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 reward 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...
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 deactivation of the striatum reward region (Hahn et al., 2013). 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.

Table 1

| Variable                  | HC (n = 12, male 6) | MDD (n = 12, male 6) | p-Value\(^*\) |
|--------------------------|--------------------|----------------------|---------------|
|                         | Mean   | sd    | Mean   | sd     | Mean   | sd     | HC vs MDD | T1 vs T2 |
| 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    | 0.003    |
| BDI2                     | 4.5    | 3.2   | 30.8   | 11.28  | 22.1   | 13.6   | < 0.001    | 0.006    |
| HRSD17                   |        |       | 20.1   | 5.14   | 13.7   | 6.42   |          |          |

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

\(^*\) t-Test.
cues were presented in pseudo-random order, for a total of 90 trials. The hit rate was targeted at 66% for each subject by an algorithm that adaptively changed target durations based on past performance within each condition (see Hahn et al., 2011). Initial target duration was determined by the mean response time in practice prior to an MRI scanning session. Stimuli presentation synchronized with fMRI trigger pulse and response logging were controlled using a personal computer with the presentation software (Neurobehavioral Systems, Inc., San Francisco, CA) (Fig. 1).

2.4. Post-MRI session

After the completion of an fMRI session, participants were presented the 5 types of cue stimuli. The participants were asked to evaluate their own motivation levels for each stimulus condition with VAS scale. The collected responses in VAS scale were translated into 101-point scale value. Due to a technical error, evaluation data from 2 participants (one healthy control and one MDD patient at T2) were lost.

2.5. Functional image acquisition

Functional brain images were acquired using a 3.0 T scanner (Signa HDxt GE Healthcare, Milwaukee, WI). During the MID task, a time course series of 370 volumes per participant was acquired with echo planar imaging sequences (TR = 2000 ms, TE = 25 ms, FA = 90 deg, Matrix size = 64 × 64, FOV = 192 mm, 3 mm slice thickness, a total of 38 slices). These functional scans lasted 12 min and 20 s.

2.6. fMRI data analysis

Data were analyzed using the statistical parametric mapping software package, SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The first 5 volumes of the fMRI run (pre-task period) were discarded to ensure a steady-state MR signal, and the remaining 365 volumes were used for the statistical analysis. Each set of functional volumes was slice timing corrected (middle slice was used for the reference), realigned, unwarped, spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain, and spatially smoothed using an 8 mm Gaussian kernel. Comparison tests of motion parameters confirmed that there was no statistically significant difference in any of the motion parameters between groups (ps ≥ 0.05).

To investigate reward-related activations, first-level general linear models included 14 regressors that modeled anticipating reward in 4 reward cue conditions, 8 feedback phase activities (4 conditions × 2 outcome), and 2 control events (neutral cue, neutral feedback). The duration of the anticipation event was set to 2 s and the feedback events were modeled with a 0 s duration. These events were then convolved with a hemodynamic response function. Using this general linear model, individual maps of parameter estimates were generated for 4 contrasts of interest: 0 yen anticipation > neutral cue, 20 yen anticipation > neutral cue, 100 yen anticipation > neutral cue, and 500 yen anticipation > neutral cue. Second-level analysis for each of these contrasts was modeled using random effects analysis. Initially, we restricted analysis to 6 striatal sub-regions (bilateral putamen, caudate, and ventral striatum). The regions of interest (ROIs) were determined by an existing anatomical atlas (Tziortzi et al., 2011). In these small-volume correction analyses, a statistical threshold for each test was set at a family wise error (FWE) corrected $p < 0.0083$ (0.05/6) in order to control for type I errors. In order to investigate the group difference of reward sensitivity, we conducted group-by-reward size mixed-model ANOVAs on neuroimaging data. In these tests, group (HC, MDD T1) was used as the between subject factor, and size (0, 20, 100, 500) was used as the within-subject factor.

2.7. Behavioral data analysis

We also conducted group-by-reward size, mixed-model ANOVAs of subjective effort ratings and reaction times to reveal the change of behavioral reward sensitivity in MDD patients.

