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Archival Report

Functional Connectivity of Corticostriatal Circuitry and Psychosis-like Experiences in the General Community

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ABSTRACT

BACKGROUND: Psychotic symptoms are proposed to lie on a continuum, ranging from isolated psychosis-like experiences (PLEs) in nonclinical populations to frank disorder. Here, we investigated the neurobiological correlates of this continuum by examining whether functional connectivity of dorsal corticostriatal circuitry, which is disrupted in psychosis patients and individuals at high risk for psychosis, is associated with the severity of subclinical PLEs.

METHODS: A community sample of 672 adults with no history of psychiatric or neurological illnesses completed a battery of seven questionnaires spanning various PLE domains. Principal component analysis of 12 subscales taken from seven questionnaires was used to estimate major dimensions of PLEs. Dimension scores from principal component analysis were then correlated with whole-brain voxelwise functional connectivity maps of the dorsal striatum in a subset of 353 participants who completed a resting-state neuroimaging protocol.

RESULTS: Principal component analysis identified two dimensions of PLEs that accounted for 62.57% of variance in the measures, corresponding to positive (i.e., subthreshold delusions and hallucinations) and negative (i.e., subthreshold social and physical anhedonia) symptom-like PLEs. Reduced functional connectivity between the dorsal striatum and prefrontal and motor cortices correlated with more severe positive PLEs. Increased functional connectivity between the dorsal striatum and motor cortex was associated with more severe negative PLEs.

CONCLUSIONS: Consistent with past findings in patients and individuals at high risk for psychosis, subthreshold positive symptomatology is associated with reduced functional connectivity of the dorsal circuit. This finding suggests that the connectivity of this circuit tracks the expression of psychotic phenomena across a broad spectrum of severity, extending from the subclinical domain to clinical diagnosis.

Keywords: Connectivity, Continuum, Corticostriatal, fMRI, Psychosis, Striatum

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Psychotic symptoms are proposed to follow a continuous distribution of severity, ranging from the absence of symptoms at one end to frank disorder at the other (1). Subthreshold psychosis-like experiences (PLEs) lie between these extremes (2). Typically characterized as attenuated (i.e., subclinical or subthreshold) forms of canonical positive symptoms (e.g., delusions and hallucinations), PLEs also encompass subclinical variation of the negative symptoms of schizophrenia, such as mild anhedonia (3–7). PLEs are predominantly transient (8,9); in cases of persistent expression, PLEs are thought to reflect an enduring personality dimension (10). The prevalence of PLEs in the general community reaches up to 8% (11), with higher incidences in the relatives of schizophrenia patients (12), suggesting that one's liability for PLEs tracks vulnerability to clinical disorder. Severe PLEs may indeed progress into a help-seeking phase, as exemplified by the at-risk mental state (ARMS) for psychosis (13–17).

The continuum model of psychosis severity accords with evidence for a polygenic contribution to schizophrenia liability, which predicts a continuous population distribution of symptomatology (18,19). It is also supported by neuroimaging evidence suggesting that subclinical and clinical phenomena share common neural correlates. The severity of PLEs in nonclinical samples correlates with variations in brain systems implicated in schizophrenia and various psychotic disorders, including frontotemporal, default mode, and cingulo-opercular systems (20–29). Alterations of white matter integrity in the corpus callosum, thalamus, and parietal, language, and visual areas have also been commonly reported in studies of clinical and nonclinical individuals with subthreshold symptomatology (30–32). These findings suggest that a continuum of neural function may underlie a broad spectrum of symptom expression.

The brain's corticostriatal (CST) circuits are particularly relevant to the various cognitive and symptom dimensions of

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schizophrenia (33,34). These parallel yet integrated circuits topographically connect frontal regions with the striatum, with feedback loops passing through the pallidum and thalamus (35,36). The two CST circuits that are most relevant to psychosis are the ventral and dorsal systems (37,38). The ventral (limbic) system connects the orbitofrontal cortex, medial prefrontal cortex, and limbic structures of the brain (e.g., the hippocampus and amygdala) with the ventral striatum (35,36,39). This system is a major pathway for mesolimbic dopamine (40) and has long been implicated in psychosis because of its role in reward processing and salience encoding (41).

