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Serum brain-derived neurotrophic factor and cortical thickness are differently related in patients with schizophrenia and controls

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) has been implicated in neuronal plasticity, a key process related to the pathophysiology of schizophrenia. However, the relationship of peripheral levels of BDNF to cortical thickness and subcortical structures has not been extensively investigated. This study aims to investigate the relationship of peripheral serum BDNF levels to cortical thickness and volumes of the hippocampus and amygdala. Twenty-nine patients with schizophrenia and 32 healthy controls were included in this study. Structural magnetic resonance imaging (MRI) scans obtained in a 1.5 T scanner were performed in all subjects. Images were processed using Freesurfer software. Blood samples were collected on the same day of the MRI scan for BDNF peripheral levels. Vertex-wise analysis revealed significantly thinner cortex in patients compared with controls. BDNF levels and cortical thickness showed different patterns of correlation for patients and healthy controls in one cluster in the right hemisphere distributed across the supramarginal, postcentral, and inferior frontal cortices.

1. Introduction

Brain-derived neurotrophic factor (BDNF) that has been implicated in neurogenesis, neuron survival, and synaptic plasticity (Vicario-Abejon et al., 2002; Nieto et al., 2013). BDNF is thought to be involved in the pathophysiology of mood disorders, anxiety disorders and psychosis (Kapczinski et al., 2008).

Studies investigating BDNF levels in schizophrenia have found conflicting results (Pedrini et al., 2011; Favalli et al., 2012; Asevedo et al., 2013; Nieto et al., 2013). A meta-analysis by Green et al. (2011) concluded that BDNF levels, despite the somewhat heterogeneous results, tend to be decreased in comparison with levels in healthy individuals. Recently, further studies have indicated a positive association between BDNF levels and clinical features of schizophrenia, such as the severity of negative symptoms (Niitsu et al., 2014).

In schizophrenia findings of decreased cortical thickness and volume relative to controls have been consistently reported. Although there are reductions in volume across many regions of the brain, volumetric reductions in specific cortical and subcortical regions tend to be more prominent (Woods et al., 2005; Haijma et al., 2013;). The actions of neurotrophins have been linked to activity-dependent synaptic plasticity with long-term modulation of synaptic connections (Poo, 2001), suggesting that imbalances of neurotrophin levels or in their molecular actions could be related to structural changes seen in schizophrenia. Nevertheless, in a post-mortem study, Durany et al. (2001) found a significant increase in BDNF concentrations in frontal, parietal, temporal and occipital cortical areas and a decrease in the hippocampus of patients with schizophrenia compared with controls. Another study found that BDNF levels were elevated in the anterior cingulate cortex and hippocampus (Takahashi et al., 2000).

BDNF gene single polymorphisms in the Val66Met have been associated with a heightened risk of developing schizophrenia (Muglia et al., 2003; Neves-Pereira et al., 2005) and with the response to antipsychotics (Zai et al., 2012). Moreover, hippocampal function appears to be affected differently by this polymorphism in patients and controls (Eisenberg et al., 2013). The BDNF

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polymorphism has also been related to cortical surface area in healthy subjects (Wang et al., 2014), as well as in neuropsychiatric conditions (Lotfipour et al., 2009; Lyoo et al., 2011; Voineskos et al., 2011). The relationship between brain structure and peripheral levels of BDNF has not been extensively studied. A study with first episode patients correlated changes in levels of peripheral BDNF to abnormalities in left hippocampal volume after 6 months of treatment with antipsychotics (Rizos et al., 2014). However, little evidence has been reported of the association of peripheral BDNF and cortical thickness, and how the effect of BDNF on cortical thickness may potentially differ in health and disease.

The aim of this study is to investigate the relationship between BDNF levels and cerebral cortical thickness in schizophrenia, using an exploratory vertex-wise approach. This approach allows for whole brain analyzes that are not restricted to *a priori* defined regions of interest (ROIs). We hypothesized that this relationship would be altered in cortical regions that have frequently been implicated in schizophrenia, that is, the dorsolateral, inferior, and orbital parts of the prefrontal cortex, and the anterior cingulate cortex. In addition these cortical regions, volumes of subcortical structures (the hippocampus and amygdala) that have previously been associated with schizophrenia and BDNF were investigated.

