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

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Abstract

Background: Psychotic symptoms are proposed lie on a continuum, ranging from isolated psychosis-like experiences (PLEs) in non-clinical populations to frank disorder. Here, we investigate neurobiological correlates of this symptomatologic continuum by examining whether functional connectivity of dorsal corticostriatal circuitry, which is disrupted in patients and high-risk individuals, 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 (PCA) estimated major dimensions of PLEs from the questionnaires. PCA dimension scores were then correlated with whole-brain voxelwise functional connectivity (FC) maps of the striatum in a subset of 353 participants who completed a resting-state neuroimaging protocol.

Results: PCA identified two dimensions of PLEs accounting for 62.57% of variance in the measures, corresponding to positive and negative PLEs. Reduced FC between the dorsal striatum and prefrontal cortex correlated with higher positive PLEs. Negative PLEs correlated with increased FC between the dorsal striatum and visual and sensorimotor areas. In the ventral corticostriatal system, positive and negative PLEs were both associated with FC between the ventro-rostral putamen and sensorimotor cortices.

Conclusions: Consistent with past findings in patients and high-risk individuals, subthreshold positive symptomatology is associated with reduced FC of the dorsal circuit. These findings suggest 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.

Introduction

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), and their persistent expression is 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 non-clinical samples correlates with variations in brain systems implicated in schizophrenia and various psychotic disorders, including frontotemporal, default mode, and cinguloopercular systems (20–30). Alterations of white matter integrity in the corpus callosum, thalamus, parietal, language and visual areas have also been commonly reported in studies of clinical and non-clinical individuals (31–33). 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 schizophrenia (34, 35). These parallel yet integrated circuits topographically connect frontal regions with the striatum, with feedback loops passing through the pallidum and thalamus (36, 37). The two most relevant CST circuits to psychosis are the ventral and dorsal systems (38, 39). The ventral, so-called limbic, system connects the orbitofrontal cortex, medial prefrontal cortex (PFC), and limbic structures of the brain (e.g. the hippocampus and amygdala) with the ventral striatum (36, 37, 40). This system is a major pathway for mesolimbic dopamine (41), and has long been implicated in psychosis due to its role in reward processing and associative learning (42).

The dorsal, so-called associative or cognitive system, links the dorsolateral prefrontal cortex (DLPFC) with the dorsal striatum (37). Positron emission tomography (PET) studies indicate that both dopamine synthesis capacity and synaptic concentration are elevated prominently in the dorsal striatum of schizophrenia patients (43), ARMS individuals (44, 45), and healthy people with increased liability for psychosis due to either genetic or environmental factors (46, 47). In ARMS, these elevations are only present in individuals who later transition to psychosis (48). These PET findings are complemented by studies of striatal functional connectivity, which report reduced coupling of the DLPFC with dorsal caudate and putamen in first-episode psychosis patients, their unaffected first-degree relatives, and ARMS individuals (49, 50). Similar changes have been found in first-episode mania patients with psychosis (51), suggesting that dorsal CST dysfunction tracks the emergence of psychotic symptoms across diagnostic categories. Other studies focusing on thalamic connectivity support the importance of dorsal CST function in risk for psychosis (52–54). Dorsal CST changes have been correlated with the severity of both positive and

negative symptoms in ARMS and clinical groups (49, 50, 53), and are often accompanied by increased coupling in the ventral CST circuit and thalamic sensorimotor systems (49, 52–54).

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 disease risk that spans genetic high-risk, ARMS, and clinically diagnosed individuals (38). Here, we investigated whether variation in CST function also tracks subclinical variation in PLEs in a large, non-clinical sample. We combined resting-state functional magnetic resonance imaging (fMRI) with an extensive battery of PLE questionnaires measuring a broad array of subclinical phenomena related to schizophrenia symptomatology. Following evidence in clinical and high-risk individuals (49, 50), 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. Secondly, we evaluated whether increased coupling in the ventral system would correlate with more severe PLEs, as suggested by work in genetic high-risk individuals (49).