The dorsal (associative or cognitive) system links the dorsolateral prefrontal cortex (DLPFC) with the dorsal striatum (36). Positron emission tomography studies indicate that both dopamine synthesis capacity and synaptic concentration are elevated prominently in the dorsal striatum of patients with schizophrenia (42), individuals in the ARMS phase (43,44), and healthy persons with increased liability for psychosis because of either genetic or environmental factors (45,46). In ARMS, these elevations are present only in individuals who later transition to psychosis (47). These positron emission tomography findings are complemented by studies of striatal functional connectivity, which report reduced coupling of the DLPFC with dorsal caudate and putamen in patients with first-episode psychosis, their unaffected first-degree relatives, and individuals with ARMS (48,49). Similar changes have been found in patients with first-episode mania experiencing psychosis (50), suggesting that dorsal CST dysfunction tracks the emergence of psychotic symptoms across diagnostic categories. Other studies focusing on thalamic connectivity support the association between changes in dorsal CST function with risk for psychosis (51–53). Changes of coupling in the dorsal CST circuit have also been correlated with the severity of both positive and negative symptoms in ARMS and clinical groups (48,49,52), and they are often accompanied by increased coupling in the ventral CST circuit and thalamic sensorimotor systems (48,51–53).

Together, these results indicate that reduced functional coupling of the dorsal CST system tracks the severity of psychotic symptom expression across a wide spectrum of illness severity that spans individuals with genetic high risk for psychosis, individuals in the ARMS phase, and individuals who were clinically diagnosed with psychosis (37). Here, we investigated whether CST function also tracks continuous subclinical variation in PLEs, ranging from the absence of PLEs to more severe experiences, in a large nonclinical sample. We combined resting-state functional magnetic resonance imaging with an extensive battery of PLE questionnaires measuring a broad array of subclinical phenomena related to schizophrenia symptomatology. Following evidence in clinical samples and individuals at high risk for psychosis (48,49), we hypothesized that reduced coupling between the dorsal striatum and prefrontal cortex would be associated with more severe PLEs, particularly those related to the positive symptoms of schizophrenia. Secondarily, we tested for other associations between dorsal and ventral striatal functional connectivity and PLE dimensions. In this exploratory analysis, we were particularly interested in determining whether increased coupling in the ventral system correlates with more severe PLEs, as suggested by work in individuals with genetic high risk for psychosis (48).

METHODS AND MATERIALS

Participants

We recruited 672 participants (274 male subjects; age, mean ± SD 23.2 ± 4.89 years [range, 18–50 years]) from the general community to complete an online battery of PLE measures. To capture a broad range of PLE variation, ranging from the absence of PLEs to more severe subthreshold experiences, we included all participants with valid data from our measurement battery. All participants were right-handed with no personal history of neurological or psychiatric illness and no significant drug use (see the Supplement for further details). Recruitment was part of a larger genetics study that required participants to have all four grandparents of European descent (54). The study was conducted in accordance with the Monash University Human Research Ethics Committee (reference number 2012001562). Each participant provided written informed consent following a thorough explanation of the study.

A subset of 379 participants with complete PLE measures underwent our resting-state functional magnetic resonance imaging protocol. Participants were subsequently excluded for scan artifacts, poor scan quality, or excessive in-scanner head motion (details in Supplement). The final sample with complete PLE measures and neuroimaging data comprised 353 participants (155 male subjects; median age [range], 22 years [18–50 years]; IQ range, 81–139, mean [SD] = 112 [11.6]).

Measures of PLEs

To sample a wide range of variation in PLEs, we used seven psychometrically validated self-report measures of subthreshold psychotic symptoms: the short-form Oxford-Liverpool Inventory of Feelings and Experiences (55); the Peters Delusion Inventory, 21-item version (56); the Community Assessment of Psychotic Experience (5); and four Chapman Scales measuring magical ideation, perceptual aberration, and social and physical anhedonia (57–59). We chose these measures not only because they are commonly used for community samples but also because they capture dimensions of PLEs based on different conceptual models of subthreshold psychosis symptomatology. For the Peters Delusion Inventory and Community Assessment of Psychotic Experience, subscales measuring distress, preoccupation, and conviction were excluded from further analysis as they were redundant with the frequency scales (all $r > .85$). The battery yielded a total of 272 items spanning 12 subscales (Supplemental Table S1).

