Biological Psychiatry: CNNI

Archival Report

Functional Connectivity of the Striatum in Schizophrenia and Psychotic Bipolar Disorder

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ABSTRACT

BACKGROUND: The striatum is abnormal in schizophrenia and possibly represents a common neurobiological mechanism underlying psychotic disorders. Resting-state functional magnetic resonance imaging studies have not reached a consensus regarding striatal dysconnectivity in schizophrenia, although these studies generally find impaired frontoparietal and salience network connectivity. The goal of the current study was to clarify the pattern of corticostriatal connectivity, including whether corticostriatal dysconnectivity is transdiagnostic and extends into psychotic bipolar disorder.

METHODS: We examined corticostriatal functional connectivity in 60 healthy subjects and 117 individuals with psychosis, including 77 with a schizophrenia spectrum illness and 40 with psychotic bipolar disorder. We conducted a cortical seed–based region-of-interest analysis with follow-up voxelwise analysis for any significant results. Further, a striatum seed–based analysis was conducted to examine group differences in connectivity between the striatum and the whole cortex.

RESULTS: Cortical region-of-interest analysis indicated that overall connectivity of the salience network with the striatum was reduced in psychotic disorders, which follow-up voxelwise analysis localized to the left putamen. Striatum seed–based analyses showed reduced ventral rostral putamen connectivity with the salience network portion of the medial prefrontal cortex in both schizophrenia and psychotic bipolar disorder.

CONCLUSIONS: The current study found evidence of transdiagnostic corticostriatal dysconnectivity in both schizophrenia and psychotic bipolar disorder, including reduced salience network connectivity, as well as reduced connectivity between the putamen and the medial prefrontal cortex. Overall, the current study points to the relative importance of salience network hypoconnectivity in psychotic disorders.

Keywords: Cortex, Psychosis, Psychotic bipolar disorder, Resting-state fMRI, Schizophrenia, Striatum

https://doi.org/10.1016/j.bpsc.2019.05.017

Multiple lines of evidence implicate the striatum in the pathophysiology of schizophrenia (1–3). The discovery that antipsychotics' efficacy relates directly to their ability to block dopamine receptors led to the dopamine hypothesis of schizophrenia, which hypothesizes that psychotic symptoms result from exaggerated dopamine signaling (4,5) in the striatum (6). The dopamine hypothesis was directly supported with the advent of positron emission tomography (PET) imaging (3). Specifically, PET studies in schizophrenia have consistently found elevated presynaptic synthesis capacity (2,7), exaggerated dopamine release following amphetamine challenge (8), and increased postsynaptic dopamine D_2 receptors (9,10).

Over the past several years, resting-state functional magnetic resonance imaging (RS-fMRI) has joined the armamentarium of neuroimaging methods for investigating psychiatric disorders (11–13). A key advantage of RS-fMRI is that it can be used to assess distributed neural networks rather than brain regions in isolation. The striatum is a key node within corticostriatal loops, or functional networks composed of cortex, basal ganglia, and thalamus (14–16). RS-fMRI studies have reliably identified five corticostriatal networks: the frontoparietal network (FPN), default mode network (DMN), limbic network (LN), salience network (SAL), and motor network (15). RS-fMRI studies of corticostriatal networks in psychotic disorders have not reached a consensus regarding the nature of dysconnectivity in these five corticostriatal networks. Research consistently finds decreased FPN connectivity [e.g., involved in goal representation (17)] in psychotic disorders (18–21). Research also generally implicates decreased SAL connectivity [e.g., information integration, salience attribution (22,23)] in psychotic disorders (24,25). Research also finds hyperconnectivity in motor networks [e.g., execution of motor plans (26)] (25,27), although the direction of connectivity in the DMN [e.g., attention to internal states, self-referential thinking (28)] (29–32) and LN (e.g., motivation) (33,34) is mixed. Furthermore, there is a lack of consistency regarding the associations among corticostriatal connectivity, clinical symptoms, and impaired cognition. In terms of associations between corticostriatal connectivity and symptoms, recent research indicates that salience network hypoconnectivity is correlated with

impaired cognition (35) and positive psychotic symptoms (24). However, other networks, such as the FPN and DMN, have also been linked to positive symptoms (18,19,36). Most previous studies involving psychotic disorders involved limited sample sizes (e.g., <30 individuals in the patient groups) (19,20,24,25,29,32,33), raising the possibility that these studies were underpowered to examine corticostriatal connectivity differences and identify reliable clinical-connectivity associations.

Psychiatry is increasingly focusing on transdiagnostic phenomena, as exemplified by the National Institute of Mental Health Research Domain Criteria initiative, which posits that common neurobiological mechanisms underlie transdiagnostic symptom domains (37). Evidence that psychotic bipolar disorder is also associated with exaggerated dopamine signaling in the striatum (38,39), consistent with schizophrenia, suggests that striatal dysfunction may be a common neurobiology underlying psychosis. Research examining connectivity in schizophrenia and bipolar groups has found mixed results. This evidence includes intact connectivity in a group at risk for bipolar disorder (40) and disorder-specific connectivity impairments in schizophrenia spectrum groups (40,41). In contrast, there is some evidence for corticostriatal impairments in bipolar groups (42), as well as transdiagnostically across psychotic disorders (43).

