# Striatal Resting-State Connectivity Abnormalities Associated With Different Clinical Stages of Major Depressive Disorder

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## ABSTRACT

***Objective:*** Reward deficits and associated striatal circuitry have been implicated in the onset and progression of major depressive disorder (MDD). This work was conducted to clarify how the striatal circuitry is involved in the established risk, acute episodes, and remission of MDD.

***Methods:*** Striatal subregion resting-state functional connectivity (RSFC) was calculated for 29 currently depressed and 28 remitted patients diagnosed with MDD per the Structured Clinical Interview for *DSM-IV*, 19 first-degree relatives of these patients, and 57 healthy controls (HCs) based on resting-state fMRI data collected between May 2007 and September 2014.

***Results:*** Compared with HCs, the other 3 groups showed increased RSFC between left dorsal caudate (DC) and right insula but reduced RSFC between right putamen and left cerebellum. The currently depressed group showed increased FC between right DC and superior frontal gyrus but reduced RSFC between putamen and right anterior cingulate as well as other striatal nuclei compared with the other 3 groups. Although no results were found in ventral striatum (VS) seeds during analysis of covariance, the comparison between currently depressed and remitted patients showed increased RSFC between right superior VS and left inferior frontal gyrus in currently depressed patients at a more linear threshold. Also, both superior and inferior VS showed increased RSFC with superior and inferior frontal gyri but reduced RSFC with cerebellum in relatives compared with HCs. Higher DC–superior frontal gyrus RSFC ($r = 0.438$, $P = .022$) was correlated with more severe depression, but lower within-putamen FC was correlated with more severe depression ($r = -0.446$, $P = .02$) and retardation ($r = -0.465$, $P = .011$).

***Conclusions:*** The findings suggest that reduced VS-frontal, within-putamen, and putamen-cingulate RSFC in currently depressed patients is dependent on current depressive episode and has implications for symptomatic monitoring, while increased caudate-insular and reduced VS-cerebellar RSFC in remitted patients and first-degree relatives might be related to the disease itself and have potential for predicting risk for and recurrence of MDD.


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Major depressive disorder (MDD) is a common psychiatric condition.[1] A large body of neuroimaging studies have investigated the biomarkers of MDD. Among the most consistent findings are hypoactivity in the dorsolateral prefrontal cortex (PFC) and hyperactivity in the ventral limbic areas.[2,3] The anterior cingulate cortex (ACC) was believed to play a mediatory role in this fronto-limbic circuit.[4] Studies[5–7] have increasingly confirmed the involvement of intrinsically connected networks in MDD, with the candidate networks commonly including the default mode, central executive, and salience networks.[5–7]

Despite increasing knowledge regarding MDD, few reliable biomarkers have been identified for monitoring the onset and progression of MDD. Biomarkers are commonly classified into "trait" and "state" markers. Given that a trait marker represents biological processes that contribute to the vulnerability to or relapse risk of diseases, it can be detected in the high-risk and remission stages of the diseases. On the other hand, a state marker represents clinical manifestations and treatment response, which can be detected during the acute episode of the diseases. Distinguishing the brain characteristics in different clinical states may lead to better understanding of the neural mechanism underlying MDD, ultimately improving its diagnosis and prognostic evaluation.[8]

Although there is large divergence between studies, the neural disturbances of MDD can converge in a cortico-striatal-thalamic-cortical circuit.[9,10] Within this circuit, the striatum receives inputs from cortical and other subcortical areas and supports reward evaluation for emotional and cognitive information.[11,12] The striatum has a high functional heterogeneity. The ventral striatum (VS) receives projections from the medial PFC and limbic structures supporting affective function and the dorsal caudate (DC) receives projections from the dorsal PFC supporting cognitive division, while the putamen receive inputs from the ACC and primary sensorimotor cortex that support cognitive and motor

**Clinical Points**

- Reward deficits and associated striatal circuitry have been implicated in the onset and progression of major depressive disorder (MDD). Yet, how striatal circuitry is distinctively involved in the established risk, occurrence, and remission of MDD remains unknown. This study examined resting-state functional connectivity (RSFC) of striatal subregions in different clinical stages of MDD.
- Lower VS-frontal, within-putamen, and putamen-frontal-dACC RSFC in currently depressed versus remitted patients may be dependent on symptom change, which has implications for prognostic evaluation and therapeutic development of MDD, while higher DC-insular and lower VS-cerebellar RSFC in first-degree relatives versus HCs may be related to the illness itself and constitutes high risk factors for individuals to develop MDD.

function.[12] This unique characteristic makes the striatum an important node for investigating reward-related network abnormalities in MDD.

Striatal dysfunction has been associated with MDD, particularly for the core symptoms of anhedonia and psychomotor retardation.[9,10] Hyporesponsivity of the striatal dopamine system related to reward processing has contributed to anhedonia,[13–16] which could be normalized with antidepressant treatment.[17] As an intermediary between the frontal and limbic areas, the ACC and its connections with striatum have been also implicated in MDD. The dorsal ACC (dACC), a structure involved in conflict monitoring,[18,19] showed reduced activation in MDD during reward anticipation,[20,21] which was considered as another mechanism contributing to anhedonia. An inflexibility in local efficiency of the dACC and reduced putamen-dACC functional connectivity (FC) has predicted poorer inhibition performance[22,23] and higher depression severity.[24] Further, studies[25–27] have suggested an involvement of all striatal divisions in MDD, including the caudate, putamen, and VS, as lower dopaminergic activity has been shown in these structures.

These studies suggest that the striatal function not only varies with symptomatic changes in MDD but also is disturbed when depressive symptoms have either not occurred or have settled. However, how the striatal circuitry is distinctively involved in the established risk, occurrence, and remission of MDD remains unknown. By measuring temporal dependency of neural signals between anatomically separated regions, resting-state functional magnetic resonance imaging (R-fMRI) has been applied to map the FC of striatal subregions in normal[12] and ill[28,29] populations. The comparison of different clinical stages facilitates the obtaining of biomarkers associated with disease risk, occurrence, and progression, and the analysis of striatal subregion connectivity has the advantage of comprehensively presenting reward-related circuitry, characterizing the seed-based resting-state functional connectivity (RSFC) of striatal subregions in different clinical stages may help to identify MDD-related biomarkers in a larger neural context.

Therefore, we conducted this study to examine striatal connectivity changes in currently depressed and remitted patients based on their R-fMRI data. The first-degree relatives of these patients were also recruited to examine the neural changes underlying vulnerability of MDD. The RSFC of striatal subregions was calculated by seed-based analyses. On the basis of the aforementioned studies of MDD and connectivity patterns of each striatal subregion, we hypothesized that reduced RSFC would be observed between the PFC and both VS and caudate seeds and within the striatal nuclei in currently depressed compared with remitted patients. We also expected to see reduced RSFC between the ACC and putamen in currently depressed patients. These RSFC changes would be correlated with depressive symptomatology.

