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Striatum-Based Circuitry of Adolescent Depression and Anhedonia

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Abstract

Objective—Striatum-based circuits have been implicated in both major depressive disorder (MDD) and anhedonia, a symptom that reflects deficits of reward processing. Yet adolescents with MDD often exhibit a wide range of anhedonia severity. Addressing this clinical phenomenon, we aimed to use intrinsic functional connectivity (iFC) to study striatum-based circuitry in relation to categorical diagnosis of MDD and anhedonia severity.

Method—A total of 21 psychotropic medication-free adolescents with MDD and 21 healthy controls (HC), group-matched for age and sex, underwent resting-state functional magnetic resonance imaging (fMRI) scans. Voxelwise maps indicating correlation strengths of spontaneous blood-oxygenation-level-dependent (BOLD) signals among 6 bilateral striatal seeds (dorsal caudate, ventral caudate, nucleus accumbens, dorsal-rostral putamen, dorsal-caudal putamen, ventral-rostral putamen) and the remaining brain regions were compared between groups. Relationships between striatal iFC and severity of MDD and anhedonia were examined in the MDD group. Analyses were corrected for multiple comparisons.

Results—Adolescents with MDD manifested increased iFC between all striatal regions bilaterally and the dorsomedial prefrontal cortex (dmPFC), as well as between the right ventral caudate and the anterior cingulate cortex (ACC). MDD severity was associated with iFC between the striatum and midline structures including the precuneus, posterior cingulate cortex, and

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dmPFC. However, distinct striatal iFC patterns involving the pregenual ACC, subgenual ACC, supplementary motor area, and supramarginal gyrus were associated with anhedonia severity.

Conclusions—Although MDD diagnosis and severity were related to striatal networks involving midline cortical structures, distinct circuits within the reward system were associated with anhedonia.

Keywords

depression; functional connectivity; functional magnetic resonance imaging (fMRI); intrinsic functional connectivity (iFC)

Adolescent major depressive disorder (MDD) is a profoundly disabling illness, yet its pathophysiology and underlying neural circuitry remain poorly defined. It has become evident that the inherent heterogeneity of psychiatric disorders has been a major impediment to the development of reliable biomarkers. Therefore, the field has emphasized the importance of investigating specific symptoms along the continuum of severity. Anhedonia, a core symptom of MDD that reflect deficits in reward processing, has been the target of such investigations.¹⁻³ Although anhedonia is highly prevalent among depressed adolescents,⁴ its extent is quite variable which results in contrasting MDD phenotypes.^{5,6} Notably, converging evidence, including recent data from the Treatment of Resistant Depression in Adolescents (TORDIA) multisite trial, indicates that anhedonia may represent a negative prognostic predictor for suicide and treatment response.⁷⁻⁹ In our previous work, we identified specific neurobiological correlates of anhedonia involving the immune system² and the major inhibitory neurotransmitter γ -aminobutyric acid (GABA).³ The current study extends this line of work by investigating striatal circuitry in adolescents with MDD as it relates to anhedonia severity.

Converging evidence suggests that anhedonia reflects disturbances in reward circuitry tied to the mesolimbic striatum-based system underlying reward processing.^{10,11} Because anhedonia is a core symptom of MDD, functional magnetic resonance imaging (fMRI) studies have used pleasant stimuli (images) or reward-related tasks to study MDD. Broadly, the most consistent findings have been hypoactivation of the ventral and dorsal striatum along with altered activation (both hyper- and hypoactivation) in the medial prefrontal cortex (PFC), specifically the dorsomedial PFC (dmPFC) and the perigenual (pg) and subgenual (sg) anterior cingulate cortex (ACC).¹²⁻¹⁸ However, most of these studies did not account for interindividual differences in anhedonia severity among the examined population. Here, we used a seed-based approach to investigate resting-state functional connectivity (RSFC) and to illuminate striatum-based circuitry related to adolescent MDD and anhedonia. RSFC identifies functional networks based on patterns of correlation in low-frequency fluctuations of blood-oxygenation-level-dependent (BOLD) signals during rest, referred to as intrinsic functional connectivity (iFC).¹⁹⁻²² The absence of a task minimizes potential floor, ceiling, and practice effects and allows recruitment of subjects who would not otherwise be able to perform a cognitive task satisfactorily (e.g., younger or more severely ill subjects). There have been multiple RSFC investigations in adult MDD and a few in pediatric MDD populations. These studies confirm task-based fMRI findings of alterations in fronto-striatal-limbic circuits along with medial wall abnormalities in both adults²³⁻²⁷ and adolescents with MDD.²⁸⁻³⁰ However, findings have been conflicting as to whether MDD is associated with increased³¹⁻³⁴ or decreased^{17,24,29,35} iFC along these circuits. This inconsistency may be related to the techniques used, as these studies have not directly examined striatal circuitry. Indeed, a recent study of striatal circuitry in adults with MDD reported decreased iFC between the ventral striatum and the sgACC but increased iFC between the dorsal caudate and dorsolateral PFC.³⁶

Building upon these observations, our aims were to study striatum-based iFC in adolescents with MDD and its relationships to severity of illness and anhedonia. We used a previously validated set of 6 bilateral striatal seeds consisting of the dorsal and ventral caudate, the nucleus accumbens (NAc), and the dorsal (caudal and rostral) and ventral putamen.³⁷⁻⁴⁰ Based on prior resting-state and task-based fMRI findings in pediatric and adult MDD,¹²⁻²¹ we hypothesized the following: that, compared to healthy controls (HC), psychotropic-medication-free adolescents with MDD would exhibit altered iFC along frontostriatal circuits involving both the dmPFC and ACC (specifically decreased iFC with ventral striatum seeds and increased iFC with dorsal caudate seeds, per prior seed-based striatal findings in adult MDD³⁶); and that, in the MDD group, anhedonia severity would be associated with strength of striatal iFC with brain regions identified in the group comparison, particularly the dmPFC and ACC. Furthermore, in light of substantial data linking the sgACC and pgACC with reward circuitry, we expected that these regions would be separately identified in relation to anhedonia severity. Analyses were repeated using a set of 3 bilateral striatal seeds corresponding to the entire caudate, putamen, and NAc, with results provided in Supplement 1, available online.

