Functional Dysconnectivity of Corticostriatal Circuitry as a Risk Phenotype for Psychosis

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**IMPORTANCE** Dysregulation of corticostriatal circuitry has long been thought to be critical in the etiology of psychotic disorders, although the differential roles played by dorsal and ventral systems in mediating risk for psychosis have been contentious.

**OBJECTIVE** To use resting-state functional magnetic resonance imaging to characterize disease-related, risk-related, and symptom-related changes of corticostriatal functional circuitry in patients with first-episode psychosis and their unaffected first-degree relatives.

**DESIGN, SETTING, AND PARTICIPANTS** This case-control cross-sectional study was conducted at a specialist early psychosis clinic, GlaxoSmithKline Clinical Unit, and magnetic resonance imaging facility. Nineteen patients with first-episode psychosis, 25 of their unaffected first-degree relatives, and 26 healthy control subjects were included in this study.

**MAIN OUTCOMES AND MEASURES** Voxelwise statistical parametric maps testing differences in the strength of functional connectivity between 6 striatal seed regions of interest (3 caudate and 3 putamen) per hemisphere and all other brain regions.

**RESULTS** Disease-related changes, reflecting differences between patients and control subjects, involved widespread dysregulation of corticostriatal systems characterized most prominently by a dorsal-to-ventral gradient of hypoconnectivity to hyperconnectivity between striatal and prefrontal regions. A similar gradient was evident in comparisons between relatives and control subjects, identifying it as a genetically inherited risk phenotype. In patients, functional connectivity in risk-affected and disease-affected dorsal frontostriatal circuitry correlated with the severity of both positive and negative symptoms.

**CONCLUSIONS AND RELEVANCE** First-episode psychosis is associated with pronounced dysregulation of corticostriatal systems, characterized most prominently by hypoconnectivity of dorsal and hyperconnectivity of ventral frontostriatal circuits. These changes correlate with symptom severity and are also apparent in unaffected first-degree relatives, suggesting that they represent a putative risk phenotype for psychotic illness.

Published online September 4, 2013.

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The striatum plays an important role in the pathophysiology of psychotic disorders. Its function is heavily modulated by dopamine and it contains a rich abundance of D2 receptors—the primary target for most antipsychotic agents. Markers of striatal dopamine are robustly elevated (by 14% on average) in patients with schizophrenia, irrespective of medication status. Similar elevations have been reported in patients' unaffected relatives and individuals in an at-risk mental state (ARMS) for psychosis, suggesting that striatal dopamine dysregulation represents a risk phenotype for psychotic illness.

However, the striatum does not function in isolation, being heavily interconnected with many other brain regions implicated in the etiology of psychotic illness. For several decades, a focal point for pharmacological models of psychosis has been a ventral circuit linking the inferior limbic division of the striatum with the orbitofrontal cortex (OFC); ventromedial prefrontal cortex (PFC); and other limbic areas such as the hippocampus, amygdala, and midline and medial intralaminar thalamus. The circuit is a major pathway for mesolimbic dopaminergic transmission and is heavily implicated in associative learning and reward-based decision making, the derailment of which are thought to result in psychotic symptoms. Accordingly, patients with psychotic disorders show aberrant activation of ventral striatal and prefrontal regions during performance of associative learning tasks, and there is complementary evidence for progressive gray matter volume loss in ventral prefrontal regions during the transition from an ARMS to frank psychosis.

Despite this ventral-system focus, recent high-resolution tomographic imaging studies have localized dopamine elevations in both medicated patients with schizophrenia and ARMS individuals to the dorsal, rather than ventral, striatum. The dorsal, so-called associative, division of the striatum forms part of a circuit linking the dorsolateral PFC and other polymodal association areas with the mediodorsal and ventral anterior thalamus. The circuit is thought to play a critical role in psychosis-related cognitive impairments. Accordingly, increased dopamine in the associative striatum of ARMS individuals has been correlated with altered dorsal prefrontal activation, poorer cognitive function, and a specific increase in the severity of psychotic, but not mood or anxiety, symptoms (see also an article by Meyer-Lindenberg et al).

