BRIEF REPORT
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Serum BDNF levels in patients with gambling disorder are associated with the severity of gambling disorder and Iowa Gambling Task indices

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Background and aims: Gambling disorder (GD) shares many similarities with substance use disorders (SUDs) in clinical, neurobiological, and neurocognitive features, including decision-making. We evaluated the relationships among, GD, decision-making, and brain-derived neurotrophic factor (BDNF), as measured by serum BDNF levels. *Methods:* Twenty-one male patients with GD and 21 healthy sex- and age-matched control subjects were evaluated for associations between serum BDNF levels and the Problem Gambling Severity Index (PGSI), as well as between serum BDNF levels and Iowa Gambling Task (IGT) indices. *Results:* The mean serum BDNF levels were significantly increased in patients with GD compared to healthy controls. A significant correlation between serum BDNF levels and PGSI scores was found when controlling for age, depression, and duration of GD. A significant negative correlation was obtained between serum BDNF levels and IGT improvement scores. *Discussion:* These findings support the hypothesis that serum BDNF levels constitute a dual biomarker for the neuroendocrine changes and the severity of GD in patients. Serum BDNF level may serve as an indicator of poor decision-making performance and learning processes in GD and help to identify the common physiological underpinnings between GD and SUDs.

Keywords: gambling disorder, brain-derived neurotrophic factor (BDNF), Iowa Gambling Task (IGT), behavioral addiction

INTRODUCTION

Gambling disorder (GD), a type of behavioral addiction, is characterized by persistent and recurrent maladaptive gambling behavior leading to significant deleterious legal, financial, and psychosocial consequences (Grant, Kim, & Kuskowski, 2004). GD shares many similar clinical and neurobiological features with substance use disorders (SUDs), such as alterations of the mesolimbic dopamine reward pathway (Potenza, 2008), as well as neurocognitive features, including impaired decision-making.

Poor performance on the Iowa Gambling Task (IGT), designed to assess risky decision-making, has been found consistently among SUDs (Noel, Bechara, Dan, Hanak, & Verbanck, 2007). Similarly, patients with GD have demonstrated high risk-taking performance on the task (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009). Although the biological basis for decision-making is poorly understood, neural systems related to executive function and memory have been implicated (Brand, Recknor, Grabenhorst, & Bechara, 2007).

One protein associated with various cognitive functions such as decision-making and memory is the brain-derived neurotrophic factor (BDNF) (Yamada, Mizuno, & Nabeshima, 2002). BDNF plays an important role in neuronal survival, neurogenesis, and synaptic plasticity. Studies have shown associations between BDNF and changes in behavior and psychopathology in psychiatric disorders such as depression, schizophrenia, and bipolar disorder (Montegia et al., 2007), as well as autism spectrum disorder (Wang et al., 2015). Increases in serum levels of BDNF have been observed in drug addictions (Angelucci et al., 2010), where the involvement of BDNF in the ventral tegmental area-nucleus accumbens (VTA-NAc)-mediated processes has been implicated (Pu, Liu, & Poo, 2006).

In contrast, only a few studies have examined the association between BDNF and GD (Angelucci et al., 2013; Geisel, Banas, Hellweg, & Muller, 2012), and how BDNF levels relate to the severity of GD and the level of impairment in neurocognitive tasks remains unclear. Reduced serum BDNF has been found to relate to poor performance on the IGT (Hori, Yoshimura, Katsuki, Atake, & Nakamura, 2014) and immediate memory (Zhang et al., 2012) in patients with schizophrenia. Associations between low BDNF levels and cognitive impairment have been further

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confirmed in a large elderly population (Shimada et al., 2014).

In this study, we examined the relationships among GD, BDNF, and decision-making performance on the IGT in a sample of GD patients and compared the serum BDNF levels in GD patients with those in healthy control subjects. We then investigated the association of serum BDNF levels with the severity of GD and IGT indices.