Principal Component Analysis

We used principal component analysis (PCA) of the subscale scores, with varimax rotation, as implemented in SPSS version 25 (IBM Corp., Armonk, NY), to derive data-driven estimates of the latent dimensions driving PLE variance in our sample. PCA was performed on the larger sample of 672 participants to obtain robust estimates of latent dimensions. The Kaiser-Meyer-Olkin test of sampling adequacy value was 0.87, indicating that the correlations between variables would yield reliable factors (60). Following PCA, component scores were extracted for all participants using the Anderson-Rubin method to ensure orthogonality (61).

Neuroimaging Data Acquisition and Preprocessing

Multiband resting-state echo-planar images (620 volumes, 754-ms repetition time, 3-mm isotropic voxels) and anatomical T1-weighted scans (1-mm isotropic voxels) were acquired for each participant. The following pre-preprocessing steps were applied to the echo-planar images: 1) basic preprocessing in FSL FEAT that included removal of the first four volumes, rigid-body head motion correction, 3-mm spatial smoothing, and high-pass temporal filter (75-second cutoff); 2) removal of artifacts using FSL-FIX; 3) spatial normalization to the MNI152 template; and 4) spatial smoothing with a 6-mm full width at half maximum Gaussian kernel. After processing, the data were subjected to rigorous quality control for motion artifacts, as per past work (62). Further details are presented in the Supplement.

Definition of Seed Regions of Interest

In each hemisphere, six striatal regions of interest (ROIs) were seeded using 3.5-mm radius spheres that were delineated using a functional parcellation of the striatum (63), as per past work (48,49). For the caudate, three ROIs were seeded along a dorsoventral axis, including the dorsal caudate (x = ±13, y = 15, z = 9), the superior ventral caudate (x = ±10, y = 15, z = 0), and the inferior ventral caudate/nucleus accumbens (x = ±9, y = 9, z = −8). Three ROIs were seeded for the putamen along a similar axis, comprising the dorsocaudal putamen (DCP) (x = ±28, y = 1, z = 3), the dorsorostral putamen (x = ±25, y = 8, z = 6), and the ventrorostral putamen (x = ±20, y = 12, z = −3). Seeds in the dorsal CST system comprise the dorsal caudate, the dorsorostral putamen, and the DCP, whereas seeds in the ventral system comprise the inferior ventral caudate/nucleus accumbens, superior ventral caudate, and ventrorostral putamen. The mean time series of each region was then used for seed-related functional connectivity mapping. Further details on ROI definition are in the Supplement.

Functional Connectivity Analysis

First-level analysis was performed using SPM8 as previously described (48,49). For each participant, a general linear model containing the six seed-region time courses as covariates was used to model blood oxygen level–dependent signal fluctuations in each voxel. Separate models were fitted for the left and right hemispheres, yielding a pair of brain maps for each striatal ROI. Parameter estimates from the first-level analysis were passed to a second-level general linear model to generate group-wide functional connectivity maps for each ROI. Covariates comprised component scores of orthogonal PLE dimensions derived from the PCA. Nuisance covariates included age, age squared, estimated full-scale IQ, sex, and mean framewise displacement as a measure of in-scanner motion (64). Our analyses focused on mean effects collapsed across left and right striatal seeds to facilitate comparison with prior work (48,49). We note, however, that this approach may limit sensitivity to identify strongly lateralized effects.

Our primary hypothesis concerned the association between dorsal circuit connectivity and positive PLEs. We thus declared any associations between positive PLEs and functional connectivity of the dorsal circuit significant if they passed a threshold-free cluster enhancement (TFCE) (65)–corrected threshold of $p < .017$, determined using 5000 permutations, as implemented in FSL Randomise (66). This threshold is a Bonferroni correction of the typical $p < .05$ threshold for the three seeds used to probe dorsal circuit connectivity. Our secondary hypotheses and other exploratory correlations were evaluated using a TFCE-corrected threshold of $p < .002$, which accounts for 24 comparisons in total (i.e., six seeds, two PLE dimensions, two contrast directions). To facilitate comparison with prior work in this area (48,49), we also report significant associations without accounting for cross-seed comparisons (i.e., those with TFCE-corrected $p < .05$). To avoid circular inference, which can inflate effect sizes, scatter plots of associations between PLEs and functional connectivity were visualized using a leave-one-subject-out approach (67). See the Supplement for our results with $p < .05$ TFCE correction and leave-one-subject-out analysis details.