Collectively, these findings point to a network-based disturbance of dorsal corticostriatal circuitry as a putative risk phenotype that predates psychosis onset. They also suggest that changes in ventral circuitry emerge after or during the onset of psychotic symptoms, in parallel with the progressive brain changes occurring in ventral regions during the transition to illness. This view is consistent with a growing consensus that psychotic disorders are a consequence of disordered connectivity within and between distributed brain networks, as well as evidence that risk for psychosis is associated with connectivity disruptions in other neural systems. However, a comprehensive systems-level characterization of how corticostriatal dysfunction relates to risk for psychosis has thus far been lacking. Moreover, it has been difficult to determine whether the dorsal circuit changes reported in ARMS individuals represent a state-independent risk marker or a secondary consequence of psychotic experiences since, by definition, ARMS individuals experience some level of psychotic symptoms.

We sought to address these limitations using established resting-state functional magnetic resonance imaging (rs-fMRI) techniques to systematically characterize functional disturbances of corticostriatal circuitry in a sample of patients with first-episode psychosis and their asymptomatic, unaffected first-degree relatives. Resting-state fMRI has emerged as a powerful tool for probing the functional integrity-specific brain circuits in vivo and corticostriatal circuits in particular. Neural dynamics recorded during the so-called resting state, in the absence of an explicit task, putatively capture a spontaneous, stable, and intrinsic property of brain functional organization. Importantly, patterns of interregional covariation in resting-state activity—termed functional connectivity—are under strong genetic control, identifying them as viable candidate intermediate phenotypes or genetic risk biomarkers.

Our aims were 3-fold. First, to characterize disease-related functional dysconnectivity of dorsal and ventral corticostriatal systems in patients with first-episode psychosis. Second, to identify risk-related dysconnectivity phenotypes by mapping alterations in corticostriatal connectivity that are common to both patients and their relatives. Finally, to investigate symptom-related predictors of corticostriatal functional connectivity by correlating measures of symptom severity with disease-related and risk-related connectivity alterations in patients. Informed by recent findings in ARMS individuals, we hypothesized that risk-related changes in functional connectivity would be localized to dorsal corticostriatal circuitry, whereas disease-related dysconnectivity would be apparent in both dorsal and ventral systems.

### Methods

#### Participants

We recruited 30 patients with first-episode psychosis, 30 of their first-degree relatives (22 siblings and 8 parents), and 31 unrelated healthy volunteers. Patients were clinically followed up through specialist clinical services in Cambridgeshire, England, and surrounding regions. Diagnostic details are presented in eTable 1 in Supplement. Details on recruitment and inclusion/exclusion criteria are presented in the eAppendix in Supplement. All participants provided written informed consent in accordance with local ethics committee guidelines (Research Ethics Committee reference number 06/Q0108/129).

Following scanning, participants were excluded for either medical reasons (1 relative), positive urine test result for an illicit substance (2 patients and 1 relative; see eAppendix in Supplement), imaging artifacts (1 patient, 1 relative, and 1 control subject), and excess head movement during scanning (>3-mm translation or 3° rotation; 8 patients, 2 relatives, and 4 control subjects). Thus, the final sample comprised 26 control subjects, 25 relatives, and 19 patients. Ten patients were
taking atypical antipsychotics, 4 were also taking antidepressants, and 2 were taking benzodiazepines. The remaining participants were unmedicated at the time of scanning. Demographic and other details are presented in eTable 1 in Supplement.

**Image Acquisition and Preprocessing**

Whole-brain T2*-weighted echoplanar images were acquired using a 3-T GE.Sega HDxt system (General Electric) located at the Magnetic Resonance Imaging and Spectroscopy Unit, Addenbrooke’s Hospital, Cambridge, England. Acquisition parameters were as follows: repetition time = 1600 milliseconds; echo time = 35 milliseconds; flip angle = 90°; in-plane resolution = 3.75 × 3.75 mm; and slice thickness = 7 mm. A total of 640 volumes were acquired as participants lay quietly in the scanner with their eyes closed. We retained only the first 400 volumes (approximately 10 minutes) for analysis owing to excess head motion in later scans. T1-weighted spoiled-gradient recall images were also acquired (repetition time = 9060 milliseconds; echo time = 3880 milliseconds; voxel dimensions = 0.47 × 0.47 × 1.1).

