Antipsychotic Treatment and Functional Connectivity of the Striatum in First-Episode Schizophrenia

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Importance: Previous evidence has implicated corticostriatal abnormalities in the pathophysiology of psychosis. Although the striatum is the primary target of all efficacious antipsychotics, the relationship between its functional connectivity and symptomatic reduction remains unknown.

Objective: To explore the longitudinal effect of treatment with second-generation antipsychotics on functional connectivity of the striatum during the resting state in patients experiencing a first episode of psychosis.

Design, Setting, and Participants: This prospective controlled study took place at a clinical research center and included 24 patients with first-episode psychosis and 24 healthy participants matched for age, sex, education, and handedness. Medications were administered in a double-blind randomized manner.

Interventions: Patients were scanned at baseline and after 12 weeks of treatment with either risperidone or aripiprazole. Their symptoms were evaluated with the Brief Psychiatric Rating Scale at baseline and follow-up. Healthy participants were scanned twice within a 12-week interval.

Main Outcomes and Measures: Functional connectivity of striatal regions was examined via functional magnetic resonance imaging using a seed-based approach. Changes in functional connectivity of these seeds were compared with reductions in ratings of psychotic symptoms.

Results: Patients had a median exposure of 1 day to antipsychotic medication prior to being scanned (mean [SD] = 4.5 [6.1]). Eleven patients were treated with aripiprazole and 13 patients were treated with risperidone. As psychosis improved, we observed an increase in functional connectivity between striatal seed regions and the anterior cingulate, dorsolateral prefrontal cortex, and limbic regions such as the hippocampus and anterior insula ($P < .05$, corrected for multiple comparisons). Conversely, a negative relationship was observed between reduction in psychosis and functional connectivity of striatal regions with structures within the parietal lobe ($P < .05$, corrected for multiple comparisons).

Conclusions and Relevance: Our results indicated that corticostriatal functional dysconnectivity in psychosis is a state-dependent phenomenon. Increased functional connectivity of the striatum with prefrontal and limbic regions may be a biomarker for improvement in symptoms associated with antipsychotic treatment.

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Disruptions in corticostriatal circuitry have been implicated in the pathophysiology of schizophrenia. Early proposals linked schizophrenia with decreases in dopamine in the prefrontal cortex and excessive dopamine in the striatum. Although elevated striatal dopamine has been shown in patients with schizophrenia, their unaffected relatives, and individuals who are at risk for developing psychotic symptoms, corticostriatal relationships have also been demonstrated to play a central role in psychosis. Early positron emission tomography work found that the severity of psychotic symptoms correlated with abnormal patterns of blood flow in limbic and prefrontal cortical regions. Studies in schizophrenia using functional magnetic resonance imaging (fMRI) have reported abnormal corticostriatal activation during reward and executive processing. Evidence from functional connectivity and multimodal studies have shown altered corticostriatal circuitry in patients with chronic schizophrenia, and in patients with prodromal psychotic symptoms. A previous family-based study suggested that altered functional connectivity between striatum and cortical regions may represent a risk phenotype in patients with first-episode psychosis (FEP) and their relatives.

Despite the evidence implicating corticostriatal links in psychosis, there is a paucity of data directly examining the relationship between corticostriatal functional connectivity and the clinical effects of antipsychotic agents. Structures of the striatum are of particular interest when considering the effects of treatment because they harbor the largest density of dopamine D2 receptors. Although antipsychotic drugs vary in their potency and effect on cortical and subcortical functions, all known antipsychotic agents bind to the D2 receptor. A few studies have used a longitudinal study design to examine the effects of antipsychotic treatment with network-based analyses and during reward processing but did not directly address the question of symptom-related changes in striatal connectivity.

In the present study, we examined the relationship between changes in striatal circuitry and reduction in psychotic symptoms after treatment with antipsychotic medications. We used a prospective study design in which resting-state fMRI scans were collected in a cohort of patients with first-episode schizophrenia and a matched healthy comparison (HC) group at 2 points. Scans in the patient group were collected at baseline and after 12 weeks of treatment with a second-generation antipsychotic; HC participants were also scanned within a 12-week interval.