2.8. Reward sensitivity parameter

We parameterized neural and behavioral reward sensitivity by modeling each response data as a function of reward size. These responses were fitted by a linear regression model, $Y = b_0 + b_1 R$, where $Y$ is the variable in each domain (i.e. striatum activities, subjective effort ratings, reaction times), $R$ is the reward size (0, 20, 100, 500), $b_1$ is the slope of regression line, and $b_0$ is the constant term. The slope indicates the intensity of modulation or sensitivity for reward size, and $b_1 = 0$ means low reward sensitivity. In this study, we considered the slope parameter as the reward sensitivity parameter. In contrast to other variables, reaction time (RT) is such that a larger amount indicates lower motivation. Thus, the fitted parameter for RT is sign reversed. As a result, a larger parameter always indicates higher reward sensitivity in this study.

3. Results

3.1. Demographic and clinical data

MDD patients showed a significantly higher BDI than HC at T1. There were no significant differences in age or verbal IQ between the patients and HC (Table 1). In comparison within MDD patients, the reduction in BDI and HRSD from T1 to T2 was significant. Of these 2 symptom scores, the number of patients who exhibited good response (% reduction > 0.5) were 4 and 3, respectively.

3.2. Behavioral results

3.2.1. Hit rate

All participants endured functional scanning and performed the MID task well. In the task, the rate of a successful response for each group subject (HC, 65%; MDD T1, 62%; MDD T2, 60%) were close to 66% as planned (see above Methods section).

3.2.2. Reaction time

Mixed model ANOVA of reaction time revealed a significant main effect of reward size $F (3,66) = 5.29, p = 0.003, \eta^2_p = 0.19$ and group-by-reward size interaction $F (3,66) = 3.17, p = 0.030, \eta^2_p = 0.12$. The main effect of group was not significant $F (1,22) = 0.37, p = 0.547, \eta^2_p = 0.02$. In post hoc analysis, simple main
effect of reward size was significant in HC \(F(3,33) = 6.90, p = 0.001, \eta_p^2 = 0.39\), but not in MDD T1 \(F(3,33) = 0.56, p = 0.648, \eta_p^2 = 0.05\) (Fig. 2B).

### 3.2.3. Subjective effort rating

Mixed model ANOVA of the subjective effort rating revealed a significant main effect of reward size \(F(3,63) = 18.01, p < 0.001, \eta_p^2 = 0.46\) and group-by-reward size interaction \(F(3,63) = 3.67, p = 0.017, \eta_p^2 = 0.15\). The main effect of group was not significant \(F(1,21) = 0.19, p = 0.668, \eta_p^2 = 0.01\). In post hoc analysis, simple main effect of reward size was significant in HC \(F(3,30) = 23.52, p < 0.001, \eta_p^2 = 0.70\), but not in MDD T1 \(F(3,33) = 2.46, p = 0.080, \eta_p^2 = 0.18\) (Fig. 2A).

### 3.3. fMRI results

#### 3.3.1. Striatum activation

Mixed model ANOVAs of brain activation during reward anticipation revealed a significant group-by-reward interaction effect in 3 ROIs (the left ventral striatum, and bilateral putamen) and no significant main effect of group (Table 2). The 3 significant clusters and extracted mean contrast estimates values for each condition are shown in Fig. 3.

#### 3.4. Behavioral and neural reward sensitivity

The results of ANOVAs for behavioral and fMRI data suggest that MDD patients have reduced modulation in responding to a variable amount of reward. We calculated the intensity of this motivational modulation as a reward sensitivity parameter for each individual using the liner least squared regression method (Table 3). In the group comparison t-tests between HC and MDD patients at T1, reward sensitivity parameters of subjective effort \(p = 0.041\), left ventral striatum \(p = 0.004\), left putamen \(p = 0.003\) and right putamen \(p = 0.001\) were significantly higher in HC than in MDD T1, and the difference in reaction time was not significant \((p = 0.186)\). In the test of treatment effect, no parameter showed significant change between MDD patients at T1 and T2 \((p > 0.05)\).

