Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 181–188

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses

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ARTICLE INFO

Article history:
Received 14 March 2013
Received in revised form 3 July 2013
Accepted 10 July 2013
Available online 19 July 2013

Keywords:
BDNF val66met
Cognition
Early trauma
Gene × environmental interaction
Psychoses
sMRI

ABSTRACT

Objective: Brain derived neurotrophic factor (BDNF) is important for brain development and plasticity, and here we tested if the functional *BDNF val66met* variant modulates the association between high levels of childhood abuse, cognitive function, and brain abnormalities in psychoses.
Method: 249 patients with a broad DSM-IV schizophrenia spectrum disorder or bipolar disorder were consecutively recruited to the TOP research study (mean ± age: 30.7 ± 10.9; gender: 49% males). History of childhood trauma was obtained using the Childhood Trauma Questionnaire. Cognitive function was assessed through a standardized neuropsychological test battery. *BDNF val66met* was genotyped using standardized procedures. A sub-sample of n = 106 Caucasians with a broad DSM-IV schizophrenia spectrum disorder or bipolar disorder (mean ± age: 32.67 ± 10.85; 49% males) had data on sMRI.
Results: Carriers of the *Methionine (met)* allele exposed to high level of childhood abuse demonstrated significantly poorer cognitive functioning compared to homozygotic *Valine (val/val)* carriers. Taking in consideration multiple testing, using a more conservative p value, this was still shown for physical abuse and emotional abuse, as well as a trend level for sexual abuse. Further, *met* carriers exposed to high level of childhood sexual abuse showed reduced right hippocampal volume ($r^2 = 0.43$; $p = 0.008$), and larger right and left lateral ventricles ($r^2 = 0.37$; $p = 0.002$, and $r^2 = 0.27$; $p = 0.009$, respectively). Our findings were independent of age, gender, diagnosis and intracranial volume.
Conclusion: Our data demonstrate that in patients with psychoses, *met* carriers of the *BDNF val66met* with high level of childhood abuse have more cognitive and brain abnormalities than all other groups.

1. Introduction

Cognitive dysfunction is a core abnormality in schizophrenia spectrum disorder (Flashman and Green, 2004). The majority of patients with schizophrenia function at a level of at least one standard deviation below healthy comparison groups, even at the time of their first-episode (Aas et al., 2010; Faerden et al., 2009; Rund et al., 2004; Zanelli et al., 2010), and the dysfunction seems to endure after successful treatment of psychotic symptoms (Rund et al., 2007; van Os and Kapur, 2010). In addition to global cognitive deficits, specific cognitive domains including episodic memory, working memory, and executive function are particularly affected (Flashman and Green, 2004). There are also patients with schizophrenia with cognitive scores in the normal or above-normal range, varying in different studies from 15% to 45% (Allen et al., 2003; Goldstein, 1990; Heinrichs and Awad, 1993; Reichenberg et al., 2009). Nevertheless, in the high cognitive function subgroup,

Abbreviations: BDNF, Brain derived neurotrophic factor; Bipolar NOS, Bipolar Not Otherwise Specified; CTQ, Childhood Trauma Questionnaire; DNA, Deoxyribonucleic acid; D-KEFS, Delis–Kaplan Executive Function Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EA, emotional abuse; EN, emotional neglect; GR, glucocorticoid receptor; IQ, intelligence quotient; met, methionine; PA, physical abuse; PANSS, Positive and Negative Syndrome Scale; PASW, Predictive Analytic software; PN, physical neglect; proBDNF, Precursor of brain-derived neurotrophic factor; Psychosis NOS, Psychosis Not Otherwise specified; RNA, Ribonucleic acid; SA, sexual abuse; SCID, Structured Clinical Interview for DSM Disorders; sMRI, structural magnetic resonance imaging; SNP, single-nucleotide polymorphism; TOP study, Thematically Organized Psychosis research study; val, valine; WASI, Wechsler Abbreviated Scale of Intelligence.

