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Brief report

# Major depressive disorder, serotonin transporter, and personality traits: Why patients use suboptimal decision-making strategies?

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**Abstract**

*Background:* Patients with major depressive disorder (MDD) show suboptimal decision-making strategy in experimental game situations. The influence of personality traits and genetic variations on decision-making is not known.
*Methods:* Contingency learning based on the cumulative effect of reward and punishment was assessed in 124 patients with unipolar MDD using the ABCD (reward sensitivity) and EFGH (punishment sensitivity) versions of the Iowa Gambling Test. All patients were genotyped for serotonin transporter promoter polymorphism (5-HTTLPR) and received the Temperament and Character Inventory (TCI).
*Results:* Patients with the ll genotype achieved higher persistence scores and used more optimal decision-making strategy on the ABCD task compared with patients with the ss genotype. Higher persistence was associated with better performance on the ABCD task, and higher harm-avoidance was associated with worse performance on the EFGH task.
*Limitations:* Healthy control volunteers were not included. Personality traits and decision-making were not assessed with multiple questionnaires and tasks. Type I errors cannot be excluded.
*Conclusions:* Decision-making strategy is influenced by personality traits and genetic variations in patients with MDD. Patients carrying the ss variant of the 5-HTTLPR show less persistence and tend to be influenced by high immediate reward.
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*Keywords:* Unipolar major depressive disorder; Serotonin transporter; Tridimensional personality model; Iowa Gambling Test; Reward

## 1. Introduction

Evidence suggests that patients with major depressive disorder (MDD) use suboptimal strategies during decision-making. We recently used the Iowa Gambling Test in order to investigate decision-making strategies in MDD (Must et al., 2006). This test is sensitive for the lesion of brain areas related to emotional regulation (ventromedial prefrontal cortex and amygdala) (Bechara et al., 1999), which are influenced by the polymorphisms of genes regulating serotonin neurotransmission (Brown and Hariri, 2006). Patients with MDD showed altered sensitivity to reward and punishment: paradoxically, immediate large reward enhanced related response patterns even when the strategy was disadvantageous

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and immediate large punishment did not prohibit related response patterns (Must et al., 2006). However, it was unclear how personality traits and genetic factors may influence decision-making performance. In this study, we investigated this question by assessing personality traits (Temperament and Character Inventory [TCI], Cloninger et al., 1993) and serotonin transporter promoter polymorphism (5-HTTLPR) (Heils et al., 1996) in patients with MDD. Previous studies indicated that participants with the short (s) allele of the 5-HTTLPR show higher anxiety-related traits (Lesch et al., 1996) and subclinical depressive symptoms (Gonda et al., 2005) (but for recent meta-analyses, see Schinka et al., 2004; Sen et al., 2004; Munafo et al., 2005). We hypothesized that patients with the s allele will show higher harm-avoidance on the TCI and increased sensitivity for immediate punishment on the Iowa Gambling Test.

## 2. Methods

### 2.1. Participants

Participants were 124 patients with DSM-IV unipolar MDD (American Psychiatric Association, 1994) (83 females, 41 males). Patients with history of neurological illness, obsessive–compulsive symptoms, recent suicide attempts (within 2 years), manic/hypomanic episode or mixed states, psychoactive substance-related disorders, impulse control disorders, and cluster A or B personality disorders were excluded. All participants received the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and the Hungarian version of the TCI (Rózsa et al., 2005). Mean Hamilton Depression Rating Scale (HAM-D) score and mean Hamilton Anxiety Rating Scale (HAM-A) scores were given for each patient (Mountjoy and Roth, 1982; Maier et al., 1988). The following medications were used: bupropion, citalopram, duloxetine, escitalopram, mirtazapine, paroxetine, sertraline, venlafaxine, alprazolam, clonazepam, and lithium. Testing was performed during maintenance therapy. All participants were genotyped for the 5-HTTLPR polymorphism using the method of Heils et al. (1996). The study was done in accordance with the Declaration of Helsinki and was approved by the local ethics board. Written informed consent was obtained from each participant.

### 2.2. Iowa Gambling Test

The computer-administered task has been described in details elsewhere (Bechara et al., 2000; Must et al., 2006). In the ABCD version, four decks of cards labeled as A, B, C, and D were presented on the computer screen. The task was to click on a card from any of the decks using the mouse. After picking a card, the amount of money the participant won or lost was depicted on the computer screen. Decks A and B were associated with high immediate reward but even higher future punishment. In the EFGH task, the four decks were labeled as E, F, G, and H. Decks E and G were associated with high immediate punishment but even higher future reward. In both versions, the 100 trials were divided into five equal blocks. The dependent measure was the number of cards selected from advantageous decks minus disadvantageous decks as calculated for the last block.

Data were analyzed using analysis of variance (ANOVA) and two-tailed *t*-tests. Pearson's correlation coefficients were calculated between TCI and Iowa Gambling Test measures. Linear regression analysis was used to determine the relationship between genetics and task performance. The level of significance was set at alpha $< 0.05$.

## 3. Results

Genotype frequencies did not deviate from Hardy–Weinberg equilibrium ($p > 0.1$). Table 1 depicts that MDD patients with the ss variant of the 5-HTTLPR achieved lower persistence scores on the TCI compared with patients with the ll variant; patients with the ls variant scored between ll and ss patients. No other TCI parameters showed significant differences as a function of 5-HTTLPR genetics (Table 1).