METHODS

Participants

Twenty-one male patients who fulfilled the DSM-5 criteria for GD were recruited from the outpatient gambling clinic of the Department of Psychiatry, Gangnam Eulji Hospital, Eulji University, Korea. The diagnoses were determined by a board-certified psychiatrist (SWC) through the examination of past medical records and a semi-structured interview that included questions about the presence of co-occurring disorders. A self-report questionnaire regarding age, weight, height, alcohol-related history, regular medication use, gambling-related history, and clinical variables was also administered. The severity of GD was assessed with the Problem Gambling Severity Index (PGSI), a nine-item self-report assessment measure reported to be useful for both clinical and non-clinical settings (Young & Wohl, 2011). Mood symptoms were assessed using the Beck Depression Inventory (BDI). The exclusion criteria for the patient group were 1) any history of a chronic physical disease, 2) regular use of any medication, and 3) presence of comorbid psychiatric disorders, including alcohol and nicotine dependence. The control group consisted of 21 age- and sex-matched healthy male volunteers who had no current or past psychiatric history or history of medication use.

Measures

Measurement of serum BDNF levels. A total of 10 ml of blood was drawn from each subject into a serum separator tube. Samples were allowed to clot for 30 minutes before centrifugation for 15 min at approximately 1000 g, after which the serum was removed. All samples were stored at −80 °C. The serum BDNF levels were determined using an ELISA protocol according to the manufacturer's instructions (DBD00; R & D Systems, Europe).

IGT. For this computer-administered task, participants were asked to draw from four decks of cards. Each deck consisted of randomly distributed cards with differing amount of gains and penalties, adding up to a pre-set net outcome. Two decks contained cards with low levels of gains (e.g. $50) and penalties (e.g. $40), but their net outcome was favorable (e.g. $100); the other two decks consisted of cards with high gains (e.g. $100) but even higher penalties (e.g. $200), so that their net outcome was unfavorable (e.g. −$250).

All participants were instructed to try to earn as much money as possible by drawing cards one at a time from a deck of their choice. They were informed that some decks were more advantageous than others but were not told the composition of the decks. The entire IGT procedure was completed upon drawing 100 cards.

Three IGT indices were derived with high scores indicating effective strategic thinking: net total score, calculated as the number of draws from advantageous decks minus that from the disadvantageous decks (Barry & Petry, 2008); proportion of advantageous deck selections from the total number of cards; and improvement score, calculated by subtracting the net score of the first block of 20 cards from that of the last block.

Statistical analyses

An analysis of covariance, with age, body-mass index (BMI), and BDI scores entered as covariates, was used to compare serum BDNF levels of the patients and controls. The correlation between serum BDNF levels and the severity of GD based on PGSI scores in the patient group was examined using Pearson partial-correlation analysis, by controlling for age, BDI scores, and the duration of problem gambling. Finally, the association between serum BDNF levels and IGT performance was analyzed using the same method. All data are presented as means ± standard deviations *(SD)*. The significance level was set at $p < 0.05$. All statistical analyses were conducted using SPSS, version 18.1 (Chicago, Illinois, USA).

Ethics

The Ethical Committee of the Eulji University, Korea, approved this study protocol. In accordance with the Declaration of Helsinki, all subjects were advised about the procedures and signed the written informed consent prior to participation.

RESULTS

The demographic data, gambling-related clinical variables, and IGT indices are listed in Table 1. The mean serum BDNF levels were significantly increased in the patients with GD (29051.44 ± 6237.42 pg/ml) compared to healthy controls (19279.67 ± 4375.58 pg/ml, $p < 0.0001$) (Figure 1). We also found a significant correlation between serum BDNF levels and PGSI scores ($r = 0.56$, $p < 0.05$) after controlling for age, BDI scores, and the duration of problem gambling.

Serum BDNF levels were also significantly negatively correlated with the IGT improvement scores ($r = –0.48$, $p < 0.05$), but not with IGT total net scores ($r = –0.163$, n.s.) or advantageous proportion ($r = –0.19$, n.s.).