Method

Study Participants

We enrolled 21 adolescents with MDD (aged 12–19 years, mean 17.1 ± 2.5 , 12 female and 9 male) and 21 HC (aged 13–19, mean 16.3 ± 1.4 , 12 female and 9 male), group-matched for age, sex, and handedness. Fourteen subjects in each group were also enrolled in a prior proton MR spectroscopy study of GABA in adolescents with MDD and anhedonia.³ Subjects with MDD were recruited from the New York University (NYU) Child Study Center, from the Bellevue Hospital Center Department of Psychiatry, and through local advertisements in the New York (NY) metropolitan area. Healthy control (HC) subjects were recruited from the greater NY metropolitan area through local advertisements and from the families of NYU staff. This study was approved by the NYU School of Medicine Institutional Review Board and the NYU University Committee on Activities Involving Human Subjects. Before baseline clinical evaluations, study procedures were explained to subjects and parents. Participants aged 18 years and older provided informed consent; those less than 18 years provided assent and a parent-provided informed consent.

Inclusion and Exclusion Criteria—Exclusion criteria for all subjects consisted of the presence of any significant medical or neurological disorder, IQ < 80, claustrophobia, or any MRI contraindication as assessed by a standard safety screening form, a positive urine toxicology test, or a positive urine pregnancy test in females.

All adolescents with MDD met the *DSM-IV-TR* diagnosis of MDD with current episode 8 weeks duration, raw severity score 40 (T score 63) on the Children's Depression Rating Scale–Revised (CDRS-R), and psychotropic-medication-free status 3 months.

Exclusionary diagnoses included a lifetime history of bipolar disorder, schizophrenia, pervasive developmental disorder, panic disorder, obsessive-compulsive disorder, conduct disorder, or Tourette's disorder; or a substance-related disorder in the past 12 months. A current diagnosis of posttraumatic stress disorder or an eating disorder was also exclusionary.

HC subjects did not meet criteria for any current or past *DSM-IV-TR* diagnoses and had never received psychotropic medication.

Clinical Assessments—Subjects and parents were interviewed by a board-certified child and adolescent psychiatrist (V.G., C.A.) at the NYU Child Study Center. Diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS-PL),⁴¹ a semistructured interview completed with subjects and parents. Additional assessments included the CDRS-R and the Beck Depression Inventory, 2nd edition (BDI-II).⁴² IQ was estimated with the Kaufman Brief Intelligence Test⁴³ or the Wechsler Abbreviated Scale of Intelligence.⁴⁴ Urine toxicology and pregnancy tests were administered on the day of the scan.

Severity of MDD Episode—The severity of MDD episodes was determined from CDRS-R scores.

Anhedonia—The anhedonia score (range 1–13) for each subject was computed, as in our previous work,³ by summing the responses associated with anhedonia on a self-rated questionnaire and a clinician-rated scale: the self-rated BDI-II (0–3 points for item 4: “loss of pleasure” and 0–3 points for item 12: “loss of interest”); and the clinician-rated CDRS-R (1–7 points for item 2: “difficulty having fun”). Thus, clinician- and self-rated assessments each contributed equally to the computed anhedonia score (0–6 points from the BDI-II and 1–7 points from the CDRS-R). Such an approach has been previously used to assess anhedonia severity in others' and our laboratories.^{1,3,7,45,46}

Data Acquisition

Imaging data were acquired on a Siemens Allegra 3.0T scanner at the NYU Center for Brain Imaging. For each participant, a high-resolution T₁-weighted anatomical image (magnetization prepared rapid acquisition gradient-echo [MPRAGE]; repetition time [TR] = 2,500 ms; echo time [TE] = 3.93 ms; inversion time [TI] = 600 ms; flip angle = 8°; 176 slices; field of view [FOV] = 256 × 256 mm²; voxel size = 1×1×1 mm³) was acquired. Resting-state fMRI data were acquired using an echo planar imaging (EPI) sequence (197 whole-brain volumes; TR = 2,000 ms; effective TE = 25 ms; flip angle = 90°; 39 contiguous 3-mm oblique axial slices parallel to the AC-PC; matrix = 64×64; FOV = 192×192 mm²; voxel size = 3×3×3 mm³). Participants were asked to relax with their eyes open while the word “Relax” was displayed.

Data Analysis

Image Preprocessing—Consistent with prior work, we used a combination of AFNI (<http://afni.nimh.nih.gov/afni>) and the FMRIB software library tool (FSL, www.fmrib.ox.ac.uk).^{47–49} Resting-state data preprocessing comprised slice time correction for interleaved slice acquisition, 3D motion correction, despiking, spatial smoothing (using a 3D spatial filter implemented in FSL with full width at half maximum (FWHM) = 6 mm), mean-based intensity normalization of all volumes by the same factor, temporal bandpass filtering (0.009–0.1 Hz) and linear and quadratic detrending. Linear registration of high-resolution structural images to the Montreal Neurological Institute MNI152 template with 2×2×2 mm³ resolution was carried out using the FSL tool FLIRT, and was then refined using FNIRT nonlinear registration.⁵⁰ Linear registration of each participant's functional data to his or her high-resolution structural image was also carried out using FLIRT.