The current study investigated corticostriatal connectivity in schizophrenia and psychotic bipolar disorder to 1) further clarify corticostriatal network dysconnectivity in schizophrenia; 2) determine if schizophrenia and psychotic bipolar disorder demonstrate similar or different patterns of corticostriatal dysconnectivity; and 3) replicate prior findings linking corticostriatal network dysconnectivity to cognitive impairment (35) and positive psychotic symptoms (24).

METHODS AND MATERIALS

Study Participants

A total of 193 individuals (61 healthy subjects, 132 individuals with a psychotic disorder) that participated in an ongoing National Institute of Mental Health–funded study on brain connectivity in psychotic disorders were initially screened for inclusion in this investigation. Sixteen participants did not meet our neuroimaging quality assurance procedures described below. Thus, the final cohort consisted of 177 study participants: 60 healthy individuals, 77 individuals with a schizophrenia spectrum illness (i.e., schizophrenia, schizoaffective, or schizophreniform disorder), and 40 individuals with bipolar disorder with psychotic features (i.e., psychotic bipolar disorder). Demographic data are presented in Table 1. Patients were recruited through the Psychotic Disorders Program within the Department of Psychiatry and Behavioral Sciences at Vanderbilt University Medical Center. Healthy individuals were recruited from Nashville and the surrounding area via advertisement and word of mouth. This study was approved by the Vanderbilt University Institutional Review Board. All study participants provided written informed consent prior to participating.

Psychiatric diagnoses were confirmed in patients and ruled out in healthy subjects using the Structured Clinical Interview for DSM-IV (44). Patients were further assessed with the Positive and Negative Syndrome Scale (PANSS) (45), Young Mania Rating Scale (46), and Hamilton Depression Rating Scale (47) to quantify severity of psychotic, mania, and depression symptoms, respectively. The Wechsler Test of Adult Reading (48) was administered to all subjects to provide an estimate of premorbid intellect. Study participants also completed the Screen for Cognitive Impairment in Psychiatry (SCIP) (49), a brief neuropsychological battery that includes a word list learning test of verbal memory, a version of the Auditory Consonant Trigrams test of working memory, a test of phonemic verbal fluency, and a coding test of processing speed. SCIP subtest raw scores were converted to *Z* scores using previously published normative data and averaged to create a "composite" *Z* score of overall cognitive functioning (49). Exclusion criteria included <16 years of age or >55 years of age, estimated premorbid IQ <70, presence of a medical illness or central nervous system disorder (e.g., multiple sclerosis, epilepsy) that would affect study results, reported pregnancy or lactation, history of significant head trauma, psychotropic drug use (healthy subjects only), substance abuse within last 3 months (patients) or lifetime history of substance abuse/dependence (healthy subjects), and MRI contraindicators (e.g., metal implants, claustrophobia).

Neuroimaging Data Acquisition, Preprocessing, and Quality Assurance

A 10-minute resting-state (eyes open, fixation) echo-planar imaging functional scan and T1-weighted anatomical scan were collected on each subject during a single scanning session on a 3T Philips Intera Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) located at Vanderbilt University Institute of Imaging Sciences. The RS-fMRI scan had the following parameters: 38 axial slices (slice thickness = 3.0 mm; gap = 0.3 mm), field of view = 80 × 80 matrix (3.0 mm × 3.0 mm in-plane resolution), 90-degree flip angle, 300 volumes, repetition time/echo time = 2000 ms/25 ms. A high-resolution T1-weighted turbo field echo structural scan (170 sagittal slices, field of view = 256 × 256 matrix, 1.0-mm isovoxel resolution, repetition time/echo time = 8.9 ms/4.6 ms) was also acquired.

T1-weighted anatomical images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using the voxel-based morphometry, version 8 toolbox (VBM8) (http://dbm.neuro.uni-jena.de/vbm/) for SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). Following segmentation, each tissue class was spatially warped to a Montreal Neurological Institute space template image comprising 550 subjects included with the VBM8 toolbox (http://dbm.neuro.uni-jena.de.libproxy.wustl.edu/vbm/) using the high-dimensional DARTEL toolbox normalization method. Functional RS scans were slice-time corrected, motion corrected, co-registered to native space structural data, and normalized to Montreal Neurological Institute space using DARTEL toolbox deformation fields obtained from spatially normalizing the T1-weighted anatomical images.

All RS data underwent quality assurance using an automated quality assurance pipeline that calculated median voxel displacement, median temporal signal-to-noise ratio (SNR), and 95th percentile signal change. Scans with log SNR and log

Table 1. Sample Demographics

		Psychosis				
	HS Group, n = 60	SCZ Group, n = 77	BPP Group, n = 40	Statistics $F/t/\chi^2$	p Value	Contrast
Male/Female, n	38/22	53/24	23/17	$\chi^2_2 = 1.52$	.47	
White/African American/Other, n	39/15/6	54/21/2	32/6/2	$\chi^2_4 = 5.81$	.21	
Clinical Status, % First Episode		44.2	40.0	$\chi^2_1 = 0.19$	.67	
Mood Stabilizer Use, %		28.6	70.0	$\chi^2_1 = 18.46$	<.001[a]	
Age, Years	29.27 ± 9.45	27.43 ± 9.71	29.20 ± 11.19	$F_{176} = 0.72$	.49	
Premorbid IQ	109.90 ± 6.73	102.01 ± 10.08	105.53 ± 9.93	$F_{175} = 12.66$	<.001	HS > SCZ
SCIP Global Cognition Z Score	0.29 ± 0.59	−0.80 ± 0.82	−0.29 ± 0.90	$F_{176} = 33.83$	<.001	HS > BPP > SCZ
Median Signal-to-Noise Ratio	58.87 ± 14.15	61.31 ± 13.85	60.49 ± 14.33	$F_{176} = 0.51$	.60	
Median Voxel Displacement	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	$F_{176} = 0.33$	.72	
PANSS Positive		14.43 ± 8.27	10.83 ± 6.26	$t_{115} = 2.42$	.02	
PANSS Negative		13.62 ± 5.41	9.80 ± 2.73	$t_{115} = 4.20$	<.001	
PANSS General		27.53 ± 7.83	23.75 ± 6.48	$t_{115} = 2.62$	.01	
CPZ Equivalents		354.64 ± 199.53	231.84 ± 160.81	$t_{83} = 2.65$	.01	
Illness Duration, Months[b]		75.00 ± 95.75	72.51 ± 88.44	$t_{113} = 0.14$	.89	

