Functional Dysconnectivity of Corticostratial Circuitry as a Risk Phenotype for Psychosis

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IMPORTANCE Dysregulation of corticostratial 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 corticostratial 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 corticostratial 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 corticostratial 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.

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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 input to the ventral 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 thought to play a critical role in psychosis-related cognitive impairments. 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 and unmedicated patients with schizophrenia to the 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 precedes 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 frontostriatal 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 Signa 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 laid 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, cerebellar 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 motion: (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 asymptomatic, 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 dorsoventral 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 neuromediator 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 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-
evations of ventral striatal dopamine function have been reported in ARMS individuals, similar changes have not been observed in patients with schizophrenia, suggesting that dorsal system abnormalities play a more prominent role in mediating 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 frontostriatal alterations.

Hyperconnectivity of the ventral system provides a plausible neurobiological basis for salience-based accounts of psychotic symptoms. These models posit that altered dopaminergic neurobiological basis for salience-based accounts of psychosis, suggesting that excess motivational salience is assigned to otherwise uninteresting stimuli, resulting in phenomenological disturbances and consequent psychotic phenomena. The ventral circuit plays a major role in reinforcement learning and updating of predictions about the value of rewarding stimuli, and hyperconnectivity of this system is consistent with an ongoing drive to assign unnecessary significance to irrelevant stimuli. One hypothesis to emerge from our data was that reduced functional connectivity within dorsal frontostriatal circuitry may lead to aberrant top-down control over the ventral system and subsequent hyperconnectivity between the ventral caudate and OFC. Such a view would be consistent with a primary dopaminergic abnormality in the dorsal system, as well as our finding that dorsal frontostriatal functional connectivity was more reliably associated with psychotic symptom severity (eAppendix in Supplement).

Notably, patients showed an additional increase of functional connectivity between the ventral caudate and dorsolateral PFC that was not shared with relatives. This circuit did not show significant functional connectivity in control subjects (eFigure 1 in Supplement), suggesting that the hyperconnectivity observed in patients represents a remapping of frontostriatal functional circuitry that promotes greater crosstalk 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 genetic liability to the emergence of psychotic symptoms. In support of this view, greater functional connectivity between the ventral caudate and left dorsolateral PFC in patients was correlated with more severe positive symptoms (eFigure 4 in Supplement). Future work should directly examine how hyperconnectivity between ventral and dorsal frontostriatal regions relates to markers of striatal dopaminergic function in patients and high-risk individuals.

Risk-related alterations of frontostriatal circuitry occurred in the context of several other changes in ventral striatal functional connectivity. Specifically, patients and relatives showed common changes in functional connectivity between posterior cortical areas and the inferior ventral caudate and ventrorostral putamen seeds. Relatives showed additional changes in corticostriatal functional connectivity that did not overlap spatially with those observed in patients. These additional changes may reflect either a psychosis-specific vulnerability that is altered by medication or disease onset in patients, or a generic, nonspecific vulnerability for psychopathology, given that some genetic risk factors for psychosis are shared with other disorders.

### Symptom-Related Corticostriatal Dysconnectivity

Lower functional connectivity in risk-affected dorsal frontostriatal 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 dorsolateral PFC independently correlated with negative symptom severity, suggesting that this pathway may play a particularly important role in the emergence of schizophrenia-like symptoms.

Although correlations between symptoms and functional 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 frontostriatal functional connectivity cannot be a consequence of psychotic 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 dysconnectivity in risk-affected circuits was more severe in patients, passing a threshold beyond which psychotic symptoms emerge. To test this hypothesis, we ran secondary analyses comparing patients and relatives on functional connectivity measures in dorsal and ventral risk-affected frontostriatal 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 connectivity in these systems when compared with control subjects, they did not differ from each other.

The second possibility is that dysconnectivity of additional corticostriatal circuits outside those affected by genetic risk is necessary for the emergence of psychotic symptoms. In other words, symptom expression is determined by a combination of both risk-related and disease-specific network changes. This view is consistent with our finding of an association between positive symptom severity and disease-related functional connectivity changes in corticostriatal circuits outside the risk-affected pathways (eFigure 4 in Supplement), although longitudinal work mapping functional connectivity alterations as symptoms emerge in high-risk individuals will be necessary to validate this conclusion.

### Limitations

Approximately half of our patients were receiving antipsychotic medication. Treatment effects cannot explain the observed risk-related changes in corticostriatal connectivity as our relative sample was unmedicated. Moreover, a comparison of patients taking ($n = 10$) and not taking ($n = 9$) antipsychotics 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-
sion owing to excess head motion and standard first-level correction procedures with a second-level, groupwise correction for individual differences in 4 additional summary measures of head motion. This procedure ensured that our findings were not attributable to group differences in head motion, an assertion further supported by the lack of significant differences between groups in any of the head-motion parameters quantified (all $P > .65$). Finally, to improve temporal resolution, our images were acquired using thick slices and our coverage of medial orbitofrontal regions was limited. This may have affected our sensitivity for detecting subtle and/or focal abnormalities, particularly in ventral circuits linked to the most inferior aspect of the caudate (ie, iVC).27,29

Conclusions

Our findings indicate that the earliest stages of psychosis are associated with a widespread dysregulation of corticostriatal 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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REFERENCES


9. Setack SR, Carr DB. Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. Physiol Behav. 2002;71(4-5):513-517.


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