Nuisance Signal Regression—As described elsewhere,³⁹ to control for motion, physiological nuisance signals (e.g., cardiac and respiratory fluctuations), and the large-scale global neural signal(s) present in all voxels throughout the cortex,⁵¹ we regressed the pre-processed data on the following 9 nuisance covariates: white matter, cerebrospinal fluid, 6 motion parameters, and the global signal. The resultant 4-dimensional residual time-series

were transformed into MNI152 2-mm standard space and used for subsequent participant-level correlation analyses.

As there remains controversy regarding whether to correct for the global signal,^{21,51-53} and how to do so without introducing artifactual findings,⁵⁴ we repeated analyses without global signal correction. These results, which are consistent with our primary findings, are presented in Supplement 1 and Table S2, available online.

Selection of Regions of Interest—We used 6 bilateral striatal seeds as described by Di Martino *et al.* (2008).³⁷ Each seed region of interest (ROI) was approximately spherical (volume = $257 \times 1 \text{ mm}^3$ voxels, radius = $\sim 4 \text{ mm}$). These were located (in MNI152 space) in the following: nucleus accumbens (NAc; $\pm 9, 9, -8$); ventral caudate (VC; $\pm 10, 15, 0$); dorsal caudate (DC; $\pm 13, 15, 9$), dorsal caudal putamen (DCP; $\pm 28, 1, 3$); dorsal rostral putamen (DRP; $\pm 25, 8, 6$), and ventral rostral putamen (VRP; $\pm 20, 12, -3$). These seed ROI were defined based on anatomical and functional subdivisions of the striatum,^{55,56} and their iFC patterns have been replicated independently.^{38-40,57} Secondary analyses, focusing on broader striatal divisions, used a set of 3 anatomically defined ROI consisting of the right and left caudate, putamen, and NAc as defined by the Harvard-Oxford Structural Atlas;⁵⁸ the results of these analyses were largely confirmatory and are available in Supplement 1, Table S1, and Figures S1–S3, available online.

Subject-Level iFC Analysis—For each participant, we first resampled the 4-dimensional EPI residuals to $1 \times 1 \times 1 \text{ mm}^3$ and applied seed masks to the resampled data to obtain representative time series from the seed ROI. Each extracted seed ROI time series was then used to calculate the correlation between it and that of every other voxel in the EPI residuals data in native (i.e., acquisition) space to derive iFC maps. The resultant participant-level correlation maps were Fisher z transformed to Z-value maps and transformed into MNI152 2 mm^3 standard space for group-level analyses.

Group-Level iFC Analysis and Brain–Behavior Associations—Analyses of group-level iFC for adolescents with MDD versus HC were carried out using a random-effects least-squares model implemented in FSL (nuisance covariates: age, sex, full-scale IQ). This group-level analysis produced thresholded Z-score maps of positive and negative iFC for each striatal ROI and for each condition. Direct voxelwise condition comparisons of the 2 groups (HC, MDD) produced thresholded Z-score maps of those voxels that showed significant iFC differences between the groups for each ROI.

To assess dimensional relationships between striatal iFC and anhedonia, voxel-wise regression analyses were carried out in the MDD group, with anhedonia scores as the covariate of interest. Since severity of MDD episode and anhedonia scores were significantly correlated, all analyses controlled for CDRS-R scores with the anhedonia question omitted to account for the nonspecific influences of depressive episode severity. Resulting relationships between iFC and our clinical variables are thus partial correlations. The HC group was excluded from this analysis because of the limited range of anhedonia scores.

For all analyses, cluster-level corrections for multiple comparisons were performed using Gaussian random field theory ($Z > 2.3$; cluster significance: $p < .008$ corrected; $p < .008$ was selected to take into account the number of independent seed regions used ($0.008 = 0.05/6$). Six, as opposed to 12, seed ROIs were considered, given the high degree of correlated activity between homotopic seed regions^{59,60}). Scatterplots found in Figures 2 and 3, and in S4, available online, demonstrating the iFC relationships for all significant clusters, are for illustrative purposes only and were not used for calculating r values.

Results

Participants

Demographic and clinical characteristics are summarized in Table 1. One subject with MDD had been treated with escitalopram for 6 months but was medication-free for 9 months before scanning. All other subjects were psychotropic-medication-naive. Nineteen subjects with MDD (90%) had experienced only 1 episode of depression, with length of episode ranging from 4 to 30 months, and 2 patients reported having 2 distinct episodes.

Anhedonia scores were positively correlated with MDD severity scores, as indexed by CDRS-R scores ($r = 0.68, p < .001$). Because our anhedonia scale included the anhedonia-related item from the CDRS-R, we retested the correlation between anhedonia scores and the CDRS-R computed without the anhedonia item. The correlation remained significant ($r = 0.56, p = .008$).