RESULTS

Principal Component Analysis

PCA was performed on 12 subscales derived from seven PLE questionnaires completed by 672 participants (descriptive statistics and pairwise correlations between subscales are in Supplemental Table S1). Based on the inflection in the scree plot (Supplemental Figure S1) (68), we retained two principal components. The first component accounted for 42.87% of the variance, with high loadings from subscales measuring the positive dimension of psychosis-related experiences, including delusional ideation, unusual experiences, perceptual aberrations, and eccentric behavior (i.e., positive PLEs). The second component accounted for 19.7% of the variance, with high loadings from subscales measuring the negative dimension of psychosis-related experiences (i.e., negative PLEs), including social and physical anhedonia. Component loadings are displayed in Table 1.

Table 1. Component Loadings of Subscales After Rotation

	Component	
Subscale	1	2
CAPE Positive	0.88[a]	0.01
Chapman Magical Ideation	0.86[a]	−0.01
sO-LIFE Unusual Experiences	0.86[a]	0.10
Peters Delusion Inventory	0.85[a]	0.05
Chapman Perceptual Aberration	0.78[a]	0.12
sO-LIFE Impulsive Nonconformity	0.63[a]	0.17
CAPE Depressive	0.53[a]	0.40
sO-LIFE Cognitive Disorganization	0.47[a]	0.49[a]
sO-LIFE Introvertive Anhedonia	0.03	0.86[a]
Chapman Social Anhedonia	0.14	0.79[a]
Chapman Physical Anhedonia	−0.19	0.74[a]
CAPE Negative	0.40	0.67[a]
Eigenvalue	5.14	2.36
% of Variance	42.87	19.70

CAPE, Community Assessment of Psychotic Experience; sO-LIFE, short-form Oxford-Liverpool Inventory of Feelings and Experiences.
[a]Loadings >0.40.

Corticostriatal Functional Connectivity

Functional connectivity analysis was performed in 353 participants with functional magnetic resonance imaging data. Each striatal region showed functional connectivity profiles consistent with known anatomy and prior findings (Supplemental Figure S3) (48,49,63).

Dorsal CST Functional Connectivity and PLEs. As predicted, higher scores on the positive PLE dimension were associated with reduced functional connectivity between the dorsorostral putamen and the right DLPFC (i.e., anterior middle frontal gyrus) (Table 2, Figure 1). Higher positive PLE scores were also associated with reduced coupling between the dorsal caudate and left dorsal anterior cingulate cortex (ACC) and reduced coupling between the DCP and the right primary motor cortex (Table 2, Figure 1). Each of these results was statistically significant at the Bonferroni-corrected TFCE threshold of $p < .017$. Additional suggestive associations between dorsal circuit functional connectivity and positive PLEs at an uncorrected threshold of $p < .05$ TFCE are presented in the Supplement.

PLEs and Functional Connectivity Across Dorsal and Ventral CST Circuits. Our exploratory analysis found a significant correlation between negative PLEs and increased functional connectivity between the DCP seeds and right primary motor area, TFCE corrected at $p < .002$ (Table 2, Figure 2). We did not find any significant association between PLEs and coupling within the ventral system after Bonferroni correction. Suggestive associations identified at an uncorrected threshold of $p < .05$ TFCE are presented in the Supplement.

DISCUSSION

Corticostriatal systems have long been implicated in the pathophysiology of psychosis. Studies in independent samples present converging evidence that reduced coupling of the dorsal CST circuit is apparent across a broad spectrum of illness severity (48,49,51–53). Here, we show that reduced functional coupling in the dorsal CST circuit correlates with subclinical variation in PLEs related to positive symptomatology, consistent with a continuum of neural function that tracks the severity of symptom expression (2,10,11) (see Figure 3 for a summary). Our comprehensive investigation of striatal functional connectivity also identified additional associations between PLEs and CST coupling that have not been observed in patients, suggesting a discontinuity for these phenotypes.

Dorsal Corticostriatal Coupling and PLEs

As hypothesized, higher levels of positive PLEs were associated with reduced coupling between the dorsal striatum and PFC. This association is broadly consistent with our past work in patients with first-episode psychosis, persons with genetic high risk for psychosis, and individuals in the ARMS phase (48,49). However, the specific regions implicated in this past work show some differences with our current findings. Specifically, we have previously reported that first-episode patients, their unaffected relatives, and individuals with ARMS show reduced coupling between the dorsal caudate and the DLPFC, with patients and relatives also showing reduced coupling between the DCP and the DLPFC (48,49). Here, we found that positive PLEs were associated with reduced coupling between the dorsal caudate and the ACC and between the dorsorostral putamen and a more anterior region of the DLPFC. A summary and comparison of these findings is provided in Figure 3.