## METHODS

Patients with a current depressive episode or remitted state were recruited from Beijing Anding Hospital of Capital Medical University between May 2007 and September 2014. First-degree relatives were recruited from the siblings of these MDD patients. Patients were diagnosed by a trained psychiatrist according to the *DSM-IV* criteria for MDD. Those with current major depressive episode were required to have moderate-to-severe illness defined by a 17-item Hamilton Depression Rating Scale (HDRS)[30] score > 17. The remitted patients were required to have an HDRS score < 7 and have been remitted for at least 2 months prior to the MRI scans. We excluded patients with comorbid Axis I disorders except for anxiety disorders as well as patients with Axis II personality disorders or intellectual disability. Among the patients enrolled, 6 currently depressed and 2 remitted patients were medication-free, while other patients were on medication. The healthy controls (HCs) were required to have an HDRS score < 7, no history of psychiatric disorders in themselves and their first-degree relatives, and no history of psychotropic drug use.

Exclusion criteria for all subjects included a history of neurologic illnesses, unstable medical conditions, substance dependence within the last year, a history of electroconvulsive therapy, current pregnancy or breastfeeding, or any contraindications to an MRI scan. We excluded subjects who had a long history of smoking or alcohol use (> 1 year) and subjects who smoked daily in the week before the MRI scan. The subjects were told not to smoke or to drink alcohol, coffee, tea, or other substances with a central nervous excitatory effect the day before the MRI scan. Through the above means, we attempted to avoid the effects of central nervous excitatory substances on brain imaging scans.

All procedures of this work comply with the ethical standards of Institutional Review Boards of Beijing Anding Hospital of Capital Medical University and Beijing Normal University Imaging Center for Brain Research. All subjects signed informed consent forms. Demographic and clinical data are provided in Table 1.

### MRI Data Acquisition

Imaging data were acquired using a 3T Siemens MRI scanner (Siemens; Munich, Germany). The resting-state functional images were obtained with an echo-planar imaging sequence: 33 slices, 3.5-mm thickness with 0.6 mm gap, 2,000-ms repetition time (TR), 30-ms echo time (TE), $64 \times 64$ in-plane resolution, $220 \times 220$ mm$^2$ field of view (FOV), 90° flip angle, 240 volumes lasted 8 min. Subjects were instructed to keep their eyes closed, remain still, not think of a specific thing consistently, and not fall into sleep during the scan. A simple questionnaire was performed after the scan to confirm that the subjects had followed instructions. T1-weighted structural images were obtained for registration purpose with the following parameters: 128 slices, 1.33-mm thickness with no gap, 2,530-ms TR, 3.39-ms TE, $256 \times 256$ mm$^2$ FOV, $256 \times 192$ resolution, 1,100-ms inversion time, and 7° flip angle.

### Data Analysis

***Image preprocessing.*** The R-fMRI data were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF, http://rfmri.org/DPARSF) based on Statistical Parametric Mapping update 12 (SPM12, http://www.fil.ion.ucl.ac.uk/spm). After the removal of the first 10 volumes, the remaining 230 volumes were corrected for different acquisition times and realigned with 6-parameter rigid-body transformation. Thenuisance signals (including linear trend, head-motion parameters based on Friston 24-parameter model[31] signals of cerebrospinal fluid, white matter, and whole brain) were then regressed out from the data. Derived images were normalized to Montreal Neurologic Institute (MNI) space and resampled with $2 \times 2 \times 2$ mm$^3$ resolution using transformation parameters estimated by unified segmentation algorithm.[32] A band-pass filtering (0.01–0.1 Hz) was applied for the transformed images.

Considering a possible effect of micromovements on RSFC,[33] we calculated the framewise displacement (FD) values for each subject using the formula from Jenkinson and colleagues.[34] Four subjects (including 3 currently depressed patients and 1 first-degree relative) in any plane of translation or rotation $>2$ and 7 subjects (including 1 remitted patient, 2 first-degree relatives, and 4 HCs) with mean FD $>0.2$ were excluded. Data from 29 acutely depressed and 28 remitted patients, 19 first-degree relatives of the depressed patients, and 57 HCs were used for the final analysis.

### Striatal RSFC

We used seed-based analysis to compute striatal RSFC according to a previous protocol.[12,35] Specifically, the seeds were defined (MNI152 space) bilaterally in the DC ($x = \pm 13$, $y = 15$, $z = 9$), superior VS (VSs) ($x = \pm 10$, $y = 15$, $z = 0$), inferior VS (VSi) ($x = \pm 9$, $y = 9$, $z = -8$), dorsal rostral putamen (DRP) ($x = \pm 25$, $y = 8$, $z = 6$), dorsal caudal putamen (DCP) ($x = \pm 28$, $y = 1$, $z = 3$), and ventral rostral putamen (VRP) ($x = \pm 20$, $y = 12$, $z = -3$), with each seed covering 27 voxels in 2-mm$^3$ space (radius = 3.5 mm). The placement of these seeds is shown in Supplementary Figure 1. We extracted the mean time courses of blood-oxygen-level–dependent (BOLD) signals of each seed and computed their correlations with the rest of the brain. This procedure generated 12 striatal RSFC images (6 per hemisphere) for each subject. The $r$ value correlation maps were $z$ value converted by Fisher $r$-to-$z$ transformation and smoothed with 6-mm Gaussian kernel.

### Statistical Analysis

***Within-group patterns.*** We performed 1-sample $t$ tests to obtain within-group RSFC patterns of each striatal subregion. The results were corrected for multiple comparison with voxel $P < .001$ ($z > 3.1$) and cluster $P < .05$ according to Gaussian random field (GRF) theory.

***Between-group differences.*** One-way analysis of covariance (ANCOVA) and post hoc tests were performed on striatal RSFC images of the 4 groups (including currently depressed patients, remitted patients, first-degree relatives, and HCs) to investigate between-group differences, with age, sex, education, and mean FD as covariates. The results were corrected for multiple comparisons with voxel $P < .001$ and cluster $P < .05$ according to GRF theory. For those clusters that survived after correction, we extracted the mean RSFC values for each subject and performed 2-sample $t$ tests to show their differences between every 2 groups, with a Bonferroni-corrected $P < .0083$ (.05/6).

***Correlations with symptoms.*** To clarify the behavioral associations of striatal RSFC, we performed correlation analysis between the RSFC values of clusters that survived after ANCOVA and the total HDRS scores, controlling for age, sex, education, and FD values within each group. To investigate the specific association with reward function, we computed correlation between striatal RSFC and retardation subscale scores, which include the items of depressive mood, work and interest, retardation, and sexual symptoms. Among the 5 factors of the HDRS, retardation best reflects the reward function.