Values are mean ± SD except where noted.

BPP, bipolar with psychotic features; CPZ, chlorpromazine; HS, healthy control subjects; PANSS, Positive and Negative Syndrome Scale; SCIP, Screen for Cognitive Impairment in Psychiatry; SCZ, schizophrenia.

[a]The groups did not differ in mood stabilizer dose ($t_{44} = -0.27$, $p = .79$).

[b]Average duration of illness was not significantly associated with any of the significant corticostriatal connectivity estimates ($ps > .45$).

median voxel displacement above the 95th percentile of the distribution of the entire dataset were excluded from the analysis, leaving (as previously mentioned) 177 subjects passing these criteria. Diagnostic groups did not differ on median SNR ($F_{2,174} = 0.51$, $p = .60$), median voxel displacement ($F_{2,174} = 0.33$, $p = .72$), and 95th percentile signal change ($F_{2,174} = 1.24$, $p = .29$).

Functional Connectivity Analysis

Prior striatal functional connectivity studies in psychosis used either cortical seeds to examine connectivity of cortical areas with the striatum (i.e., cortex seed–based analysis) (27,50–52) or striatal seeds to examine connectivity of striatal subregions with the rest of the brain (i.e., striatum seed–based analysis) (18,19,53). We used both approaches to comprehensively map functional connectivity of the striatum and facilitate comparison of our results to prior studies. Each approach is described in detail below.

Functional connectivity maps of cortex and striatum seeds were generated using the CONN-fMRI toolbox v.17.f (http://www.nitrc.org/projects/conn). The mean blood oxygen level–dependent time series was extracted from seeds and entered as a predictor in a multiple regression general linear model. Regressors corresponding to the 6 motion correction parameters and their first temporal derivatives, along with gray matter, white matter, and CSF, were included to remove variance related to head motion, the global gray matter signal, white matter, and CSF, respectively. In addition to 12 nuisance regressors related to motion (6 translations/rotations and their temporal first derivatives), the first 6 principal components were extracted from each subject's white matter and CSF segmentations (i.e., anatomical CompCor) (54). Anatomical CompCor has been shown to be at least as effective as another commonly used approach, the "scrubbing" procedure described by Power *et al.* (55), at mitigating the residual effects of head motion on functional connectivity (56). Motion correction parameters were regressed out prior to temporal bandpass filtering. Performing these steps in reverse order (i.e., bandpass filtering before nuisance regression) reintroduces nuisance-related variation, thereby overestimating connectivity estimates and exacerbating the effects of head motion (57).

In addition, a mask was created for each subject's mean fMRI image to identify in-brain voxels (i.e., an in-brain mask) and exclude voxels with low SNR. Briefly, after rescaling and standardizing each subject's voxel intensity, the mean voxel intensity for all 177 subjects was calculated and a threshold was identified using the SPM12's antimode function to estimate a brain–nonbrain threshold (58). Any voxels that did not meet this in-brain threshold were removed, after applying the mask to Montreal Neurological Institute space. This mask was used in all cortical analyses in to remove nonbrain and low-SNR voxels from the analyses.

Cortex Seed–Based Analysis. The 7-network cortical parcellation identified by Yeo *et al.* (59) was used to define seeds for the cortical seed–based analysis (see Figure 1A). Briefly, the Yeo *et al.* 7-network cortical parcellation comprises the DMN, FPN, SAL, LN, sensorimotor, dorsal attention, and visual networks. Functional connectivity maps were generated for each of the Yeo *et al.* networks, except the dorsal attention network and visual network, which have minimal functional connectivity with the striatum (15). The functional connectivity maps were masked to only include voxels in the striatum. To maximize statistical power, we first performed a region-of-interest (ROI) analysis that generated a single value approximating overall functional connectivity of each cortical seed with the striatum. Specifically, the unsmoothed cortical seed–