To interrogate the functional networks of the striatum, we used a seed-based approach first proposed by Di Martino et al. We tested the effect of antipsychotic treatment on the functional connectivity of the striatum by comparing changes in connectivity of our striatal seed regions and changes in psychotic symptoms. Our primary hypothesis was that functional connections with cortical regions would be strengthened and normalized as psychotic symptoms resolved, specifically with prefrontal and limbic regions that had been impaired in schizophrenia. To test this hypothesis, we first needed to create functional maps from our HC group at baseline. We hypothesized that our functional maps would replicate the anteroposterior separation of positive and negative striatal correlations previously observed. At baseline, we expected to see frontostriatal decoupling in our patients relative to the HC group, which would then normalize as a function of successful treatment. By contrast, we did not expect to see changes associated merely with the passage of time.

### Table 1. Baseline Demographics and Clinical Ratings

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Healthy Comparison Group (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>21.4 (5.0)*</td>
<td>20.0 (3.1)</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17*</td>
<td>17</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Education</td>
<td>12.3 (1.8)*</td>
<td>13.0 (2.5)</td>
</tr>
<tr>
<td>Handedness (Edinburgh)</td>
<td>0.76 (0.32)*</td>
<td>0.51 (0.58)</td>
</tr>
<tr>
<td>Interval between scans, d</td>
<td>87.3 (4.9)*</td>
<td>89.1 (6.7)</td>
</tr>
<tr>
<td>Prior antipsychotic exposure, d</td>
<td>4.5 (6.1)</td>
<td>NA</td>
</tr>
<tr>
<td>BPRS total score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>43.1 (9.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up</td>
<td>27.3 (6.9)*</td>
<td>NA</td>
</tr>
<tr>
<td>PSx rating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.0 (2.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up</td>
<td>5.6 (2.6)*</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations:** BPRS, Brief Psychiatric Rating Scale; NA, not applicable; PSx, psychotic symptoms.

* No significant difference (P < .05) from values for the comparison group (2-tailed t test).

**Methods**

**Participants**

Patients aged 15 to 40 years old with FEP underwent resting-state fMRI scanning and symptom ratings at baseline and after 12 weeks of treatment, with either risperidone or aripiprazole as part of a National Institute of Mental Health (NIMH)-funded double-blind, randomized clinical trial. First-episode psychosis includes a variety of diagnostic categories; our investigation was limited to patients with first-episode schizophrenia spectrum disorders (ie, schizophrenia, schizophreniform disorder, schizoaffective disorder, or a psychotic disorder not otherwise specified). All patients were required to have 2 weeks or less of cumulative lifetime exposure to antipsychotics to enter the clinical trial. An HC group was also scanned at 2 points within a 12-week interval (Table 1). Patient diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders, supplemented by information from clinicians and, when available, family members. After a complete description of the study was given to the participants, written informed consent (written assent and written parental/guardian consent for individuals younger than 18 years) was obtained per a protocol that was approved by the institutional review board of the North Shore-
Long Island Jewish Health System. Additional details regarding exclusion criteria for our study participants are available in the eAppendix in the Supplement.

After providing informed consent, all patients received double-blind treatment with either risperidone (dose range, 1-6 mg) or aripiprazole (5-30 mg) for 16 weeks. Details regarding allowed supplemental medications taken by our patients are available in the eAppendix in the Supplement. Clinical ratings were administered weekly for the first month and then every 2 weeks thereafter until week 12. To evaluate psychotic symptoms, the Brief Psychiatric Rating Scale–Anchored version was used. For our analyses, we were concerned only with symptoms reflective of psychosis. We used the following 3 items from the Brief Psychiatric Rating Scale–Anchored version that assess positive psychotic symptoms: unusual thought content, hallucinations, and conceptual disorganization to obtain a measure of psychotic symptoms (PSx), termed by previous studies as a thought-disturbance rating.23

**Resting-State Functional Magnetic Resonance Image Acquisition**

All functional magnetic resonance imaging exams were conducted on a 3-T scanner (GE Signa HDx). Further details are provided in the eAppendix in the Supplement. During resting state scanning, participants were asked to close their eyes and instructed not to think of anything in particular. All participants were spoken to between scan sequences to ensure they were not asleep; no behavioral differences were observed between groups during scanning.

