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Influence of BDNF and COMT polymorphisms on emotional decision making

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ABSTRACT

Decision making is an important brain function. Although little is known about the genetic basis of decision making, it has been suggested that it is mediated by the modulation of neurotransmitter systems. We investigated how the BDNF Val66Met and COMT Val158Met polymorphisms affect emotional decision making using the Iowa Gambling Task (IGT). One hundred sixty-eight healthy Korean college students (93 males, 75 females) with a complete dataset were included in the data analysis. The IGT and genotyping for the polymorphisms of BDNF Val66Met and COMT Val158Met were performed. Both Met/Met and Val/Met of the BDNF Val66Met polymorphism were significantly associated with a lower mean score of blocks 3–5 of the IGT and with less improvement from block 1 to block 3–5 than the Val/Val. However, the BDNF was not significantly associated with the score of block 1, and the COMT Val158Met polymorphism produced no significant effect on IGT performance. No interaction effect was observed between the BDNF and the COMT for the IGT. These findings suggest the BDNF Val66Met may affect the emotional decision making performance.

1. Introduction

In most situations, it is not easy to exactly predict the consequences of a decision. The decision making of which we can predict the result is called “decision under risk” (Brand et al., 2006), and the decision making of which we cannot easily predict the result is called “decision under ambiguity” (Bechara and Martin, 2004).

The Iowa Gambling Task (IGT) is widely used to measure a person's ability to make decisions and is thought to simulate a real-world decision making (Bechara et al., 1997) situation. There are suggested to be two phases of the IGT. The earlier blocks of the IGT represent a “decision under ambiguity” phase in which subjects are supposed to make a decision without any explicit knowledge of the contingencies of the task. Implicit information largely affects the decision with a minimal effect on one's executive function. The later blocks of the IGT reflect a “decision under risk” phase in which subjects learn more about the results of their choices but still make decisions under uncertain conditions (Brand et al., 2007).

Although the biological basis for decision making is not well known, it has been suggested to be heavily dependent on neural systems related to executive functions (Brand et al., 2007). The IGT requires emotional processing and its related neural systems such as the orbitofrontal cortex and amygdala. It also requires cognitive processing and its related neural systems affecting memory, the understanding of probabilities and the gain or loss of information from prior trials (Buelow and Suhr, 2009). In addition, neurotransmitter systems, such as the serotonin and dopamine systems, may play a role in decision making processes (Bechara et al., 2001; Rogers et al., 2003). Recently, we reported the interaction effects of the triallelic serotonin transporter-linked polymorphic region (5-HTTLPR) and the dopamine receptor D4 (DRD4) 48-bp variable number of tandem repeat (VNTR) polymorphisms on IGT (Ha et al., 2009).

There are several pieces of evidence suggesting that the brain-derived neurotrophic factor (BDNF) gene is a potential candidate for emotional decision making. First, BDNF has an important effect on the proliferation of neurotransmitter systems, including dopamine and serotonin (Berton et al., 2006; Deltheil et al., 2008). Second, it plays a major role in neuronal survival, neurogenesis, and synaptic plasticity (Lu, 2003) and has been implicated in various higher cognitive processes, including decision making, learning, and memory (Gasic et al., 2009; Yamada et al., 2002). Several genetic studies have suggested that the Met variant of the BDNF Val66Met polymorphism is associated with poor performance on memory and executive function tests (Gong et al., 2009; Rybakowski et al., 2003). Third, the BDNF gene has been reported to be associated

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with various neuropsychiatric conditions such as obsessive–compulsive disorder (Hemmings et al., 2008), eating disorders (Monteleone et al., 2006), and substance dependence (Gratacos et al., 2007), which result in impaired IGT performance (Buelow and Suhr, 2009).

The catechol-O-methyltransferase (COMT) gene, which is involved in the inactivation of dopamine in the synaptic cleft, is another candidate. A polymorphism in the human COMT gene (472G > A) results in a valine (Val) to methionine (Met) amino acid substitution (Val158Met), and reduces the enzyme activity to one-quarter of what is originally encoded by the Val allele (Lachman et al., 1996), and thus has an impact on the dopamine level in the prefrontal cortex. Evidence suggests that the COMT variants affect various cognitive domains such as memory, executive function, and decision making (Sheldrick et al., 2008). Recently, Roussos et al. (2008) reported that the G allele of COMT rs4818 (high COMT activity, low prefrontal dopamine level) was associated with higher performance on the IGT but poorer performance on planning tasks. Van den Bos et al. (2009) reported that subjects with the Met/Met of COMT Val158Met polymorphism chose more disadvantageously than did subjects with Val/Val. They also found an interaction effect between the COMT and 5-HTTLPR genes and that subjects with Met/Met of COMT and short allele/short allele of 5-HTTLPR showed the poorest IGT performance among all genotypic combinations of COMT and 5-HTTLPR.

