Abnormalities in Hemispheric Specialization of Caudate Nucleus Connectivity in Schizophrenia

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Hemispheric specialization is a prominent feature of the human brain and appears to be a marker of successful neurodevelopment. Altered brain asymmetry that has been repeatedly reported in schizophrenia may represent consequences of disrupted neurodevelopment in the disorder. However, a complete picture of functional specialization in the schizophrenic brain and its connectional substrates is yet to be unveiled.

OBJECTIVES To quantify intrinsic hemispheric specialization at cortical and subcortical levels and to reveal potential disease effects in schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS Resting-state functional connectivity magnetic resonance imaging has been previously used to quantitatively measure hemispheric specialization in healthy individuals in a reliable manner. We quantified the intrinsic hemispheric specialization at the whole brain level in 31 patients with schizophrenia and 37 demographically matched healthy controls from November 28, 2007, through June 29, 2010, using resting-state functional magnetic resonance imaging.

RESULTS The caudate nucleus and cortical regions with connections to the caudate nucleus had markedly abnormal hemispheric specialization in schizophrenia. Compared with healthy controls, patients exhibited weaker specialization in the left, but the opposite pattern in the right, caudate nucleus (P < .001). Patients with schizophrenia also had a disruption of the interhemispheric coordination among the cortical regions with connections to the caudate nucleus. A linear classifier based on the specialization of the caudate nucleus distinguished patients from controls with a classification accuracy of 74% (with a sensitivity of 68% and a specificity of 78%).

CONCLUSIONS AND RELEVANCE These data suggest that hemispheric specialization could serve as a potential imaging biomarker of schizophrenia that, compared with task-based functional magnetic resonance imaging measures, is less prone to the confounding effects of variation in task compliance, cognitive ability, and command of language.

Hemispheric specialization is a prominent feature of the human brain and appears to be a marker of successful neurodevelopment. Higher-order cognitive functions, such as memory and language, are lateralized (ie, subserved by one hemisphere more than the other) early in neurodevelopment, and associated differences exist between the 2 hemispheres in anatomy, activity, and connections. Because hemispheric asymmetry may occur as early as the second trimester of pregnancy, abnormalities in hemispheric specialization may provide crucial evidence of neurodevelopmental mechanisms of disease and clues about their timing. Schizophrenia is suggested to be a disorder of neurodevelopment, and abnormal development of hemispheric specialization could play an important role in the pathophysiology of the illness. During the past several decades, hemispheric specialization in schizophrenia has been investigated with increasingly powerful neuroanatomical, neurobehavioral, and neurophysiologic measures.

Emerging from this work, convergent evidence indicates that cerebral asymmetry is altered in schizophrenia. The prevalence of non–right-handedness has been reported to be significantly higher in patients with schizophrenia than in healthy individuals, which may indicate a failure to establish cerebral asymmetry (but also see the article by Deep-Soboslay et al.). Diminished laterality in gray matter volume of the planum temporale has been reported in schizophrenia; however, negative findings (ie, normal planum temporale laterality in schizophrenia) have also been reported. Task-
dependent functional magnetic resonance imaging (fMRI) studies have found, more consistently than structural studies, reduced left lateralization in schizophrenia\textsuperscript{21,26-28} and impairment of functions that are known to depend on right hemispheric specialization, such as attention modulation.\textsuperscript{29} Moreover, reduced functional laterality in schizophrenia has been repeatedly correlated with symptom severity.\textsuperscript{15,21,30} Impaired functional laterality has been found in patients with schizophrenia experiencing their first episode of illness\textsuperscript{28,31} and paired functional laterality has been found in patients with brain cerebral specialization based on resting-state fMRI.\textsuperscript{33} The neurodevelopmental injury in people at risk for or affected by the illness.

We applied a novel approach to the exploration of whole brain cerebral specialization based on resting-state fMRI.\textsuperscript{33} The degree of specialization is quantified using the autonomy index (AI), defined as the difference between intrahemispheric and interhemispheric connectivity. Regions with preferential intrahemispheric connectivity rather than interhemispheric connectivity are considered more specialized. This approach does not rely on comparing homologous regions of interest (ROIs) in 2 hemispheres, thereby avoiding the potential confounder of anatomical asymmetry. The AI was recently evaluated in a large cohort of 1000 healthy individuals and was able to predict asymmetric brain activation during language processing.\textsuperscript{33} With this novel approach, we explored the connectional underpinnings of hemispheric specialization in schizophrenia.