***Between-group differences accounting for medication effects.*** Given that the medication may be a confounding factor for the imaging results, we compared striatal RSFC between the patients who were currently medicated and those who were not within the currently depressed group. This comparison was not performed in the remitted group given that this group included only 2 unmedicated patients.

We also compared the striatal RSFC between currently depressed and remitted patients as well as between first-degree relatives and HCs. We hypothesized that the results repeatedly observed in this analysis would largely exclude medication effects. A more libear threshold of 2-tailed voxel $P < .01$ and cluster $P < .05$ corrected according to the GRF theory was used.

## RESULTS

### Sample Characteristics

As shown in Table 1, HDRS scores were higher in currently depressed patients than in remitted patients, first-degree relatives, and HCs ($P < .001$), while no significant differences

**Table 1. Sample Characteristics[a]**

| Characteristic | Acute MDD (n = 29) | Remitted MDD (n = 26) | First-Degree Relatives (n = 18) | Healthy Controls (n = 57) | *F*/*t* | *P* |
|---|---|---|---|---|---|---|
| Sex, male/female | 15/14 | 16/10 | 11/7 | 32/25 | 8.000 | .333 |
| Age, y | 34.0 ± 11.7 | 34.8 ± 12.0 | 39.5 ± 11.8 | 36.0 ± 11.6 | 0.911 | .438 |
| Education, y | 11.6 ± 2.9 | 11.9 ± 2.3 | 12.2 ± 2.5 | 11.5 ± 2.2 | 0.500 | .638 |
| Total duration, mo | 7.1 ± 9.1 | 7.8 ± 6.5 | … | … | −0.301 | .765 |
| Duration of current episode, mo | 4.7 ± 5.0 | 8.5 ± 14.8 | … | … | −1.31 | .196 |
| No. of previous episodes | 3.3 ± 1.4 | 3 ± 2 | … | … | 0.604 | .549 |
| HDRS total score | 22.7 ± 4.4 | 5.4 ± 2.1 | 1.4 ± 1.6 | 0.8 ± 0.7 | 539.33 | < .001 |
| Framework displacement | 0.08 ± 0.04 | 0.07 ± 0.04 | 0.08 ± 0.03 | 0.07 ± 0.03 | 0.557 | .644 |

[a]Data are expressed as mean ± SD unless otherwise noted.
Abbreviations: HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder.

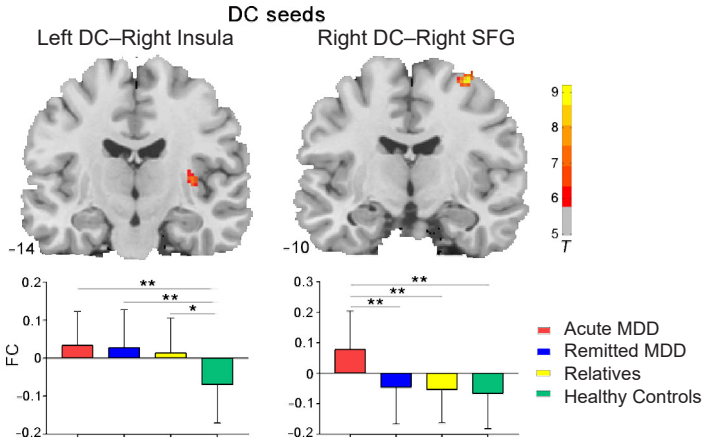
were observed in age, sex, and education level among the 4 groups.

We also compared demographic and clinical data between 23 medicated and 6 unmedicated currently depressed patients, with no significant differences found (Supplementary Table 1). The comparison between currently depressed and remitted patients showed no differences in medication status ($t = 0.141$, $P = .253$). The medication status of each subject is listed in Supplementary Table 2.

### Within-Group Patterns

As shown in Supplementary Figure 1, the RSFC patterns of each seed were basically consistent with those reported in other normal[12] and ill[28,29] populations. On the whole, each of the striatal seeds showed positive RSFC with their adjacent regions. In particular, the DC and VS showed positive RSFC with the medial PFC, while the putamen showed positive RSFC more extensively with the dorsal PFC, inferior frontal gyrus, and insula. We also show the correlation matrix for the 12 seeds in Supplementary Table 3.

**Figure 1. Between-Group Differences in Dorsal Caudate Resting-State Functional Connectivity (RSFC)[a]**




[a]The brain maps show the clusters with significant group differences in RSFC of the left and right DC seeds obtained by analyses of covariance. The bar graphs show the mean RSFC values of clusters and their differences between every 2 groups determined by independent-sample *t* tests with a Bonferroni-corrected $P < .0083$. The data are expressed as mean ± SD.
*$P < .0083$.
**$P < .001$.
Abbreviations: DC = dorsal caudate, FC = functional connectivity, MDD = major depressive disorder, SFG = superior frontal gyrus.

### Between-Group Differences

We found significant group differences in the RSFC of the DC (Figure 1, Table 2) and putamen (Figure 2, Table 2) seeds. Details are described as follows.

***DC seeds.*** Compared with HCs, increased RSFC was found between the left DC and right insula in currently depressed and remitted patients as well as in first-degree relatives, while increased RSFC between the right DC and right superior frontal gyrus was found in currently depressed patients compared with the other 3 groups.

***Putamen seeds.*** Suggesting a state-dependent effect, the currently depressed patients showed lower RSFC in the right DCP and bilateral DRP seeds to right dACC, the left DRP seed to right lentiform nucleus, the left DCP seed to left putamen, and bilateral VRP to right putamen compared with remitted patients and HCs. Conversely, the 3 MDD-related groups showed lower RSFC in the left DCP seed to right thalamus and in the right DCP seed to left cerebellum compared with HCs, suggesting a possible vulnerability or trait finding.

### Between-Group Differences Accounting for Medication Effects

No significant differences were observed in striatal RSFC between the patients currently medicated and those not within the currently depressed group.