One explanation for these discrepancies is that variations in sample characteristics and image processing techniques may lead to slight changes in the localization of clinically relevant effects. Another possibility is that our findings reflect a weak continuum model, in which PLEs are broadly related to the activity of the dorsal CST system, but the onset of frank illness arises only with dysfunction in very specific elements of this system—putatively, those involving the dorsal caudate and the DLPFC. It is also possible that our use of PCA to measure PLE severity, while capturing the dominant modes of variance across a wide battery of measures, may miss a more specific component of positive symptomatology that shows high behavioral and neurobiological continuity with clinical disorder. Better models of the latent dimensions underlying psychosis-related psychopathology across the full range of illness severity will be required to clarify the relationship between clinical and subclinical phenotypes.

Nevertheless, the associations with dorsal circuit function and PLE severity implicate areas that have been shown in other work to be affected by schizophrenia and subthreshold

Table 2. Regions Where Striatal Functional Connectivity Was Associated With Psychosis-like Experiences

Seed	Region	MNI Coordinates, x, y, z	Max *t* Value	Cluster Extent	*p* Value
Dorsal Circuit and Positive PLEs[a]					
DRP	R anterior middle frontal gyrus	24, 54, 26	5.70	110	.002
DC	L dorsal anterior cingulate cortex	−8, 28, 26	4.98	26	.011
DCP	R primary motor cortex	22, −16, 74	4.88	22	.01
Dorsal Circuit and Negative PLEs[b]					
DCP	R primary motor cortex	34, −24, 52	5.07	44	.001

Clusters in the dorsal circuit that are associated with positive PLEs are thresholded at $p < .017$, threshold-free cluster enhancement corrected. The cluster associated with negative PLEs is thresholded at $p < .002$, threshold-free cluster enhancement corrected.

DC, dorsal caudate; DCP, dorsocaudal putamen; DRP, dorsorostral putamen; L, left; Max, maximum; MNI, Montreal Neurological Institute; PLE, psychosis-like experience; R, right.

[a]Reduced coupling is associated with PLEs.

[b]Increased coupling is associated with PLEs.