Data were analyzed using Statistical Parametric Mapping version 8, running in Matlab version 7.4 (Mathworks Inc). The functional data were first corrected for slice-timing differences and then head motion via rigid-body alignment of each volume to the first scan. These realigned images were spatially normalized to the Statistical Parametric Mapping echoplanar image template in Montreal Neurological Institute space using a nonlinear warping algorithm and subsequently spatially smoothed (8-mm full-width half-maximum Gaussian kernel).

**Definition of Seed Regions of Interest**

Following prior work,27,36 we seeded 3 caudate and 3 putamen regions per hemisphere along a dorsal-ventral axis using 3.5-mm-radius spherical regions of interest. For the caudate, a horizontal plane at stereotactic coordinate z = 7 mm distinguished the dorsal caudate (DC) (x = ±13, y = 15, z = 9) from 2 ventral regions—the superior ventral caudate (sVC) (x = ±10, y = 15, z = 0), and inferior ventral caudate (iVC) (x = ±9, y = 9, z = −8). For the putamen, a plane at z = 2 mm distinguished the dorsocaudal putamen (dcPT) (x = ±28, y = 1, z = 3) and dorso-rostral putamen (drPT) (x = ±25, y = 8, z = 6) from the ventro-rostral putamen (vrPT) (x = ±20, y = 12, z = −3).

**First-Level Statistical Analysis**

For each seed and each participant, mean activity time courses were extracted and used as covariates in a general linear model. Six head-motion parameters (3 translation and 3 rotation) and time courses representing mean signal fluctuations in white matter, cerebrospinal fluid, and the entire brain were also included (further details in the eAppendix in Supplement). Low-frequency drifts were removed via a high-pass filter (128-second cutoff). The general linear models were fitted to each voxel’s time series to generate participant-specific contrast images representing the functional connectivity of each striatal seed region with the rest of the brain. Separate models were fitted for left and right hemisphere striatal regions.

**Second-Level Analysis**

Group effects were estimated using a 3 × 2 factorial model with group (patients, relatives, and control subjects) and hemisphere (left seed and right seed) as factors. Separate models were used for each seed. Nuisance covariates included age, sex, and National Adult Reading Test IQ, as well as 4 parameters modeling residual differences in head motion37: (1) the number of significant micromovements (instances of >0.10-mm relative displacement between adjacent volumes); (2) mean head displacement; (3) maximum head displacement; and (4) mean head rotation.

To identify disease-related changes in striatal functional connectivity, we used a clusterwise-corrected threshold of P < .05 determined using the AlphaSim permutation procedure implemented in the REST toolbox (http://pub.restfmri.net). Risk-related changes were identified by contrasting relatives with control subjects within a mask of disease-affected regions, thus mapping common connectivity alterations in patients and relatives. Differences between relatives and control subjects that were not shared with patients were also explored (eFigure 2 in Supplement). For simplicity, we focused on results averaged across left and right seed regions. Further details about thresholding procedures are provided in the eAppendix in Supplement.

Correlations with symptom ratings were assessed in patients only (symptoms were virtually absent in the other groups). For each seed, a general linear model was constructed that included Brief Psychiatric Rating Scale factor scores for positive, negative, depressive, and manic symptoms.38 Modeling the effects of all symptoms simultaneously ensured that any resulting associations were unique to that symptom dimension. This analysis was conducted within the mask of significant disease-related functional connectivity changes observed for each seed. The results were thresholded using the procedure just described. We focused on Brief Psychiatric Rating Scale ratings because the uniformly low scores registered for other symptom scales (eTable 1 in Supplement) resulted in insufficient variance for meaningful analysis.