As indicated in Supplementary Figures 2 and 3 and Supplementary Tables 4 and 5, increased RSFC was found between the left DC and right insula in first-degree relatives compared with HCs. For the VS seeds, increased RSFC was found between the right VSs and left inferior frontal gyrus in currently depressed compared with remitted patients. Both the VSs and VSi showed increased RSFC with the superior and inferior frontal gyri but reduced RSFC with the bilateral cerebellum in first-degree relatives compared with HCs. For the putamen, we found reduced RSFC between all of the seeds and bilateral lentiform nucleus/putamen, between both the bilateral DRP and right DCP seeds

**Table 2. Between-Group Differences in Striatal Resting-State Functional Connectivity**

| Seed | Regions With FC Peak | Voxels | Statistics (*F*) | MNI Coordinates x, y, z | Post Hoc Analysis |
|---|---|---|---|---|---|
| Left DC | Insula | 81 | 8.330 | 34, −14, 6 | aMDD, rMDD, relative > HC |
| Right DC | Precentral gyrus | 102 | 9.209 | 34, −8, 64 | aMDD > rMDD, HC, relative |
| Left DRP | Anterior cingulate cortex | 87 | 8.332 | 12, 18, 26 | aMDD, relative < rMDD, HC |
| | Lentiform nucleus | 81 | 7.556 | 32, 8, −10 | aMDD < rMDD, HC |
| Right DRP | Anterior cingulate cortex | 49 | 9.681 | 8, 32, 16 | aMDD < rMDD, HC, relative |
| Left DCP | Putamen | 106 | 7.252 | −28, 8, 2 | aMDD < rMDD, HC |
| | Thalamus | 135 | 5.819 | 10, −18, −2 | aMDD, rMDD, relative < HC |
| Right DCP | Anterior cingulate cortex | 185 | 7.712 | 10, 32, 14 | aMDD < rMDD, HC, relative |
| | Cerebellum anterior lobe | 152 | 6.364 | −6,–64, −34 | aMDD, rMDD, relative < HC |
| Left VRP | Putamen | 70 | 9.485 | −28, 14, 2 | aMDD < rMDD, HC |
| Right VRP | Putamen | 83 | 7.455 | 28, 10, 12 | aMDD < rMDD, HC |
| | Cerebellum posterior lobe | 111 | 8.567 | −46, −56, −38 | rMDD, relative < HC |

Abbreviations: aMDD = acute MDD, DC = dorsal caudate, DCP = dorsal caudal putamen, DRP = dorsal rostral putamen, FC = functional connectivity, HC = healthy control, MDD = major depressive disorder, MNI = Montreal Neurologic Institute, rMDD = remitted MDD, VRP = ventral rostral putamen.

and right dACC, and between both the left DRP and the right DCP seeds and left middle frontal gyrus in currently depressed compared with remitted patients. We observed increased RSFC only between the left VRP and left middle frontal gyrus in first-degree relatives compared with HCs. Thus, as we hypothesized, the ANCOVA results largely exclude medication effects.

### Correlation Between Striatal RSFC and Depressive Severity

As shown in Figure 3, the analysis showed that lower left-sided RSFC between the VRP seed and the putamen/lentiform nucleus was correlated with higher HDRS and retardation scores. Higher right-sided RSFC between the DC seed and superior frontal gyrus was correlated with higher HDRS scores.

## DISCUSSION

This study provides a comprehensive examination of striatal RSFC in MDD populations with different clinical statuses. Consistent with our hypothesis, altered RSFC was observed in the DC, VS, and putamen seeds. Specifically, reduced RSFC in VS-frontal circuitry, within and between putamen and dACC, was observed in currently depressed compared with remitted patients, which indicates symptom-dependent changes, while increased DC-insular and reduced VS-cerebellar RSFC in first-degree relatives compared with HCs seem to be related to the illness itself and the onset of MDD.