Methods and Materials

Participants

We recruited 672 participants (274 males; age range = 18–50 years old, mean [SD] age = 23.2 [4.89]) from the general community to complete an online battery of PLE measures. All participants were right handed with no personal history of neurological or psychiatric illness and no significant drug use (see Supplemental Information for further details). Recruitment was part of a larger genetics study that required participants to have all four grandparents of European descent. 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 fMRI protocol. Participants were subsequently excluded for either scan artifacts, poor scan quality, or excessive in-scanner head motion (details in Supplemental Information). The final sample with complete PLE measures and neuroimaging data comprised 353 participants (155 males; median age [range] = 22 [18–50 years]; IQ range = 81–139, mean [SD] = 112 [11.6]).

Measures of Psychosis-Like Experiences

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 (sO-LIFE) (55), the Peter Delusion Inventory (PDI-21) (56), the Community Assessment of Psychotic Experience (CAPE) (5), and four Chapman Scales measuring magical ideation, perceptual aberration, and social and physical anhedonia (57–59). For the PDI and CAPE, subscales measuring distress and frequency were excluded from further analysis as they were redundant with the severity scales (all $p > .9$). 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 IBM SPSS version 25, 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 (EPI; 620 volumes, 754 milliseconds repetition time, 3mm isotropic voxels) and anatomical T1-weighted scans (1mm isotropic voxels) were acquired for each participant. The following pre-preprocessing steps were applied to the EPI images: (1) basic preprocessing in FSL FEAT which included removal of the first four volumes, rigid-body head motion correction, 3mm spatial smoothing, and high-pass temporal filter (75 seconds cut-off); (2) removal of artifacts using FSL-FIX; (3) spatial normalization to the MNI152 template; and (4) spatial smoothing with a 6mm full-width 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 in Supplemental Information.

Definition of Seed Regions of Interest

In each hemisphere, six striatal regions-of-interest (ROI) were seeded using a 3.5mm radius spheres, as per past work (49, 50, 63). For the caudate, three ROIs were seeded along a dorsoventral axis, including the dorsal caudate (DC; $x = \pm 13$, $y = 15$, $z = 9$), the superior ventral caudate ($x = \pm 10$, $y = 15$, $z = 0$), and the inferior ventral caudate/nucleus accumbens ($x = \pm 9$, $y = 9$, $z = -8$). Three ROIs were seeded for the putamen along a similar axis, comprising the dorso-caudal putamen (DCP; $x = \pm 28$, $y = 1$, $z = 3$), the dorso-rostral putamen (DRP; $x = \pm 25$, $y = 8$, $z = 6$), and the ventro-rostral putamen (VRP; $x = \pm 20$, $y = 12$, $z = -3$). Seeds in the dorsal CST system comprise the DC, DRP, and DCP; whereas seeds in the

ventral system comprise the inferior ventral caudate/nucleus accumbens, superior ventral caudate, and VRP. The mean time series of each region was then used for seed-related functional connectivity mapping.

Functional Connectivity Analysis

First-level analysis was performed using SPM8 as previously described (49, 50). For each participant, a general linear model containing the six seed region time courses as covariates was used to model BOLD signal fluctuations in each voxel. Separate models were fitted for the left and right hemispheres, yielding a pair of 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, age², IQ, sex, and mean framewise displacement as a measure of in-scanner motion (64). Correlations between PLEs and seed-related functional connectivity, collapsed across hemispheres, were declared significant if they passed a threshold-free cluster enhancement (TFCE) (65) correction of $p < .05$, determined using 5000 permutations, as implemented in FSL Randomise (66). Scatterplots of associations between PLEs and functional connectivity were visualized using a leave-one-subject-out (LOSO) approach that circumvents circular inference (67) (details in Supplemental Information).

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 Supplement Table S1). Based on the inflection in the scree plot (Supplement 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.

Corticostriatal Functional Connectivity

Functional connectivity analysis was performed in 353 participants with fMRI data. Each striatal region showed functional connectivity profiles consistent with known anatomy and prior findings (Supplement Figure S3) (49, 50, 63).