To investigate the relationship between behavioral and neural reward sensitivity parameters, we conducted correlation analyses between these parameters in each subject group (Table 4). As summarized in Fig. 4, in healthy controls, reward sensitivity in subjective effort and 3 neural striatum activities were positively correlated. In MDD patients at T1, there was a significant correlation between the left ventral striatum and the left putamen. In MDD patients at T2, neural reward sensitivity parameters in 3 striatum clusters were correlated.

#### 3.5. Relationship between treatment response and neural reward sensitivity

To investigate the relationship between SSRI treatment responses and change of neural reward sensitivity of MDD patients, we conducted Pearson’s correlation analyses between these variables. Treatment responses were defined as % reduction \((\text{score at T1} - \text{score at T2}) / \text{score at T1}\) of HRSD. The change of neural reward sensitivity was calculated as delta values \((\text{score at T2} - \text{score at T1})\). As a result, only the left ventral striatum showed significant positive correlation \((r = 0.59, p = 0.045)\) (Fig. 5), and both left and right putamen showed weak positive correlations, but the correlations did not reach statistical significance \((r = 0.36\) and 0.11, \(p = 0.253\) and 0.734).

### 4. Discussion

We examined the change in the modulatory ability of reward system response to a variable amount of reward in MDD patients and its relationship to treatment response.

We found that patients with MDD exhibit a reduced ability to regulate effort, motor response, and neural activity in the striatum.

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Table 2

| Test | ROI       | FWE-corrected peak p value | Size (voxel) | Expected size (voxel) | Peak F | Peak Z | MNI coordinates |
|------|-----------|---------------------------|--------------|-----------------------|--------|--------|-----------------|
|      |           |                           |              |                       |        |        | x    | y    | z    |
| Main effect of group | Left VST | ns                        |              |                       |        |        |      |      |      |
|      | Right VST | ns                        |              |                       |        |        |      |      |      |
|      | Left caudate | ns                  |              |                       |        |        |      |      |      |
|      | Right caudate | ns                 |              |                       |        |        |      |      |      |
|      | Left putamen | ns                   |              |                       |        |        |      |      |      |
| Group-by-Reward Size interaction | Left VST | 0.003                     | 51           | 28                    | 16.52  | 3.71   | -10  | 12   | 8    |
|      | Right VST | ns                        |              |                       |        |        |      |      |      |
|      | Left caudate | ns                   |              |                       |        |        |      |      |      |
|      | Right caudate | ns                  |              |                       |        |        |      |      |      |
|      | Left putamen | 0.002                | 44           | 21                    | 19.87  | 4.06   | -22  | 10   | 4    |
|      | Right putamen | < 0.001              | 119          | 22                    | 24.2   | 4.46   | 28   | -6   | 6    |

(Small volume correction analysis, FWE corrected \(p < 0.0083\).)

ROI, Region of Interest; VST, ventral striatum; ns, not significant.
compared to healthy volunteers. The left ventral striatum and bilateral putamen exhibit a significant group-by-reward size interaction effect, but not a main effect of group, which indicates that these nodes in the reward system reflect reduced neural reward sensitivity in MDD patients. Furthermore, the T1 to T2 increase of reward sensitivity in the left ventral striatum correlated with reduction of depression severity.

These results suggest that MDD patients experience motivational anhedonia at the neural level as indicated by reduced reward sensitivity parameters in the left ventral striatum, and the bilateral putamen. Although both regions are rich in projections from DA neurons, the pathways they connect and their proposed roles are different. Previous literature suggests that the ventral striatum is particularly important for motivation and that the putamen and caudate have important roles in motor planning and execution of movement (Dunlop and Nemeroff, 2011). Together, these results suggest that the reduced reward sensitivity at the left ventral striatum reflects the disrupted value representation itself, and restoration of this system may alleviate several depressive symptoms including anhedonia. On the other hand, the reduced reward sensitivity at the bilateral putamen may reflect the reduced capability of executing motivated behavior based on biased reward representation at the left ventral striatum. Unlike in the left ventral striatum, the change of the neural reward sensitivity in these two regions did not correlate significantly with the treatment effect. A possible reason of this result is the difference in the time course of recovery between the primary value representation system and following value-to-action translation system. This interpretation is supported by the results of the correlation analyses between reward sensitivity parameters. In MDD T1 patients, the relationships between striatum regions and between motor responses and striatum responses were diminished. In MDD T2 patients, the relationships between striatum regions reappeared, however, the relationships between motor responses and striatum responses remained diminished. This result suggests that the neurobehavioral coupling in motivated response regulation recovers slowly. Assuming that normalization of response execution is preceded by normalization of value representation, it is reasonable to expect that the relationship between the recovery of the response