Movement

Head movement during resting-state scans was approximated using 5 estimators: mean head displacement, maximum head displacement, number of micromovements (> 0.1 mm), head rotation,⁶¹ and mean framewise displacement (FD).⁶² These estimators were calculated from the 6 translation and rotation parameters of 3-dimensional motion correction during data preprocessing. Independent-samples *t* tests were conducted to compare these estimators between MDD and HC groups, and no significant differences were found for any of the movement measures (all $p > 0.5$; Table 2). Although motion was relatively low in the sample used for the present work and was unrelated to diagnostic status or our covariates of interest (i.e., MDD severity and anhedonia), we repeated our analyses with mean FD⁶² as a nuisance covariate at the group level to rule out any motion sensitivities for our findings (Table S3 and Figures S5–S7, available online). Nearly all findings remained unchanged; a notable exception was the relationship between anhedonia and NAc/sgACC iFC, which fell below threshold. Reassuring overall, we recommend some caution regarding the sgACC finding until replicated in future work. Given the relatively low occurrence of motion in the present sample, we avoided use of higher-order regression models for motion correction at the individual subject level.⁶³

Primary Hypothesis Testing: Striatal iFC Group Comparisons

MDD Group versus HC—Consistent with our hypothesis, group analyses revealed that adolescents with MDD manifested increased iFC between striatal seeds and the dmPFC, regardless of the hemisphere in which the seed was located. Decreased iFC in the MDD group was identified between striatal seeds and mainly the occipital cortex. Additional findings are detailed below, based on seed locations, as well as in Table 2 and Figure 1. Similar findings from our secondary analysis are presented in Table S1 and Figure S1, available online. Baseline connectivity maps for each seed region (based on the HC group) and overlays of findings for each seed are available in Figure S8, available online.

Caudate—Adolescents with MDD compared to HC exhibited increased iFC between the right ventral caudate and the ACC, including both the pregenual (pgACC) and subgenual (sgACC) regions of the ACC. Adolescents with MDD exhibited decreased iFC between the left dorsal caudate and the superior temporal lobe, as well as between the left ventral caudate and the postcentral gyrus.

Putamen—Within the putamen, adolescents with MDD also manifested increased iFC between the right ventral rostral putamen and the paracingulate gyrus, and between the right dorsal rostral putamen and the inferior frontal gyrus.

Nucleus Accumbens—Relative to HC, adolescents with MDD exhibited decreased iFC between the right NAc and the middle temporal gyrus.

Associations of Striatal iFC With Clinical Variables in the MDD Group

MDD Severity—As indexed by CDRS-R scores, MDD severity was positively correlated with iFC strength between the right ventral rostral putamen seed and the precuneus/posterior cingulate cortex (PCC). Interestingly, negative correlations with MDD severity were observed for iFC strength between the bilateral dorsal caudate and the precuneus/PCC. Negative correlations between MDD severity and iFC were also observed between the right NAc seed and the dmPFC. Findings are detailed in Table 2 and presented in Figure 2. Severity findings from our secondary analysis were largely consistent and are presented in Table S1 and Figure S2, available online.

Anhedonia Severity—As noted, because anhedonia scores were positively correlated with the severity of current depressive episode, we carried out analyses adjusted at the cluster level for CDRS-R scores with the anhedonia question omitted. The majority of anhedonia-related findings were in the caudate. Specifically, anhedonia scores were positively correlated with iFC strength of the ventral and dorsal caudate seeds with the supplementary motor area (SMA), middle frontal gyrus, supramarginal gyrus, precuneus, and pgACC, as well as between the right dorsal rostral putamen and the supramarginal gyrus. Negative correlations were found between the left NAc and both the sgACC and the left caudate, and between the right NAc and the occipital fusiform cortex. Anhedonia correlations are detailed in Table 2 and presented in Figure 3, with additional correlation plots provided in Figure S4, available online. Our secondary analysis yielded similar results (Table S1 and Figure S3, available online).

Discussion

Our hypotheses that adolescents with MDD would manifest altered iFC along frontostriatal circuits were confirmed; however, we detected only increased iFC compared to HC. Similarly, we were able to detect distinct patterns of striatum-based circuitry that were related to illness and anhedonia severity beyond our specific hypotheses. These findings are discussed below.

Striatal Circuitry Based on a Categorical Diagnostic Approach

In group comparisons, adolescents with MDD manifested increased iFC between striatal seeds and the dmPFC bilaterally, and between the right ventral caudate seed and the ACC. Unexpectedly, we also found that adolescents with MDD manifested decreased iFC in circuits connecting the striatum with the occipital cortex.

Our finding of increased connectivity between the striatum and dmPFC/ACC implies a higher degree of coordination between these regions in adolescents with MDD. As noted, there have been reports of both increased³¹⁻³⁴ and decreased^{17,24,29,35} striatum-PFC iFC in MDD patients compared to HC. However, most relevant to the current study is a recent striatal-seed iFC investigation in adult MDD reporting increased striatum-PFC iFC for dorsal striatum seeds versus decreased striatum-PFC iFC for ventral striatum seeds.³⁶ In contradiction to this study in adult MDD, we found only increased striatal-PFC iFC, and our hypothesis that patients would exhibit decreased iFC between ventral striatum seeds and the PFC was not supported. Interestingly, we did find a negative correlation between MDD severity and iFC strength of the ventral-striatal NAc seed within the same network, suggesting that the lower the coordination between the ventral striatum and the dmPFC, the greater the illness severity. Our finding of increased increased iFC within the fronto-striatal

circuits observed in adolescents with MDD compared to HC may reflect an earlier manifestation or compensatory process of the disease. As such, this finding may be used in the future to assess early stages of the disorder or at-risk individuals.

The coordinates of peak cluster activity also differ substantially between the NAc group comparison and MDD severity correlation findings, with the left dmPFC involved in group differences and the right dmPFC associated with MDD severity (Table 2). Past research has indicated that the dmPFC responds to self-referential words with both positive and negative valence bilaterally, but the right dmPFC is more involved in positive self-referential processing.⁶⁴ These opposing findings may therefore be driven by functional differences in the distinct dmPFC regions detected.

