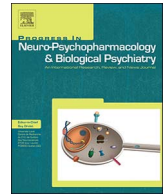




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## Patients with major depressive disorder exhibit reduced reward size coding in the striatum



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### ABSTRACT

**Background:** Anhedonia is a core symptom of major depressive disorder (MDD). While recent evidence suggests that reduced motivation for reward may be a core feature of anhedonia, the abnormalities in modulatory neural responses to variable amounts in MDD patients remain unclear. We investigated whether MDD patients' ability to represent variable-sized monetary rewards in the striatum is disrupted.

**Methods:** Twelve MDD patients and 12 healthy volunteers completed an assessment of psychometric status and participated in a functional magnetic resonance imaging (fMRI) task that involved the anticipation of financial reward (monetary incentive delay task). The size of the monetary reward was varied among trial conditions and was cued with geometric stimuli. Patients participated in additional fMRI sessions after a 6-week pharmacological treatment with escitalopram, an SSRI.

**Results:** In healthy volunteers, striatal activity increased in proportion to the size of the monetary reward during reward anticipation. This pattern was altered in MDD patients, and significant group-by-reward size interaction effects were observed in the bilateral putamen and the left ventral striatum. Reward sensitivity in motor response and striatum activity at three regions were correlated in healthy controls. In MDD patients, this neurobehavioral coupling was not observed. In addition, changes in the neural reward sensitivity parameter at the left ventral striatum in response to treatment were positively correlated with a reduction of depressive symptoms.

**Conclusions:** Patients with MDD exhibit reduced ability to modulate neural response when adjusting for variable amount of reward. This result suggests that reward size coding in the striatum may represent a neural correlate of motivational anhedonia in MDD patients.

### 1. Introduction

Decline of motivation (anhedonia) is a core symptom of major depressive disorder (MDD). Although this symptom is known to be related to poor treatment outcomes for MDD (Spijker et al., 2001), first line antidepressants such as SSRIs have a limited treatment effect for anhedonia (Dunlop and Nemeroff, 2011). Thus, elucidating the neuro-pathology of anhedonia is important to develop an effective treatment method for major depression.

In recent years, the concept of anhedonia has been clarified, and it is proposed that 2 types of anhedonia, motivational and consummatory anhedonia, should be discriminated (Treadway and Zald, 2011; Whitton et al., 2015). Consummatory anhedonia represents a deficit in the experience of pleasure, and is considered a traditional conceptualization of anhedonia. However, recent reviews have suggested inconsistencies in observations concerning consummatory anhedonia in MDD (Treadway and Zald, 2011; Whitton et al., 2015). Motivational anhedonia in MDD is characterized by an inability to modulate

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behavior in response to intermittent rewards (Whitton et al., 2015), and there is growing evidence of the existence of motivational anhedonia in MDD patients. Previous behavioral studies showed that healthy people exhibit a biased response for a large reward relative to a small reward during a probabilistic reward task (Pizzagalli et al., 2005), while MDD patients exhibit a reduced biased response (Pizzagalli et al., 2008). Treadway et al. (2012) also reported a disrupted modulation of effort for large reward in MDD patients. In addition, motivational reward processing has been investigated extensively in animal studies, and evidence suggests that motivational reward processing is strongly related to dopamine (DA) system function (Treadway and Zald, 2011). Thus, investigating the disrupted motivational reward processing of MDD patients is a promising approach to clarify the neuropathology of anhedonia in MDD.

Previously, an fMRI study using a monetary incentive task demonstrated proportional activation of the striatum in humans anticipating increasing financial gain in healthy individuals (Knutson et al., 2001). A meta-analysis (Bartra et al., 2013) examined the neural correlates of subjective value, and supported the relationship between ventral striatum activity and subjective reward representation. If coding of reward becomes inaccurate, maladaptive behavior, such as a destruction of reward learning, may occur. A previous study (Vrieze et al., 2013) reported that MDD patients showed reduced reward learning, and that this impairment predicts poor treatment response.