**Methods**

**Participants**

Thirty-one patients with DSM-IV diagnosed schizophrenia and 37 controls completed the study from November 28, 2007, through June 29, 2010. All patients were outpatients at the time of the scan. Twenty-three patients were being treated with an antipsychotic medication but had not been taking medication for at least 4 weeks before the scan. All patients were right-handed\textsuperscript{34} and native speakers of English. The healthy controls were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders.\textsuperscript{35} Written informed consent was obtained from all participants in accordance with the guidelines of the Partners Healthcare Institutional Review Board, which approved this study. The 2 groups were matched with respect to age, sex, premorbid verbal IQ, and parental socioeconomic status (eTable 1 in the Supplement). Severity of schizophrenia symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS).\textsuperscript{36} Chlorpromazine equivalents were calculated based on the criteria of Woods.\textsuperscript{37}

**fMRI Data Acquisition and Preprocessing**

Resting-state fMRI data were collected on a 3-T Tim Trio scanner (Siemens Healthcare) using a 12-channel head coil. Functional images were acquired using an echo planar imaging pulse sequence (repetition time, 5000 milliseconds; echo time, 30 milliseconds; flip angle, 90°; 2 × 2 × 2-mm\textsuperscript{3} voxels; and 76 time points per run). A total of 13 healthy controls and 15 patients underwent 2 resting-state scans; all other study participants had 1 resting-state scan. Only resting-state scans with a mean slice signal-to-noise ratio higher than 100 were included in the analyses. All but one scan (of a patient with schizophrenia) passed this criterion. Structural MRI scans were acquired using a sagittal 3-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. Resting-state functional and structural MRI data were processed according to procedures previously described\textsuperscript{33,38} (eAppendix in the Supplement).

**Hemispheric AI**

We uniformly subsampled the cerebrum in the FreeSurfer nonlinear volumetric space (voxel size, 8 × 8 × 8 mm\textsuperscript{3}). For each seed voxel, the degree of within- and cross-hemisphere connectivity was computed by summing up the number of voxels strongly correlated (\( r > 0.25 \)) to the seed in the ipsilateral and contralateral hemispheres, respectively. We have previously tested different selections of correlation threshold and found that the distribution of the AI could be robustly estimated.\textsuperscript{33}

The AI was calculated as the difference between the normalized within- and cross-hemisphere connectivity according to the following equation:

\[
AI = N_l/H_l - N_r/H_r,
\]

where \( N_l \) and \( N_r \) are the numbers of voxels significantly correlated with the seed in the ipsilateral and contralateral hemispheres, respectively, and \( H_l \) and \( H_r \) are the total number of voxels in the ipsilateral and contralateral hemispheres, respectively. Because the connectivity degree is normalized by the total number of vertices in each hemisphere, the AI is denoted as a percentage. For further details, see the eAppendix in the Supplement.

For each study participant, the AI values were averaged within important subcortical structures, including the caudate nucleus, putamen, thalamus, amygdala, and hippocampus. The anatomical masks for these subcortical structures were generated using FreeSurfer segmentations.\textsuperscript{39} The AI values were also averaged within a cortical mask, which was generated by identifying the cerebral voxels strongly correlated (\( r > 0.25 \)) to the caudate nucleus based on 1000 healthy controls.

**Group Effects**

For any between-group comparisons reported in this article, the overall threshold for significance is \( P < .05 \). In Figure 1, the AI maps of the patient and control groups only show voxels with \( P < .05 \) (F test, false discovery rate corrected). The uncorrected mean difference between these 2 groups is shown in Figure 1C. The group comparison based on the AI values averaged within each of the 5 subcortical ROIs (caudate nucleus, putamen, thalamus, amygdala, and hippocampus) was performed using a nonparametric Wilcoxon rank sum test at
Relation to Developmental Cortical Expansion
A map of regional developmental cortical expansion between term-born infants and young adults was published previously\(^40,41\) and made publicly available. The map of right hemispheric developmental cortical expansion and the map of hemispheric specialization in 1000 healthy controls\(^33\) were projected to the Conte69 164k_fs_LR mesh\(^42\) (http://sumsdb.wustl.edu/sums/directory.do?id=8291494&dir_name=CONTE69). The data were extracted using the Caret Surface Statistics Toolbox\(^43\) for correlation analysis.