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![Image](image.png)

**Fig. 3.** Result of striatum activation. (A) Clusters showing significant group-by-reward size interaction effect ($p_{FWE} < 0.0083$). (B) Extracted parameter estimates from 3 significant clusters.

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Table 3

| Behavioral and neural reward sensitivity parameters in the 3 groups. |
|---|---|---|---|---|
| Behavioral reward sensitivity | HC | MDD | p-Value |
| | Mean | sd | T1 | T2 | HC vs MDD | T1 vs T2 |
| Subjective effort rating | 0.086 | 0.051 | 0.032 | 0.063 | 0.052 | 0.046 | 0.041 | 0.409 |
| Reaction time | 0.027 | 0.027 | 0.012 | 0.040 | 0.023 | 0.028 | 0.186 | 0.739 |
| Neural reward sensitivity | Left ventral striatum | 0.0027 | 0.0014 | 0.0012 | 0.0008 | 0.0011 | 0.0009 | 0.004 | 0.811 |
| | Left putamen | 0.0028 | 0.0017 | 0.0011 | 0.0006 | 0.0007 | 0.0007 | 0.003 | 0.202 |
| | Right putamen | 0.0019 | 0.0013 | 0.0003 | 0.0004 | 0.0006 | 0.0006 | 0.001 | 0.296 |

HC, healthy controls; MDD, major depressive disorder patients; T1, time 1; T2, time 2; sd, standard deviation.
modulatory system based on the putamen and the treatment response will be clear at later treatment stages.

In contrast to our present results, a previous study examined RT and brain activity in response to a variable amount of reward using the MID task, but they did not detect a group-by-reward size interaction effect in the brain activity in response to a variable amount of reward using the MID task revealed the existence of alternative incentive conditions (Cooper et al., 2009). Cooper et al. (2009) demonstrated that anticipatory activity at the ventral striatum for large uncertain rewards and large uncertain punishment conditions is elevated by the addition of the certain large punishment conditions, and that differences between activation for uncertain gain and loss were reduced. This result suggests that the worst incentive condition acted as an anchor for value computation of possible options. Thus, under a gain-and-loss setting, the dynamic range of ventral striatum activation between several gain conditions may be more narrow than that of the gain-only setting. We speculate that because of this narrower dynamic range using both gain and loss conditions, the MDD patients’ response characteristics during gain condition can be obscured. Thus, our findings should be replicated in the gain-only setting MID task or another kind of reward task that has a simple reward condition structure.

While the present results provide new evidence of a correlation between motivational anhedonia and the disruption of striatum function in MDD patients, in a broader context, the background of this disruption and the relationship with consummatory anhedonia are important questions. A growing body of literature suggests a decline of reinforcement learning in patients with MDD (Huys et al., 2013). The DA system including striatum is known to be involved in the learning process (e.g. O’Doherty, 2004), and an abnormality of this neural processing in MDD patients has been reported (Kumar et al., 2008). Given the intact or inconsistent deficits of consummatory response to rewards, it is suggested that the disruption of reward processing in MDD patients is not expressed by a reduction in response to reward per se, but rather by a failure to learn the value of the cue based on the reward (i.e. outcome). As a result, an anticipation of reward is made based on cue value, anticipatory activity in MDD patients may be reduced (see also Admon and Pizzagalli, 2015).