Based on the findings reported in the literature, we examined the effects of BDNF Val66Met and COMT Val158Met variants on emotional decision making. We determined the influences of BDNF and COMT genes on IGT performance by analyzing 1) the scores of five 20-card blocks and 2) the scores of the decision under ambiguity phase (earlier blocks), the scores of the decision under risk phase (later blocks), and the difference between the two mean scores of the two phases.

2. Materials and methods

2.1. Subjects

One hundred eighty-four healthy Korean college students (100 males, 84 females) were recruited through an advertisement. Most of them (n = 173, 94%) were the same subjects as in our earlier study (Ha et al., 2009), and eleven subjects were newly recruited. Subjects with any current or lifetime Axis I psychiatric disorders according to the Structured Clinical Interview for the DSM-IV (First et al., 1997) or with an immediate family history of mental disorders were excluded. Sixteen participants were excluded because of a family history of psychiatric illness (n = 14) or genotyping failure (n = 1 for BDNF and n = 1 for COMT). The remaining 168 subjects (93 males, 75 females) were included in the analysis. We collected written informed consent from all participants. All subjects were compensated $10 for their participation. The study was approved by the local ethics committee.

2.2. BDNF and COMT genotyping

Genomic DNA was extracted from peripheral blood leukocytes. The genotyping of the functional polymorphisms of BDNF Val66Met (rs6265) and COMT Val158Met (rs4680) was screened using a single-base primer extension assay using the ABI PRISM SNaPShot Multiplex kit (ABI, Foster City, CA, USA). The forward and reverse primer pairs used for the SNaPshot assay were 5′-TGATGACCATCCTTTTCC TT-3′ (forward) and 5′-CACTGGGAGTTCCAATGC-3′ (reverse) for the BDNF and 5′-ATCAACCCCGACTGTGCC-3′ (forward) and 5′-CTTTTTCCAGGTCTGACAACG-3′ (reverse) for the COMT.

2.3. IGT

Subjects completed the computerized version of the IGT (Kim et al., 2006) which is made according to the original design (Bechara et al., 1997). The task ends when the subject has chosen 100 cards, but the subject does not know when the game ends. A virtual reward of $100 was given for selecting a card from either deck A or B, and a $50 reward was given for cards from decks C and D. However, at some points, a form of punishment unpredictably followed the selection of a card in any of the four decks. For every ten cards chosen from deck A or B, subjects earned $1000 but lost $1250 in unpredictable punishments. While for every ten cards chosen from deck C or D, subjects earned $500 but lost $250 in punishments. The IGT net scores were calculated by subtracting the total number of cards selected from decks A and B from the total number selected from decks C and D for each five 20-card block.

2.4. Statistics

Associations between IGT performance and three other potential covariates (gender, age, and education level) were analyzed by t-test or Pearson's correlation test. Repeated measures- and two-way ANOVA with subsequent one-way ANOVA were used to examine the effects of BDNF or COMT polymorphism on IGT performances. In all analyses, significance was held at $p < 0.05$. NS indicates non-significant p value. All tests were two tailed. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. Results

The demographic data and total IGT score are listed in Table 1. There was no effect of gender ($t = 0.26$, NS), age ($r = -0.08$, NS), and education level ($r = -0.01$, NS) for the total IGT score. Therefore, those factors were not controlled in subsequent analyses.

Table 1 also lists the genotype distributions of BDNF and COMT. These distributions were similar to those reported in other Korean populations (Kim et al., 2008a,b). Neither of them deviated from Hardy–Weinberg equilibrium (χ^2 = 1.99, NS and χ^2 = 1.09, NS). Because the frequency of Met/Met of COMT was only 8.9% (n = 15), we grouped the COMT genotypes into two categories of Val/Val (n = 92, 54.8%) and Val/Met + Met/Met (n = 76, 45.2%) to conserve statistical power.