Results
Hemispheric Specialization of the Cerebral Cortex
Hemispheric specialization of the cerebral cortex revealed a characteristic spatial distribution in the patients with schizophrenia and the healthy controls (Figure 1A and B). Strong hemispheric specialization was observed in the association cortices, including the lateral prefrontal, inferior parietal, and temporal regions, whereas visual, somatosensory, and motor cortices exhibited minimal specialization. In addition, hemispheric specialization in the 2 hemispheres revealed different patterns, replicating previous findings based on 1000 healthy controls.\(^33\) In the left hemisphere, strong specialization was observed in regions overlapping the default network and involved in language processing. In the right hemisphere, strong specialization was observed in regions engaged in attention control. This characteristic distribution was grossly preserved in the patient group (Figure 1B). However, when contrasting the patient group with the control group, several brain regions revealed a moderate difference. Compared with patients with schizophrenia, healthy controls had stronger specialization in the left anterior cingulated cortex (ACC) and left medial prefrontal cortex (mPFC). In addition, the inferior frontal gyrus (likely the Broca area) had reduced specialization in patients with schizophrenia compared with healthy controls, possibly related to prior evidence of altered language specialization in this illness.\(^44-46\) In contrast, patients with schizophrenia had stronger specialization in the right ACC and the right mPFC (Figure 1C).

Decreased Left Hemispheric and Increased Right Hemispheric Specialization of the Caudate Nucleus
We then investigated the hemispheric specialization of subcortical structures. The AI was quantified within the caudate nucleus, putamen, amygdala, hippocampus, and thalamus. Hemispheric specialization of the right and left caudate nucleus and right thalamus was significantly altered in patients (Figure 2). While the patients had significantly weaker specialization in the left caudate nucleus \((P < .005)\), specialization of the right caudate nucleus and right thalamus was sig-
Figure 2. Decreased Left Hemispheric and Increased Right Hemispheric Specialization of the Caudate Nucleus

The autonomy index (AI) values were averaged within 5 subcortical regions, including 2 striatal structures (caudate nucleus and putamen), 2 limbic structures (hippocampus and amygdala), and the thalamus. Error bars indicate 2 SEs. Patients with schizophrenia exhibited significantly decreased left but increased right hemispheric specialization of the caudate nucleus compared with the healthy controls. *P < .005.

significantly stronger (P < .005) in the patient group than in the control group. Accordingly, a significant group by hemisphere interaction of the AI in the caudate nucleus (P < .001, univariate analysis of variance in SPSS statistical software [SPSS Inc]) and in the thalamus (P = .02) was found.

For any functional network with a strong interhemispheric interaction, a strong negative correlation between the AI values in the left and right hemisphere portions of the network would be expected (for a detailed explanation, see the eAppendix in the supplement). However, if the subregions in 2 hemispheres become disconnected, the negative correlation will diminish. In the healthy control group, all 5 subcortical structures had strong negative correlations between the left and right hemisphere AI values (Figure 3), suggesting that the functions of the subcortical structures in the 2 hemispheres are tightly integrated. Remarkably, patients with schizophrenia did not show this characteristic anticorrelation in the caudate nucleus (P = .02) and the putamen (P = .04), whereat the significance of the difference between the anticorrelations of the 2 groups was established by interactive analysis of covariance using MATLAB (The MathWorks Inc; www.mathworks.com/help/stats/aocctool.html). However, the patients had the normal pattern of anticorrelated AI values in the thalamus, amygdala, and hippocampus (Figure 3). These results suggest that in schizophrenia the network associated with the left striatum may be segregated from the network associated with the right striatum.