Our finding of increased iFC between the striatum and both the dmPFC and the ACC in adolescents with MDD is consistent with mounting evidence implicating these specific circuits in MDD across the lifespan,^{10,12,13,65-67} using a wide range of imaging techniques.^{3,10,39,68-71} fMRI studies further support such findings through a wide range of task paradigms⁷²⁻⁷⁴ as well as diverse iFC approaches in adolescent,^{12,13,29,30,67} adult,^{27,74-76} geriatric,^{31,77} and postpartum patients.⁷² Histopathological reports have confirmed findings in the medial PFC and ACC, documenting reduction in neuron size and/or loss of glia in these regions in MDD.⁷⁸⁻⁸⁰ A possible explanation for the consistent involvement of striatum-dmPFC/ACC circuits in MDD is their critical role in the cognitive control of reward, reappraisal, mood, and reasoning: processes that contribute to key symptoms of MDD.⁸¹⁻⁸³ A germane meta-analysis supports the view that these cortical midline structures, along with their striatal connections, mediate self-referential processes and constitute the core of both our sense and our feeling of self.⁸⁴ Findings from a recent iFC study in adults with MDD provide additional support for this notion by identifying a “dorsal nexus” region centered around the dmPFC that exhibits increased iFC with 3 distinct networks involved in cognitive control, affect, and the default mode.²⁷ Recent work has further identified the dmPFC as a distinct subsystem within the default mode network that is activated in spontaneous cognition involving self-referential thoughts about one's mental state and affective information, as well as those that involve spontaneous social cognition—processes that are disturbed in MDD.⁸⁵⁻⁸⁸

We also found decreased iFC between striatal seeds and the occipital cortex in adolescents with MDD compared to HC. Albeit unexpected, a large body of evidence has pointed to the possible role of the occipital lobe in MDD. Findings include changes in metabolism,^{89,90} white matter alterations,^{91,92} and increased BOLD signal in response to neutral faces⁹³ and during a working memory task.⁹⁴ Adding to this literature is a recent iFC study that examined the topological properties of brain networks in adults with MDD and documented reduced nodal centrality in the occipital lobe among other relevant visual regions in MDD.⁹⁵ These findings are most likely related to the critical role of the occipital cortex in processing emotionally relevant visual stimuli.^{96,97} It is important to note that although occipital findings in resting-state fMRI can be affected by whether eyes are open or closed during scans,^{98,99} there is not a 1:1 relationship that would provide a direct explanation. Previous studies, including a key meta-analysis of emotional task-based fMRI paradigms,¹⁰⁰ noted the presence of an occipital network linked to the PCC. In addition, a growing body of literature suggests the presence of a functional hub based in cuneus, once again arguing against a simple explanation based on eyes-open status.¹⁰¹

Neural Circuitry Related to Illness and Anhedonia Severity

MDD Severity—In our dimensional analysis, MDD severity was associated with iFC strength between striatal seeds and both the precuneus/PCC and the dmPFC.

Both the precuneus and PCC are considered a major connectivity hub along with the dmPFC; together, they form the midline core of the default-mode network that is involved in spontaneous cognition, self-referential processing, and affective decision-making.^{88,101} Multiple investigations have repeatedly implicated these circuits in MDD.^{16,25-27,31,32}

In our study, we documented both positive and negative relationships between MDD severity and iFC strength in circuits linking the striatum and the precuneus/PCC, depending on the seed: positive correlations were identified with the right ventral putamen seed, and negative correlations with the dorsal caudate seeds. These opposite directions with different seeds suggest that the function of the ventral-putamen– based circuit differs from the caudate/NAc-based circuit. Indeed, in our prior investigation of the striatum, we concluded that a ventral-putamen– based network is involved with executive functioning, whereas the caudate is involved with cognition and reward.³⁷

Anhedonia—When we related striatum-based iFC to anhedonia severity, distinct circuits within the neural reward system were identified. Specifically, positive associations with anhedonia were found for circuits connecting the striatum and the pgACC, SMA, and supramarginal gyrus. In addition, anhedonia was negatively associated with circuits connecting the NAc with the sgACC and caudate. Intriguingly, these circuits and regions have been previously linked to anhedonia as well as to reward processes across several neuropsychiatric disorders, indicating that the circuitry underlying anhedonia is independent of the specific MDD diagnosis.^{11,102-106}

Furthermore, in our current investigation, we also documented 2 opposing striatum-ACC circuits that related to anhedonia severity: a positive association with ventral-caudate-pgACC iFC, and a negative association with NAc-sgACC iFC. We hypothesize that these contrasting associations represent independent circuits that participate in distinct reward processes. Supporting this notion are recent fMRI findings documenting pgACC activation during decisions that entail large versus small rewards, as opposed to sgACC activation during decisions with positive versus negative outcomes.¹⁰⁷ Similarly, our finding of a positive association of striatum-SMA iFC with anhedonia severity fits with current literature identifying the SMA as a key region in reward processing. The SMA has often been activated along with the pgACC in reward task-based fMRI studies, particularly during the anticipation/decision phase of reward.¹⁰⁸⁻¹¹⁰ We also found positive correlations between striatum-supramarginal-gyrus iFC and anhedonia severity; these findings are akin to a previously reported correlation between activation of this region in response to sad stimuli and anhedonia severity in adults with MDD.¹⁵ Interestingly, the supramarginal gyrus has also been implicated in adult obesity, where alterations within the reward circuitry are hypothesized to play a key role.¹⁰⁵