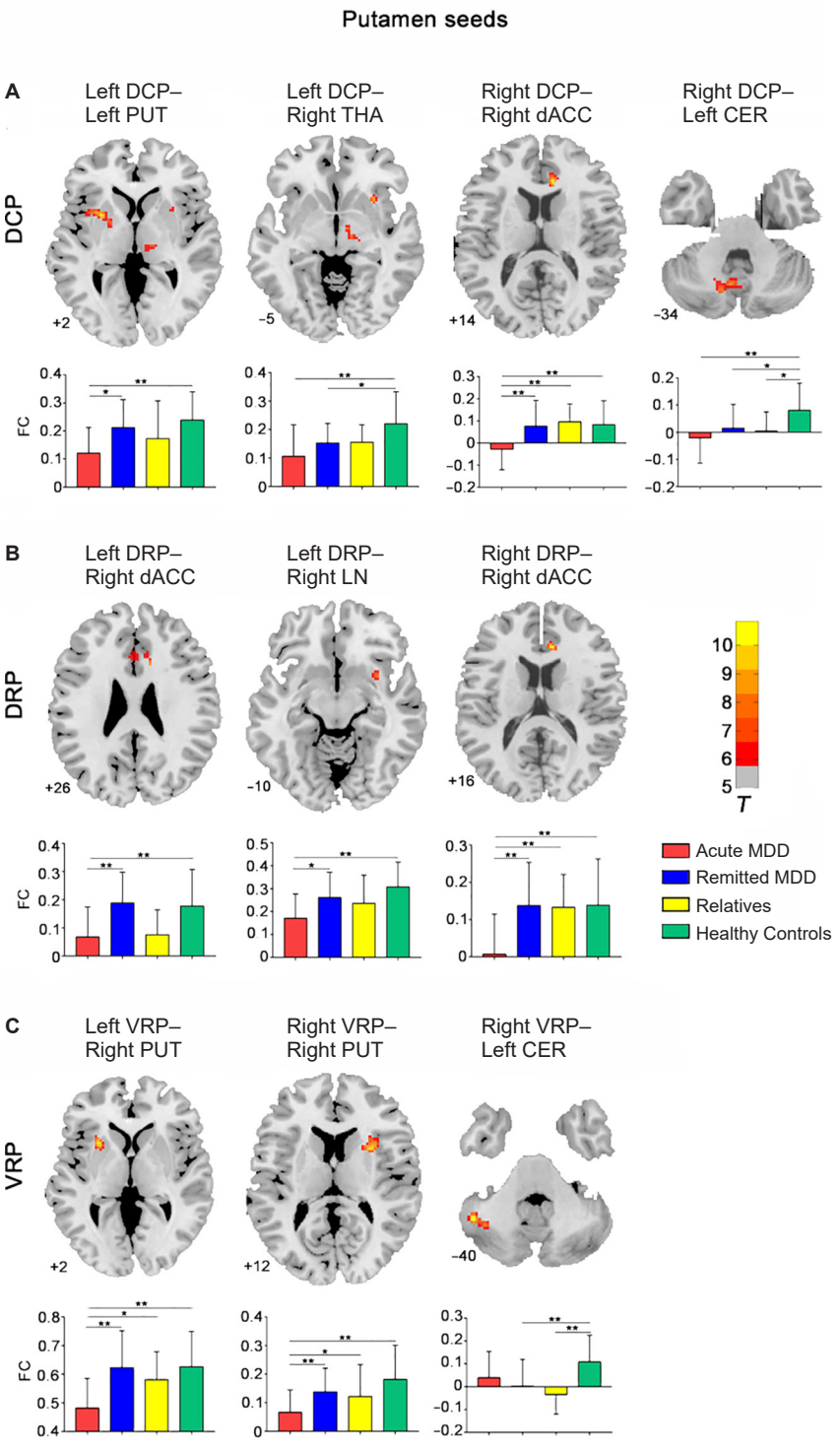
### DC-Insular Circuitry

We found increased RSFC between the left DC and right insula in the 3 MDD groups compared with HCs, which was also observed in the first-degree relatives compared with HCs after direct comparison of RSFC images between these 2 groups. The insula is one of the primary cortical structures underlying interoceptive awareness.[36] It is suggested that the core symptoms of MDD (eg, anhedonia, social deficits) may be products of disturbed interoceptive-exteroceptive integration.[37] Researchers found greater insula activity in treatment-resistant depressed patients in response to positively valenced pictures.[38] In support of our result, a study[39] showed that young daughters of mothers with a history of MDD had greater right insular response during reward anticipation compared with those of healthy mothers. Combined, increased insular activity and connectivity may be a high risk factor for individuals to develop MDD, one that is associated with oversensitivity to interoceptive and exteroceptive-related stimuli seen in MDD patients. We also found increased right-sided RSFC between the DC and precentral gyrus in currently depressed patients compared the other 3 groups, but this was not observed during direct comparisons of striatal images between the 2 groups, which might be explained by a medication effect.

### VS-Frontal-Cerebellar Circuitry

Although no results were observed in the VS seeds during ANCOVA, the 2-group comparisons in VS RSFC images at a more libear threshold showed significant group differences. Specifically, reduced RSFC was observed between the right VSs and left inferior frontal gyrus in currently depressed compared with remitted patients. Conversely, increased RSFC between the VSs and VSi seeds and the superior and inferior frontal gyri was observed in first-degree relatives compared with HCs. In support of these results, a study[40] found reduced superior and inferior frontal activation during loss outcome in remitted MDD. Diminished frontostriatal activation has been associated with reduced capacity to sustain positive emotion.[41] Further, the frontostriatal RSFC may be associated with treatment effects of antidepressants, as depressed patients showing the largest increase in sustained frontostriatal RSFC after treatment were those showing the largest increase in positive affect.[42] Combined with this evidence, our findings of reduced frontostriatal RSFC may reflect that a negative emotional bias persistently exists in MDD patients when their symptoms are not active, while this bias may become prominent when a depressive episode begins.

**Figure 2. Between-Group Differences in Putamen Resting-State Functional Connectivity (RSFC)[a]**



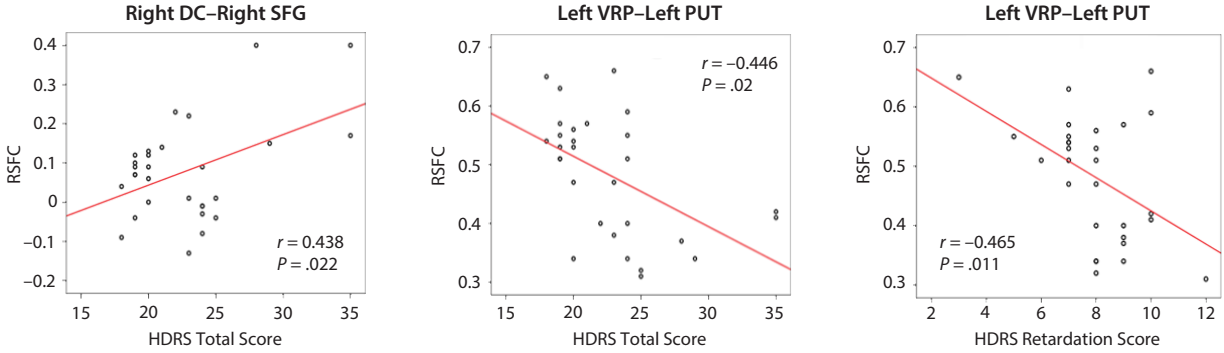

[a]The brain maps show the clusters with significant group differences in RSFC of the left and right seeds of the putamen, including (A) the DCP, (B) the DRP, and (C) the VRP, obtained by analyses of covariance. The bar graphs show the mean RSFC values of these clusters and their differences between every 2 groups determined by 2-sample *t* tests with a Bonferroni-corrected $P < .0083$.

*$P < .0083$.

**$P < .001$.

Abbreviations: CER = cerebellum, dACC = dorsal anterior cingulate cortex, DCP = dorsal caudal putamen, DRP = dorsal rostral putamen, LN = lentiform nucleus, MDD = major depressive disorder, PUT = putamen, THA = thalamus, VRP = ventral rostral putamen.

**Figure 3. Relationships Between Striatal Resting-State Functional Connectivity (RSFC) and Clinical Variables[a]**




[a]The scatter plots show significant correlations in right-sided RSFC between the DC seed and SFG with the HDRS total scores and in left-sided RSFC between the VRP seed and another cluster within the putamen with both the total HDRS total and retardation subscale scores in currently depressed patients.
Abbreviations: DC = dorsal caudate, HDRS = Hamilton Depression Rating Scale, PUT = putamen, SFG = superior frontal gyrus, VRP = ventral rostral putamen.

In contrast, we found increased VS-frontal RSFC in first-degree relatives compared with HCs. Researchers have observed less bilateral middle frontal gyrus activation during commission errors in patients with future recurrence of MDD compared with those without recurrence.[43] Also, at-risk resilient adolescents exhibited greater activation than did remitted depressed adolescents in the middle frontal gyrus during reward anticipation.[44] This evidence raises the possibility that increased VS-frontal RSFC observed in our study might be a mechanism protecting high-risk individuals from future depressive relapse. Those at a high risk of MDD may benefit from preventive treatment by strengthening the VS-frontal connections.

We also found reduced RSFC between both the right VSs and left VSi seeds and bilateral cerebellum in first-degree relatives compared with HCs. In addition to a role in motor coordination and behaviors, the cerebellum also participates in cognition and emotion by its connections with cortical and limbic areas.[45,46] A growing number of studies have paid attention to the role of the cerebellum in MDD.[47–49] The cerebellum may be related to the remitted process of MDD.[47] Moreover, reduced cerebellar-cerebral RSFC and regional homogeneity in the cerebellum have been observed in individuals at high risk for MDD,[48,49] possibly supporting our proposal of reduced striatal-cerebellar RSFC as a neural substrate underlying the vulnerability to MDD.