We first tested the hypothesis that BDNF levels would differ in patients with schizophrenia and controls. We then tested the hypothesis that cortical thickness would be smaller in patients than in controls. Finally, we tested the hypothesis that the relationship between BDNF levels and cortical thickness in these regions would be altered in schizophrenia. We used a similar approach to investigate the relationship between the volumes of the amygdala and the hippocampus with BDNF levels, using linear regression to verify if the volume of these subcortical structures had a different relation to BDNF in individuals with schizophrenia versus controls.

2. Methods

The study protocol was approved by Ethical Committee of the Federal University of São Paulo (ethical committee number 1737/06), and all subjects provided written informed consent before their enrollment in this study.

2.1. Studied population

The diagnosis of schizophrenia diagnosis was established based on clinical interviews and confirmed using the Structured Clinical interview for DSM-IV (SCID-I) (Del-Ben et al., 2001). Patients were also assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993; Bressan et al., 1998), the Clinical Global Impression (CGI) and the Global Assessment of Functioning (Haro et al., 2003; Lima et al., 2007). Antipsychotic dose was converted to chlorpromazine equivalents using previously published guidelines for both first generation antipsychotics (American Psychiatric Association, 1997) and second generation antipsychotics (Woods, 2003). For depot haloperidol, fluphenazine, paliperidone, and risperidone, we used the manufacturers' recommended equivalent for the depot to oral conversion for the same drug and then converted those values to oral chlorpromazine equivalents.

For the comparison group, we selected volunteers from the community with no current or lifetime psychiatric diagnosis according to DSM-IV, as well no first degree relative with a history of psychiatric disorders. All interviews were conducted by expert psychiatrists using the SCID-I. Exclusion criteria for both groups included history of severe head trauma or neurological illness; drug and alcohol dependence or abuse; acute and chronic general medical conditions associated with imbalances in inflammatory response such as infections, HIV, allergies, rheumatologic, or immunological conditions; and immunomodulatory treatments. All subjects were required to undergo magnetic resonance imaging (MRI) and provide blood samples for inclusion in this study. One subject initially enrolled in the schizophrenia group was excluded due to low quality of MR images (see Section 2.3).

The patient group comprised 29 subjects with schizophrenia according DSM-IV-TR (American Psychiatric Association, 2000), and the comparison group consisted of 32 healthy volunteers. All patients had been treated with atypical antipsychotics at stable doses for at least 6 weeks preceding their inclusion in the study. The patients represent a subset of a previously described sample (Noto et al., 2011; Asevedo et al., 2013; Zugman et al., 2013), selected because they had both peripheral BDNF values and MRI scans available.

2.2. Blood sample collection and BDNF analysis

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The samples were centrifuged at 2000*g* during 10 min and serum was kept frozen at −80 °C until assayed. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Milipore, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h at 4 °C with the samples diluted 1:75 in sample diluents and the standard curve ranged from 7.8 to 500 pg/ml of BDNF. Plates were then washed four times with wash buffer, biotinylated mouse anti-human BNDF monoclonal antibody (diluted 1:1000 with sample diluents) was added, and plates were incubated for 3 h at room temperature. After washing, a second incubation with streptavidin–horseradish peroxidase conjugate solution (diluted 1:1000) for 1 h at room temperature was carried out. After addition of substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration.

2.3. MRI acquisition and data processing

Images were acquired in a Siemens 1.5 T scanner using a 3DSPGR sequence for volumetric analysis (T1, sagittal, echo time = 3.4 ms; repetition time = 2000 ms; field of view = 256 mm; matrix size = 256 × 256; flip angle = 15°; slice thickness = 1 mm). Cortical reconstruction and volumetric segmentation were performed with the Freesurfer 5.1 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/).

Freesurfer processing includes the removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002, 2004), intensity normalization (Sled et al., 1998), tessellation of the gray matter-white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 1999b). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl et al., 1999a), registration to a spherical atlas which uses individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999b), and