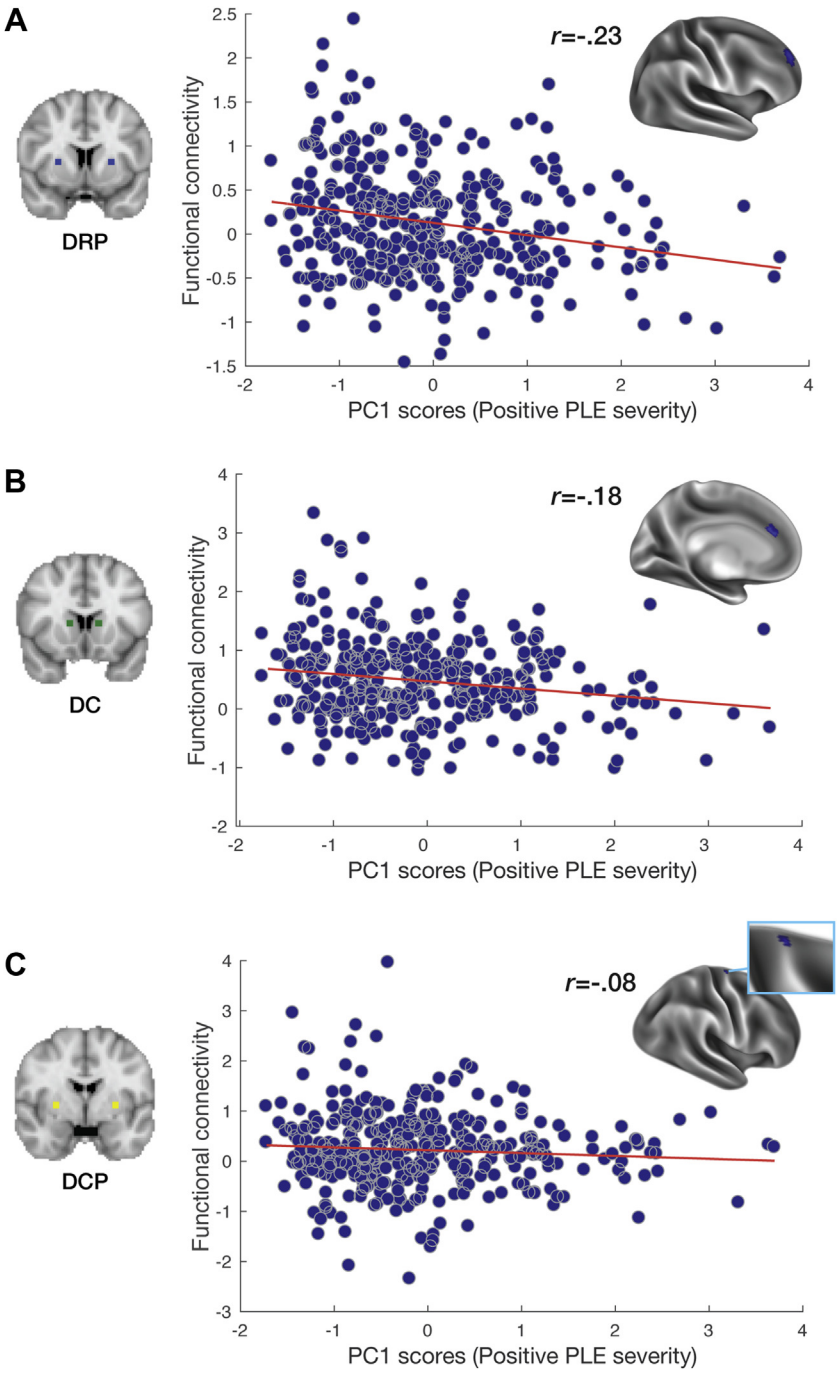

Figure 1. Associations between dorsal circuit functional connectivity and positive psychosis-like experiences (PLEs) ($p < .017$, threshold-free cluster enhancement corrected). Coronal slices in the left panels depict the location of striatal seed regions in the dorsal circuit. Cortical surface maps in the right panels depict the cortical sites for which functional connectivity with each seed correlates with positive PLE severity. Scatter plots depict the associations between positive PLE severity and functional connectivity between **(A)** the dorsorostral putamen (DRP) and right dorsolateral prefrontal cortex; **(B)** the dorsal caudate (DC) and left dorsal anterior cingulate cortex; and **(C)** dorsocaudal putamen (DCP) and primary motor cortex. Clusters on cortical surfaces are thresholded at $p < .017$ threshold-free cluster enhancement corrected. For visualization purposes, functional connectivity estimates and correlation coefficients were obtained using leave-one-subject-out analysis, thresholded at $p < .05$, threshold-free cluster enhancement corrected. PC, principal component.

symptomatology. Abnormal structure and function of the ACC are frequently reported in both patients and individuals at high risk for psychosis (28,69–74). In addition, ACC dysfunction is linked to a failure to update prior beliefs based on sensory experience, which may induce hallucinations (75). Adolescents with high PLEs also show altered dorsal circuit activity during reward processing (76). Together, these findings motivate the need to develop a more refined understanding of how distinct elements of dorsal CST circuitry relate to specific types of PLEs and clinical symptoms.

After correcting for multiple comparisons, we also found that stronger negative PLEs were associated with increased functional connectivity between the DCP and the right sensorimotor cortex. This association was weak, however, with <1% of variance shared between the two measures. This finding differs from our prior report that negative symptoms correlate with reduced