**Results**

**Disease-Related Corticostriatal Functional Dysconnectivity**

Each striatal region showed a characteristic pattern of functional connectivity that replicated prior analyses27,29 and recapitulated known anatomical connectivity31 (eFigure 1 and eAppendix in Supplement). Compared with control subjects, patients showed disease-related hypoconnectivity and hyperconnectivity of each striatal region with the cortex, indicative of a widespread dysregulation of corticostriatal function (Figure 1; eTable 2 in Supplement). For the caudate, patients showed a dorsal-to-ventral gradient of hypoconnectivity to hyperconnectivity with prefrontal regions. Specifically, they showed reduced functional connectivity between the DC and dorsolateral and medial PFC bilaterally, accompanied by increased connectivity between the sVC and bilateral OFC/
anteroventral insula and left dorsolateral PFC. This last finding of increased connectivity between the sVC and dorsolateral PFC suggests greater functional integration (ie, a relative de-segregation) of dorsal and ventral circuits in patients, as significant functional connectivity between these regions was not observed in control subjects (eFigure 1 in Supplement).

The dorsal-to-ventral, hypoconnectivity-to-hyperconnectivity gradient observed for frontostriatal systems was reversed for posterior cortical areas. Specifically, patients showed increased connectivity between the DC and right inferior temporal cortex and reduced connectivity between the sVC and left superior temporal gyrus. Patients additionally showed altered functional connectivity between posterior brain regions and the iVC (Figure 1 and eTable 2 in Supplement).

A gradient of hypoconnectivity to hyperconnectivity of frontostriatal circuits was also evident for the putamen seeds, although this time along a dorsocaudal to rostroventral axis. Specifically, patients showed hypoconnectivity between the dcPT and bilateral dorsal medial and lateral PFC, accompanied by hyperconnectivity between similar prefrontal regions and the drPT. Once again, these prefrontal circuits did not show significant functional connectivity in control subjects (eFigure 1 in Supplement), suggesting a reorganization of frontostriatal systems in patients. Other disease-related changes in putamen functional connectivity are summarized in Figure 2 and eTable 2 (Supplement).

Risk-Related Corticostriatal Functional Dysconnectivity

Risk-related changes in corticostriatal functional connectivity, reflecting alterations shared by patients and their unaffected relatives, were identified for all striatal regions except the drPT (Figure 2; eTable 3 in Supplement). Most prominently, relatives showed a comparable dorsal-to-ventral gradient of hypoconnectivity to hyperconnectivity between caudate regions and the PFC. Specifically, in comparison with
control subjects, relatives showed reduced functional connectivity between the DC and dorsal medial and lateral PFC, accompanied by increased connectivity between the sVC and bilateral clusters extending from the OFC into the anteroventral insula. A similar pattern was also evident for the putamen seeds, with relatives showing reduced functional connectivity between the dcPT and right medial and lateral PFC, accompanied by increased connectivity between the vrPT and ventromedial PFC. Additional risk-related alterations of putamen functional connectivity are summarized in Figure 2 and eTable 3 (Supplement). Striatal functional connectivity differences between relatives and control subjects that were not shared with patients are reported in the eAppendix and eFigure 2 (Supplement). Variations in age and sex could not explain our findings (see eAppendix in Supplement).

Symptom Correlates
In patients, we found a significant association between positive symptom severity and functional connectivity in a circuit linking the DC and regions of dorsolateral PFC and left medial PFC. These prefrontal regions overlapped with areas showing disease-related and risk-related dysconnectivity (Figure 3). In this circuit, both patients and relatives showed reduced functional connectivity compared with control subjects, and lower connectivity in patients correlated with more severe positive symptoms (Figure 3). Lower connectivity in the left dorsolateral PFC region was also correlated with more severe negative symptoms (Figure 3B, arrow; see eAppendix in Supplement).