First, we analyzed the effects of BDNF and COMT genotypes on IGT performance per block. In within-subjects analyses, all subjects improved their performance from block 1 to block 5 [$F(4,159) = 6.40$, $p < 0.001$]. The pattern of IGT scores change over block was significantly linear [$F(1,162) = 24.21$, $p < 0.001$], with less quadratic pattern [$F(1,162) = 4.75$, $p < 0.05$].

However, no significant interaction was found between a block and BDNF genotype [$F(8,320) = 1.56$, NS]; block and COMT genotype [$F(4,159) = 0.58$, NS]; and block and BDNF × COMT genotypes [$F(8,320) = 0.37$, NS]. In between-subjects test, we found no main effect of BDNF [$F(1,162) = 1.96$, NS] and COMT [$F(1,162) = 0.003$, NS] and no interaction effect of BDNF and COMT [$F(2,162) = 1.96$, NS] on overall IGT scores.

Then, we analyzed the effects of BDNF and COMT genotype on the mean scores of the decision under ambiguity phase, the mean scores of the decision under risk phase, and the difference between them. In our study, the IGT score of block 1 was not correlated with those of blocks 3, 4, and 5. The IGT scores of blocks 3, 4 and 5 were significantly correlated with each other (all $p < 0.01$). The IGT score of block 2 was significantly correlated with both block 1 and blocks 3–5 (all $p < 0.01$)(Table 2). These suggested that block 1 and blocks

Table 1
Demographic data, BIS-11 scores, IGT scores, and genotype distributions of BDNF and COMT.

Age (years)	23.14±2.25	
Education (years)	15.42±1.03	
Sex (male/female)	93 (55.4%)/75 (44.6%)	
Total IGT score (male/female)	−3.20±27.51/-4.23±22.00	t=0.26, df=166, p = 0.79
Genotype Frequencies		
BDNF	Val/Val 56 (33.4%)	Met/Met 38 (22.6%)
	Val/Met 74 (44.0%)	HWE; X^2=1.99, df=1, p = 0.16
COMT	Val/Val 92 (54.8%)	Met/Met 15 (8.9%)
	Val/Met 61 (36.3%)	HWE; X^2=1.09, df=1, p = 0.30

IGT: Iowa gambling task
BDNF: brain-derived neurotrophic factor
COMT: cathechol-O-methyltransferase
HWE: Hardy-Weinberg equilibrium

Table 2
Correlations between scores on IGT blocks ($n = 168$).

Block	1	2	3	4	5
1	–	0.23*	0.13	0.15	0.12
2		–	0.42*	0.39*	0.30*
3			–	0.35*	0.32*
4				–	0.37*

*$p < 0.01$.

3–5 reflect different phases of IGT and that block 2 is a transition period between them. Therefore, after excluding block 2, we categorized the IGT performance into block 1 (decision under ambiguity phase) and block 3–5 (decision under risk phase). The improvements in IGT score were calculated by subtracting the IGT score of block 1 from the mean IGT score of blocks 3–5. In within-subjects analyses, there was a significant block effect [$F(1,162) = 11.22$, $p = 0.001$], a block and BDNF genotype interaction effect [$F(2,162) = 3.33$, $p < 0.05$], but not a block and COMT genotype interaction [$F(1,162) = 0.14$, NS]. In between-subjects analyses, no main effect of COMT genotype was found [$F(1,162) = 1.96$, NS]. Subsequent one-way ANOVA showed a significant correlation between the BDNF genotype and the mean IGT score of block 3–5 [$F(2,167) = 3.63$, $p < 0.05$]. Post-hoc analyses indicated that the Val/Val genotype had a higher IGT score on block 3–5 than the Val/Met ($p < 0.05$) and the Met/Met genotypes ($p < 0.05$), but there was no difference between the Val/Met and Met/Met ($p =$ NS). In addition, the Val/Val genotype had a higher IGT improvement than Val/Met ($p < 0.05$) and Met/Met ($p < 0.05$) (Table 3, Fig. 1).