**Image Analysis and Preprocessing**

We used the FMRIB Software Library (http://www.fmrib.ox.ac.uk) and the Analysis of Functional Neuroimages–based script libraries (http://afni.nimh.nih.gov/afni) from the 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000) for preprocessing of resting-state scans (fcon scripts). Details regarding preprocessing steps are provided in the eAppendix in the Supplement.

**Functional Connectivity Analyses**

To test the functional connectivity of subregions of the striatum within the putamen, caudate nucleus, and nucleus accumbens, we used a seed-based approach. We used methods described in the Di Martino et al study.22 The central coordinates of the regions of interest (ROIs) were taken from that study and used to create 3.5 × 3.5 × 3.5-mm spherical ROIs. The ROIs were defined bilaterally in the following: dorsal caudate (x = ±13, y = 15, and z = 9), ventral caudate (x = ±10, y = 15, and z = 0), ventral caudate/nucleus accumbens (x = ±9, y = 9, and z = −8), dorsal rostral putamen (x = ±25, y = 8, and z = 6), dorsal caudal putamen (x = ±28, y = 1, and z = 3), and the ventral rostral putamen (x = ±20, y = 12, and z = −3).

Once ROIs were defined, the Analysis of Functional Neuroimages–based scripts from the 1000 Functional Connectomes Project were used to create correlation maps for each participant for all 12 of our ROIs. Mean activity time courses were extracted from each seed region. Whole-brain voxelwise correlation maps for each ROI were created with the extracted waveform as a reference. The resulting correlation maps were z transformed.

For group-level analyses, we used SPM5 (http://www.fil.ioin.ucl.ac.uk/spm). One-sample t tests were performed with group level correlation maps for each ROI in our baseline HC group. Results were visualized at P < .05, uncorrected for both positive and negative correlations for each of our ROIs. A relatively liberal threshold was used for these initial analyses because these were used to create masks for subsequent analyses testing our primary hypothesis. We found a good separation of networks with our ROIs in both the positive and negative directions, consistent with results from the Di Martino et al study.22 Results for other analyses were considered significant if they surpassed a threshold of P < .05, corrected for false discovery rate by the standard function provided with the SPM5 package.24 Baseline and follow-up scans within each group and between groups were compared by 2-sample t tests in SPM.

To compare changes in Psx ratings with longitudinal changes in the functional connections of our striatal ROIs in our FEP group, we subtracted the baseline scan from the follow-up scan (follow-up minus baseline) using FSLMATHS. This image representing the change in correlation at each voxel was then taken into a group-level multiple regression analysis with reduction in Psx (baseline Psx minus follow-up Psx) as a regressor. This analysis was performed separately for each ROI, explicitly masked within the binary mask from the corresponding HC network. To visualize our correlations, we extracted and plotted data from the most significant voxel within clusters that surpassed our threshold for significance.

**Results**

**Demographics**

A total of 24 patients with FEP and an age-, sex-, education-, and handedness-matched cohort of 24 HC participants were included in the present study (Table 1). Patients had a median exposure of 1 day to antipsychotic medication prior to being scanned (mean [SD] = 4.5 [6.1]; Table 1). Eleven patients were treated with aripiprazole and 13 patients were treated with risperidone. Owing to the limited power, we did not perform analyses to separate drug-specific effects (eAppendix in the Supplement).

**Baseline Correlations**

All 12 of our striatal seed ROIs (6 per hemisphere) showed well-delineated patterns of positive and negative functional connectivity (Figure 1), similar to those described by Di Martino and colleagues.22 Across all seeds, we observed a general anteroposterior pattern of correlative activity; positive correlations were limited to more frontal regions and negative correlations were generally observed in more posterior regions (Figure 1). Additionally, we observed laterality of functional maps. In particular, the dorsal caudate showed ipsilateral functional connectivity with more dorsal prefrontal regions.
Figure 1. Locations of Seed Regions and Their Representative Connectivity Maps

Both left and right seed regions of interest are displayed in green in the first column. The corresponding positive (red) and negative (blue) functional connectivity maps of each of these seeds from the right hemisphere in the healthy comparison group at baseline are displayed in subsequent columns. Maps are shown with a threshold of $P < .001$, uncorrected for the purpose of visualization.
Both positive and negative masks were created from all 12 connectivity maps in our HC group at baseline with a threshold of $P < .05$, uncorrected. Our subsequent analyses that involved psychotic symptom ratings were limited within these reference masks.