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http://dx.doi.org/10.1016/j.pnpbp.2013.07.008

64% still have abnormal scores on at least one cognitive domain, compared to 35% of healthy controls (Allen et al., 2003). Parallel, but less severe cognitive dysfunctions, specifically in memory, executive function/working memory and processing speed, are also observed in affective psychoses and bipolar disorder (Simon et al., 2007; Simonsen et al., 2011; Zanelli et al., 2010). It is also widely accepted that patients with schizophrenia and bipolar disorder show brain structural abnormalities compared to healthy controls, in the direction of smaller whole brain and hippocampus volumes, and larger ventricles (Shenton et al., 2001, 2010; Shepherd et al., 2012; Steen et al., 2006). The most profound abnormalities when comparing patients with psychosis to controls are enlargement of the ventricles, with reports of up to 30% larger ventricles in patients with schizophrenia (Hulshoff Pol et al., 2002). Also bipolar disorder is characterized by whole brain and prefrontal lobe volume reductions, and by increases in lateral ventricles, however to a lesser degree than observed in schizophrenia (Arnone et al., 2009). The knowledge is still sparse about possible mechanisms behind these cognitive and brain abnormalities; here we hypothesize that early stress exposure combined with genetic factors of variations of the *BDNF val66met* gene may play a role behind at least some of these abnormalities.

On the cellular level, both acute—and chronic high levels of stress exposure are linked to atrophy of dendrites and suppression of neurogenesis (Sapolsky et al., 1986; Wolf, 2003), possibly mediated by stress-based reductions in neurotrophic factors, including the Brain Derived Neurotropic Factor (BDNF) (Calabrese et al., 2009). This may explain some of the volumetric changes seen in the cerebral cortex and the limbic system in persons exposed to trauma. Here, particularly chronic stress in early life have more severe effect on brain development and plasticity compared to short-term stress and to chronic stress later in life (De Bellis et al., 1999; Teicher et al., 2012). The neurobiological explanation could be stress-induced programming of the glucocorticoid, and the noradrenergic system, which again may produce effects on neurogenesis, synaptic overproduction and pruning, and myelination during specific sensitive periods (Teicher, 2002). Perinatal, postnatal and early childhood are believed to be periods of specific interest for long-term consequences of stress (Andersen et al., 2008; Heim et al., 2008). Studies have shown that childhood abuse has a long-lasting effect on the HPA axis, and BDNF levels compared to adult recent stressful events (Heim et al., 2000, 2008; Jensen et al., 2012).

Brain derived neurotrophic factor is important for growth and differentiation of neurons during brain development, as well as synaptic plasticity and maintenance of neurons in adult life (Lewin and Barde, 1996). The *BDNF* gene has at least one functional variant, the SNP (rs 6265), resulting in a *Valine to Methionine* substitution at codon 66 of the proBDNF, with the low active *Methionine (met)* variant being related to reduced BDNF release (Egan et al., 2003). The *BDNF val66met* functional polymorphism and its effect on neural plasticity and hence neuronal fate could lead to global changes in brain structure, specifically in patients with early trauma experiences. Indeed recent review articles show reduced hippocampal volume in *met* carriers (here without taking into account childhood trauma), though with small effect sizes (Hajek et al., 2012). Patients with psychosis show reduced BDNF levels in the brain (Durany et al., 2001), serum and plasma (Buckley et al., 2007; Durany et al., 2001; Ikeda et al., 2008). They also report increased incidences of childhood trauma compared to the general population (Aas et al., 2011; Fisher et al., 2011; Mondelli et al., 2010; Read et al., 2005). Interestingly, childhood trauma has further been linked to reduction of BDNF levels in both first-episode psychosis and bipolar disorders (Kauer-Sant'Anna et al., 2007; Mondelli et al., 2011), as well as reduced of hippocampal volume (Mondelli et al., 2011). In animals, stressful upbringing with low maternal care is associated with reduction of BDNF hippocampal RNA levels in pups, especially when low maternal care is expressed in the pups puberty phase (Jensen et al., 2012), again supporting the role of childhood trauma and changes in BDNF levels. As suggested by Mondelli et al. (2011), childhood trauma may represent a significant factor influencing brain structure and function in psychosis, through an effect on BDNF. Thus, it may be that carriers of the low active *met allele* of the *BDNF val66met* are more vulnerable to this effect due to a genetically lower secretion of BDNF compared to the high active *val* carriers. So far only one study by Savitz et al. (2007) comprised of both individuals with bipolar disorder and their relatives (n = 225), has investigated the relationship between *BDNF val66met*, childhood trauma and cognition in severe mental disorders. They found that *met* carriers (both patients and relatives) who had been exposed to childhood trauma performed worse on a memory task compared to *val/val* carriers. There are to our knowledge, no studies in the literature investigating this relationship in patients with a schizophrenia spectrum diagnosis, and no studies investigating associations between childhood abuse, *BDNF val66met* and brain structures.

