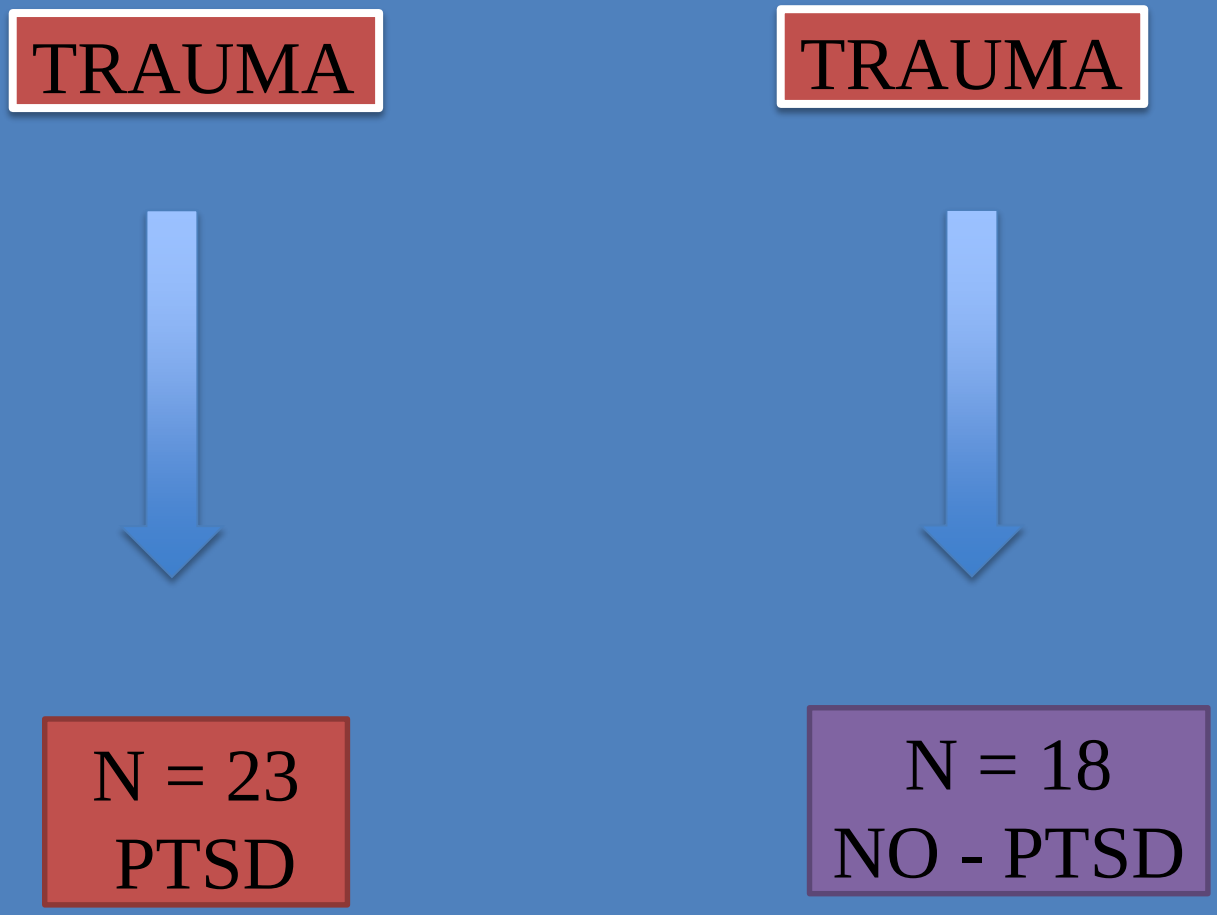
Study Design



Study Design

- The assessment included: the Structured Clinical Interview for DSM-IV Axis-I disorders Patient Version (SCID-I/P, First et al., 1997) and the Clinician Administered PTSD Scale CAPS, (Blake et al, 1995). The SCID-I/P was administered to patients and control subjects by psychiatrists trained and certified in the use of the instruments.