We then investigated whether this loss of AI anticorrelation in the caudate nucleus is driven by specific subdivision(s) of the caudate nucleus. Choi et al38 segmented the human caudate nucleus according to its connection strength to different cortical networks39 and found that ventromedial parts of the caudate nucleus are strongly connected to limbic cortical regions, whereas dorsal portions of the caudate nucleus are connected to association networks, specifically to the default network and the frontoparietal network, as seen in the monkey.48 We quantified the specialization in these subdivisions of the caudate nucleus. The absence of AI anticorrelation in patients with schizophrenia was more prominent in the association relative to the limbic portion of the caudate nucleus (eFigure 1 in the Supplement). The strongest group effect within the association portion of the caudate nucleus was in the segment showing connectivity to the default network, where patients with schizophrenia had a complete absence of AI anticorrelation compared with the healthy controls (P = .005). Group comparisons of the frontoparietal network- and limbic-connected segments of the caudate nucleus revealed no significant differences (P = .20 and P = .56, respectively). To control for potential outliers driving this differential AI anticorrelation of the caudate nucleus or subportions of the caudate nucleus, we performed a standardized analysis of outliers (for detailed methods and results, see the eAppendix in the Supplement).

Alteration of Hemispheric Specialization in the Large-Scale Functional Network Connected to the Caudate Nucleus

Hemispheric specialization of the caudate nucleus revealed significant changes in schizophrenia, with patients having decreased left hemispheric but increased right hemispheric specialization. Consequently, the difference between left and right caudate nucleus specialization was significantly decreased in patients compared with healthy controls (Figure 4A; P < .001).

Previous studies47,49 have indicated that the medial prefrontal regions that had reduced AI values in schizophrenia (Figure 1C) are tightly connected to the caudate nucleus. As a post hoc analysis, we investigated whether hemispheric specialization was similarly altered in the cortical regions connected to the caudate nucleus. The cortical regions functionally associated with the caudate nucleus included the ACC and mPFC (Figure 4B) and therefore mainly fell within the de-
Abnormal Hemispheric Specialization of the Caudate Nucleus

Next we determined whether the specialization difference between the left and right caudate nucleus could accurately categorize the study participants into patient and control groups. We trained a support vector machine classifier based on the AI values in the caudate nucleus and tested the classification accuracy. With the difference between left and right hemispheric caudate nucleus AI values used as the input, the classifier yielded an accuracy rate of 74% (with a sensitivity of 68% and a specificity of 78%). In contrast, classification accuracy based on volume estimates of several subcortical structures derived from Freesurfer parcellation ranged from 43% to 63% (Table).

Association of Hemispheric Specialization and Cortical Expansion During Neurodevelopment

To test whether hemispheric specialization is associated with cortical expansion during neurodevelopment, we compared the hemispheric specialization map derived from 1000 healthy controls to a map of regional developmental cortical expansion between term-born infants and healthy young adults (eFigure 4 in the Supplement) (http://sumsdb.wustl.edu/sums/directory.do?id=7601585). On a whole surface level, developmental expansion and...
hemispheric specialization revealed a moderate yet significant correlation (Spearman rank correlation $r = 0.39$, $P < .001$), indicating that the extent of hemispheric specialization is related to the developmental cortical expansion.

**Examination of Potential Confounds**

To investigate a potential anatomical confound, we compared the intracranial volume–corrected caudate nucleus volumes of all participants. No significant patient-control differences were found ($P = .39$ for the left caudate nucleus and $P = .42$ for the right caudate nucleus, respectively). We further explored whether duration of illness or antipsychotic medication dose confounded our findings. The AI values in the left and right caudate nucleus and their difference revealed no correlation with the duration of illness ($P = .72$ for the left caudate nucleus, $P = .86$ for the right caudate nucleus, and $P = .69$ for the difference) or medication dose ($P = .91$ for the left caudate nucleus, $P = .95$ for the right caudate nucleus, and $P = .95$ for the difference). Furthermore, we tested whether there were any differences in our outcomes between the unmedicated ($n = 8$) and medicated ($n = 23$) patients with schizophrenia. The absence of anticorrelation between the left and right caudate nucleus AI and the weakened difference between them were found in the unmedicated and medicated patients (eTable 3 in the Supplement). To ensure that our conclusions were not affected by variable data acquisition length across the participants, we replicated the main results in 26 patients and 24 healthy controls who had a single resting-state run (eTable 4 in the Supplement). Last, we performed an additional correlation analysis, which revealed that there was no significant correlation between head motion (mean relative displacement in millimeters$^{53}$) and the AI of the caudate nucleus (left caudate nucleus: $r = -0.16, P = .20$; right caudate nucleus: $r = 0.17, P = .15$; but see previous discussions on the potential biological basis of head motion$^{52}$).