A significant association was found between increased positive symptom severity and higher functional connectivity in a risk-affected circuit linking the sVC and left OFC/anteroventral insula, although this result may have been driven by a single outlying value (eFigure 3 and eAppendix in Supplement). Significant associations with positive symptom severity were also found in several circuits showing disease-related but not risk-related changes in functional connectivity (eFigure 4 in Supplement). An exploratory analysis of associations with other symptom dimensions is reported in the eAppendix (Supplement).

Discussion
Corticostriatal dysfunction has long been implicated in the pathophysiology of psychosis, although the differential roles played by dorsal and ventral systems in mediating disease risk have been unclear. In this study, we used rs-fMRI to systematically characterize disease-related, risk-related, and symptom-related functional dysconnectivity of corticostriatal circuits in patients with first-episode psychosis and their symptomatic, unaffected relatives. Patients showed widespread dysregulation of corticostriatal dynamics implicating all 6 striatal subregions examined. This dysregulation was characterized by the simultaneous presence of hypoconnectivity and hyperconnectivity compared with healthy control subjects. At a broad level, a similar pattern was also evident in patients’ unaffected relatives. More specifically, however, changes common to both relatives and patients, thus reflecting a putative risk phenotype, were only found for select corticostriatal circuits. Most prominently, these changes involved a dorsal-to-ventral gradient of hypoconnectivity to hyperconnectivity with frontal regions. Changes in each of these risk-affected circuits also correlated with psychotic symptom severity in the patient group. Collectively, these results indicate that functional abnormalities of corticostriatal systems are apparent from the earliest stages of psychosis and may be more extensive than previously thought. They also indicate that dysconnectivity of specific corticostriatal circuits represents a candidate risk phenotype for psychotic disorders.
Risk-Related Hypoconnectivity of Dorsal Frontostriatal Circuitry
As hypothesized, both patients and relatives showed a common pattern of dysconnectivity in dorsal frontostriatal circuitry. Specifically, when compared with control subjects, patients and relatives both showed reduced connectivity between the dorsal caudate and dorsal medial and lateral PFC. Functional connectivity between the dorsocaudal putamen and more posterior medial and lateral prefrontal regions was also reduced. These risk-related changes in dorsal frontostriatal circuitry are consistent with reports of selective dopamine elevations in the associative striatum of schizophrenic patients and ARMS individuals, as well as reports that such changes correlate with prefrontal activity. Our results extend this work by directly demonstrating that genetic risk for psychosis is associated with a functional decoupling of dorsal frontostriatal systems. They also demonstrate that such changes are not a secondary consequence of psychotic symptoms or treatment since our sample of first-degree relatives was unmedicated and virtually symptom free at the time of scanning.

Decoupling of frontostriatal dynamics is a plausible consequence of altered dopamine levels, given that either too little or too much of the neuromodulator is thought to increase noise in prefrontal information-processing systems. Reduced interregional functional connectivity is a predictable result of increased noise since adding noise to 2 variables will generally decrease the correlation between them. However, caution must be exercised in ascribing a causal role to excess striatal dopamine in this context. Although we seeded striatal regions, our measures of functional connectivity were inherently undirected, making it unclear whether striatal abnormalities caused changes in prefrontal activity or vice versa. Although there is robust evidence for abnormal striatal dopamine transmission in patients with psychotic disorders, evidence of dopamine deficits in the prefrontal cortex has also been reported. Animal studies have shown both that prefrontal lesions can lead to excess striatal dopamine release and that excess striatal dopamine can lead to behavioral changes consistent with prefrontal dysfunction. Our findings shed some preliminary light on a possible site of primary pathology in risk-affected circuitry. The dorsal, associative striatum receives direct afferents from the PFC, but only projects back to the PFC indirectly via the pallidum and thalamus. The fact that we observed a risk-related reduction in functional connectivity between the PFC and dorsal caudate, but not along the striato-pallido-thalamic pathway, suggests that the abnormality lies in the direct afferent input provided to the dorsal caudate from the PFC rather than efferent outflow emanating from the striatum. However, our resolution to detect changes in the striato-pallido-thalamic pathway may have been limited. Ongoing developments in causal modeling techniques for fMRI may prove useful in testing this hypothesis.