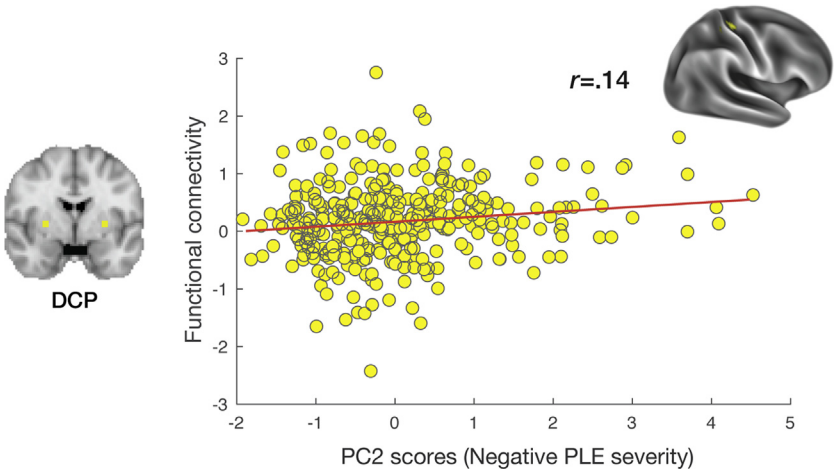

Figure 2. Association between dorsal functional connectivity and negative psychosis-like experiences (PLEs) ($p < .002$). Striatal seeds are shown in the axial slice in the leftmost panel. The scatter plot depicts the association between negative PLEs and functional connectivity between the dorsocaudal putamen (DCP) seed and right primary motor cortex. The cluster on the cortical surface was thresholded at $p < .002$, threshold-free cluster enhancement corrected. For visualization purposes, functional connectivity estimates and correlation coefficients were obtained using leave-one-subject-out analysis, thresholded at $p < .05$, threshold-free cluster enhancement corrected. PC, principal component.

coupling between the dorsal caudate and DLPFC in patients with first-episode psychosis (48). This divergence may be due to the nature of negative symptoms, which are complex and can be difficult to assess via self-report (77). Detailed investigation of the concordance between self-report and clinician-rated assessments of negative symptoms in both clinical and subclinical domains will be required to further clarify this phenotype.

Ventral Corticostriatal Coupling and PLEs

We did not find an association between PLEs and functional connectivity of the ventral circuit following multiple-comparison correction. At a reduced threshold, we found associations between PLEs and ventral CST coupling that were restricted to the ventrorostral putamen–sensorimotor and visual circuit, such that increased functional connectivity was associated with higher negative and lower positive PLE scores (Supplemental Figure S5). The association with positive PLEs is consistent with disrupted frontostriatal connectivity leading to increased thalamic outflow to sensory cortices (37,78). The concomitant association with negative PLEs implies that this increased outflow may be accompanied by psychomotor difficulties, which characterize many negative symptoms of schizophrenia (79–81), given that CST circuits modulate goal-directed behavior involving immediate physical action by coordinating motor with executive functions (81). However, these results should be regarded as tentative, and they require replication.