In the ABCD version of the Iowa Gambling Test, patients with the ss variant selected less advantageous decks compared with patients carrying the ll variant; the

Table 1
Demographical, clinical, TCI, and Iowa Gambling Test results as a function of 5-HTTLPR

| | ll ($n=31$) | ls ($n=58$) | ss ($n=35$) | $p$ |
|---|---|---|---|---|
| Age (years) | 42.3 (8.5) | 43.6 (9.2) | 41.0 (7.7) | 0.82 |
| Education (years) | 14.3 (4.8) | 15.2 (5.0) | 15.5 (6.3) | 0.86 |
| Duration of illness (years) | 12.4 (4.2) | 11.0 (9.5) | 13.4 (7.6) | 0.72 |
| HAM-D | 22.3 (7.5) | 21.5 (8.4) | 23.0 (6.3) | 0.57 |
| HAM-A | 4.5 (4.7) | 4.9 (3.2) | 4.9 (3.8) | 0.84 |
| Harm avoidance | 23.9 (7.4) | 23.3 (8.8) | 24.8 (9.9) | 0.69 |
| Reward dependence | 15.0 (2.9) | 15.0 (3.2) | 15.1 (2.8) | 0.99 |
| Novelty seeking | 17.3 (6.1) | 16.5 (6.1) | 15.8 (4.9) | 0.64 |
| Persistence | 4.5 (1.6) | 3.7 (1.9) | 3.0 (1.6) | 0.01* |
| Self-directedness | 25.9 (5.7) | 26.1 (6.0) | 25.1 (5.3) | 0.82 |
| Cooperativeness | 28.0 (5.8) | 28.4 (5.9) | 27.1 (6.5) | 0.73 |
| Transcendence | 13.8 (7.1) | 14.7 (7.0) | 15.1 (6.5) | 0.53 |

Data are mean (standard deviation).
*One-way ANOVA: $F(1,122)=4.62$, $p=0.01$; ll>ss: $t(64)=3.21$, $p<0.005$.

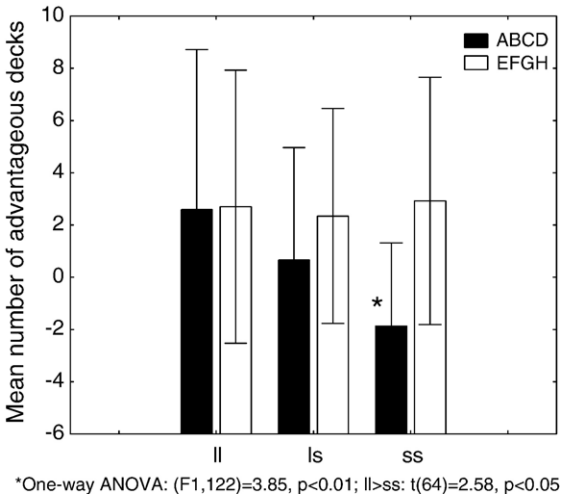


Fig. 1. The figure shows the mean number of advantageous decks selected in the ABCD and EFGH versions of the Iowa Gambling Test in patients with ll, ls, and ss versions of the 5-HTTLPR. Error bars indicate standard deviation of the mean.

value of ls patients was between the scores of the ss and ll patients (Fig. 1). The genetic variant of the 5-HTTLPR accounted for 10.8% of variance in the ABCD task (beta=0.33, $p<0.05$), whereas persistence accounted for 1.9% of variance (beta=−0.14, $p=0.26$). In the case of the EFGH version, there was no such relationship ($p>0.1$) (Fig. 1). This differential deficit was confirmed by a MANOVA test, including task type as a within-subject factor (ABCD vs. EFGH). This test revealed a significant genotype by task type interaction ($F(2,122)=4.58$, $p<0.05$).

There was a negative relationship between harm-avoidance and performance on the EFGH task ($r=-0.40$, $p<0.05$), whereas the relationship between persistence and ABCD performance was positive ($r=0.35$, $p<0.05$). Depressive symptoms did not correlate with performance on the ABCD task ($p>0.1$), but showed inverse correlation with EFGH performance ($r=-0.47$, $p<0.05$). All other correlations were not significant ($p>0.1$). Finally, male and female patients did not differ in any measure ($p>0.1$).

## 4. Discussion

This study demonstrated that MDD patients with the ll version of the 5-HTTLPR displayed higher persistence and performed better on the ABCD task compared with patients with the ss variant. Less persistence may be associated with a reduced ability to acquire or to maintain a decision-making strategy that did not lead to immediate high reward. However, the relationship between persistence and task performance was weak.

The EFGH task investigated the possibility that decision-making problems were due to the failure of high reward to outweigh immediate punishment (Bechara et al., 2000). If the patient was too heavily influenced by immediate punishment, the decision-making strategy would have not been optimal. Patients with high trait anxiety, harm-avoidance, and depressive symptoms may have shown such enhanced sensitivity to punishment. Several studies demonstrated that Cloninger's temperament factors are associated with depression (e.g. Cloninger et al., 2006). In our sample, the frequency of the ss genotype was high comparing to other European populations, which may indicate its role in depression (Lesch and Mossner, 1998).

Surprisingly, our data indicated that the genetic variants of the 5-HTTLPR did not influence trait anxiety and sensitivity to punishment. This is consistent with the recent meta-analysis of Munafo et al. (2005) who found that the association between 5-HTTLPR polymorphism and anxiety traits, if present, is weak. However, it depends on the instrument used for the personality assessment (Sen et al., 2004). Similarly to our results, Kim et al. (2005) found significant association between 5-HTTLPR polymorphism and persistence in a Korean population, but in their case the s allele was associated with higher persistence.

The main limitation of our study is that healthy control participants were not included. In addition, because of multiple testing, our results are vulnerable to type I errors. Because of the relatively small sample size, the statistical power was not strong. Further studies with larger samples and more extensive test batteries are warranted.

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