The Clinician Administered PTSD Scale

- The CAPS distinguishes between the estimated frequency (range: 0–4) and intensity (range: 0–4) of the various symptoms. Frequency and intensity scores are added up to a total CAPS score (range: 0–136)

- In the current study, the most distressing potentially traumatic event (the index event) reported by a participant was assessed at the beginning of the interview to determine whether it met the diagnostic criteria for a traumatic event (Criterion A)

- The frequency and intensity of each of 17 PTSD symptoms associated with the index event were rated on 5-point scales ranging from 0 (Never [frequency], Not at all [intensity]) to 4 (Daily or almost daily, Extremely).

BDNF, trauma e PTSD

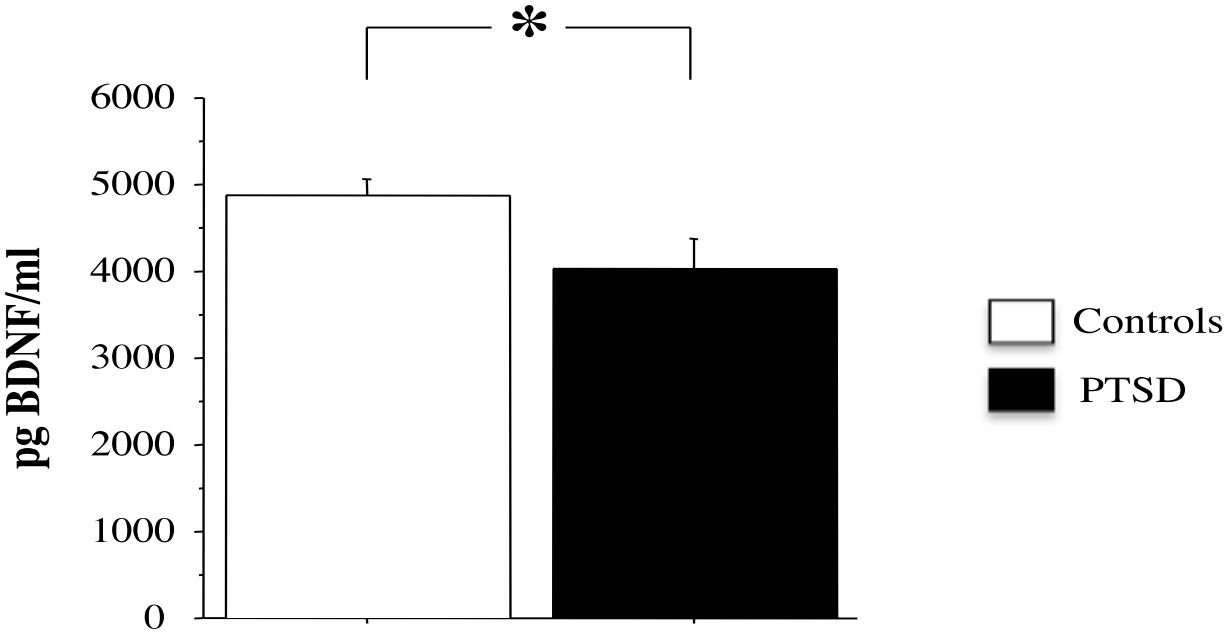
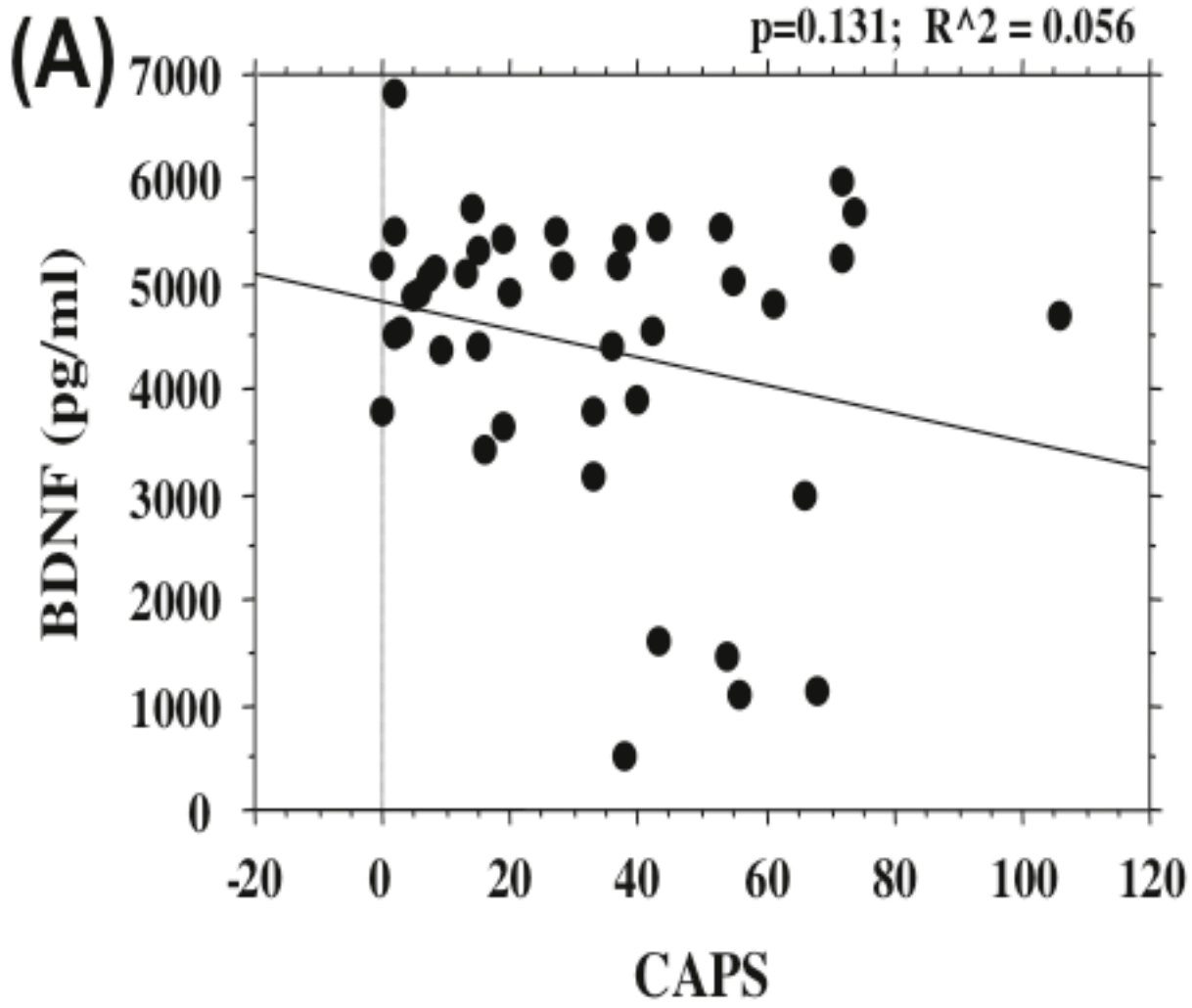
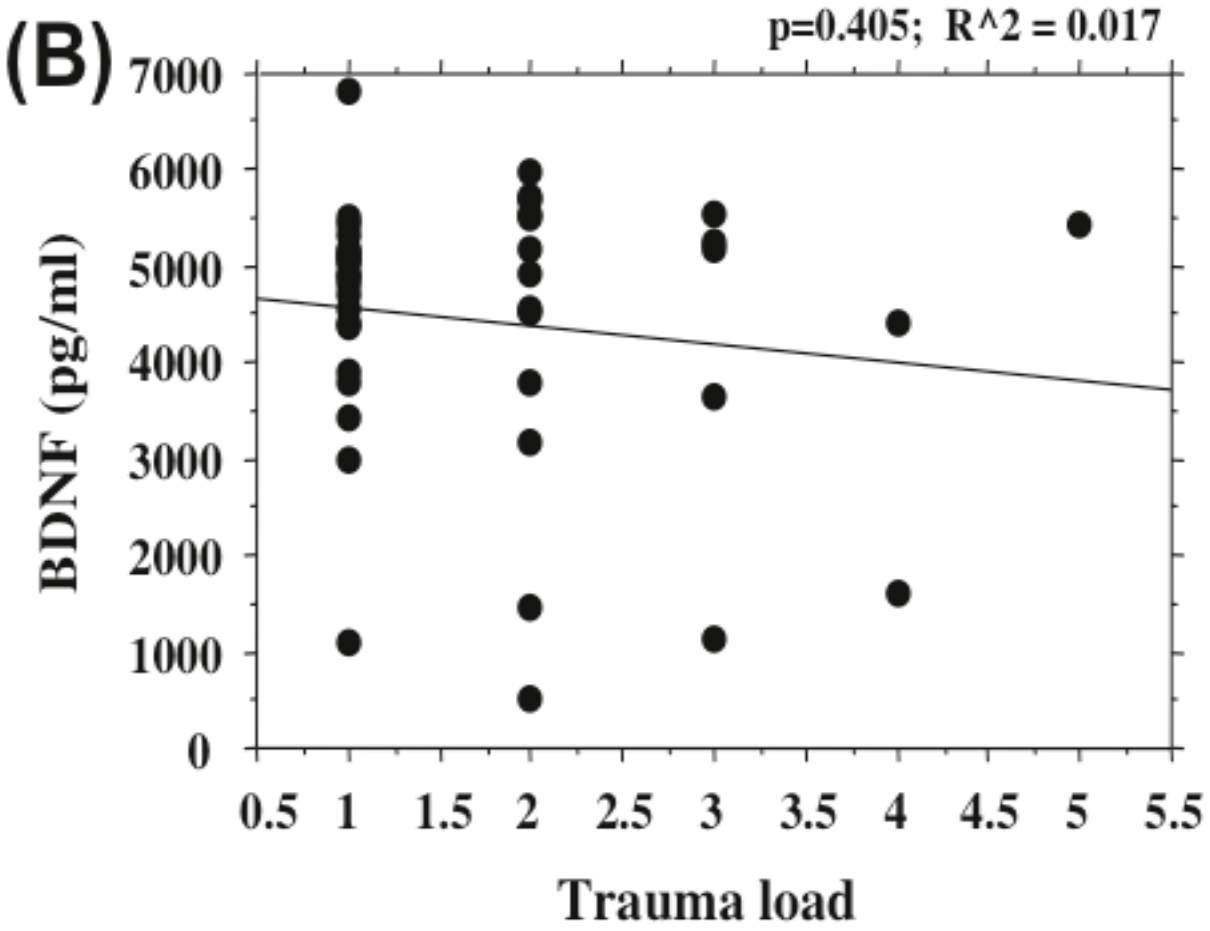