Although our sample size is comparable to those of other studies of clinical populations in the functional neuroimaging literature, definitive interpretation must be deferred until findings are replicated independently. A possible limitation of the current study is the use of an anhedonia scale that was based on questions from the BDI (self-rated) and the CDRS-R (clinician-rated). However, this approach has been used in many other investigations in both adults and adolescents, including in the multisite Treatment of Resistant Depression in Adolescents (TORDIA) trial, and seems to adequately assess anhedonia severity in MDD populations.^{3,7,46} Importantly, Leventhal *et al.* (2006) demonstrated that a similar scoring approach based on self-administered questionnaires correlated with other several anhedonia measures (e.g., the Snaith-Hamilton Pleasure Scale).¹¹¹ Furthermore, in our study we were able to capture a wide range of anhedonia severity (1–10) in a moderately to severely depressed population. Future studies should use measures that are more sensitive and applicable to both patients and controls, to fully explore the nature of anhedonia

neurobiology quantitatively. Similarly, the present work relied on task-independent approaches. Although this is an attractive option because of the relative ease of data collection and the benefits detailed above, future work should include task-activation probes with demonstrated utility in the examination of reward circuitry during distinct phases of a pleasurable activity (i.e., anticipatory versus attainment phases). Simultaneous assessment of neurotransmitters such as GABA and glutamate would also have enhanced our understanding of the involved circuits, particularly in light of our recent finding of a negative relationship between ACC GABA concentrations and anhedonia severity.³ Although the present work focused on striatal connectivity because of the sizeable literature implicating striatal dysfunction in MDD and anhedonia, it is not our intention to dissuade others from examining alternative circuits. In fact, our findings suggest the need to expand neural models of MDD, as our analyses revealed alterations in regions such as the occipital cortex and precuneus/PCC—prominent functional hubs in the brain.¹⁰¹

Our investigation of striatal iFC in medication-free adolescents with MDD revealed a consistent pattern of altered iFC between striatal seeds and the dmPFC/ACC, as well as the visual cortex, in adolescents with MDD. However, when we examined striatal circuits as they related to severity of depressive episode and anhedonia, we were able to distinguish specific connections. Although the precuneus along with the midline core of the default mode network (i.e., the PCC and dmPFC) was related to MDD severity, striatal circuits connecting to the SMA, pgACC, and sgACC were instead related to anhedonia severity. Importantly, our findings suggest that several previously established striatal networks, including cortical associations, motor, and limbic, are involved in the phenomenology of adolescent MDD (comprehensively reviewed by Choi *et al.*).¹¹² Our findings suggest that distinct circuits may contribute to different aspects of MDD. Consistent with prior work,^{3,20} this study further emphasizes that assessing symptoms as dimensions in addition to binary categories can enrich our understanding of the underlying neurobiology of psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Findings support the incorporation of both categorical and dimensional approaches in neuropsychiatric research. *J. Am. Acad. Child Adolesc.*

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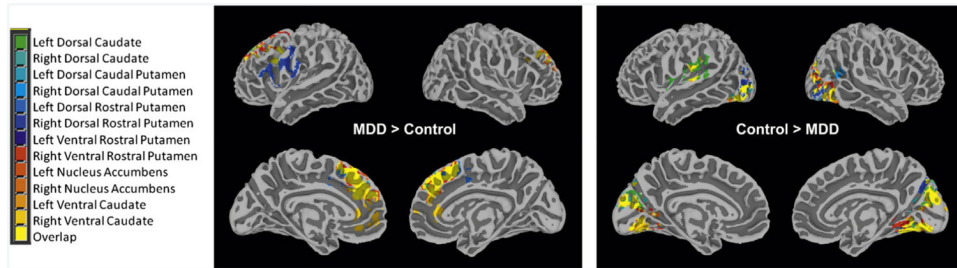


Figure 1. Intrinsic functional connectivity (iFC) group comparison between adolescents with major depressive disorder (MDD) and healthy controls. Note: Maps showing regions with (left) increased iFC in MDD versus controls, and (right) increased iFC in controls versus MDD. Significant iFC with each seed is color coded, with regions functionally connected with more than 1 seed indicated in yellow. Display threshold: $Z > 2.3$.