DISCUSSION

In this study, we found significantly higher serum BDNF levels among patients with GD than in healthy controls, as well as a positive association between the serum BDNF levels and severity of GD. Such findings are in partial agreement with previous studies showing that serum BDNF levels increased in GD (Angelucci et al., 2013;

Table 1. Demographic data, BDI, BDNF, IGT index, and GD related variables

Variable	GD (n = 21) *M (SD)*	Control (n = 21) *M (SD)*	Test statistics	p-value
Age	40.52 (12.35)	39.29 (3.96)	t = 0.438	0.664
BMI	25.17 (3.42)	22.54 (2.43)	t = 2.873	< 0.01
BDI	18.48 (11.78)	4.10 (3.03)	t = 5.420	< 0.0001
BDNF (pg/ml)	29051.44 (6237.42)	19279.67 (4375.58)	t = 5.877	< 0.0001
IGT total net score	9.14 (21.81)			
Advantageous proportion	0.55 (0.11)			
IGT improvement score	2.86 (5.08)			
CPGI-PGSI	20.10 (4.79)			
GD duration (years)	8.14 (5.30)			
No. of gambling methods*			χ^2 = 0.048	0.827
One	10 (47.6%)			
Multiple (two or more)	11 (52.4%)			
GD type*			χ^2 = 2.333	0.127
Action type	14 (66.7%)			
Escape type	7 (33.3%)			
Gambling category[a]*			χ^2 = 2.333	0.127
Strategic	7 (33.3%)			
Analytic	14 (66.7%)			

Note: *Marked variables are categorical variables with *N* (%), therefore Chi-square test was used. GD: gambling disorder; BMI: body mass index (weight / height^2); BDI: Beck Depression Inventory; BDNF: brain-derived neurotrophic factor; IGT total net score: total advantageous deck counts minus total disadvantageous deck counts; Advantageous proportion: advantageous deck counts / total card selection (100 cards); IGT improvement score: block5 IGT net score minus block1 IGT net score; CPGI-PGSI: Canadian Problem Gambling Index-Problem Gambling Severity Index.

[a]Strategic: casino gambling (e.g. Black-Jack); Analytic: sports betting, horse racing, bicycle racing, motor boat racing, stock-trading.

Geisel et al., 2012), although these studies present different results regarding the association between serum BDNF levels and severity of GD. Such discrepancies might be related to external factors that affect serum BDNF levels, including BMI, depression, and other confounding factors (Piccinni et al., 2008). Together with these two previous studies (Angelucci et al., 2013; Geisel et al., 2012), our findings suggest that behavioral addictions might be associated with neural plasticity similar to alterations observed in SUDs. Increased serum BDNF levels might then represent a compensatory mechanism to normalize dopaminergic transmission in VTA and the NAc (Geisel et al., 2012). Another plausible explanation is that increased BDNF plays a role in neuroprotective and stress-preventive processes in patients with GD, especially during stressful situations, as found in those with SUDs (Bhang, Choi, & Ahn, 2010; Geisel et al., 2012).