There are several limitations to this study. First, we should assess the motivational aspects of anhedonia using a psychological test such as TEPs (Temporal Experience of Pleasure Scale, Gard et al., 2006) in order to confirm the relationship of neural modulatory capacity and motivational anhedonia. Second, the results of correlation analyses for reward sensitivity parameters (Table 4 and Fig. 4) are a concern. In HC, a significant neurobehavioral coupling between parameters of motor response and striatum activity was observed, and this coupling may reflect adaptive collaborative functioning of the reward system in the striatum and peripheral motor system. However, no significant correlations between subjective effort and other variables were observed. We speculate this is due to differences in the methods used to capture the responses. The motor responses (as RT) and striatum activity during the trial were recorded in a trial-by-trial manner after being averaged. In contrast, the effort rating was conducted retrospectively after the MRI scanning session, and may contain some additive errors from the real response during the trials. These errors may increase the difficulty in detecting relationships between retrospective effort rating and trial-by-trial data. Although the effort rating data may contain such errors, they do capture data of the traits of the participants, and there were significant group effects in the analyses of effort rating. A third limitation is the effect of drug taking in patients at T1. Although the average

### Table 4

| Variable | 1       | 2       | 3       | 4       | 5       |
|----------|---------|---------|---------|---------|---------|
| HC       |         |         |         |         |         |
| 1. Left ventral striatum | 2. Left putamen | 0.68<sup>⁎</sup> |         |         |         |
| 2. Left putamen | 0.66<sup>⁎</sup> 0.83<sup>⁎⁎</sup> | 0.64<sup>⁎</sup> 0.79<sup>⁎</sup> 0.80<sup>⁎</sup> |         |         |         |
| 3. Right putamen | 0.52 0.23 |         |         |         |         |
| 4. Reaction time | −0.16 −0.10 −0.10 |         |         |         |         |
| 5. Subjective effort | −0.54 −0.34 −0.48 0.31 |         |         |         |         |
| MDD T1   |         |         |         |         |         |
| 1. Left ventral striatum | 2. Left putamen | 0.81<sup>⁎</sup> |         |         |         |
| 2. Left putamen | 0.59 0.85<sup>⁎</sup> |         |         |         |         |
| 3. Right putamen | 0.18 0.14 0.07 |         |         |         |         |
| 4. Reaction time | −0.09 −0.27 −0.13 −0.17 |         |         |         |         |
| 5. Subjective effort |         |         |         |         |         |
| MDD T2   |         |         |         |         |         |
| 1. Left ventral striatum | 2. Left putamen | 0.60<sup>⁎</sup> |         |         |         |
| 2. Left putamen | 0.59 0.85<sup>⁎</sup> |         |         |         |         |
| 3. Right putamen | 0.18 0.14 0.07 |         |         |         |         |
| 4. Reaction time | −0.09 −0.27 −0.13 −0.17 |         |         |         |         |
| 5. Subjective effort |         |         |         |         |         |

Values are Pearson’s correlation coefficients; HC, healthy controls; MDD, major depressive disorder patients; T1, time 1; T2, time 2. 
<sup>⁎</sup> p < 0.05. 
<sup>⁎⁎</sup> p < 0.01.

Fig. 4. Summary of correlation analyses between behavioral and neural reward sensitivity parameters in the 3 groups.

Fig. 5. Correlation analysis between change of neural reward sensitivity at left ventral striatum and treatment response. Treatment response is indicated as % reduction of HRSD score. HRSD, Hamilton rating scale for depression; T1, time 1; T2, time 2.
duration of medication at T1 was < 1 week, initial medications may influence the result of this study. Finally, the small sample size is an important limitation of this study. Consequently, additional studies with a larger patient cohort and drug-naïve patients are needed to confirm the relationship between reward size coding in the striatum and anhedonia.

In conclusion, although further study is needed, we identified a candidate of the neural correlates of motivational anhedonia in MDD patients, and this neurobehavioral feature may be important in personalized pharmacological treatment of MDD patients.

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All authors report no financial interests or potential conflicts of interest.

Author declaration

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Author MT undertook the data analysis and wrote the manuscript. Authors MT, ST, TY, HM, YT, YS, AK, and YK acquired the data. Authors MT, YO, ST, and Y’ designed the study. Authors YO, NI, AM, and GO supervised the data analysis. Author KA provided infrastructure. All authors contributed to and have approved the final manuscript.

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