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Gray matter volume and rapid decision-making in major depressive disorder

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ABSTRACT

Background: Reduced motivation and blunted decision-making are key features of major depressive disorder (MDD). Patients with MDD show abnormal decision-making when given negative feedback regarding a reward. The brain mechanisms underpinning this behavior remain unclear. In the present study, we examined the association between rapid decision-making with negative feedback and brain volume in MDD.
Methods: Thirty-six patients with MDD and 54 age-, sex- and IQ-matched healthy subjects were studied. Subjects performed a rapid decision-making monetary task in which participants could make high- or low-risk choices. We compared between the 2 groups the probability that a high-risk choice followed negative feedback. In addition, we used voxel-based morphometry (VBM) to compare between group differences in gray matter volume, and the correlation between the probability for high-risk choices and brain volume.
Results: Compared to the healthy group, the MDD group showed significantly lower probabilities for high-risk choices following negative feedback. VBM analysis revealed that the MDD group had less gray matter volume in the right medial prefrontal cortex and orbitofrontal cortex (OFC) compared to the healthy group. The right OFC volume was negatively correlated with the probability that a high-risk choice followed negative feedback in patients with MDD. We did not observe these trends in healthy subjects.
Conclusions: Patients with MDD show reduced motivation for monetary incentives when they were required to make rapid decisions following negative feedback. We observed a correlation between this reduced motivation and gray matter volume in the medial and ventral prefrontal cortex, which suggests that these brain regions are likely involved in the pathophysiology of aberrant decision-making in MDD.

1. Introduction

Reduced motivation for reward and loss of interest are key symptoms of major depressive disorder (MDD) (DSM-IV-TR). Furthermore, these features are related to depression severity (Eugene et al., 2010), the number of recurring severe episodes (Nolen-Hoeksema, 2000), and the prognosis of MDD (Pine et al., 1999). Patients with MDD show abnormal responses to negative feedback in reward and gambling tasks (Beats et al., 1996; Elliott et al., 1996, 1997b), and compared to healthy subjects, these patients demonstrate poorer problem solving in response to negative feedback (Elliott et al., 1997a, 1997b). Among patients with MDD, those without recovery show poorer responses to negative feedback than those with recovery (Elliott et al., 1997b). In the Trail Making Test part B, the proportion of subjects making multiple and consecutive errors was higher among subjects with depression than among healthy subjects at baseline, and at both 1- and 2-year follow-up assessments. It is believed that abnormal response to negative feedback in MDD reflects an impaired ability to use knowledge of outcomes to monitor performance. Beck's cognitive vulnerability model (Beck, 2008) may explain such aversive cognitive behavior following negative feedback, however, the underlying neurobiological mechanisms for these behaviors remain unclear.

A meta-analysis of functional neuroimaging studies in healthy people suggests that negative rewards increase activity in the anterior cingulate (ACC), lateral orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (PFC), amygdala, anterior insula, and ventral striatum (Liu et al., 2011). In contrast, functional neuroimaging studies in patients with MDD reveal abnormal activity in the inferior and ventromedial

Abbreviations: MDD, major depressive disorder; OFC, orbitofrontal cortex; VBM, voxel-based morphometry; ACC, anterior cingulate cortex; PFC, prefrontal cortex; JART, Japanese Adult Reading Test; HRSD, Hamilton Rating Scale for Depression; ANOVA, analysis of variance; ROI, region of interest.

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prefrontal cortex, including the OFC, ACC, and striatum, during decision-making/reward processing following feedback (Dichter et al., 2012; Knutson et al., 2008; Remijnse et al., 2009; Smoski et al., 2009). However, these studies have yielded inconsistent results probably due to the differences in the tasks employed in the studies. Compared to healthy subjects, remitted patients with MDD showed decreased activity in the right frontal pole, left insula, left thalamus, and the OFC bilaterally during the outcome phase of the monetary incentive delay task (Dichter et al., 2012). When compared to healthy subjects, patients with MDD also showed increased activity in the left inferior frontal gyrus and thalamus bilaterally during the positive reward in outcome phase of the Wheel of Fortune task, but showed decreased activity in the medial frontal cortex, the right caudate, and auditory cortex combined with increased activity in the OFC, inferior frontal cortex, and middle frontal cortex during the negative reward in outcome phase (Smoski et al., 2009). Finally, patients with MDD showed increased activity in the ACC when they anticipated increasing gains, whereas euthymic patients showed increased activity in the ACC when they anticipated increasing losses (Knutson et al., 2008).

Healthy subjects that receive negative feedback indicating a loss generally show increased activity in the medical frontal cortex, whereas patients with depression receiving the same negative feedback fail to show this activity pattern (Steele et al., 2007). In a monetary incentive delay task, patients with MDD showed weaker activity in the left nucleus accumbens and dorsal caudate than healthy subjects in response to gain versus no-change feedback (Pizzagalli et al., 2009). The same patients also showed a correlation between a small caudate volume and both anhedonic symptoms and depression severity.