However, to our knowledge, previous clinical neuroimaging studies of MDD have not investigated or detected maladaptive neural responses to variable amounts of monetary rewards. Some studies examined abnormal brain activity during anticipating reward in MDD patients using similar tasks as that of Knutson et al. (2001), but those studies did not demonstrate or directly examine deficits in proportional response to increasing monetary rewards in the striatum reward region (Hahn et al., 2011; Knutson et al., 2008; Pizzagalli et al., 2009; Stoy et al., 2012). For example, Pizzagalli et al. (2009) demonstrated differences in striatal activity during anticipating and receiving reward between MDD patients and healthy controls. However, only one reward or punishment condition was used and the adjustment ability of the subjects for variable amount of reward was not examined.

In this study, to determine whether MDD patients suffer from impaired reward size coding in the striatum, we investigated neural activation during the anticipation of different amounts of monetary rewards and the relationship between reward size coding ability and SSRI treatment response. From previous behavioral results, we hypothesize that patients with MDD exhibit a disruption of the adaptive, modulatory response to variable reward amount, and that this abnormality is related to SSRI treatment response.

## 2. Methods

### 2.1. Participants

Twelve MDD patients participated in this study. Patients were recruited from a local clinic, and were examined during the acute phase of illness (within 2 weeks of administration of treatment; T1) and after approximately 6 weeks of treatment with escitalopram, an SSRI (10–20 mg/day; T2). All of the patients were screened with the DSM-IV criteria for MDD diagnosis, using the MINI-International Psychiatric Structural Interview (MINI) (Otsubo et al., 2005; Sheehan et al., 1998). No patient had current or past bipolar disorder or schizophrenia episodes.

Healthy volunteers (12 healthy control subjects, 6 males) that responded to local newspaper and public notices were recruited for the study. All healthy control (HC) subjects were investigated thoroughly by experienced psychiatrists and psychologists to ensure that they did not have a history of psychiatric disorders according to DSM-IV criteria (Otsubo et al., 2005; Sheehan et al., 1998). Table 1 lists the demographic and questionnaire data of the study participants. The Ethics Committee of Hiroshima University approved the study. After a complete description of the study to the participants, written informed consent was obtained.

### 2.2. Questionnaires

The 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) was administered to measure each patients' severity of depression at each session. The Beck Depression Inventory (BDI) (Beck et al., 1996; Kojima et al., 2002) was administered to measure the severity of depression of both HC and patients at each session. The Japanese version of the Adult Reading Test (JART) (Matsuoka et al., 2006) was used to assess each participants' verbal IQ equivalent. Mean scores and standard deviations of these scales are shown in Table 1.

### 2.3. Monetary incentive delay task

During each fMRI scanning session, subjects participated in a modified version of the monetary incentive delay (MID) task (Knutson et al., 2003, also described in Mori et al., 2016). In each trial, subjects viewed 1 of 5 types of cues indicating the trial condition (no response, 0 yen gain, 20 yen gain, 100 yen gain, or 500 yen gain). This was followed by a fixation cross (2000–2500 ms; “anticipation phase”), after which a target was rapidly presented on the screen (150–500 ms). If the subject pressed the button before target offset, they gained the cued amount of money. Feedback indicating the trial outcome was then presented. Immediately after the feedback offset, the cue stimulus of the next trial was presented. Eighteen repetitions of each of the 5 trial type

**Table 1**  
Demographics of study participants.

Variable	HC (n = 12, male 6)		MDD (n = 12, male 6)				p-Value*	
			T1		T2		HC vs MDD	T1 vs T2
	Mean	sd	Mean	sd	Mean	sd		
Age (years)	44.0	13.2	38.3	8.46	–	–	0.243	–
Verbal IQ	111.5	6.13	110.4	9.39	–	–	0.739	–
Dose of escitalopram (mg)	–	–	12.5	4.33	13.3	4.71	–	0.339
Duration of medication (days)	–	–	6.9	5.16	49.4	7.31	–	< 0.001
BDI2	4.5	3.2	30.8	11.29	22.1	13.6	< 0.001	0.003
HRSD17	–	–	20.1	5.14	13.7	6.42	–	0.006

BDI2, Beck Depression scale-II; HRSD, Hamilton Rating Scale for Depression 17-item; sd, standard deviation.

\* t-Test.

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