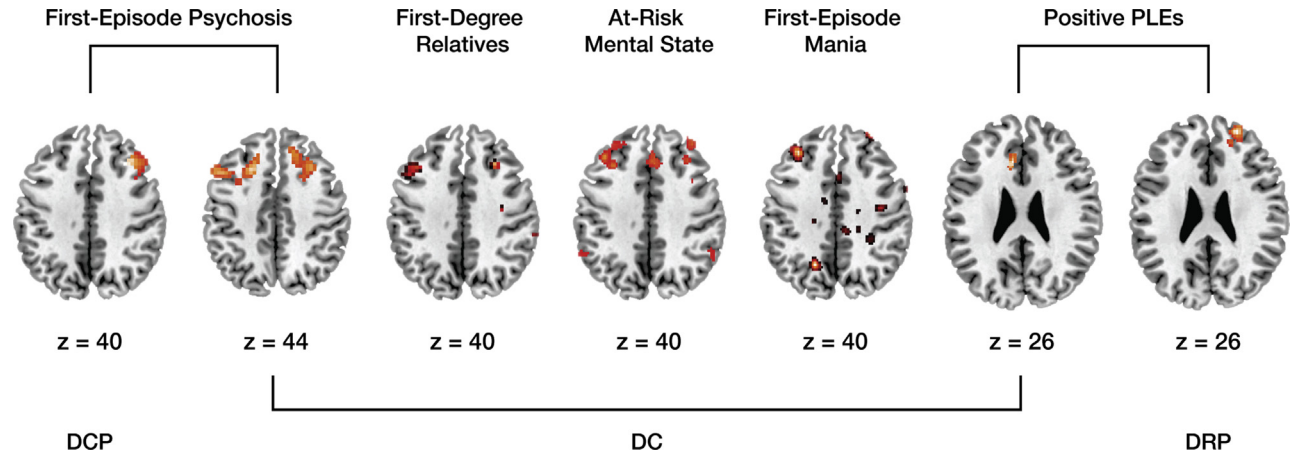

Figure 3. Functional connectivity of the dorsal circuit in persons experiencing different levels of illness severity. Axial slices show prefrontal regions where coupling within the dorsal circuit was reduced across a broad spectrum of severity, as identified in the current study and past findings. From left to right: regions in which coupling with the dorsocaudal putamen (DCP) and dorsal caudate (DC) were reduced in patients with first-episode psychosis compared with those in healthy control subjects [data from Fornito *et al.* (48)]; regions of reduced coupling with the DC in healthy first-degree relatives of patients, individuals with at-risk mental state, and patients with first-episode mania with psychosis compared with those of healthy control subjects [data from Fornito *et al.* (48), Dandash *et al.* (49), and Dandash *et al.* (50)]; and findings from this study, showing regions where lower coupling with the DC and the dorsorostral putamen (DRP) was associated with more severe positive psychosis-like experiences (PLEs) (thresholded at $p < .05$, threshold-free cluster enhancement corrected, for visualization). The z-axis slice in Montreal Neurological Institute coordinates is shown beneath each image. The left hemisphere is on the left side of the images.

In contrast to our prior report that first-episode psychosis patients and their unaffected relatives showed increased coupling between the nucleus accumbens and the ventral frontal cortex (48), we found no evidence for an association between the connectivity of this system and PLE severity. There is some evidence to suggest that this system may be tied to specific aspects of negative PLEs such as social anhedonia in subclinical groups (82). Our focus on dominant modes of PLE variance may have missed such specific effects.

Limitations

Over 90% of our sample was <30 years of age; hence, most participants have not passed through the maximal period of risk for schizophrenia (83). As psychotic experiences in early adulthood have been found to predict later psychopathology (15,84), it is possible that some people in our cohort may develop the illness at a later stage. Our exclusion of individuals with a personal history of mental health treatment ensured that we sampled the subclinical range of symptom expression, but this means that we may not have sampled the more severe end of the PLE spectrum. Our sample also included only right-handed individuals of European descent, which may limit the generalizability of the results.

Our two-component PCA solution parallels the well-known distinction between positive and negative symptoms in clinical populations, but it should be interpreted with some caveats. The simple two-factor solution may reflect an implicit bias in the PLE questionnaires to (over-)sample experiences related to positive and negative symptom dimensions of psychotic illness, which may inadvertently exclude other dimensions. A comprehensive assessment of clinical and subclinical symptomatology of psychosis may lead to a more refined model of the psychosis-risk phenotype.

Many of the associations between functional connectivity and PLEs were weak to moderate. It is possible that the strength of these association may increase with a more extensive sampling of the extreme end of the PLE spectrum. It is also likely that our PCA method, which focuses on common variance across instruments, may miss stronger associations with specific symptom domains. The strength of the associations identified here indicate that striatal functional connectivity cannot be used as a reliable predictor of PLE severity. However, when taken with findings in first-episode psychosis patients and individuals at high-risk for psychosis (48,49), our findings do suggest that dorsal corticostriatal dysconnectivity may represent a neurobiological mediator of a broad spectrum of psychosis symptom severity. Finally, in-scanner head motion exerts a pernicious effect on functional connectivity estimates (62,64,85,86), but our extensive quality control procedures indicate that our findings could not be explained by motion artifact (see the Supplement).

Conclusions

Our findings indicate that variation in dorsal CST function tracks subclinical expression of positive PLEs in a nonclinical sample, paralleling the circuit-level changes seen in patients and high-risk groups. Together, these findings are consistent with a continuum of psychosis symptom severity that is apparent at the level of overt behavior and underlying neurobiology, and which spans a broad spectrum of liability ranging from isolated experiences or attributional biases in otherwise healthy individuals to frank disorder in clinical populations.

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KS and AFo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. AFo, MB, BJH, AZ, and CP were responsible for the study concept and design. KS and AFo drafted the manuscript. JT, AFi, BJ, AP, KS, MB, and AFo acquired the data. KS, AFo, JT, LP, and FS were responsible for the analysis and interpretation of the data. MB, JT, VC, BJH, AZ, and CP conducted a critical revision of the manuscript for important intellectual content. KS, JT, and AFo were responsible for statistical analysis. JT, AFi, and BJ provided administrative, technical, or material support. MB and AFo supervised.

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ARTICLE INFORMATION

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