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Serum brain-derived neurotrophic factor and cognitive functioning in underweight, weight-recovered and partially weight-recovered females with anorexia nervosa

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ABSTRACT

Several studies support the assumption that the brain-derived neurotrophic factor (BDNF) plays an important role in the pathophysiology of eating disorders. In the present cross-sectional and longitudinal study, we investigated BDNF levels in patients with anorexia nervosa (AN) at different stages of their illness and the association with cognitive functioning.

We measured serum BDNF in 72 acutely underweight female AN patients (acAN), 23 female AN patients who successfully recovered from their illness (recAN), and 52 healthy control women (HCW). Longitudinally, 30 acAN patients were reassessed after short-term weight gain. The association between BDNF levels and psychomotor speed was investigated using the Trail Making Test.

BDNF serum concentrations were significantly higher in recAN participants if compared to acAN patients and increased with short-term weight gain. In acAN patients, but not HCW, BDNF levels were inversely associated with psychomotor speed. AcAN patients with higher BDNF levels also had lower life time body mass indexes. Taken together, our results indicate that serum BDNF levels in patients with AN vary with the stage of illness. Based on the pleiotropic functions of BDNF, changing levels of this neurotrophin may have different context-dependent effects, one of which may be the modulation of cognitive functioning in acutely underweight patients.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a protein that promotes the growth, differentiation and survival of neurons and synapses of the central and peripheral nervous system (Huang and Reichardt, 2001; Xiao et al., 2010). BDNF is expressed in brain regions responsible for higher cognitive and executive functions, such as the hippocampus, and it plays a crucial role in activity-dependent forms of synaptic plasticity (Waterhouse and Xu, 2009; Yamada and Nabeshima, 2003). Previous animal studies have highlighted the importance of BDNF for hippocampal long term potentiation, a phenomenon underlying synaptic plasticity (Cunha et al., 2010). In line with that, hippocampal LTP and hippocampus-dependent learning is drastically reduced in BDNF mutant mice (Cunha et al., 2010; Tyler et al., 2002). Exogenous BDNF administration or restoring BDNF by adenoviral mediated re-expression can transiently reverse both, the neurophysiological and learning deficits (Korte et al., 1996; Patterson et al., 1996).

Several studies found evidence supporting an association between BDNF levels and neurocognitive functions in humans. Chung et al. (2012) could show improvements in cognitive performance and increased plasma BDNF levels in healthy high school students when treated with a mixed-grain diet. Further, a study in patients with bipolar disorder demonstrated a positive relationship between verbal fluency and serum BDNF levels (Dias et al., 2009), and BDNF levels in schizophrenia patients were shown to increase under neuroplasticity-based cognitive training (Vinogradov et al., 2009). However, negative findings have been published as well, e.g. plasma BDNF was not associated with cognitive function or rates of age-related change in performance across several cognitive domains in older, non-demented adults (Driscoll et al., 2012), and there were no correlations between plasma BDNF and executive functioning in patients with bipolar disorder (Barbosa et al., 2012).

In addition to the aforementioned cognitive functions, BDNF is also a determinant of food intake and weight regulation. Animal experiments have demonstrated obesity phenotypes in BDNF heterozygous mice

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with one functional BDNF allele, and in mice in which the BDNF gene has been deleted in excitatory neurons of the brain (Kernie et al., 2000; Rios et al., 2001). These mutants also show hyperactivity, hyperleptinaemia, hyperinsulinaemia, hyperglycaemia, and increased linear growth (Chourbaji et al., 2004; Kernie et al., 2000; Lyons et al., 1999; Rios et al., 2001). Conversely, exogenous BDNF treatment transiently reverses these abnormalities (Kernie et al., 2000). Moreover, it could be demonstrated that food deprivation leads to significant changes of brain BDNF expression in mice. While food deprivation in C57BL/6 mice is associated with increased BDNF expression in the hippocampus, in food-deprived mice of the A/J strain (a strain which is highly vulnerable to the mouse model "activity-based anorexia") BDNF expression is reduced (Gelegen et al., 2008). Most ex vivo studies demonstrated decreased serum BDNF levels in acutely underweight patients with anorexia nervosa (AN) or bulimia nervosa (BN) (Monteleone et al., 2004, 2005; Nakazato et al., 2003, 2006). However, our previous work provides some evidence suggesting increased BDNF levels in AN patients who are weight-recovered (recAN) (Ehrlich et al., 2009). Additional data from recAN patients as well as longitudinal data are needed to verify these findings.

Numerous neuropsychological studies in patients with acute AN (acAN) have demonstrated severe deficits in cognitive functioning, in particular in the areas of verbal learning, visuo-spatial thinking, psychomotor speed, and attention (Duchesne et al., 2004). These changes may be related to the well documented cortical atrophy and decreased grey and white matter volumes in these patients (Kerem and Katzman, 2003; Mainz et al., 2012; Ohrmann et al., 2004). Longitudinal studies of cognitive and executive functioning in AN provide evidence for substantial improvements in several domains (i.e. overall intelligence, attention, working memory, verbal fluency, number processing, sensory-motor speed) after weight gain (Hatch et al., 2010; Neumärker et al., 2000). Although some deficits may persist for many years (Gillberg et al., 2010), the majority of reports suggest that both, brain atrophy and the cognitive impairments are at least partially reversible with weight recovery (Kerem and Katzman, 2003).