### Putamen-Lentiform-ACC-Frontal RSFC

In addition to in the VS and caudate, altered RSFC was also found in the putamen. Specifically, we found reduced RSFC between all of the putamen seeds and other striatal nuclei (eg, lentiform nucleus, putamen) in currently depressed compared with remitted patients but not in the comparison between first-degree relatives and HCs. Lower left-sided VRP-putamen RSFC was correlated with higher HDRS total and retardation scores. These results suggest a symptom-dependent impairment of functional synchronization within the striatum, compatible with studies[13–17] showing reduced striatal response to positive stimuli and its normalization with antidepressant treatment in MDD. Specifically for the putamen, aging in this region has been accelerated in MDD,[50] and aberrant putamen network topology was associated with the number of depressive episodes.[51] In support of our results of correlation analysis, studies have found associations of lower striatal activation with reduced capacity to sustain positive emotion[41] and higher anhedonia scores.[38] Overall, the abnormality in putamen-striatal RSFC may be dependent on the depressed symptom changes and might be used to monitor the psychomotor-related symptoms typically seen in MDD patients, such as retardation and reduced energy.

We also found reduced RSFC between the DRP and DCP seeds and right dACC and left middle frontal gyrus in currently depressed compared with remitted patients. Connected with the regions in central executive and salience networks, the dACC is implicated in conflict monitoring, attentional orienting, and behavioral selection.[18,19] In MDD, researchers found reduced dACC activation and striatum-to-dACC synchronization during reward anticipation.[20,21,52] An inflexibility in local efficiency of the dACC predicted cognitive inhibition performance.[22,23] These studies[22,23] have found associations between dysregulated ACC function and impaired ability to deal with conflicts, which may contribute to disruption in goal-directed behaviors that characterizes MDD. Further, a study of MDD[52] showed impaired fiber tracts in the internal capsule connecting striatum and ACC. We therefore speculate that dysregulated RSFC in the putamen-dACC-frontal pathway may contribute to the cognitive flexibility impairment seen in MDD, which is dependent on symptom change in MDD and has implications in progression monitoring and treatment target selection for MDD. In contrast to the dACC, increased RSFC between the left VRP and left middle frontal gyrus in first-degree relatives compared with HCs might indicate another neural mechanism for protecting the high-risk individuals from the occurrence of MDD.

Despite these important findings, several issues need be further addressed. Current medications may have had a confounding effect on the observation of between-group differences in striatal RSFC. The ideal means of excluding

the medication effects would be to enroll drug-naive patients. Instead, we performed a comparison analysis in striatal RSFC between currently depressed and remitted patients as well as between first-degree relatives and HCs. The results observed in this analysis largely excluded the effects of medication. Another limitation is a lack of a reward-orientated scale, which limits the specific speculation of behavioral implication of brain imaging results. As an alternative solution, we divided the HDRS into 5 factors and correlated the retardation subscale scores with striatal RSFC values. Further, the high heterogeneity of depressive syndrome may bias the results, given that although MDD in general has been associated with reward deficits, the reward function is mostly impaired in melancholic depression.[53] Recruiting a larger sample with a subtype assessment in the future would help to clarify the effect of different clinical syndromes on striatal RSFC. In addition, while the overall sample is robust and the control sample size is reasonable, the depressed subgroups are relatively small, particularly the relatives cohort, possibly contributing to false-positive findings. Another limitation is the low sampling rate of MRI, which impedes us from analyzing the causal relationship of brain activity and makes it difficult to form a model of relationship of abnormal brain activity. In the future, combining MRI with high time resolution technology such electroencephalography and magnetoencephalography would help to obtain temporal information on brain activity and construct a model of depressed brain. Finally, future longitudinal studies tracking the pathway from high-risk condition to depressive episode and to remission could help to verify the speculations of this study.

In conclusion, this study provides the first evidence of the involvement of striatal circuitry in different clinical stages of MDD by examining the striatal RSFC at a subregion level. Lower VS-frontal, within-putamen, and putamen-dACC-frontal RSFC in currently depressed versus remitted patients may be dependent on symptom change, which has implications for prognostic evaluation and therapeutic development of MDD, while higher DC-insular and lower VS-cerebellar RSFC in first-degree relatives versus HCs may be related to the illness itself and constitute high risk factors for individuals to develop MDD.

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# Supplementary Material

**Article Title:** The Striatal Resting-State Connectivity Abnormalities Associated With Different Clinical Stages of Major Depressive Disorder

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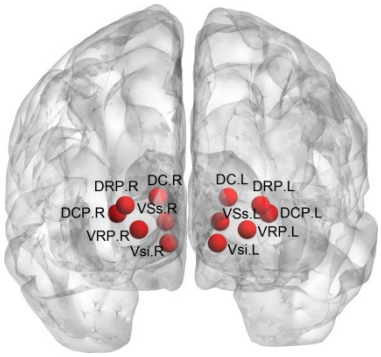


**Figure 1. Definition of the striatal subregions**.

DC, dorsal caudate; VSs, superior ventral striatum; VSi, inferior ventral striatum; DRP, dorsal rostral putamen; DCP, dorsal caudal putamen; VRP, ventral rostral putamen. L, left; R, right.