Risk-Related Hyperconnectivity of Ventral Frontostriatal Circuitry
Contrary to expectations, we also found evidence for risk-related hyperconnectivity between the ventral caudate and inferior frontal and anterior insula regions. Ventral circuit changes have been found in patients with established illness and during the transition to psychosis. While nonsignificant el-

Figure 3. Correlations Between Positive Symptom Severity in Patients and Functional Connectivity in Risk-Affected Dorsal Frontostriatal Circuitry

A. The location of the dorsal caudate (DC) seed region. B. Prefrontal regions in which individual differences in functional connectivity with the DC were correlated with positive symptom severity. The yellow regions indicate where more severe positive symptoms were associated with reduced striatal functional connectivity. The magenta regions highlight where positive symptom correlations spatially overlapped with regions showing significantly reduced functional connectivity in patients and relatives compared with control subjects. The arrow highlights a prefrontal region where reduced functional connectivity with the DC was also predicted by negative symptom severity. The left hemisphere is on the right. C. Scatterplot of the association between positive symptom scores and average functional connectivity between the DC and all prefrontal regions depicted in part A showing significant voxelwise correlations. In this plot, positive symptom scores were orthogonalized via linear regression, with respect to negative, depressive, and manic symptoms, to depict the specific association between positive symptoms and frontostriatal functional connectivity. Also shown is the Spearman rank correlation coefficient for the association. This correlation remained significant after removal of the potential outlier apparent in the bottom right-hand corner of the graph ($P = -0.46$ and $P = 0.04$; see eAppendix in Supplement for further details).
evations of ventral striatal dopamine function have been re-
ported in ARMS individuals, similar changes have not been
observed in patients with schizophrenia,\textsuperscript{6,18} suggesting that
dorsal system abnormalities play a more prominent role in me-
diating specific risk for psychosis. As such, the ventral circuit
hyperconnectivity shown by our genetic high-risk sample may
represent a dysfunction that is secondary to dorsal fronto-
striatal alterations.

Hyperconnectivity of the ventral system provides a plau-
sible neurobiological basis for salience-based accounts of psy-
chotic symptoms.\textsuperscript{12,13} These models posit that altered dopa-
mine in the ventral circuit causes a derailment of normal associativ
learning processes, such that excess motivational salience is assigned to otherwise uninteresting stimuli, result-
ing in phenomenological disturbances and consequent psy-
chotic phenomena. The ventral circuit plays a major role in re-
inforcement learning and updating of predictions about the
value of rewarding stimuli,\textsuperscript{44} and hyperconnectivity of this sys-
tem is consistent with an ongoing drive to assign unne-
cessary significance to irrelevant stimuli. One hypothesis to
emerge from our data was that reduced functional connectiv
ity within dorsal frontostriatal circuitry may lead to aberrant
top-down control over the ventral system and subsequent hy-
perconnectivity between the ventral caudate and OFC. Such
a view would be consistent with a primary dopaminergic ab-
normality in the dorsal system, as well as our finding that dor-
sal frontostriatal functional connectivity was more reliably as-
associated with psychotic symptom severity (eAppendix in
Supplement).

Notably, patients showed an additional increase of func-
tional connectivity between the ventral caudate and dorso-
lateral PFC that was not shared with relatives. This circuit did
not show significant functional connectivity in control sub-
jects (eFigure 1 in Supplement), suggesting that the hypercon-
nectivity observed in patients represents a remapping of fron-
tostriatal functional circuitry that promotes greater cross-
talk between, or relative desegregation of, dorsal and ventral
systems. The fact that this change was disease-specific and not
apparent in relatives suggests that it may act as a catalyst
through which vulnerabilities in dorsal and ventral circuits
compound each other in mediating the transition from ge-
netic liability to the emergence of psychotic symptoms. In sup-
port of this view, greater functional connectivity between the
ventral caudate and left dorsolateral PFC in patients was cor-
related with more severe positive symptoms (eFigure 4 in
Supplement). Future work should directly examine how hy-
perconnectivity between ventral and dorsal frontostriatal re-

gions relates to markers of striatal dopaminergic function in
patients and high-risk individuals.

