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Could BDNF be involved in compensatory mechanisms to maintain cognitive performance despite acute sleep deprivation? An exploratory study

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ABSTRACT

Background: Neuroimaging studies suggest that acute sleep deprivation can lead to adaptations, such as compensatory recruitment of cerebral structures, to maintain cognitive performance despite sleep loss. However, the understanding of the neurochemical alterations related to these adaptations remains incomplete.
Objective: Investigate BDNF levels, cognitive performance and their relations in healthy subjects after acute sleep deprivation.
Methods: Nineteen sleep deprived (22.11 ± 3.21 years) and twenty control (25.10 ± 4.42 years) subjects completed depression, anxiety and sleep quality questionnaires. Sleep deprived group spent a full night awake performing different playful activities to keep themselves from sleeping. Attention, response inhibition capacity and working memory (prefrontal cortex-dependent) were assessed with Stroop and Digit Span tests. Declarative memory (hippocampus-dependent) was assessed with Logical Memory test. Serum BDNF was measured by sandwich ELISA. Data were analyzed with independent samples T-test, ANOVA, ANCOVA and curve estimation regressions. $p < 0.05$ was deemed statistically significant.
Results: The sleep deprived group showed higher BDNF levels and normal performance on attention, response inhibition capacity and working memory. However, declarative memory was impaired. A sigmoidal relation between BDNF and Stroop Test scores was found.
Conclusions: Increased BDNF could be related, at least in part, to the maintenance of normal prefrontal cognitive functions after sleep deprivation. This potential relation should be further investigated.

1. Introduction

The socio-economic demands of modern life are one of the major pressures related to sleep loss (Orzeł-Gryglewska, 2010) and the consequences of sleep deprivation on cognition have been examined in both chronic and acute sleep deprivation conditions (Banks and Dinges, 2007; Lo et al., 2012; Philip et al., 2012). The main conclusion of these studies is that sleep loss can impair different cognitive domains, such as executive function (attention, response inhibition capacity and working memory) and declarative memories (Chee et al., 2006; Goerke et al., 2013; Linde and Bergstrom, 1992; Smith, 2001; Tucker et al., 2010). However, there are also indications that the effects of sleep loss on these functions are related with the sleep deprivation length, the type and complexity of the cognitive task evaluated (Harrison and Horne, 2000; Lim and Dinges, 2010). In this respect, different neuroimaging studies suggest that sleep deprivation can lead to adaptive mechanisms, such as compensatory recruitment of cerebral structures, to maintain cognitive performance despite sleep loss (Drummond and Brown, 2001; Drummond et al., 2005). Even so, the understanding of the neurochemical alterations related to these adaptive mechanisms is sparse and incomplete (Tafti and Franken, 2007).

Brain-derived neurotrophic factor (BDNF) is a neurogenesis, synaptic plasticity and cell survival promoter and has a pivotal role in neuroprotection and cognition (Lu et al., 2014; Wang et al., 2012). It is normally assumed, based on animal (Klein et al., 2011; Calabrese et al., 2013) and human (Carlino et al., 2011; Rasmussen et al., 2009) studies, that peripheral and central BDNF levels are correlated. Until

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now, a significant number of studies also showed that serum BDNF levels are positively correlated with cognitive performance in healthy subjects (Gunstad et al., 2008; Komulainen et al., 2008; Zhen et al., 2013), although some controversies exist on this issue (Driscoll et al., 2012; Tsai et al., 2014).

Animal studies suggest that genes coding for BDNF are wakefulness related, that is, they are selectively expressed in the awake state (Cirelli et al., 2006; Faraguna et al., 2008). Moreover, some studies suggest that BDNF could be a sleep regulatory substance, since activity-dependent increments in its expression during the awake state were related with an increase in slow-wave activity (one of the best characterized markers of sleep need available) during the subsequent sleep period (Faraguna et al., 2008; Martinowich et al., 2011).

Despite the evidences discussed above, until now there are no studies directly investigating the effects of sleep deprivation on BDNF levels in humans, nor its relation with the cognitive performance of healthy subjects submitted to such an intervention. The only existing knowledge about the interactions between sleep disturbances, BDNF levels and cognition come from studies of chronic sleep disorders (sucha as insomnia, dyssomnia, narcolepsy and obstructive sleep apnea/hypopnea syndrome), in which patients show cognitive impairments and decreased BDNF levels (Giese et al., 2013; Klein et al., 2013; Wang et al., 2012). However, beside sleep disturbances, chronic sleep disorders are related to a number of structural, metabolic and neurochemical brain dysfunctions (Goel et al., 2009; McCoy and Strecker, 2011). Thus, these pathologies are not adequate models to investigate the adaptative mechanism recruited to face the challenges imposed by sleep deprivation. In order to investigate this issue, we analyzed the effects of acute sleep deprivation on cognitive performance and serum BDNF levels of young healthy adults. Our hypothesis were that sleep deprived subjects would have (I) higher BDNF levels and (II) similar or impaired cognitive performance (depending on the evaluated task) in relation to non-sleep deprived subjects. Moreover, we expected to find a significant relation between BDNF levels and cognitive performance.