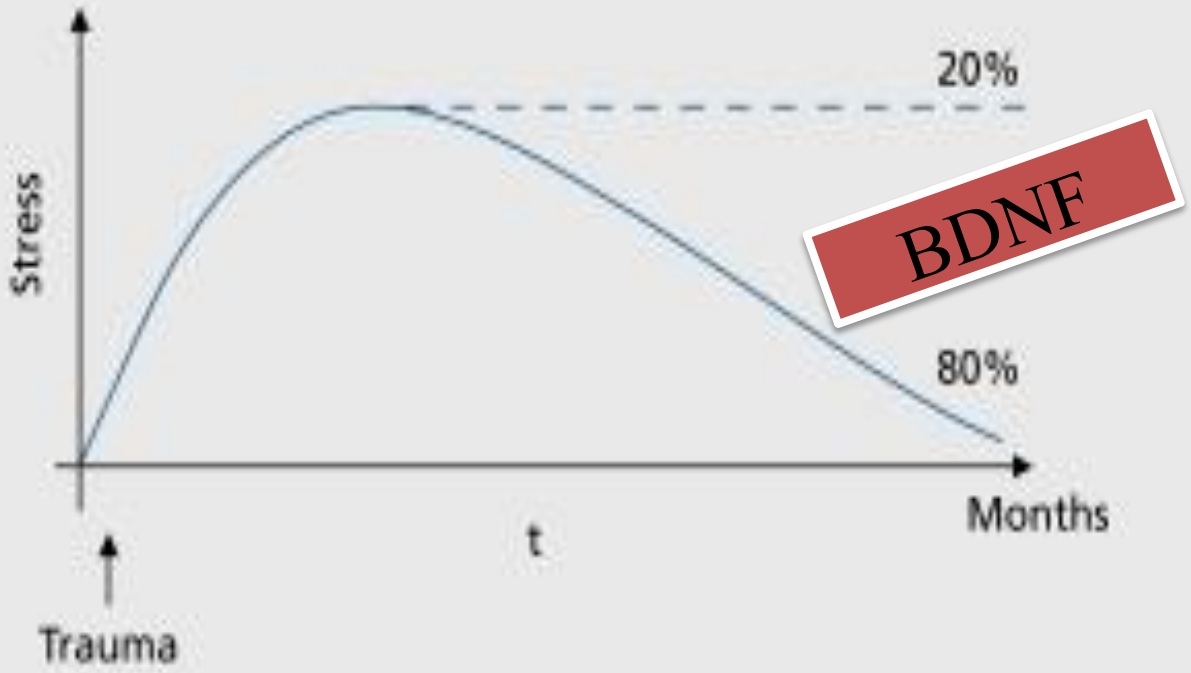
Fig. 1. BDNF serum levels in PTSD patients and controls. Data are the mean ± SEM. Values are expressed in pg/ml. Asterisk (*) indicates significant difference between the groups. $^{*}p < 0.05$.