4. Discussion

Our results showed the BDNF Val66Met polymorphism affects IGT performance, but no association between the COMT gene and IGT performance was observed. The IGT measures the ability to learn to sacrifice immediate rewards in favor of long-term gains. IGT performance changes from the initial phase, in which a participant has no explicit knowledge of reward/punishments, to the later phase. Our findings revealed that the Met polymorphism of the BDNF (Met/Met or Val/Met) was significantly associated with a lower mean score of blocks 3–5, while it was not associated with block 1. Furthermore, the Met polymorphism of the BDNF was significantly associated with a lack of improvement in IGT score. IGT improvement requires gradual learning through accumulated experience about the choice-outcomes of rewards and punishments. Subjects therefore pass through an initial, potentially adverse, exploration phase and move on to the phase where they can learn about choices with long-term rewards (Brand et al., 2007). Thus, the Met polymorphism of the BDNF may be associated with poor IGT performance through reduced learning ability and impaired reward processing. In order to make advantageous decisions in IGT, subjects must maintain and update a representation of the contingencies associated with multiple decks of card over time. Therefore, the memory function plays a critical role in IGT performance, although it is still controversial whether advantageous decisions require conscious or nonconscious knowledge of previous behavioral choices (Maia and McClelland, 2004).

In particular, the later phase of the IGT may depend more on mechanisms related to explicit memory and executive functions, in contrast with the earlier phase, even if conditions remain uncertain (Brand et al., 2007). Therefore, given the complexity of decision making, the present findings suggest that the Met/Met or Val/Met of BDNF may be involved in reduced decision making ability, particularly with regard to explicit memory and/or executive function.

This finding is interesting because there are several pieces of evidence suggesting an association between BDNF Val66Met polymorphisms and learning/memory-related brain structures such as the hippocampus. Met-BDNF allele has been reported to be associated with reduced hippocampal volume (Bueller et al., 2006), less hippocampal engagement during episodic memory processing (Hariri et al., 2003), and decreased encoding-related brain activity in the bilateral hippocampi (Hashimoto et al., 2008). Since the hippocampus is an essential structure for learning and memory, our results showing an association between the Met allele and poor IGT performance are consistent with previous studies. In addition, it has been suggested that BDNF Val66Met variants are related to the prefrontal cortex, which plays a key role in guessing rules and understanding probabilities (Pezawas et al., 2004). The Met allele of BDNF Val66Met variants has been reported to be associated with poor working memory or executive function (Chen et al., 2008), although there are studies with contradicting results (Beste et al., 2009). Rybakowski et al. (2003) demonstrated that the Met allele of BDNF was associated with poor performance on the Wisconsin Card Sorting Test in bipolar patients. Recently, Gong et al. (2009) found that individuals with the Met allele of BDNF showed poorer performance in digital working memory and spatial localization than Val/Val homozygotes. Considering these findings, the association between Met polymorphism of BDNF and lower IGT score on later blocks in our study might be related to the Met-BDNF variant being associated with poor explicit memory or executive function. However, it is still unclear how the BDNF polymorphism affects neuronal functioning, brain structure and human behavior. Further investigation is warranted to elucidate the biological mechanism of the BDNF polymorphism in brain structures and functions.

As mentioned, it is still controversial whether the learning required by the IGT is implicit, explicit, or both. Therefore, our results might also reflect, at least partially, some influences of the BDNF Val66Met polymorphism on the implicit learning/memory

Table 3
IGT performance according to genotype of the BDNF Val66Met and the COMT Val158Met polymorphisms.

Mean IGT scores	BDNF			COMT	
	Val/Val ($n = 56$)	Val/Met ($n = 74$)	Met/Met ($n = 38$)	Val/Val ($n = 92$)	Met carrier ($n = 76$)
Block 1	−2.46 ± 5.09	−1.86 ± 6.19	−1.83 ± 7.30	−2.15 ± 5.73	−1.94 ± 6.55
Block 3–5	1.68 ± 5.80[a]	−0.37 ± 5.57[a]	−1.45 ± 6.43[a]	0.26 ± 0.66	−0.17 ± 5.46
IGT improvement	4.15 ± 6.49[b]	1.49 ± 6.84[b]	0.38 ± 9.17[b]	2.41 ± 7.38	1.78 ± 7.52

Data are mean ± SD.
IGT: Iowa gambling task.
BDNF: brain-derived neurotrophic factor.
IGT improvement: mean score of block 3–5 minus score of block 1.
NS: non-significant.
[a] One-way ANOVA, $F(2,167) = 3.63$, $p < 0.05$; post-hoc (LSD method) Val/Val vs. Met/Met ($p < 0.05$), Val/Val vs. Val/Met ($p < 0.05$), Val/Met vs. Met/Met ($p =$ NS).
[b] One-way ANOVA, $F(2,167) = 3.50$, $p < 0.05$; post-hoc (LSD method) Val/Val vs. Met/Met ($p < 0.05$), Val/Val vs. Val/Met ($p < 0.05$), Val/Met vs. Met/Met ($p =$ NS).