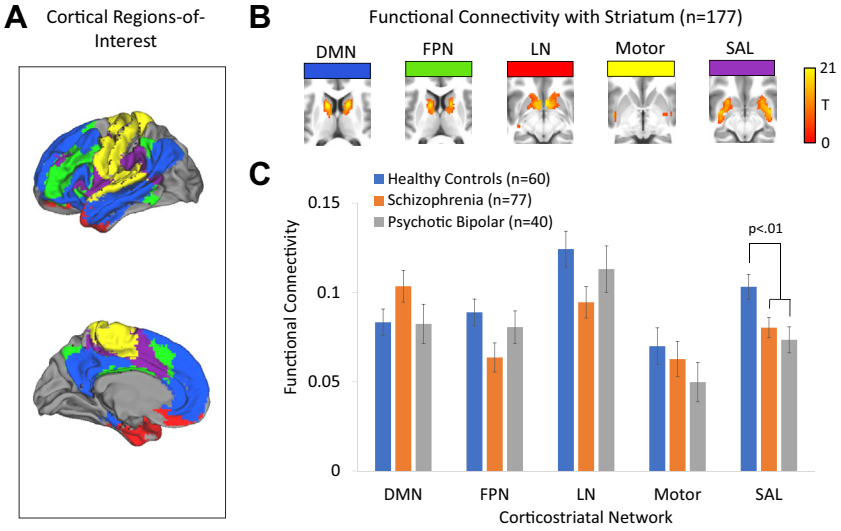

Figure 1. Cortical seed–based analysis of corticostriatal functional connectivity in healthy subjects, patients with schizophrenia, and patients with psychotic bipolar disorder. **(A)** The cortex was partitioned into 5 nonoverlapping regions of interest that were used as seeds in a seed-based functional connectivity analysis. **(B)** Average corticostriatal functional connectivity within the striatum for each of the 5 cortical regions of interest. **(C)** Average corticostriatal functional connectivity within the striatum for each of the 5 cortical regions of interest for each of the 3 diagnostic groups (i.e., healthy control subjects, patients with schizophrenia, patients with psychotic bipolar disorder). Error bars indicate SEM. DMN, default mode network; FPN, frontoparietal network; LN, limbic network; SAL, salience network.

based connectivity maps were entered into separate 1-sample voxelwise *t* tests to identify voxels in the striatum exhibiting positive functional connectivity with each cortical seed. This analysis included the entire cohort of study participants, including healthy subjects and individuals with a psychotic disorder. The resultant statistical parametric maps were thresholded at voxelwise familywise error–corrected $p = .05$, minimum cluster size = 10 voxels, and the eigenvariate function in SPM12 was used to extract the first principal component from the voxels that survived thresholding. This yielded a single measure of functional connectivity with the striatum for each cortical seed for each subject. These measures served as dependent variables in a repeated-measures analysis of covariance with network entered as a repeating variable and diagnostic group (healthy control subjects, schizophrenia, psychotic bipolar disorder) entered as a between-subjects factor, along with age and gender as covariates. Significant main effects and interactions were followed up with post hoc *t* tests.

The well-powered ROI approach described above was followed up with voxelwise analyses comparing functional connectivity of each cortical seed within the striatum between groups to examine the specific locations of connectivity differences between the groups. Briefly, the unsmoothed cortical seed–based connectivity maps were analyzed separately using 1-way analyses of variance with group (healthy control subjects, schizophrenia, psychotic bipolar disorder) entered as a between-subjects variable, along with age and gender as covariates. Voxelwise analyses of variance were masked with the 1-sample *t*-test results described above, such that only voxels that demonstrated positive functional connectivity with the cortex-based seeds were included in the analysis. Results were thresholded at cluster-level familywise error–corrected $p = .05$ for voxelwise $p = .001$.

Striatum Seed–Based Analysis. We used the striatum seeds from previous striatal seed–based connectivity research (18,19,60). These striatum seeds comprised six 3.5-mm-radius spherical ROIs, totaling 3 bilateral caudate and 3 bilateral putamen regions corresponding to the dorsal caudate ($x = \pm13$, $y = 15$, $z = 9$), superior ventral caudate ($x = \pm10$, $y = 15$, $z = 0$), inferior ventral caudate ($x = \pm9$, $y = 9$, $z = -8$), dorsocaudal putamen ($x = \pm28$, $y = 1$, $z = 3$), dorsorostral putamen ($x = \pm25$, $y = 8$, $z = 6$), and the ventrorostral putamen (vrPT) ($x = \pm20$, $y = 12$, $z = -3$). Functional connectivity maps were generated for each of these striatum seeds. Functional connectivity maps were masked to only include voxels in the cortex (using the in-brain mask) and smoothed (6 mm). A 1-sample voxelwise *t* test was performed for each striatum seed to identify voxels in the cortex exhibiting positive functional connectivity with each striatum seed. The resultant statistical parametric maps were thresholded at voxelwise $p = .001$. Group differences in functional connectivity of each striatum seed were then analyzed using a 1-way analysis of variance with group (healthy control subjects, schizophrenia, psychotic bipolar disorder) entered as a between-subjects variable, along with age and gender as covariates. These analyses were masked with the 1-sample *t*-test results described above, such that only voxels that demonstrated positive functional connectivity with striatum-based seeds were included in the analysis. Results were thresholded at cluster-level familywise error–corrected $p = .05$ for voxelwise $p = .001$.

Testing Associations Between Striatal Connectivity and Clinical Variables

Next, we examined whether there were associations between connectivity impairments and both cognitive impairment and symptoms (and specifically positive psychotic symptoms), as has been found in previous research (24,35). To test these hypotheses, we examined whether there were significant associations between each significant corticostriatal connectivity finding and both cognitive impairment on the SCIP and PANSS symptoms. These regressions included the following predictors: gender, age, diagnostic group (i.e., healthy control subjects, schizophrenia, psychotic bipolar disorder), the

variable of interest (e.g., SCIP "composite" *Z* score), and an interaction between diagnostic group and the variable of interest. For the cortex seed–based ROI analysis described above, overall connectivity between each cortical network and the striatum served as the dependent variable in regression analyses. For the voxelwise analyses, mean functional connectivity was extracted from the clusters that survived thresholding using the eigenvariate function in SPM12, and this served as the dependent variable in regression analyses. Regression analyses were corrected for multiple comparisons (using false discovery rate [FDR] correction) based on the number of associations examined (i.e., FDR corrected for every cognitive impairment and symptom variable of interest, for a total of four FDR-corrected comparisons) for each significant corticostriatal connectivity finding.