To provide a rough estimate of test-retest reliability of cortical and subcortical AI estimates, we performed additional analyses (eFigure 5 and eAppendix in the Supplement), which resulted in a mean reliability of cortical AI values of approximately 0.87 and a mean reliability of subcortical AI values of approximately 0.75.

**Correlation With Clinical Measures**

Symptom severity of the patients was evaluated using clinical measures, including PANSS total, PANSS negative symptoms, PANSS positive symptoms, and trait anxiety. However, their associations with cortical and subcortical AI measures failed to reach statistical significance ($P = .59, .34, .72, .83$ for the caudate AI for PANSS total, PANSS negative PANSS positive, and trait anxiety, respectively, and $P = .78, .17, .88, .97$ for the caudate-connected prefrontal AI for PANSS total, PANSS negative PANSS positive, and trait anxiety, respectively). One possible reason is that the patients involved in the present study were stable and compliant outpatients with little variability in symptom severity. Most patients with schizophrenia had a PANSS total score of approximately 50, which resembles a rather mild symptom severity$^{56}$ (mean [SD] score, 50.0 [13.6]).

**Discussion**

This study investigated hemispheric specialization in schizophrenia. First, we found that the physiologic left-over-right asymmetry of hemispheric specialization in the caudate nucleus and caudate-connected prefrontal regions was reduced in patients with schizophrenia. Second, patients with schizophrenia also had disrupted coordination between the 2 hemispheres, as manifested by the weakened inverse correlation between the left and right hemispheric specialization in the caudate nucleus. Third, within the caudate nucleus, the subdivision with connections to the association cortex had the strongest differences between the 2 groups, whereas subdivisions connected to limbic regions did not have significant group effects.

**Caudate Nucleus and Prefrontal Function**

In the present study, the strongest alterations in hemispheric specialization in schizophrenia were found in the caudate nucleus and the medial prefrontal regions connected to the caudate nucleus. These findings are generally consistent with prior findings of structural,$^{20,54}$ functional,$^{55,56}$ and postmortem$^{57-59}$ abnormalities of the striatum in schizophrenia. It has been long noted that the striatum and the associated cortical circuits play a key role in many of the cognitive and affective processes that are disrupted in schizophrenia.$^{59-61}$ Deficits in these functional domains have been linked to the classic symptoms of schizophrenia: cognitive impairment, negative symptoms, and positive symptoms. Thus, altered function of frontostriatal circuitry may
represent a fundamental pathophysiologic feature of schizophrenia. Although previous studies have reported both decreased and increased frontostriatal connectivity in schizophrenia, our results suggest that the changes in caudate nucleus and mPFC may correspond to the alteration in hemispheric specialization in schizophrenia. This specific alteration is the result of both increased cross-hemispheric connectivity and reduced within-hemispheric connectivity, rather than an absolute change in magnitude. One structural correlate for the reduced left-sided within-hemispheric connectivity found in this study might be the decreased integrity of the frontal and temporal white matter, affecting important intrahemispheric connections, such as the cingulate bundle and the inferior longitudinal fasciculus. Although our findings in the caudate nucleus depend on the precision of anatomical parcellation, a prior study on the reliability of subcortical segmentations has found caudate nucleus results to be most reliable, followed by the hippocampus, putamen, thalamus, and amygdala.

**Relating Alterations in Hemispheric Specialization to Dopamine Asymmetry**

Our study revealed that the left caudate nucleus is more specialized than the right caudate nucleus in healthy controls, but this asymmetry was significantly diminished in patients. In healthy controls, presynaptic dopamine levels, dopamine transporters, and D2-receptor density had a right-over-left lateralization. Previous studies have indicated a loss of this physiologic asymmetry of presynaptic striatal dopamine, striatal dopamine transporters, and striatal D2-receptor density in schizophrenia. Our results suggest that the right-over-left asymmetry of striatal dopamine metabolism is accompanied by a left-over-right asymmetry of striatal hemispheric specialization in healthy individuals, and these asymmetries are significantly diminished in patients. The fact that dopaminergic drugs model frontostriatal connectivity further supports the assumption that altered specialization of the caudate nucleus and connected frontal regions might relate to changes in dopamine signaling.