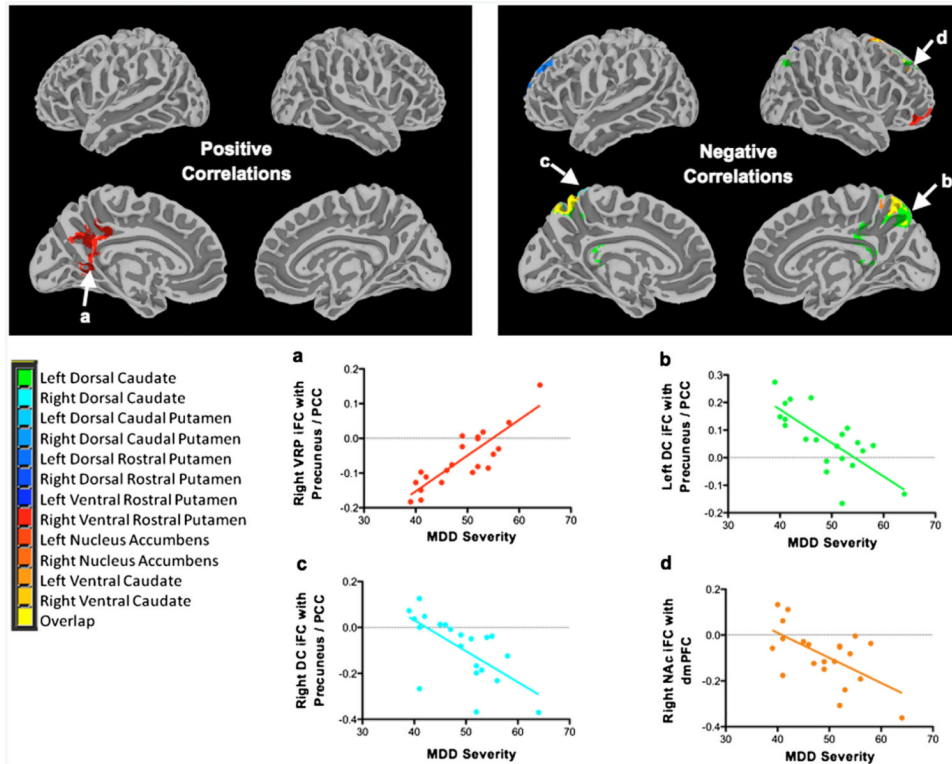


Figure 2. Intrinsic functional connectivity (iFC) correlations with major depressive disorder (MDD) severity and associated plots. Note: Maps showing regions with iFC (left) positively correlated with MDD severity and (right) negatively correlated with MDD severity. Plots a–d below demonstrate these relationships. Display threshold: $Z > 2.3$. DC = dorsal caudate; dmPFC = dorsomedial prefrontal cortex; NAc = nucleus accumbens; PCC = posterior cingulate cortex; VRP = ventral rostral putamen.

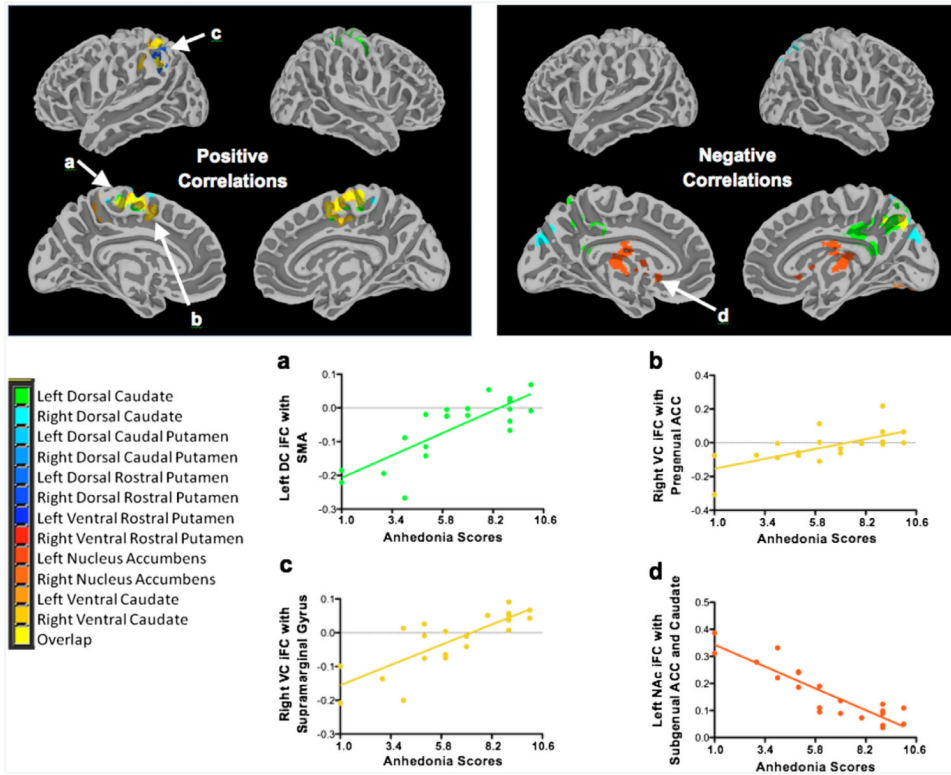


Figure 3. Intrinsic functional connectivity (iFC) correlations with anhedonia scores and representative plots. Note: Maps showing regions with iFC (left) positively correlated with anhedonia severity and (right) negatively correlated with anhedonia severity. Plots a–d below demonstrate several of these relationships. Additional plots are available in Figure S4, available online. Display threshold: $Z > 2.3$. ACC = anterior cingulate cortex; DC = dorsal caudate; NAc = nucleus accumbens; SMA = supplementary motor area; VC = ventral caudate.

Table 1
Demographic and Clinical Characteristics of Adolescents With Major Depressive Disorder (MDD) and Healthy Controls

Characteristic	MDD Subjects n = 21	Healthy Controls n = 21
Age, y (Range)	17.1 ± 2.5 (12–19)	16.3 ± 1.4 (13–19)
Gender (female/male), n (%)	12/9 (57/43)	12/9 (57/43)
Ethnicity (white/African American/Hispanic/Asian/other), n (%)	10/3/6/0/2 (48/14/29/0/10) ^a	10/5/1/2/3 (48/24/5/10/14) ^a
Illness history		
Current episode duration, mo (Range)	13.6 ± 7.9 (4–30)	0
No. of MDD episodes (n)	1 (n = 19), 2 (n = 2)	0 (n = 21)
History of suicide attempts (Range)	0.2 ± 0.5 (0–2)	0
Medication-naïve/medication-free, n (%)	20/1 (95/5)	21/0 (100/0)
CDRS-R (Range)	48.9 ± 6.8 (39–64)	19.1 ± 2.2 (17–27)
BDI-II (Range)	25.3 ± 12.5 (11–51)	1.9 ± 2.4 (0–9)
BSSI (Range)	5.6 ± 9.7 (0–37)	0.1 ± 0.2 (0–1)
MASC (Range)	50.0 19.5 (11–85)	31.2 13.1 (6–52)
Anhedonia scores (Range)	6.3 ± 2.7 (1–10)	1.3 ± 0.6 (1–3)
Current comorbidity		
ADHD, n (%)	3 (14)	0
Any anxiety disorder, n (%)	10 (48)	0
GAD, n (%)	8 (38)	0

Note: ADHD = attention-deficit/hyperactivity disorder; BDI-II = Beck Depression Inventory, 2nd ed.; BSSI = Beck Scale for Suicidal Ideation; CDRS-R = Children's Depression Rating Scale–Revised; GAD = generalized anxiety disorder; MASC = Multidimensional Anxiety Scale for Children.