Dorsal CST functional connectivity and PLEs

As predicted, higher scores on the positive PLE dimension were associated with reduced functional connectivity between the DRP 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 DC and left dorsal anterior cingulate cortex (ACC); reduced coupling between the DCP and left visual cortex, left posterior cingulate sulcus, and the right primary motor and sensory regions (Table 2; Figure 1). Higher positive PLE scores were also linked with increased coupling between the DCP and regions of right medial PFC, frontal eye

fields and frontal pole; and increased coupling between the DC and the lateral occipital cortex (Table 2).

Higher scores on the negative PLE dimension were associated with increased functional connectivity between the dorsal striatum and sensorimotor areas; namely, between the DCP and right primary motor cortex, right superior temporal gyrus, and left occipital and somatosensory areas; and between the DC seed and right occipital cortex (Table 2; Figure 1).

Ventral CST functional connectivity and PLEs

Associations between PLEs and ventral system functional connectivity were limited to the VRP seeds. Specifically, higher positive PLEs were associated with lower functional connectivity between this region and left visual cortex (Table 2; Figure 2). Higher negative PLEs were associated with higher coupling between the VRP and bilateral sensorimotor cortex (Table 2; Figure 2), and lower coupling between the VRP and the right paracentral lobule (Table 2).

Discussion

Corticostriatal systems have long been implicated in the pathophysiology of psychosis. Converging evidence from studies in independent samples report that reduced coupling of the dorsal CST circuit is apparent across a broad spectrum of disease risk (49, 50, 52–54). Here, we show that reduced functional coupling in the dorsal CST circuit tracks 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

identified several other 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, genetic high-risk, and ARMS individuals (49, 50). 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 ARMS individuals show reduced coupling between the dorsal caudate and DLPFC, with patients and relatives also showing reduced coupling between the dorso-caudal putamen and DLPFC (49, 50). Here, we found that positive PLEs were associated with reduced coupling between the dorsal caudate and ACC, and between dorso-*rostral* putamen and a more anterior region of DLPFC (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 only arises with dysfunction in very specific elements of this system (putatively involving the dorsal caudate and 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.

Other associations with dorsal circuit function and PLE severity implicate areas that are known to be affected by schizophrenia and subthreshold symptomatology. Abnormal structure and function of the ACC are frequently reported in both patients and high-risk individuals (29, 69–74). Concordantly, ACC dysfunction is linked to a failure to update prior beliefs based on sensory experience, which may induce hallucinations (75). Positive PLE severity was also associated with increased coupling between the dorsal striatum and regions involved in visual processing and oculomotor control which are processes that are disrupted in schizophrenia (36, 76, 77). Our findings of reduced coupling between the dorsal seeds and the PFC in association with higher positive PLEs are consistent with a report of simultaneously decreased and increased activation in the dorsal striatum and PFC, respectively, in healthy adolescents with high PLEs during a reward processing task (78).

Negative PLE severity was generally associated with increased dorsal circuit coupling. The implicated regions involve the dorsal caudate, dorso-caudal putamen, and sensorimotor systems. This finding is distinct from our prior report that negative symptoms correlated with reduced coupling between the dorsal caudate and DLPFC in first-episode patients (49). Negative symptoms are complex and can be difficult to assess via self-report, with such measures varying in their sensitivity to quantifying different constructs of the dimension (79). 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 refine this phenotype.

Ventral Corticostriatal Coupling and PLEs

Associations between PLEs and ventral CST coupling were restricted to the VRP-sensorimotor and visual circuit, such that increased functional connectivity was associated with higher negative and lower positive PLE scores. The association with positive PLEs is consistent with disrupted fronto-striatal connectivity leading to increased thalamic outflow to sensory cortices (38, 80). The concomitant association with negative PLEs implies that this increased outflow may be accompanied by psychomotor difficulties, which characterize many negative symptoms of schizophrenia (81–83), given that CST circuits modulate goal directed behavior involving immediate physical action by coordinating motor with executive functions (83).

In contrast with our prior report that first-episode psychosis patients and their unaffected relatives showed increased coupling between the nucleus accumbens and ventral frontal cortex (49), 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 (84), which may not have been identified in our analysis that focused on dominant modes of PLE variance.