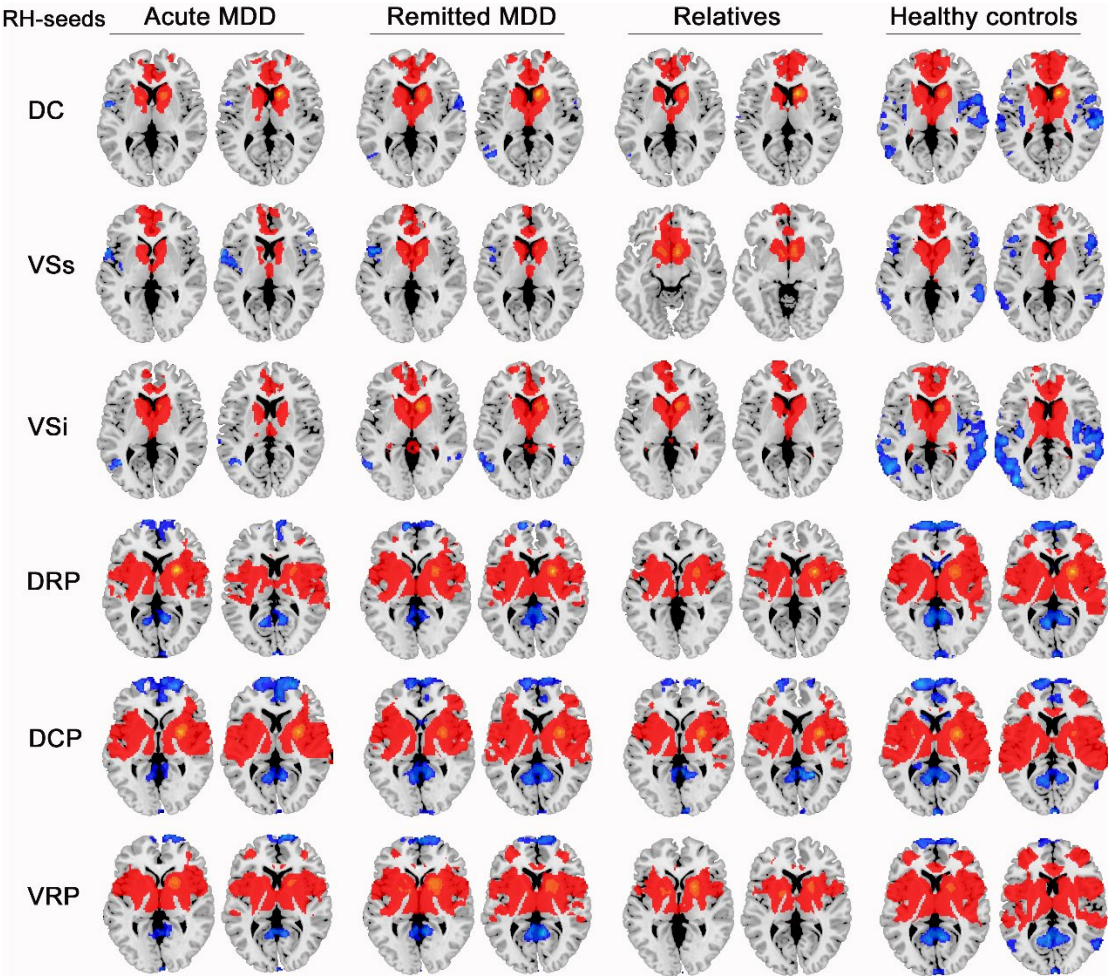


**Figure 2. Within-group striatal RSFC.**

The images displayed the corresponding positive (red) and negative (blue) resting-state functional connectivity (RSFC) of each striatal subregion from the right hemisphere (RH) in the 4 groups. DC: dorsal caudate, VSs: superior ventral striatum, VSi: inferior ventral striatum, DRP: dorsal rostral putamen, DCP: dorsal caudal putamen, VRP: ventral rostral putamen.

**Table 1. The correlation matrix for the 12 striatal seeds.**

| | R.DC | L.DC | R.VSs | L.VSs | R.VSi | L.VSi | R.DRP | L.DRP | R.DCP | L.DCP | R.VRP | L.VRP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R.DC | 1.00 | 0.35 | 0.26 | 0.26 | 0.04 | 0.04 | 0.13 | -0.07 | -0.08 | -0.08 | 0.11 | 0.13 |
| L.DC | 0.35 | 1.00 | 0.14 | 0.16 | -0.04 | -0.03 | 0.09 | -0.05 | 0.03 | 0.04 | 0.10 | 0.13 |
| R.VSs | 0.26 | 0.14 | 1.00 | 0.40 | 0.45 | 0.49 | 0.01 | -0.03 | -0.10 | -0.07 | 0.21 | 0.11 |
| L.VSs | 0.26 | 0.16 | 0.40 | 1.00 | 0.25 | 0.53 | 0.00 | -0.03 | -0.01 | -0.07 | -0.11 | 0.09 |
| R.VSi | 0.04 | -0.04 | 0.45 | 0.25 | 1.00 | 0.65 | -0.04 | -0.02 | -0.08 | 0.00 | 0.13 | 0.04 |
| L.VSi | 0.04 | -0.03 | 0.49 | 0.53 | 0.65 | 1.00 | -0.07 | -0.05 | -0.10 | -0.07 | 0.01 | 0.02 |
| R.DRP | 0.13 | 0.09 | 0.01 | 0.00 | -0.04 | -0.07 | 1.00 | 0.50 | 0.66 | 0.51 | 0.65 | 0.49 |
| L.DRP | -0.07 | -0.05 | -0.03 | -0.03 | -0.02 | -0.05 | 0.50 | 1.00 | 0.46 | 0.73 | 0.46 | 0.52 |
| R.DCP | -0.08 | 0.03 | -0.10 | -0.01 | -0.08 | -0.10 | **0.66** | 0.46 | 1.00 | 0.52 | 0.41 | 0.37 |
| L.DCP | -0.08 | 0.04 | -0.07 | -0.07 | 0.00 | -0.07 | **0.51** | **0.73** | **0.52** | 1.00 | 0.41 | 0.50 |
| R.VRP | 0.11 | 0.10 | 0.21 | -0.11 | 0.13 | 0.01 | **0.65** | 0.46 | 0.41 | 0.41 | 1.00 | 0.57 |
| L.VRP | 0.13 | 0.13 | 0.11 | 0.09 | 0.04 | 0.02 | 0.49 | **0.52** | 0.37 | 0.50 | **0.57** | 1.00 |

**Table 2. Medication status of each subject within the currently depressed and remitted groups.**

| aMDD | Medication(type/dose) | rMDD | Medication(type/dose) |
|---|---|---|---|
| sub_001 | Sertraline(SSRI, 50mg/day) | sub_001 | Citalopram(SSRI, 50mg/day) |
| sub_002 | Sertraline(SSRI, 50mg/day) | sub_002 | Paroxetine(SSRI, 10mg/day) |
| sub_003 | Trazodone(TeCAs, 150mg/day) | sub_003 | Sertraline(SSRI, 50mg/day) |
| sub_004 | Citalopram(SSRI, 40mg/day) | sub_004 | Sertraline(SSRI, 100mg/day) |
| sub_005 | Venlafaxine(SNRI, 150mg/day) | sub_005 | Maprotiline(TeCAs, 150mg/day) |
| sub_006 | Mirtazapine(NaSSA, 15mg/day) | sub_006 | Sertraline(SSRI, 50mg/day) |
| sub_008 | Sertraline(SSRI, 50mg/day) | sub_007 | Escitalopram(SSRI, 10mg/day) |
| sub_010 | Venlafaxine(SNRI, 150mg/day) | sub_008 | Paroxetine(SSRI, 40mg/day) |
| sub_012 | unmedicated | sub_010 | Paroxetine(SSRI, 50mg/day) |
| sub_013 | unmedicated | sub_011 | unmedicated |
| sub_014 | Escitalopram(SSRI, 20mg/day) | sub_012 | Venlafaxine(SNRI, 150mg/day) |
| sub_017 | Paroxetine(SSRI, 20mg/day) | sub_014 | Citalopram(SSRI, 40mg/day) |
| sub_018 | unmedicated | sub_015 | Paroxetine(SSRI, 20mg/day) |
| sub_019 | unmedicated | sub_016 | Fluvoxamine(SSRI, 75mg/day) |
| sub_020 | unmedicated | sub_017 | Escitalopram(SSRI, 40mg/day) |
| sub_021 | Escitalopram(SSRI, 20mg/day) | sub_019 | Sertraline(SSRI, 50mg/day) |
| sub_022 | Venlafaxine(SNRI, 75mg/day) | sub_020 | unmedicated |
| sub_023 | unmedicated | sub_021 | Maprotiline(TeCAs, 150mg/day) |
| sub_024 | Venlafaxine(SNRI, 150mg/day) | sub_022 | Fluoxetine(SSRI, 20mg/day) |
| sub_025 | Venlafaxine(SNRI, 75mg/day) | sub_023 | Venlafaxine(SNRI, 75mg/day), Deanxit(OToA, 0.5gmg/day) |