RESULTS

Striatum Functional Connectivity: Cortical Seed–Based Analysis

ROI Analysis. Results of the ROI analysis are shown in Figure 1B. Repeated measures analysis of covariance revealed a main effect of diagnostic group ($F_{2,172} = 3.82$, $p = .02$) and a network-by-diagnosis interaction ($F_{8,340} = 2.06$, $p = .04$). Bonferroni-corrected post hoc comparison of estimated marginal means indicated that the main effect of diagnostic group was due to the schizophrenia group overall, showing reduced corticostriatal connectivity with the striatum compared with healthy subjects (mean difference = 0.14, SE = 0.005, $p = .04$). Connectivity was not significantly different between patients with psychotic bipolar disorder and healthy subjects (mean difference = 0.14, SE = 0.006, $p = .09$). Connectivity was also similar between patients with schizophrenia and psychotic bipolar disorder (mean difference = 0.001, SE = 0.006, $p > .99$ (see Figure 1C). Post hoc univariate analysis indicated that the network-by-diagnosis interaction effect was due to group differences in SAL connectivity with the striatum ($F_{2,172} = 5.24$, $p = .006$) (see Figure 2). SAL connectivity with the striatum was greater in healthy subjects than in patients with schizophrenia ($p = .007$) and psychotic bipolar disorder ($p = .005$), which did not differ from one another ($p = .58$) (see Figure 2B). Although not significant, there were also trends toward diagnostic effects for the FPN ($F_{2,172} = 2.87$, $p = .06$) and LN ($F_{2,172} = 2.41$, $p = .09$). Post hoc contrasts indicated that FPN and LN connectivity with the striatum was significantly lower in patients with schizophrenia than in healthy subjects ($p = .02$ and $p = .03$, respectively), whereas connectivity in patients with psychotic bipolar disorder was similar to that in healthy subjects ($p = .53$ and $p = .41$, respectively).

Median voxel displacement was not significantly associated with SAL connectivity ($\beta = .30$, $p = .20$). In a regression that included the combined patient sample examining the association between connectivity and antipsychotic dose in chlorpromazine equivalents (61), SAL connectivity did not significantly correlate with antipsychotic dose ($\beta = -.04$, $p = .74$). With respect to associations with cognitive functioning and symptoms, SAL connectivity was not significantly related to cognitive functioning (i.e., SCIP composite *Z* score [$\beta = .03$, $p = .89$]; there was also no evidence that the relation between connectivity and cognitive functioning varied by group [$\beta = .08$, $p = .75$]). Nor was SAL connectivity significantly related to PANSS positive, negative, or general symptoms (βs $< -.67$, FDR-corrected ps $> .45$; there was no evidence that the relation between connectivity and PANSS symptoms varied by group [βs $< .58$, FDR-corrected ps $> .47$]).

Voxelwise Analysis. Consistent with the ROI analysis presented above, connectivity between the SAL cortical seed and striatum was decreased in schizophrenia and psychotic bipolar disorder in a cluster located in the putamen (see Table 2 and Figure 2). No additional cortical seeds demonstrated altered connectivity with the striatum. Post hoc univariate analysis revealed that the significant effect of diagnostic group for this cluster was due to greater SAL cluster connectivity in healthy subjects compared with both patients with schizophrenia ($p < .001$) and patients with psychotic bipolar disorder ($p < .001$). Connectivity was similar in schizophrenia and psychotic bipolar disorder ($p = .53$) (see Figure 2). Median voxel displacement was not significantly associated with SAL cluster connectivity ($\beta = -.18$, $p = .42$). In a regression that included the combined patient sample examining the association between connectivity and antipsychotic dose in chlorpromazine equivalents, SAL cluster connectivity did not significantly correlate with antipsychotic dose ($\beta = -.11$, $p = .33$). SAL cluster connectivity was not significantly related to cognitive functioning ($\beta = .24$, $p = .32$; there was also no evidence that the relation between connectivity in this cluster and cognitive functioning varied by group [$\beta = -.12$, $p = .60$]). SAL cluster connectivity was not significantly related to PANSS positive, negative, or general symptoms (βs $< -.80$, FDR-corrected ps $> .39$; there was also no evidence that PANSS symptoms varied by patient group [βs $< .69$, FDR-corrected ps $> .54$]).