Risk-related alterations of frontostriatal circuitry oc-
curred in the context of several other changes in ventral stria-
tal functional connectivity. Specifically, patients and rela-
tives showed common changes in functional connectivity
between posterior cortical areas and the inferior ventral cau-
date and ventrooral putamen seeds. Relatives showed ad-
ditional changes in corticostriatal functional connectivity that
did not overlap spatially with those observed in patients. These
additional changes may reflect either a psychosis-specific vul-
nerability that is altered by medication or disease onset in pa-
ients, or a generic, nonspecific vulnerability for psychopa-
thology, given that some genetic risk factors for psychosis are
shared with other disorders.\textsuperscript{45}

**Symptom-Related Corticostriatal Dysconnectivity**

Lower functional connectivity in risk-affected dorsal fronto-
striatal circuitry was correlated with more severe positive
symptoms in patients. Lower functional connectivity in a
part of this circuit linking the dorsal caudate and left dorso-
lateral PFC independently correlated with negative symptom
severity, suggesting that this pathway may play a particu-
larly important role in the emergence of schizophrenia-like
symptoms.

Although correlations between symptoms and func-
tional connectivity in risk-affected circuits were observed in
patients, our sample of relatives was virtually symptom free
at the time of scanning. Thus, risk-related changes in fronto-
striatal functional connectivity cannot be a consequence of psy-
chotic experiences. Rather, they likely reflect a state-
independent vulnerability marker. The fact that individual
differences in the functional connectivity of these pathways
also correlated with symptom severity in patients suggests 2
possibilities. The first is that the extent of functional dyscon-
nectivity in risk-affected circuits was more severe in pa-
ients, passing a threshold beyond which psychotic symp-
toms emerge. To test this hypothesis, we ran secondary
analyses comparing patients and relatives on functional con-
nectivity measures in dorsal and ventral risk-affected fronto-
striatal circuits but found no group differences, even when
using a liberal threshold of $P < .05$, uncorrected. Thus, while
both patients and relatives showed altered functional connectiv
ity in these systems when compared with control subjects,
they did not differ from each other.

The second possibility is that dysconnectivity of addi-
tional corticostriatal circuits outside those affected by ge-
etic risk is necessary for the emergence of psychotic symp-
toms. In other words, symptom expression is determined by
a combination of both risk-related and disease-specific net-
work changes. This view is consistent with our finding of an
association between positive symptom severity and disease-
related functional connectivity changes in corticostriatal cir-

cuits outside the risk-affected pathways (eFigure 4 in Supple-
ment), although longitudinal work mapping functional
connectivity alterations as symptoms emerge in high-risk in-
dividuals will be necessary to validate this conclusion.

**Limitations**

Approximately half of our patients were receiving antipsy-
chotic medication. Treatment effects cannot explain the ob-
erved risk-related changes in corticostriatal connectivity as
our relative sample was unmedicated. Moreover, a compari-
son of patients taking (n = 10) and not taking (n = 9) antipsy-
chotics revealed no significant differences in disease-
affected circuits, although a larger sample is required to better
characterize treatment effects.

Head motion poses a problem for rs-fMRI analyses. To
combat this problem, we supplemented participant exclu-
Conclusion

Our findings indicate that the earliest stages of psychosis are associated with a widespread dysregulation of corticostral systems, primarily characterized by dorsal hypoconnectivity and ventral hyperconnectivity of frontostriatal functional circuitry. This dorsal-to-ventral gradient of hypoconnectivity to hyperconnectivity was also apparent in patients' symptom-free, unmedicated relatives, suggesting that it represents a candidate risk phenotype for psychotic illness. Further work will be required to determine whether this putative risk biomarker represents a viable intermediate phenotype for psychotic illness.16

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Original Investigation Research


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