| | | | |
|---|---|---|---|
| sub_026 | Escitalopram(SSRI, 5mg/day) | sub_024 | Venlafaxine(SNRI, 75mg/day) |
| sub_027 | Paroxetine(SSRI, 20mg/day) | sub_025 | Venlafaxine(SNRI, 75mg/day) |
| sub_028 | Citalopram(SSRI, 20mg/day) | sub_026 | Paroxetine(SSRI, 20mg/day), Mirtazapine(NASSA, 15mg/day) |
| sub_029 | Citalopram(SSRI, 20mg/day) | sub_027 | Sertraline(SSRI, 100mg/day) |
| sub_030 | Escitalopram(SSRI, 20mg/day) | sub_028 | Citalopram(SSRI, 40mg/day) |
| sub_032 | Paroxetine(SSRI, 50mg/day) | sub_030 | Amitriptyline(TCAs, 150mg/day) |
| sub_034 | Escitalopram(SSRI, 10mg/day) | | |
| sub_035 | Escitalopram(SSRI, 10mg/day) | | |
| sub_036 | Escitalopram(SSRI, 10mg/day) | | |

**Table 3. Sample characteristics.**

| | Medicated depressed patients(n=23) | Unmedicated depressed patients(n=6) | F/t | p |
|---|---|---|---|---|
| Gender (M/F) | 8/13 | 5/1 | 0.082 | 0.169 |
| Age (years) | 32.8±12.2 | 42.5±8.2 | -1.826 | 0.079 |
| Education (years) | 11.3±3.0 | 12.5±2.1 | -0.871 | 0.391 |
| Duration (months) | 82.9±107.5 | 95.7±126.1 | -0.249 | 0.805 |
| Duration of current episode (months) | 5.1±5.5 | 9.2±6.2 | -1.615 | 0.118 |
| Previous depressive episode | 3.3±1.4 | 3.2±1.5 | 0.217 | 0.830 |
| Total HAMD | 21.8±3.2 | 22.8±2.6 | -0.716 | 0.480 |
| FD | 0.08±0.04 | 0.08±0.05 | -0.254 | 0.801 |

Data are expressed as mean ± SD.

Abbreviations: M, male; F, female; FD, framewise displacement; HAMD, Hamilton Rating Scale for Depression.

**Table 4. Between-group differences in striatal RSFC.**

| Seed | Regions with FC peak | Voxels | Statistics (F) | MNI coordinates x, y, z | Post-hoc analysis |
|---|---|---|---|---|---|
| Left DC | Insula | 81 | 8.330 | 34, -14, 6 | aMDD, rMDD, relative > HC |
| Right DC | Superior frontal gyrus | 102 | 9.209 | 34, -8, 64 | aMDD > rMDD, HC, relative |
| Left DRP | Anterior cingulate cortex | 87 | 8.332 | 12, 18, 26 | aMDD, relative < rMDD, HC |
| | Lentiform nucleus | 81 | 7.556 | 32, 8, -10 | aMDD < rMDD, HC |
| Right DRP | Anterior cingulate cortex | 49 | 9.681 | 8, 32, 16 | aMDD < rMDD, HC, relative |
| Left DCP | Putamen | 106 | 7.252 | -28, 8, 2 | aMDD < rMDD, HC |
| | Thalamus | 135 | 5.819 | 10, -18, -2 | aMDD, rMDD, relative < HC |
| Right DCP | Anterior cingulate cortex | 185 | 7.712 | 10, 32, 14 | aMDD < rMDD, HC, relative |
| | Cerebellum anterior lobe | 152 | 6.364 | -6 -64 -34 | aMDD, rMDD, relative < HC |
| Left VRP | Putamen | 70 | 9.485 | -28, 14, 2 | aMDD < rMDD, HC |
| Right VRP | Putamen | 83 | 7.455 | 28, 10, 12 | aMDD < rMDD, HC |
| | Cerebellum posterior lobe | 111 | 8.567 | -46, -56, -38 | rMDD, relative < HC |

aMDD, acute major depressive disorder; rMDD, remitted MDD; HC, healthy control; DC, dorsal caudate; DRP, dorsal rostral putamen; DCP, dorsal caudal putamen; VRP, ventral rostral putamen.

**Table 5. The comparisons in striatal RSFC between currently depressed and remitted patients as well as between HCs and first-degree relatives.**

| | aMDD-rMDD | Relative-HC |
|---|---|---|
| | **Regions(coordinates), voxels, F** | **Regions(coordinates), voxels, F** |
| L.DC | No | R.Insula(46,-16,6), 278, 4.016 |
| | | L.Inferior frontal gyrus(-22,38,-22), 426, -5.043 |
| R.DC | | No |
| L.VSs | No | No |
| R.VSs | L.Inferior frontal gyrus(-14,24,-22), 457, -4.413 | L.Superior frontal gyrus(-14,62,28), 4.866, 275 |
| R.VSi | No | No |
| L.VSi | | R.Cerebellum(54,-66,-30), -4.957, 399 |
| | | L.Cerebellum(-16,-88,-36), -3.606, 320 |
| L.DRP | R.Lentiform nucleus/Putamen(16,-6,10), 161, -4.515 | No |
| | L.Lentiform nucleus/Putamen(-30,18,-2), 339, -6.123 | |
| | R.Anterior cingulate cortex(10,30,24), 113, -4.777 | |
| | L.Anterior cingulate cortex(-2,12,44), 878, -5.159 | |
| R.DRP | R.Lentiform nucleus/Putamen(30,16,-10), 1061, -4.725 | No |
| | L.Lentiform nucleus/Putamen(-26,6,0), 682, -4.468 | |
| L.DCP | L.Lentiform nucleus/Putamen(-26,6,0), 476, -4.353 | No |
| R.DCP | R.Anterior cingulate cortex(10,28,16), 507, -4.346 | No |
| | L.Lentiform nucleus/Putamen(-12,-12,16), 366, -4.281 | |
| L.VRP | R.Lentiform nucleus/Putamen(12,4,12), 637, -4.521 | L.Middle frontal gyrus(-40,18,48), 624, 4.633 |
| R.VRP | R.Lentiform nucleus/putamen(24,10,-10), 225, -5.177 | No |