Striatum Functional Connectivity: Striatum Seed–Based Analysis

The between-group analyses (see Figure 3) revealed a main effect of diagnostic group between the vrPT striatal seed and cortical regions in a cluster located in the medial prefrontal cortex (PFC) (see Figure 3C; Table 2). Bonferroni-corrected post hoc univariate analysis revealed that the significant effect of diagnostic group for this cluster was due to greater vrPT cluster connectivity in healthy subjects compared with both patients with schizophrenia ($p < .005$) and patients with psychotic bipolar disorder ($p < .001$), whereas cluster connectivity was similar in patients with schizophrenia and patients with psychotic bipolar disorder ($p = .89$) (see Figure 3C). Median voxel displacement was not significantly associated with vrPT cluster connectivity ($\beta = -.13$, $p = .57$). In a regression that included the combined patient sample, examining the association between connectivity and antipsychotic dose in chlorpromazine equivalents, vrPT cluster connectivity did not significantly correlate with antipsychotic dose ($\beta = -.05$, $p = .66$). In terms of cognitive functioning, greater vrPT cluster connectivity was not significantly related to SCIP composite *Z* scores, $\beta = .23$, $p = .34$ (there was also no evidence that the relation between connectivity and SCIP scores varied by group [$\beta = -.19$, $p = .45$]). In terms of PANSS symptoms, vrPT cluster connectivity was not significantly related to PANSS positive, negative, or general symptoms (βs $< |.74|$, FDR-corrected ps

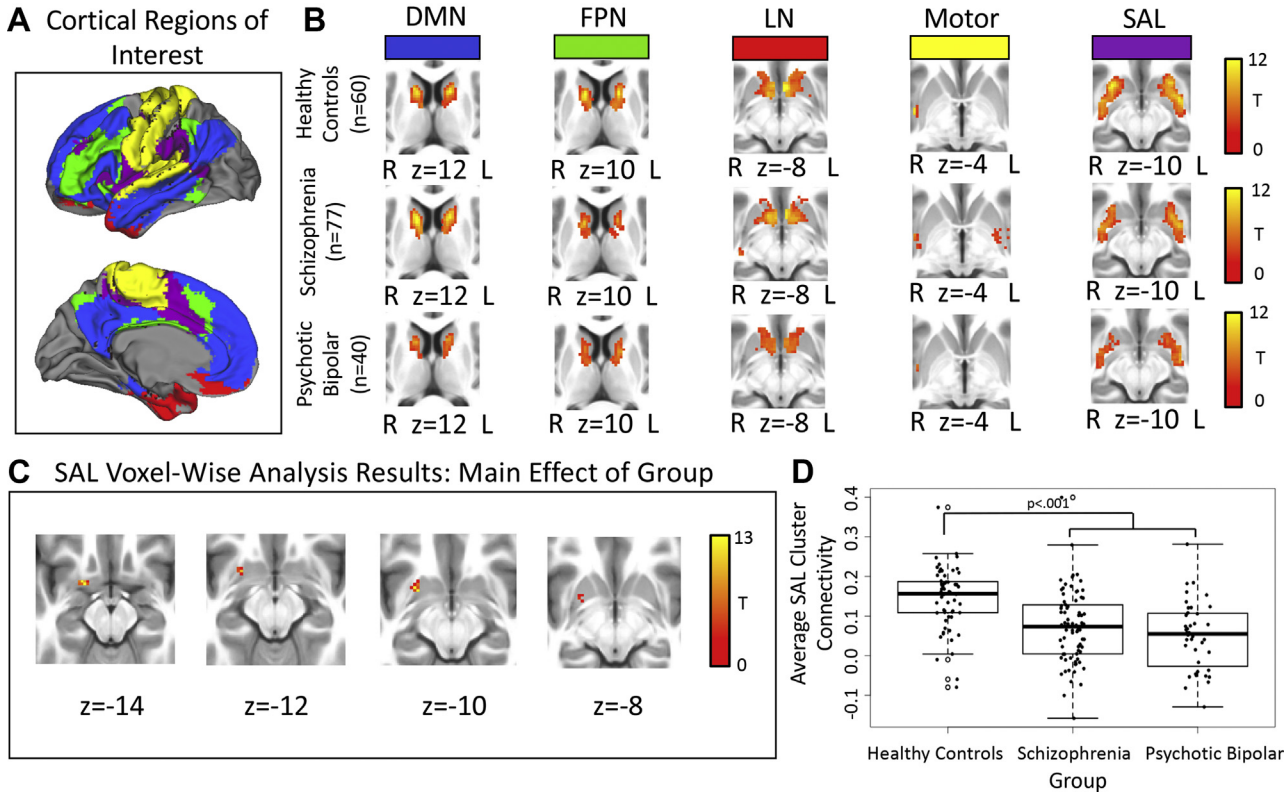

Figure 2. **(A)** Cortical parcellation used to define the 5 cortical regions of interest. **(B)** The pattern of functional connectivity within the striatum for each cortical region of interest in healthy control subjects, patients with schizophrenia, and patients with psychotic bipolar disorder. Results were thresholded at cluster-level familywise error–corrected $p = .05$ for voxelwise p (uncorrected) = .001. **(C)** Voxelwise results for the salience network (SAL) cortical seed within the striatum revealed a main effect of group for the SAL cortical seed within the striatum, thresholded at whole-brain voxelwise p (uncorrected) = .001. **(D)** Direct comparison between groups revealed decreased SAL connectivity in the striatum in schizophrenia and psychotic bipolar disorder. DMN, default mode network; FPN, frontoparietal network; L, left; LN, limbic network; R, right.

$> .49$; there was also no evidence that PANSS symptoms varied by patient group [βs $< |.71|$, FDR-corrected ps $> .56$]).