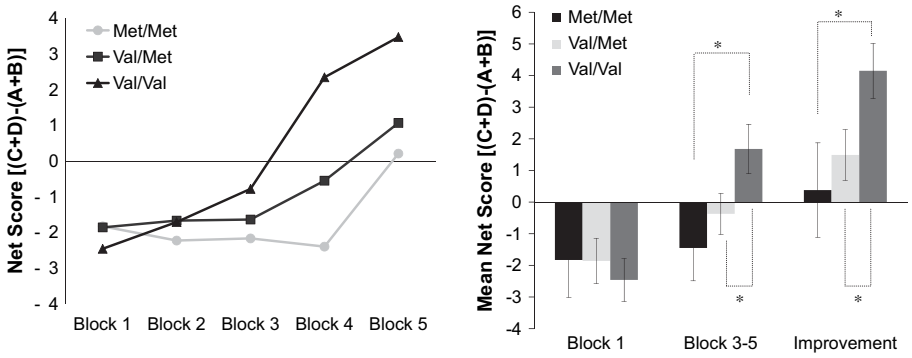

Fig. 1. (Left panel) The net score calculated by subtracting the total number of cards selected from the advantageous decks (C and D) from the number selected from the disadvantageous decks (A and B) across the three genotypes of the BDNF Val66Met polymorphism. (Right panel) Mean net score of the block 1, block 3–5, and improvement (mean IGT score of block 3–5 minus IGT score of block 1) of the IGT scores for different BDNF genotypes. Error bars represent the standard errors of the means. $^{*}p < 0.05$.

system as well. Along these lines, it is notable that a recent study reported that the BDNF Val66Met polymorphism also influences implicit motor learning function in the human brain (McHughen et al., 2009).

As for the COMT Val158Met polymorphism, our results did not replicate the previous findings of van den Bos et al. (2009) in which individuals with the Met/Met genotype chose more disadvantageously than those with the Val/Val genotype. However, it should be noted, the sample size ($n = 70$) of this study was too small (van den Bos et al., 2009). Roussos et al. (2008) reported that the C allele of COMT rs4818 was associated with decreased performance on the IGT. Those two studies suggest that low COMT activity and a high prefrontal dopamine level may be related to poor IGT performance. However, substantial evidence has shown that the Met allele of the COMT Val158Met and high prefrontal dopamine level are related to higher cognitive functions in other cognitive tasks that require working memory (Sheldrick et al., 2008). To explain this discrepancy, van den Bos et al. (2009) proposed the tonic–phasic dopamine theory, in which the COMT Met allele results in increased dopamine transmission in the cortex, increased tonic dopamine levels and reciprocally decreased phasic dopamine levels in subcortical regions. This leads to excessive rigidity and greater difficulty in emotion-related tasks such as the IGT. However, if COMT variants have such opposite effects on the cognitive and emotional processes as mentioned above, their net effect on IGT performance might not be robust because IGT contains both cognitive and emotional components of decision making. For this reason, it may be possible that we did not find any effect of COMT Val158Met polymorphism on IGT performance. Moreover, the two previous studies are different from our study in terms of sample size, genotype frequencies, gender distribution, and/or COMT variants (rs4818). Our study reported a lower mean score and a larger standard deviation (SD) on the IGT than those of the two studies. Although the scores were similar to those in other Korean studies (Lee et al., 2007), it is also possible that some subjects did not do their best since they were paid a fixed $10 reward regardless of their performance. In addition, this study might not have enough statistical power to detect the effects of COMT on IGT performance, considering large SDs. Another possible interpretation is that the profiles of IGT performance might vary according to the ethnocultural backgrounds of the subjects. Obviously, further studies with larger samples in various populations are needed to elucidate the effect of COMT Val158Met polymorphism on IGT performance.

Our study had some limitations. The sample size of this study was not large enough. Other main or interaction effects of genes on IGT performance might have been overlooked because of insufficient statistical power. In addition, only one of the well-known polymorphisms in each of the COMT and BDNF genes was chosen for this study. Therefore, further investigation needs to be conducted on various polymorphisms of these genes to determine more definitively what influence the genes have on decision making.

In conclusion, the present results suggest that the Val/Val of BDNF Val66Met polymorphism has a positive effect on emotional decision making in healthy Korean subjects. This study may be a step toward defining the genetic contribution to emotional decision making.

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