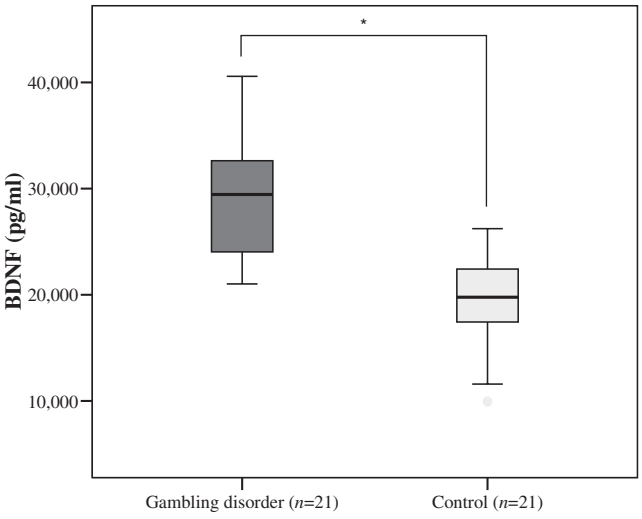

Figure 1. The mean serum BDNF levels were significantly increased in the patients with gambling disorder (29051.44 ± 6237.42 pg/ml) compared to healthy controls (19279.67 ± 4375.58 pg/ml, $p < 0.0001$) by ANCOVA with age, BMI, and the scores of BDI as covariates. The box plots show the median and quartiles, and the whisker caps of the box plots show the mean 5th and 95th percentile values.; * Indicates statistical significance ($F = 12.11$, $p \leq 0.001$)

Although a recent study (Kang et al., 2010) showed that the BDNF Val66Met polymorphism may affect decision-making performance as measured by IGT, to the best of our knowledge, our study is the first to demonstrate a significant association between serum BDNF levels and IGT improvement scores. The IGT improvement score particularly reflects learning processes based on the evaluation of choice-outcomes of rewards and penalties leading to long-term gain or loss. This learning involves discounting immediate rewards while formulating an advantageous strategy based on previous cumulative outcomes. A recent study (Kräplin et al., 2014) found that problem gamblers showed higher overall impulsivity compared to healthy controls and higher 'choice impulsivity' compared to a Tourette syndrome group, but similar levels of impulsivity as an alcohol-dependent group. Higher BDNF concentration has also been positively correlated with higher impulsivity in PTSD patients (Martinotti et al., 2015) suggesting that impulsiveness may be associated with greater BDNF expression. Additionally, in murine models, BDNF has been implicated in the actions of serotonergic neurons, particularly in

aggression and impulsivity (Lyons et al., 1999). Both BDNF and serotonin regulate the development and plasticity of neural circuits in mood disorders (Martinowich & Lu, 2008). In humans, BDNF Val66Met polymorphism in schizophrenia patients has been associated with aggressive behavior (Spalletta et al., 2010), while serotonin has been found to play a significant role in learning and memory (Meneses & Liy-Salmeron, 2012). Taken together, our results suggest that BDNF may also play a role in learning processes, and that the relationship between BDNF and serotonin needs to be further examined.

Some limitations of this study warrant discussion; our sample size was modest and contained only male GD patients, thus limiting the generalizability of our results. Serum BDNF levels were examined rather than central nervous system BDNF levels. Although BDNF regulation in peripheral blood is still poorly understood, peripheral concentrations are widely used as a mirror of the same brain parameter (Yamada et al., 2002). Because BDNF is known to cross the blood-brain barrier in both directions, a substantial part of peripheral BDNF might originate from neuronal cells of the central nervous system (Karege, Schwald, & Cisse, 2002). At the present, the relationships among BDNF, severity of disorder, and decision-making in GD patients are not clearly delineated, and future studies should consider these limitations in their designs for a better understanding of such relationships. In addition, we did not take into account personality factors in our study design. Previous studies have suggested relationships between pathological gambling and personality characteristics such as novelty-seeking and self-directness (Jiménez-Murcia et al., 2010; Martinotti et al., 2006), but consensus on the relationship between the BDNF levels and these personality traits has yet to be reached due to inconsistent results (Maclaren, Fugelsang, Harrigan, & Dixon, 2011). The results of our study should be interpreted carefully in light of such a limitation.

CONCLUSIONS

The findings of this study support the hypothesis that serum BDNF levels may serve as a candidate biomarker for neural plasticity and the severity of GD in these patients. Furthermore, heightened serum BDNF levels in GD may indicate poor decision-making performance, a characteristic feature of SUDs. This study, therefore, is a meaningful addition to the growing body of research supporting the common neurobiological underpinnings of SUDs and GD.

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Conflict of interest: The authors declare no conflict of interest.

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