Gehring and Willoughby (2002) developed a gambling task so they could use event-related potentials to evaluate rapid decision-making and brain function. They suggested that a rapid assessment of an event's motivational impact contributes to the evaluation of preceding outcomes; especially those based on negative feedback. They further suggested that these assessments were associated with the medial PFC and the ACC. Their gambling task has been used in only 1 additional study, which examined ERPs in healthy subjects (Masaki et al., 2006). To the best of our knowledge, no study has used a gambling task to examine risky behavior and brain volume in patients with MDD.

Here, we examined the neural correlates for a gambling task using voxel-based morphometry. Our aim for this study was to determine whether patients with MDD show abnormal rapid decision-making in response to negative feedback, and to test whether volumetric brain abnormalities are associated with decision-making in these patients. Medial PFC was defined as an a priori region of interest (ROI) based on previous findings (Gehring and Willoughby, 2002). We had 3 hypotheses: 1) compared to healthy subjects, patients with MDD will make less high-risk choices in the gambling task following negative feedback, 2) compared to healthy subjects, patients with MDD will have less gray matter volume in the medial PFC, and 3) patients with MDD who show poorer gambling task performance will have less gray matter volume in the medial PFC.

2. Methods

2.1. Participants

Study participants included 36 patients who met DSM-IV-TR criteria for MDD and 54 healthy subjects. Patients with MDD were recruited from Yamaguchi University Hospital, and healthy subjects were recruited from the local area. All participants were interviewed using the International Neuropsychiatric Interview (M.I.N.I., Japanese version 5.0.0) (Otsubo et al., 2005). MDD was diagnosed by clinical interview, M.I.N.I., and case conferences with psychiatrists; a senior psychiatrist (K.M.) confirmed the diagnosis by reviewing the clinical information. We obtained demographic information for each participant through a clinical interview. All participants were right handed (Oldfield, 1971). A physical examination, including blood tests, was performed to rule out physical illness. Patients with comorbid anxiety disorders or other psychiatric disorders were excluded from the study. Current mood states were measured using the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). The patients with MDD were remitted and depressed (range of HRSD; 0–35). The participants' IQ scores were estimated using a Japanese Adult Reading Inventory (JART) (Matsuoka et al., 2006). Any subject having endocrinological disease, head trauma, neurological disease, family history of hereditary neurological disorder, or other medical conditions (i.e., hypertension, diabetes, active liver disease, kidney problems, and respiratory problems) was also excluded from the study. The Institutional Review Board of Yamaguchi University approved this study, and written informed consent was obtained from all subjects after a complete description of the study was provided.

We examined the participant demographic data using Student's *t*-test or Pearson's chi-square test. Distributions for sex, age, and total IQ were not significantly different between the 2 groups (Table 1). For patients with MDD, the mean number of depressive episodes was 2.4 ± 1.7. One subject reported episodes that were "too numerous to count," and was excluded from the mean number of episode calculation. Most patients took antidepressants ($n = 19$ for selective serotonin reuptake inhibitors, $n = 16$ for serotonin–norepinephrine reuptake inhibitors and $n = 9$ for tricyclic antidepressants), antipsychotics ($n = 4$ for atypical and $n = 2$ for typical) and lithium ($n = 5$) while they participated in the study; 5 patients were unmedicated. The mean imipramine-equivalent dose was 203.4 ± 105.9 mg and the mean chlorpromazine-equivalent dose was 77.6 ± 64.2 mg.

2.2. Gambling task

We used a monetary gambling task (Fig. 1) that was modified from previous studies (Gehring and Willoughby, 2002; Masaki et al., 2006). The participants were given a hypothetical 2000 yen at the beginning of the task and were instructed to accumulate as much money as possible. Each task trial began when 2 cards labeled with the number 10 or 50 were presented on a screen. The numbers 10 and 50 represented a monetary value in Japanese Yen. Participants selected 1 of the 2 cards, and following a 2.5 s delay, the cards turned either red or green. Red indicated a monetary loss, and green indicated a monetary gain. For example, if the participant selected the 10 card, and after the delay the 10 card turned red and the 50 card turned green, then the participant lost 10 yen and missed an opportunity to gain 50 yen. Overall, there were 4 trial types based on their outcomes: loss of 50, loss of 10, gain of 50, and gain of 10. These trials were presented randomly, and the outcome probabilities for gains and losses were equal. Hence, subjects were unable to develop task strategies based on the trial order. Each participant performed 3 blocks of 32 trials (96 trials), and were informed of the cumulative sum of money earned at the end of each block to help maintain their motivation for monetary incentives (Gehring and Willoughby, 2002).

Table 1
Demographic and characteristics of participants.

	MDD (n = 36)		Healthy (n = 54)		Statistics	*P*
	Mean	SD	Mean	SD		
Age (yr)	49.0	11.4	45.4	16.1	$t = -1.29$	0.23
Gender (male/female)	14/22		27/27		$\chi = 1.08$	0.30
Total IQ	100.4	9.4	103.5	9.8	$t = 1.50$	0.14
HRSD	15.4	10.2	0.3	0.7	$t = -8.80$	<0.001
Onset age of illness (yr)	40	19.4	N/A			
Length of illness (m)	66.7	80.9	N/A			
Number of episodes	2.4	1.7	N/A			

HRSD; Hamilton Rating Scale for Depression.
Statistics were done by Student's *t* test or Pearson's chi-square test.