**Between-Group Comparisons**

In our between-group analyses, we compared connectivity maps of all 12 ROIs at baseline in our FEP and HC groups. No results in either masked or whole-brain analyses were observed at our level of significance ($P < .05$, corrected for false discovery rate).

**Between-Scan Comparisons**

Our HC group showed no significant changes in functional connectivity in masked or whole-brain analyses of all 12 of our seed ROIs when baseline scans were compared with follow-up scans in a paired manner. Our FEP group showed only 1 significant masked finding between baseline and follow-up scans in paired comparisons; the right ventral caudate/nucleus accumbens.
caudate showed increased connectivity with the thalamus on the left side and a cluster of voxels adjacent to the seed within the nucleus accumbens on the right side (see the eTable in the Supplement for details).

**Increase in Striatal Functional Connectivity With Treatment Response**

Antipsychotic treatment in our cohort of patients with FEP resulted in an overall significant reduction in positive symptoms (Mean [SD] PSx score at baseline = 11 [2.6], 12 weeks = 5.6 [2.6]; t = 7.35; P < .001), as measured by our PSx score, a composite of items reflective of psychosis from the Brief Psychiatric Rating Scale. We performed multiple regression analyses in our FEP group to compare PSx at baseline and follow-up, as well as the reduction in PSx with changes in functional connectivity of each of our seed ROIs. No significant correlations were observed between PSx and the functional connectivity of our ROIs at baseline or follow-up. Greater reduction in PSx showed a robust positive correlation with functional connectivity between the right dorsal caudate and prefrontal regions that included the orbitofrontal cortex, anterior cingulate, and the right dorsolateral prefrontal cortex (Figure 2; Table 2). As psychosis resolved, the right ventral caudate/nucleus accumbens seed showed a significant increase in connectivity with a cluster of voxels located in the left hippocampus (Figure 2; Table 2). Similarly, as symptoms improved, the right ventral rostral putamen seed showed increased functional connectivity with the anterior cingulate and right anterior insula (Figure 2; Table 2). No other seed regions showed results that survived correction for multiple comparisons. We observed no significant findings at the whole-brain level outside of the space within our masks derived from our HC group.

**Decrease in Striatal Functional Connectivity With Treatment Response**

Conversely, in several ROIs, we observed significant negative correlations between symptom improvement and changes in functional connectivity with posterior regions. This pattern mirrored the negative correlation maps we observed with our seeds in the HC group at baseline (Figure 1). With improvement in PSx, we observed significantly less connectivity between the right ventral caudate/nucleus accumbens and bilateral superior parietal lobule and supramarginal gyrus (Figure 3; Table 2). Similarly, as psychosis improved, the left ventral caudate showed less connectivity with the superior parietal lobe (Figure 3; Table 2). No additional findings were observed at the whole-brain level outside of the space within our masks.

**Discussion**

We used resting-state fMRI to examine the effects of treatment with either aripiprazole or risperidone on functional networks of striatal regions in a unique cohort of patients with FEP. Scans were collected in a longitudinal study design before and after 12 weeks of controlled treatment. With improvement of psychosis, we observed a significant increase in functional connectivity between the right dorsal caudate and several prefrontal regions including the anterior cingulate, right dorsolateral prefrontal cortex, and orbitofrontal cortex. Additionally, as psychotic symptoms resolved, we observed an increase in functional connectivity between the right ventral caudate/nucleus accumbens and hippocampus, as well as between a seed region placed within the ventral putamen with the anterior insula. Finally, we also found that as symptoms improved, the ventral caudate showed decreased functional con-
nectivity with posterior regions. These regions in the superior parietal lobe and supramarginal gyrus were negatively connected with striatal regions at the baseline in our HC group (Figure 1).