Although several papers have compared brain volumes and BDNF val66met—*val/val* carriers and *met*-carriers (Hajek et al., 2012), our study is the first to investigate associations to childhood trauma. The brain structures investigated (hippocampus and ventricles) were chosen based on previous studies linking these structures to psychosis, *BDNF val66met*, childhood abuse, and chronic stress exposure (Arnone et al., 2009; De Bellis et al., 1999; Hajek et al., 2012; Steen et al., 2006; Teicher et al., 2012). Our overall aim is to investigate if *BDNF val66met* moderates the association between childhood abuse and cognitive and brain abnormalities in psychoses. Our hypotheses are: 1) *BDNF val66met* will moderate the relationship between high levels of childhood abuse and cognitive performance (specifically working memory/executive function, and memory), in the direction of *met* carriers with high level of abuse showing the lowest performance, compared to all other groups; 2) *BDNF val66met* will moderate associations between high levels of childhood abuse and brain abnormalities in psychoses, in the direction of *met* carriers with high level of childhood abuse showing significant smaller hippocampal volume and larger ventricles, than all other groups.

2. Methods

2.1. Subjects

2.1.1. Whole sample

The participants were recruited consecutively from psychiatric units (outpatient and inpatient) in four major hospitals in Oslo, as part of the larger Thematically Organized Psychosis (TOP) Research study. All patients included in this study were Caucasians. For the present study, 249 DSM-IV-diagnosed patients were recruited between 2007 and 2012: 99 had a diagnosis of schizophrenia spectrum disorders (82 schizophrenia or schizophreniform disorder, 17 schizoaffective disorder); 106 had a diagnosis of bipolar disorders (81 bipolar I disorder, 17 bipolar II disorder, 8 bipolar NOS, 8 major depressive disorder with mood incongruent psychotic features) and 36 were classified as other psychoses (delusional disorder, brief psychotic disorder or psychosis NOS).

In addition, 476 persons without severe mental disorders or ongoing illicit drug abuse were recruited from the same geographical areas to serve as healthy controls for the cognitive test battery (Controls' age mean ± SD: 34.79 ± 10.25; years of education mean ± SD:14.09 ± 2.20). Exclusion criteria for all groups were: unstable or uncontrolled medical condition that interferes with brain function, and age outside the range of 18–65 years. The study was approved by the Regional Committee for Medical Research Ethics, and the Norwegian Data Inspectorate. All participants gave written informed consent.

2.1.2. Subsample (MRI)

The participants were recruited consecutively from psychiatric units (outpatient and inpatient) in four major hospitals in Oslo, as part of the larger Thematically Organized Psychosis (TOP) Research study. All patients included in this study were Caucasians. For the present study, 106 DSM-IV-diagnosed patients were recruited between 2007 and 2012: 48 schizophrenia spectrum disorder [26 schizophrenia; 4