^aRespective percentages (may not add up to 100% because of rounding).

Table 2
Intrinsic Functional Connectivity (iFC) Group Comparisons (Major Depressive Disorder [MDD] vs. Controls) and Correlations With MDD and Anhedonia Severity (MDD Only)

Intrinsic Functional Connectivity		Seed	Connectivity Peak	Cluster Size	Peak (MNI)			Peak Z	P
Region					X	Y	Z		
MDD > Controls									
Caudate	Right DC	dmPFC	2,430	-12	42	38	4.83	2.3×10^{-7}	
	Right VC	dmPFC and ACC	5,911	-18	40	36	4.82	1.07×10^{-11}	
Putamen	Left DRP	dmPFC	903	8	26	52	4.10	4.66×10^{-4}	
	Right DRP	Inferior frontal gyrus	951	-60	28	14	4.06	2.81×10^{-3}	
	Right VRP	dmPFC and paracingulate gyrus	2,618	6	24	48	4.25	1.79×10^{-7}	
Nucleus Accumbens	Right NAc	dmPFC	2,945	-22	46	26	4.69	5.96×10^{-8}	
Controls > MDD									
Caudate	Left DC	Superior temporal lobe	1,614	-66	-26	12	4.51	1×10^{-5}	
	Left DC	Occipital cuneal cortex	771	8	-78	30	3.78	5.27×10^{-3}	
	Left VC	Postcentral gyrus	656	-62	-22	16	4.08	6.06×10^{-3}	
	Right DC	Occipital cuneal cortex	1,750	-10	-90	26	4.48	1×10^{-5}	
	Right DC	Occipital lingual gyrus	877	-26	-60	-2	3.88	3.36×10^{-3}	
	Right VC	Occipital cuneal cortex	2,799	-22	-68	24	4.59	9.54×10^{-7}	
	Right VC	Occipital fusiform cortex	1,646	-28	-78	-14	4.13	1.82×10^{-4}	
Putamen	Left DRP	Occipital fusiform cortex	867	36	-72	-18	4.45	6.42×10^{-4}	
	Right DRP	Occipital fusiform cortex	1,300	36	-78	-18	4.55	2.87×10^{-4}	
	Right DRP	Lateral occipital cortex	1,029	34	-80	12	4.57	1.65×10^{-3}	
	Right DRP	Lateral occipital cortex	988	-40	-90	2	4.71	2.18×10^{-3}	
	Right VRP	Occipital fusiform cortex	1,172	-24	-74	-10	3.89	5.64×10^{-4}	
	Right VRP	Occipital cuneal cortex	3,591	18	-80	24	4.72	1×10^{-9}	
Nucleus Accumbens	Right NAc	Middle temporal gyrus	1,277	50	-54	-2	4.14	3.63×10^{-4}	
MDD: Positive CDRS-R Correlations									
Putamen	Right VRP	Precuneus and PCC	889	-2	-56	32	4.19	3.46×10^{-4}	

Intrinsic Functional Connectivity							
Region	Seed	Connectivity Peak	Cluster Size	Peak (MNI)			p
				X	Y	Z	
MDD: Negative CDRS-R Correlations							
Caudate	Left DC	Precuneus and PCC	1,716	6	-66	62	4.29 1.70×10 ⁻⁵
	Right DC	Precuneus and PCC	656	-4	-62	62	4.38 2.×10 ⁻³
Nucleus Accumbens	Right NAc	dmPFC	652	24	12	50	4.36 1.74×10 ⁻³
MDD: Positive Anhedonia Correlations							
Caudate	Left DC	Supplementary motor area	2,248	10	2	52	4.18 <.001
	Left VC	Supplementary motor area	679	10	2	52	4.14 <.001
	Left VC	Precuneus	620	-30	-52	52	3.88 <.001
	Right DC	Middle frontal gyrus	600	-18	-16	54	4.92 .001
	Right VC	Pregenuel ACC	607	16	-6	44	4.06 .004
	Right VC	Supramarginal gyrus	648	-54	-38	42	3.58 <.001
Putamen	Right DRP	Supramarginal gyrus	431	-52	-46	34	4.01 .003
MDD: Negative Anhedonia Correlations							
Nucleus Accumbens	Left NAc	Subgenual ACC and left caudate	939	-8	10	14	4.70 <.001
	Right NAc	Occipital fusiform cortex	391	24	-70	-12	3.82 .005
Motion Estimators							
Estimator	MDD Mean	MDD SD	Control Mean	Control SD			p
Mean relative displacement (mm)	0.039	0.006	0.044	0.009			>.6
Max relative displacement (mm)	0.353	0.053	0.443	0.141			>.5
No. of micro movements	17.857	5.084	19.810	5.619			>.7
Mean relative rotation (degrees)	0.011	0.001	0.012	0.002			>.6
Mean framewise displacement (mm)	0.72	0.016	0.88	0.019			>.5

Note: ACC = anterior cingulate cortex; CDRS-R = Children's Depression Rating Scale-Revised; DC = dorsal caudate; DCP = dorsal caudal putamen; dmPFC = dorsomedial prefrontal cortex; DRP = dorsal rostral putamen; MNI = Montreal Neurological Institute; NAc = nucleus accumbens; PCC = posterior cingulate cortex; VC = ventral caudate; VRC = ventral rostral caudate; VP = ventral rostral putamen.