Limitations

Over 90% of our sample was aged under 30 years, hence most participants have not passed through the maximal period of risk for schizophrenia (85). As psychotic experiences in early adulthood have been found to predict later psychopathology (15, 86), 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 two-component PCA solution parallels the well-known classification of clinical positive and negative symptomatology, but should be interpreted with some caveats. First, as stated, the leading components from the PCA encompass common variance across measures and may miss subtle aspects of PLEs that are unique to each questionnaire. Second, 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 psychotic and non-psychotic symptomatology in subclinical populations may lead to a more refined model of the psychosis risk phenotype.

Our scatterplots show small-to-moderate associations between PLEs and coupling estimates. We note that these were generated using a LOSO analysis for visualization purposes to avoid circular inference (67), and do not directly correspond to the general linear model used to estimate the main functional connectivity results. Finally, in-scanner head motion exerts a pernicious effect on functional connectivity estimates (62, 64, 87, 88), but our extensive quality control procedures indicate that our findings could not be explained by motion artifact (see Supplemental Information).

Conclusions

Our findings indicated that variation in dorsal CST function tracks subclinical expression of PLEs in a non-clinical sample, paralleling the circuit-level changes seen in patients and high-risk groups. Together, these findings are consistent with a continuum of

psychosis risk that is apparent at the level of overt behavior and underlying neurobiology, and which spans across a broad spectrum of liability ranging from isolated experiences or attributional biases in otherwise healthy individuals, to frank disorder in clinical populations. Early interventions targeting the function of this circuit may thus be a fruitful strategy for mitigating disease risk.

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Disclosures

The authors declare no competing interests

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Figure Legends

Figure 1. Associations Between Dorsal Circuit Functional Connectivity and Psychosis-Like Experiences

Coronal slices in the center of the bottom row depict the location of striatal seed regions in the dorsal circuit. Cortical surface maps depict the cortical sites for which functional connectivity with each seed correlates with PLE severity. Blue scatterplots depict the associations between positive PLE severity and (A) DRP and right DLPFC functional coupling (B) DC and left mPFC coupling; and (D) DCP and right sensorimotor coupling. Yellow scatterplots depict the associations between negative PLE severity and (C) DC and right visual cortex coupling and (E) DCP and right sensory cortex coupling. Clusters are thresholded at $p < .05$ TFCE corrected. For visualization purposes, functional connectivity estimates were obtained using Leave-One-Subject-Out analysis. DRP: dorso-rostral putamen; DC: dorsal caudate; DCP: dorso-caudal putamen; PC: principal component; PLEs: Psychosis-Like Experiences.

Figure 2. Associations Between Ventral Circuit Functional Connectivity and Psychosis-Like Experiences

Coronal slice in the center of the left column depicts the location of striatal seed regions in the ventral circuit. Cortical surface maps show the cortical sites for which functional connectivity with the ventral seeds correlate with PLE severity. Blue scatterplot depicts the association between positive PLE and the functional coupling of VRP and left visual area. Yellow scatterplot depicts the association between negative PLEs and VRP and left somatosensory area. Clusters are thresholded as $p < .05$ TFCE corrected. For visualization purposes, functional connectivity estimates were obtained using a Leave-One-Subject-Out

analysis. VRP: ventro-rostral putamen; PC: principal component; PLEs: Psychosis-Like Experiences.

Figure 3. Functional Connectivity of the Dorsal Circuit Across a Broad Spectrum of Disease Risk

Axial slices showing prefrontal regions where coupling within the dorsal circuit was reduced across a broad spectrum of disease risk, as identified in the current study and past findings. From left to right: regions in which coupling with the DCP and DC were reduced in first-episode psychotic patients compared to healthy controls (data from reference (49)); regions of reduced coupling with the DC in healthy first-degree relatives of patients, ARMS individuals and first-episode mania patients with psychosis compared to healthy controls (data from references (49–51)); and findings from the present study, showing regions where lower coupling with the DC and DRP was associated with more severe positive PLEs. The z-axis slice in MNI coordinates is shown beneath each image. Left hemisphere is on the left. DCP: dorso-caudal putamen; DC: dorsal caudate; DRP: dorso-rostral putamen.