**Abnormalities of the Associative Striatum**

We found that changes in hemispheric specialization of the caudate nucleus in schizophrenia are mainly limited to alterations in the associative subdivision of the caudate nucleus, whereas the limbic subdivision does not have a significant effect. This finding is in line with the results of several previous molecular imaging studies. Woodward et al found a correlation between schizotypal traits in healthy individuals and striatal dopamine release was particularly strong in the associative subdivision of the striatum. Similarly, among individuals at ultrahigh risk for psychosis, those who later transitioned to psychosis had a significantly higher level of striatal dopamine synthesis than those who did not, again with the greatest effect size seen in the associative striatum. Furthermore, another study found that compared with healthy controls, patients with schizophrenia had a greater D2-receptor availability increase in the associative striatum after dopamine depletion, whereas there were no between-group differences observed in the limbic and sensory motor striatum. These findings of selective abnormalities of the associative striatum in schizophrenia converge with evidence (including the current data) of abnormalities in the cortical regions projecting to this segment of the striatum, such as the ACC. Thus, a dorsomedial frontal caudate associative network may be particularly affected in schizophrenia, accounting for the abnormalities seen in higher-order cognitive and affective functions served by this network.

**Neurodevelopment of Hemispheric Specialization and Its Relation to Schizophrenia as a Developmental Disorder**

Multiple lines of evidence suggest that schizophrenia is a neurodevelopmental disorder that might be characterized by impaired establishment of cerebral asymmetry. We investigated abnormalities in hemispheric specialization that may provide crucial evidence of a neurodevelopmental mechanism of the illness and clues about its timing. Asymmetry in brain structures become recognizable by 31 weeks of gestation. Differential gene expression levels between the left and right hemisphere can even be detected as early as 12 weeks of gestation, suggesting that transcriptional asymmetry might set the stage for hemispheric specialization at very early stages of brain development. Successful development of hemispheric specialization requires asymmetric pruning of dispensable connections and maturation of functionally specialized connections. Thus, failure to establish hemispheric specialization may occur very early in development but only become clinically apparent much later, when highly specialized connectional hubs, such as the prefrontal cortex, would normally have reached their full functionality.

**Alterations in Hemispheric Specialization as an Imaging Biomarker for the Exploration of Schizophrenia Risk Genes**

Neuroimaging measures are increasingly used as intermediate phenotypes to investigate the effect of genetic variants on brain structure and function. Because hemispheric specialization per se is a heritable trait that has been related to symptom severity in schizophrenia, hemispheric specialization of the caudate nucleus might serve as an imaging endophenotype for schizophrenia risk variants. The classification accuracy and specificity indicate that the caudate AI alone is already a strong discriminative feature that might be a valuable contributor to a multivariate classifier or prediction model in the future. Hemispheric specialization of medial prefrontal regions connected to the associative striatum might also be a meaningful endophenotype, especially because functional network efficiency of the medial frontal cortex is known to be highly heritable. As this measurement does not depend on the performance of a cognitive task, it is less prone, compared with task-based fMRI measures, to the confounding effects of variation in task compliance, cognitive ability, and command of language. Thus, if abnormal caudate nucleus specialization is present before the onset of the illness and linked to genetic variants associated with schizophrenia risk, this phenotype...
may prove useful for detecting the illness early and understanding how risk genes contribute to neurodevelopmental changes that lead to the emergence of symptoms. Although the AI is a meaningful measure of hemispheric specialization that captures biologically plausible associations with task-based language lateralization, evolution, and neurodevelopment, its association with symptom severity in schizophrenia remains to be investigated.

Conclusions

Hemispheric specialization of the caudate nucleus and cortical regions with connections to the caudate nucleus was significantly altered in schizophrenia. Hemispheric specialization in these brain structures may serve as a potential imaging biomarker for schizophrenia risk.