DISCUSSION

We examined both cortical connectivity between the striatum and predefined cortical seeds, and connectivity of striatal seeds with the rest of the brain in a large sample. We found that evidence for reduced SAL connectivity observed in several prior investigations of patients with schizophrenia (22,33,35) is also present in psychotic bipolar disorder. We also replicated evidence for hypoconnectivity between the vrPT and the SAL portion of the medial PFC in both schizophrenia and psychotic bipolar disorder. This research supports evidence for a transdiagnostic neurobiology underlying psychosis (39), providing evidence that the SAL may be specifically associated with

Table 2. Voxelwise Analysis Results for the Cortical and Striatal Regions of Interest

Cortical Target	Brain Region	MNI Coordinates x	y	z	Peak F Value	Cluster p[a]	Cluster Size, Voxels
Cortical Region of Interest							
SAL	L putamen/L olfactory cortex	−20	6	−14	12.37	<.001	28
SAL	L putamen	−24	6	−6	9.50		
Striatal Region of Interest							
vrPT	R medial prefrontal cortex	4	14	48	11.62	.003	208
vrPT	L medial prefrontal cortex	−2	8	46	8.47		
vrPT	R anterior cingulate cortex	8	20	28	8.35		

Regions of interest not presented had no clusters that survived the cluster-level threshold.
L, left; MNI, Montreal Neurological Institute; R, right; SAL, salience network; sVC, superior ventral caudate; vrPT, ventrorostral putamen.
[a]Cluster familywise error–corrected $p = .05$ for voxelwise p (uncorrected) = .001.

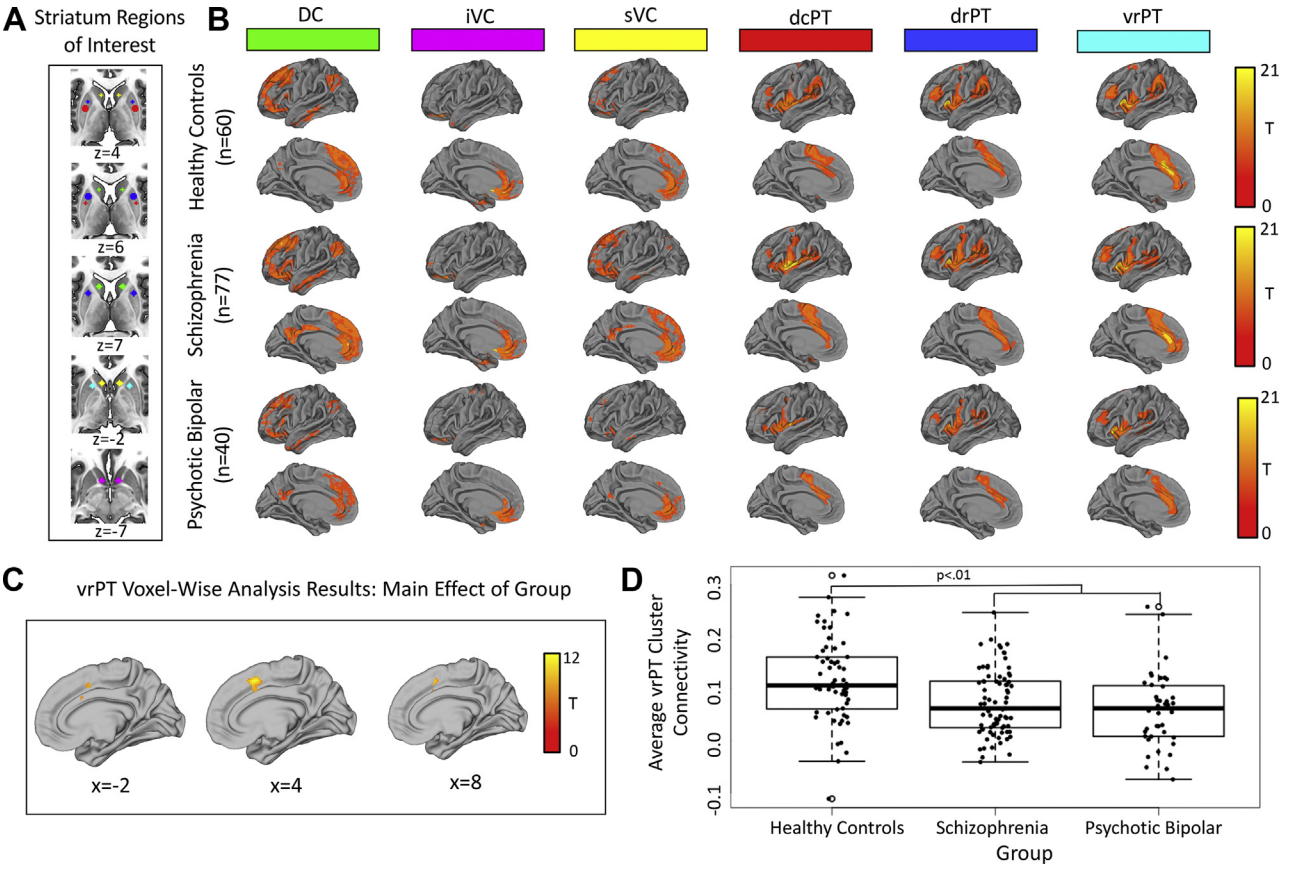

Figure 3. **(A)** The 6 striatum seeds used as regions of interest in seed-based functional connectivity analyses. **(B)** The pattern of functional connectivity within the cortex for each striatum region of interest in healthy control subjects, patients with schizophrenia, and patients with psychotic bipolar disorder, thresholded at whole-brain voxelwise *p* (uncorrected) = .001. **(C)** Voxelwise results for the main effect of group for the ventrorostral putamen (vrPT) striatum seed, thresholded at whole-brain voxelwise *p* (uncorrected) = .001. **(D)** Direct comparison between groups revealed decreased vrPT connectivity in schizophrenia and psychotic bipolar disorder. DC, dorsal caudate; dcPT, dorsocaudal putamen; drPT, dorsorostral putamen; iVC, inferior ventral caudate; sVC, superior ventral caudate.

hypoconnectivity across psychotic disorders. Thus, the current study helps clarify corticostriatal dysconnectivity in psychotic disorders.