The BDNF Val66Met polymorphism has been associated with changes in cognitive functioning in humans. More specifically, the BDNF Met66 allele, which results in reduced secretion of BDNF, has been associated with impaired short-term episodic memory (Egan et al., 2003; Kambeitz et al., 2012) and lower performance on the Wisconsin Card Sorting Test as well as the Trail Making Test (Brooks et al., 2014; Rybakowski et al., 2006). In a large cohort of elderly participants, BDNF Met66 carriers were characterized by lower fluid intelligence and processing speed (Miyajima et al., 2008). Although the cognitive effects of BDNF Val66Met seem to be well established (Kambeitz et al., 2012), effects on regional brain volumes are still a matter of debate (Molendijk et al., 2012a).

Given the aforementioned findings we pursue two main goals in the present study. First, we aim to verify our previous results regarding increased BDNF levels after weight-recovery. Therefore, we study an enlarged cross-sectional and a substantial longitudinal sample. Second, regarding the cognitive functions of BDNF, we seek to answer the question whether altered BDNF levels in underweight AN patients may explain deficits in psychomotor speed.

2. Methods

2.1. Study population

The study population consisted of female patients with acAN, recAN, and healthy control women (HCW). We recruited 72 participants with acAN according to DSM-IV criteria within 1 week after admittance to eating disorder programs of two university child and adolescent psychiatry and psychosomatic medicine departments (Berlin = Site A, and Dresden = Site B). The acAN group consisted of 55 participants from Site A and 17 participants from Site B. During the study period, all acAN patients were enrolled in a behaviourally oriented, nutritional rehabilitation program and were encouraged to gain a minimum of 500 g of body weight weekly. Following a weight gain of 10% or more, we reassessed the patients. We refer to them as patients with "short-term/partially weight-restored AN."

We also included 23 participants who had been previously treated for AN, and who had successfully recovered from their illness (recAN; recruited from Site A). To be considered "recovered", participants had to (1) maintain a body mass index (BMI) greater than 18.5 kg/m^2 (patients older than 18 years) or less than the tenth BMI percentile (patients younger than 18 years) (Kromeyer-Hauschild et al., 2001) for at least 3 months before the study, (2) menstruate, and (3) refrain from binging, purging or engaging in substantially restrictive eating patterns.

The control group consisted of 52 normal-weight, eumenorrhoeic HCW who we recruited (all from Site A) through advertisement among middle school, high school and university students.

We obtained information on possible confounding variables using the Structured Interview of Anorexia Nervosa and Bulimic Syndromes [SIAB-EX] (Fichter and Quadflieg, 1999) and by physical examination. We derived information on comorbid psychiatric diagnoses other than eating disorders from medical records. We excluded controls if they had any history of psychiatric illness. We excluded patients if they had a lifetime history of any of the following clinical diagnoses: organic brain syndrome, schizophrenia, substance dependence, bipolar disorder, bulimia nervosa or binge eating disorder. Further exclusion criteria for all participants were IQ lower than 85, current inflammatory, neurologic or metabolic illness, chronic bowel diseases, cancer, anaemia, pregnancy, breast feeding, current use of acetylsalicylic acid, cortisone, antibiotics or antihypertensive medication, and use of antidepressants, antipsychotics or any other psychotropic medications or substances within the 6 weeks preceding the study.

The local Institutional Review Boards of the Charité Berlin-Universitätsmedizin Berlin and the Faculty of Medicine, Technische Universität Dresden approved our study, and all participants, or their guardians if the participants were underage, provided written informed consent.

2.2. Blood collection and biochemical assessments

Within the first days of treatment initiation, venous blood samples of 9 ml were collected into vacutainer tubes between 7:30 and 9:30 a.m. after the participants had fasted overnight. After centrifugation of the blood (800 g for 15 min) serum samples were frozen and stored at −80 °C until analyzed.

We measured endogenous levels of BDNF in the thawed serum samples using commercial Enzyme-Linked Immunosorbent Assay kits (ELISA; Promega Inc., Madison, WI, USA) according to the manufacturer's instructions but adapted to the fluorometric technique as described in detail previously (Deuschle et al., 2013). We measured the BDNF content as equivalents of recombinant human BDNF. The detection limit of the assay was 1 pg/ml.

Previous studies have shown that long term storage of serum is associated with significantly lower BDNF concentrations (Bus et al., 2011; Trajkovska et al., 2007). Since the average storage time of the frozen serum samples in our study varied between a few weeks and more than 3 years we adjusted for these effects statistically (see point 2.6 below).

2.3. Assessment of BMI

In order to take account of the height and weight changes during adolescence it is important to determine age-adapted BMI scores (Hebebrand et al., 2004). Therefore, we estimated BMI standard deviation scores (BMI-SDS) for all participants (Kromeyer-Hauschild et al., 2001).

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