BDNF, trauma e PTSD



BDNF, trauma e PTSD




20%
BDNF
80%
Stress
Months
t
Trauma

BDNF and Impulsivity

- Furthermore, a difference was observed in BIS 11 total score between PTSD patients and controls, but the different doesn't reach the significance (patients higher score than controls, $p=0.09$).

- Pearson coefficient revealed a positive correlation between BDNF levels and BIS 11 total score, that is, higher the impulsivity index, higher the BDNF level ($r=0.476$, $p<0.05$). No correlation was observed between the BDNF values and BIS 11 score in control group.

Discussion

- We found that while NGF serum levels were unchanged, BDNF serum levels were lower in PTSD patients as compared to related control subjects.

- Our findings are in line with another study showing a reduction of BDNF plasma levels in a small sample of PTSD patients as compared with healthy controls (Dell'Osso et al., 2009). On the other hand, Hauck et al demonstrated elevated serum BDNF levels in patients with recent trauma raising the possibility that BDNF serum levels increase in early stages of trauma (Hauck et al., 2010).

- Since in our study we included subjects with trauma exposure not developing PTSD as control group, we provided an additional evidence for a direct involvement of BDNF in PTSD.

CONSIDERAZIONI CONCLUSIVE

La valutazione del BDNF può rappresentare un futuro indicatore diagnostico e prognostico sia nel PTSD che nei disturbi dell'umore

L'aumento del BDNF sierico, riscontrabile nelle fasi immediatamente successive ad un trauma, è probabilmente indotto in seguito alla attivazione del ciclo del cortisolo, a sua volta elicitato dall'esposizione al trauma

La presenza di elevati livelli di BDNF potrebbe essere implicata nella contro-reazione al trauma, rappresentando, dal punto di vista neurobiologico, un fattore di resilienza

Il mancato aumento di BDNF in relazione al trauma potrebbe differenziare i soggetti che sviluppano un PTSD da quelli che reagiscono fisiologicamente al trauma

GRAZIE PER L’ATTENZIONE