Table 1. Component Loadings of Subscales After Rotation

	Component	
	1	2
CAPE Positive	.88	.01
Chapman Magical Ideation	.86	-.01
sO-LIFE Unusual Experiences	.86	.10
Peters Delusion Inventory	.85	.05
Chapman Perceptual Aberration	.78	.12
sO-LIFE Impulsive Nonconformity	.63	.17
CAPE Depressive	.53	.40
sO-LIFE Cognitive Disorganization	.47	.49
sO-LIFE Introvertive Anhedonia	.03	.86
Chapman Social Anhedonia	.14	.79
Chapman Physical Anhedonia	-.19	.74
CAPE Negative	.40	.67
Eigenvalues	5.14	2.36
% of variance	42.87	19.70

Loadings over .40 appear in bold.

Table 2. Regions Where Striatal Functional Connectivity Was Associated with Psychosis-Like Experiences ($p < .05$ TFCE Corrected)

Seed	Contrast	Region	MNI coordinates (x, y, z)	Max T-value	Cluster extent (voxels)	p
DC	Pos PLEs -	L dorsal anterior cingulate cortex	-8, 28, 26	4.98	128	.001
	Pos PLEs +	R lateral occipital cortex	42, -60, 24	4.98	37	.02
	Neg PLEs +	R occipital cortex	26, -82, 8	4.92	216	<.01
DCP	Pos PLEs -	R primary motor cortex	22, -16, 74	4.88	569	<.001
		R supplementary motor area	6, -4, 62	3.95	95	.03
		L visual association area	-6, -96, 24	4.71	68	.03
		R primary sensory area	10, -38, 78	4.18	57	.03
		L posterior cingulate sulcus	-16, -34, 50	4.32	56	.02
	Pos PLEs +	R medial prefrontal cortex	2, 44, 34	4.12	166	.03
		L frontal eye fields	-24, 30, 44	4.15	84	.03
		R frontal pole	16, 70, 2	4.97	33	.03
	Neg PLEs +	R primary motor area	34, -24, 52	5.07	3567	<.001
		R superior temporal gyrus	66, -2, 6	4.74	91	.02
		L intraparietal sulcus	-26, -78, 24	5.14	66	.01
		L superior occipital gyrus	-20, -84, 38	4.05	47	<.01
		L primary somatosensory area	-60, -14, 34	4.25	14	.04
		L parietal opercular	-52, -18, 18	4.66	11	.03
DRP	Pos PLEs -	R anterior middle frontal gyrus	24, 54, 26	5.7	213	<.01
VRP	Pos PLEs -	L visual association area	-38, -92, 2	5.4	505	<.01
	Neg PLEs -	R paracentral lobule	2, -76, 42	4.72	58	.02
	Neg PLEs +	L primary somatosensory area	-60, -14, 30	4.78	890	<.01
		R postcentral sulcus	44, -30, 40	4.18	320	.01
		R precentral gyrus	12, -26, 68	5.16	240	.001
		R premotor cortex	50, -2, 26	4.19	201	.02
		R primary somatosensory area	44, -36, 62	4.44	114	.02
		R mid cingulate cortex	8, -18, 52	4.58	75	.02
		R primary somatosensory area	40, -12, 66	3.57	36	.04
		L frontal opercular	-58, -10, 6	4.35	28	.03
		R supplementary motor area	8, -14, 62	3.44	13	.04
		L posterior cingulate	-8, -26, 44	3.66	11	.04

Only clusters with more than 10 voxels are listed. '+' sign indicates increased coupling in

association with PLEs, while '-' indicates reduced coupling associated with PLEs. PLEs:

Psychosis-Like Experiences; R: right; L: left; DRP: dorso-rostral putamen; DC: dorsal

caudate; DCP: dorso-caudal putamen; VRP: ventro-rostral putamen.

VRP

First-Episode Psychosis

First-Degree
Relatives

At-Risk
Mental State

First-Episode
Mania

Positive PLEs

$z = 40$

$z = 45$

$z = 40$

$z = 40$

$z = 40$

$z = 26$

$z = 26$

DCP

DC

DRP