As hypothesized, our results demonstrated that symptomatic improvement of psychosis was associated with alterations in functional connections of the striatum, a structure consistently implicated in the pathophysiology of psychosis and a shared site of D2 receptor binding of all antipsychotic agents. One region that showed robust changes in functional interactions as psychosis improved was the dorsal caudate, also known as the associative caudate. This region has been shown to be anatomically and functionally connected to the dorsolateral prefrontal cortex. A large body of evidence has linked the striatum with the dorsolateral prefrontal regions in psychosis. Our results extended these findings and demonstrated that this link was modulated by pharmacologic intervention in a manner that correlated with symptom reduction. Additionally, our finding of significantly increased connectivity between striatal regions and the dorsal anterior...
cingulate implicated a role for error monitoring and cognitive control in recovery from psychotic symptoms. Our work supported previous results that demonstrated second-generation antipsychotic treatment–based alterations in blood flow to the anterior cingulate.28

Psychosis has been characterized as the result of abnormal assignment of salience to internal and external stimuli.29,30 Several brain regions from the present study that demonstrated increased striatal connectivity in response to treatment were implicated in the normal attribution of salience. Specifically, as psychotic symptoms remitted, the ventral putamen showed increased connectivity with the anterior insula and anterior cingulate, regions that have been linked to the salience network.31 Findings in the present study suggested that changes in the functional coordination between the striatum and prefrontal and limbic systems may influence salience processing as psychotic symptoms are reduced. In support of this hypothesis, induction of psychosis by cannabis has been shown to modulate activation of the caudate and prefrontal cortex during salience processing.32

We did not observe significant baseline differences in functional connectivity of the striatum between healthy individuals and patients with psychosis. A previous study by Fornito and colleagues15 suggested that frontostriatal dysconnectivity is an endophenotype for psychosis by showing decreased coupling between the striatum and dorsolateral prefrontal cortex in unaffected relatives of patients. While our study did not address familiality, baseline differences in connectivity patterns between studies may be related to differences in clinical variables, imaging parameters, and statistical approaches.

While previous fMRI studies have reported cross-sectional evidence linking reduced striatal signal and psychotic symptoms,23,34,35 our study used a longitudinal approach to examine the effects of antipsychotic medications on network-based functional connectivity measures. To our knowledge, only 1 resting-state fMRI study has been reported that examines antipsychotic treatment and functional connectivity in first-episode schizophrenia. Lui and colleagues18 observed treatment-based disruption in connectivity between brain regions and functional circuits in conjunction with altered low-frequency fMRI signals within the cortical regions and striatum. They did not report changes in functional circuitry that correlated with treatment efficacy; furthermore, the study did not specifically examine corticostriatal connectivity with an anatomically driven approach. Additionally, 1 longitudinal positron emission tomography study observed decreased connectivity of the medial frontal cortex with the hippocampus and ventral striatum after treatment,36 while a task-based fMRI study reported alterations in default mode network connectivity after olanzapine treatment.20 Other neuroimaging studies have also taken a longitudinal approach to test the effects of antipsychotic treatment on task-based activation and generally report normalization of the signal after treatment.37,38

The present study contributes to the evolving field of biomarkers for psychotic disorders and treatment response. Previous studies have shown differential neuroimaging signals based on treatment response.39 Additionally, differences in the response to treatment with antipsychotic medications have been associated with polymorphisms in the gene coding for the D2 receptor.38,39 Independently, variation in the DRD2 gene has been shown to be related to functional engagement of frontostriatal circuits.40 Further studies are required to clarify the association between our finding of treatment-related modulation of corticostriatal interactions and genetic variation.

Limitations of the present study included a relatively modest sample size; however, our sample size was comparable with other recent studies that examined patients with first-episode schizophrenia at 2 points21 or used functional connectivity.15,41,42 Larger sample sizes would have been useful to examine differential effects of various antipsychotic agents. Additionally, we examined a select group of psychotic patients and were unable to extend our results to other groups of patients experiencing psychosis. Future studies are required to examine striatal connectivity in illnesses such as bipolar disorder. By examining changes in psychotic symptoms, our results focused on state-dependent changes in corticostriatal circuitry that are reflective of successful treatment rather than the effect of treatment alone. Further studies are required to separate trait-related abnormalities in circuitry.

Conclusions

The present study provided evidence that the efficacy of treatment of psychosis with second-generation antipsychotic medications is associated with a neurophysiological level with alterations in functional corticostriatal circuitry. To the extent that psychosis successfully improves, functional connectivity between the striatum and the prefrontal—as well as limbic regions—are strengthened. These data further characterize the pathophysiology of psychosis and support the role of neuroimaging as a potential biomarker for clinical response.
Antipsychotic Treatment and the Striatum


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REFERENCES