2. Material and methods

Young adults (18 to 34 years, n = 39, 29 women), recruited from the University's undergraduate and graduate programs, were randomly divided into two groups, sleep deprived (SD) and control. All subjects were fully aware of the experimental procedures and provided written consent. The sleep deprivation protocol was designed to be as similar as possible to sporadic real life situations in which younger subjects willingly abstain to sleep during one night. Thus, SD group spent a full night awake executing playful activities (e.g. movies, music, board and video games, books) to keep themselves from sleeping. Both groups (SD and control) went through the same neuropsychological tests and underwent blood sampling for BDNF analysis.

Exclusion criteria were neurological or major medical disorders and current treatment with cognitive, hypothalamic–pituitary–adrenal axis (HPA) and sleep-modulating medication or use of psychoactive drugs. Depressive and anxiety symptomatology was measured with the Brazilian-version of the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) (Cunha, 2011), and subjects with moderate to severe symptomatology (score > 22) were excluded.

All subjects were asked to refrain from any kind of sleep deprivation for 72 h prior the experiment and to stop any stimulant ingestion (e.g. caffeinated drinks or foods) 18 h before the neuropsychological tests. Adherence to these recommendations was investigated through a questionnaire that evaluated the routine of the subjects in the last seven days before the sleep deprivation (for sleep deprived group) or neuropsychological testing and BDNF sampling (for the control group). Only subjects that correctly followed the instructions were included in the study.

The sleep deprivation was conducted in groups (ranging from four to six subjects per night), in a controlled environment and under the supervision of the research group team. The sleep deprivation protocol lasted all night until 07 AM of the next morning (totaling 24 h of uninterrupted wakefulness), when the application of the neuropsychological tests started. Meanwhile, the control subjects went through the same daily routine they were used to (adherence to this recommendation was also evaluated with the routine questionnaire described above) and performed the tests at the same laboratory.

After the neuropsychological tests, subjects underwent the blood sampling (at 08 AM) and the serum was stored at −80 °C for further analysis. All procedures were approved by the Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul/Brazil.

2.1. Assessment instruments

A socio demographic questionnaire was used to survey volunteers' age, gender, marital status and medical history. The Beck Depression Inventory (BDI-II) (Beck et al., 1996) and the Beck Anxiety Inventory (BAI) (Beck et al., 1988) are self-reported inventories that include 21 subjective items each, with scores ranging from 0 to 3. The items of each inventory are summed in order to obtain the total score, which can range from 0 to 63. BDI evaluates emotional, cognitive and motivational symptoms of depression, whereas BAI measures the frequency of psychological and other anxiety symptoms. Both inventories were adapted to Brazilian population (Cunha, 2011) and have the same cutoff (score > 22) for moderate to severe symptoms. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) adapted for the Brazilian population (Bertolazi et al., 2011) was used to assess the volunteer's sleep quality during the last month. The 19 self-rated questions of this inventory are divided into seven components and comprise general sleep-related topics, from time to go to bed and wake up to sleep medicine used and overall sleep quality in the last month. Each component score ranges from 0 to 3 and the full range score goes from 0 to 21. A PSQI score below 5 indicates a good sleep quality.

2.2. Neuropsychological measurements

Attention and response inhibition capacity performance were analyzed with the Stroop Color–Word test (Selnes, 1991). In this task, the participant receives three sheets, each with 100 different stimuli. At the first sheet (Stroop Word), the subject must read aloud a sequence of words written in black ink. At the second sheet (Stroop Color), the participant must name the ink color in which sequences of neutral letters are presented. At the third sheet (Stroop Color/Word), the name of a color is printed in a different color ink (e.g. word red written in blue). Subjects are asked to name the ink in which the word is printed, inhibiting the normal tendency to read the written word. The two first sheets analyze attention and the third sheet assesses response inhibition capacity. For each sheet, participants are required to read words or name colors as fast and accurate as possible within 45 s. The number of correct responses after subtracting the wrong ones measures the subject's performance.

For working memory assessment we used the Digit Span, a Wechsler Adult Intelligence Scale subtest where the volunteer must retain a growing string of numbers read once, and repeat them in the same (forward) or reverse order (backwards) ((Wechsler, 1997). The test begins with a three-digit string, increasing one digit every two strings. The test finishes after the subject makes two consecutive errors. Each correct sequence equals to one point, and the final score is the sum of both forward and backwards scores. This test is already validated for use in the Brazilian population (Nascimento, 2004).

Immediate and delayed recall of declarative memory was assessed with the Wechsler Logical Memory Test, in which the subject must freely recall two short stories. Each story is read once and the participant is informed that he should retell them immediately and 30 min after listening (Wechsler, 1987). Each story has 25 key elements that the subject must recall to score. Each key element equals one point, and the