With regard to cortical connectivity to striatal regions, there was a main effect of group, whereby the schizophrenia group overall showed reduced connectivity compared with healthy subjects. Furthermore, we replicated previous findings of SAL hypoconnectivity (22,33,35), as the voxelwise analysis helped localize the SAL connectivity differences to the putamen. The SAL is consistently linked to functions associated with impairment in psychotic disorders, including directing attention toward important stimuli (23), making the SAL a likely suspect for impaired connectivity across psychotic disorders. SAL-related dysfunction in psychotic disorders has been found in neuroimaging studies, including reductions in gray matter volume in SAL regions (62), impairments in task-related activation (63,64), and altered structural connectivity in key SAL regions (65,66). Likewise, and consistent with this study, reduced SAL connectivity in psychotic disorders has been found in a number of studies, including reduced connectivity within the insula (24,52,67) and dorsal anterior cingulate cortex (34,51), as well as overall reduced SAL within-network connectivity (29,66,68). Last, post hoc analyses indicated that the FPN and LN showed reduced connectivity specifically for the schizophrenia group, replicating findings from previous corticostriatal connectivity work (18,19,21,69). Thus, while the SAL exhibited transdiagnostic connectivity impairments across psychotic disorders, the FPN and LN connectivity impairments were unique to schizophrenia. The post hoc findings of cortical seed–based impairments in the FPN and LN in this group indicate that there are connectivity impairments that perhaps represent more proximal risk factors unique to the diagnosis of schizophrenia (70).

With regard to striatal connectivity to cortical regions, the vrPT seeds showed reduced connectivity to the medial PFC. This hypoconnectivity between the ventrorostal putamen and a salience network portion of the medial PFC is consistent with the current study's cortical seed–based findings of salience network hypoconnectivity and provides further evidence that salience network dysfunction is specifically associated with transdiagnostic impairment across psychotic disorders. This medial PFC hypoconnectivity is also consistent with several studies finding that hypoconnectivity of this region linked to self-referential thinking is associated with schizophrenia

spectrum symptoms (25,33,34). Furthermore, the vrPT hypoconnectivity extended into the anterior cingulate cortex, a region that has been heavily implicated in psychotic disorders (32,71,72), including recent research indicating that increased connectivity between the anterior cingulate cortex and putamen is associated with more favorable treatment response (73).

Hypoconnectivity in SAL regions in both the cortical and striatum seed–based analyses is also consistent with the dopamine hypothesis of psychotic disorders (6). As noted in the introductory paragraphs, hyperdopaminergic functioning is heavily implicated in psychosis (40–42), and the dopaminergic system is also broadly implicated in corticostriatal circuits (43). The dopaminergic system likely has multiple influences on the development and expression of psychotic symptoms, including influencing salience misattribution and failures in information integration, functions associated with reduced SAL connectivity (44,45). Such a model could, if supported by future studies designed to test it explicitly, unify behavioral, functional, and neural correlates of psychotic symptoms. However, inconsistent with previous research and perhaps the dopamine hypothesis of psychosis, we did not replicate previous correlations between SAL connectivity (or vrPT-medial PFC connectivity) and cognition (35) and positive symptoms (24).

Our investigation has several limitations. First, it is unclear if the functional dysconnectivity found in the current study is a consequence of compromised structural connectivity, as has been reported in previous studies (22,65,66). Multimodal investigations will be helpful in clarifying the nature of corticostriatal dysconnectivity. Second, the relatively small number of psychotic bipolar patients (n = 40) included in our sample is another limitation. Third, the schizophrenia sample was quite heterogeneous (i.e., 42.7% first episode, 6.2% schizoaffective). Future research should replicate these transdiagnostic effects in other homogeneous psychotic samples [e.g., first episode, medication naïve (32)] to examine the generalizability of results. Last, and somewhat surprisingly, the cortical patterns of connectivity for each of the putamen seeds (i.e., dorsocaudal putamen, dorsorostral putamen, and vrPT) were very similar (see Figure 3), and therefore it will be important for future research to replicate these patterns of corticostriatal connectivity using other striatum parcellations.

In conclusion, using a combination of cortical and striatal seed–based approaches, we confirmed that SAL hypoconnectivity is present in both schizophrenia and psychotic bipolar disorder, perhaps representing a transdiagnostic biomarker. According to striatum seed–based approach, there is evidence for transdiagnostic hypoconnectivity between the ventrorostral putamen and salience network portion of the medial PFC. Thus, overall, the current study points to the relative importance of salience network hypoconnectivity in psychotic disorders.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by National Institute of Mental Health Grant Nos. R01 MH102266 (to NDW) and T32 MH014677 (to NRK), the Charlotte and Donald Test Fund, and Vanderbilt Institute for Clinical and Translational Research from the National Center for Research Resources/National Institutes of Health Grant No. 1-UL-1-TR000445.

This work was conducted in part using the resources of the Advanced Computing Center for Research and Education at Vanderbilt University, Nashville, Tennessee.

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Feb 9, 2019; revised May 9, 2019; accepted May 29, 2019.

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