Impaired Prefrontal-Basal Ganglia Functional Connectivity and Substantia Nigra Hyperactivity in Schizophrenia

Jong H. Yoon, Michael J. Minzenberg, Sherief Raouf, Mark D’Esposito, and Cameron S. Carter

Background: The theory that prefrontal cortex (PFC) dysfunction in schizophrenia leads to excess subcortical dopamine has generated widespread interest because it provides a parsimonious account for two core features of schizophrenia, cognitive deficits and psychosis, respectively. However, there has been limited empirical validation of this model. Moreover, the identity of the specific subcortical brain regions and circuits that may be impaired as a result of PFC dysfunction and mediate its link to psychosis in schizophrenia remains unclear. We undertook this event-related functional magnetic resonance imaging study to test the hypothesis that PFC dysfunction is associated with altered function of and connectivity with dopamine regulating regions of the basal ganglia.

Methods: Eighteen individuals with schizophrenia or schizoaffective disorder and 19 healthy control participants completed event-related functional magnetic resonance imaging during working memory. We conducted between-group contrasts of task-activated, univariate activation maps to identify regions of altered function in schizophrenia. We also compared the groups on the level of functional connectivity between a priori identified PFC and basal ganglia regions to determine if prefrontal disconnectivity in patients was present.

Results: We observed task-evoked hyperactivity of the substantia nigra that occurred in association with prefrontal and striatal hypopactivity in the schizophrenia group. The magnitude of prefrontal functional connectivity with these dysfunctional basal ganglia regions was decreased in the schizophrenia group. Additionally, the level of nigrostriatal functional connectivity predicted the level of psychosis.

Conclusions: These results suggest that functional impairments of the prefrontal striatonigral circuit may be a common pathway linking the pathogenesis of cognitive deficits and psychosis in schizophrenia.

Key Words: Basal ganglia, fMRI, prefrontal cortex, psychosis, schizophrenia, substantia nigra

Two cornerstones of our emerging understanding of schizophrenia are the role of excess subcortical dopamine (DA) and prefrontal cortex (PFC) dysfunction in the pathogenesis of psychosis and cognitive deficits, respectively. However, since their co-occurrence rather than the presence of either core symptom alone is more characteristic of schizophrenia, the elucidation of how these symptoms are pathophysiologically linked could help to uncover disease mechanisms.

One of the most influential theories of schizophrenia proposes that PFC dysfunction leads to disinhibited DAergic activity, enhanced subcortical DA neurotransmission, and psychosis (8). Indirect support for this model comes from the demonstration that lesioning of the rodent PFC analogue results in increased subcortical DA levels (9) and the observation that cognitive deficits usually predate psychosis onset in schizophrenia (10). A small number of in vivo schizophrenia studies have confirmed an association between markers of PFC dysfunction or pathology and neurochemical markers of enhanced subcortical DA function (11,12). However, many aspects of the mechanisms by which PFC dysfunction may lead to enhanced DA function remain unclear.

We undertook this study to increase our understanding of the specific brain regions and circuits mediating the hypothesized impaired PFC regulation of the DA system in schizophrenia. In particular, we wanted to determine whether specific basal ganglia (BG) structures could be involved in this process. The BG contains some of the most important DA regulatory regions. They include the midbrain nuclei, ventral tegmental area (VTA), and substantia nigra (SN), which produce and release the majority of brain DA (13), and other structures, such as the striatum, which sends gamma-aminobutyric acidergic projections to, and may exert inhibitory control of, midbrain DA neurons (14,15). While a small number of studies have reported altered BG function (including of the midbrain) in schizophrenia (16,17), none, to our knowledge, has specifically examined the hypothesis of an association between dysfunction of DA regulating structures of the BG and the PFC.

We tested this hypothesis with an event-related working memory (WM) functional magnetic resonance imaging (fMRI) experiment. We first mapped regions of abnormal activity in schizophrenia to determine if we could detect concomitant dysfunction in the PFC and DA regulating regions of the BG. To more directly test our hypothesis, we then measured prefrontal functional connectivity with the BG regions showing abnormal activity. If the BG abnormalities were due to deficits in prefrontal regulation, impaired prefrontal-BG connectivity in schizophrenia would be expected. We employed WM because it is an effective driver of not only the PFC but also of BG function and DA signaling (18,19). Moreover, since WM-associated PFC dysfunction in schizophrenia is commonly observed (20), WM would be an effective means of testing the hypothesis of an association...
between PFC and BG dysfunction. We report evidence of task-evoked SN hyperactivity and striatal hypofunction in schizophrenia occurring in the context of PFC hypofunction, as well as diminished prefrontal connectivity with these BG regions.

Methods and Materials

Subjects

We obtained results from 18 subjects with chronic schizophrenia or schizoaffective disorder (SZ) and 19 healthy control subjects (C). Groups were well matched on demographic variables except for lower IQ and education in patients (Table 1). The Structured Clinical Interview for DSM-IV-TR Axis I Disorders confirmed the diagnosis of schizophrenia or schizoaffective disorder in patients and excluded the presence of Axis I conditions in control subjects. Negative symptoms and psychosis severity were quantified using the Scale for the Assessment of Negative Symptoms, and Scale for the Assessment of Positive Symptoms total scores, respectively. We derived a disorganization index from Brief Psychiatric Rating Scale, Scale for the Assessment of Negative Symptoms, and Scale for the Assessment of Positive Symptoms subscores (21). Details of diagnostic and symptom quantification procedures can be found in Supplement 1. Exclusion criteria for all subjects were IQ < 70, drug/alcohol dependence history or abuse in the previous 3 months, a positive urine drug screen on test day, significant head trauma, or any magnetic resonance imaging contraindication. Control subjects with psychotic first-degree relatives were excluded. We obtained written informed consent after providing a complete study description. University of California Davis Institutional Review Board approved this study. All subjects were paid for participation.

fMRI Paradigm

Subjects completed a delayed-response face WM paradigm. It entailed encoding a cue face presented for 1 second at the beginning of each trial, maintaining its mental image throughout the 15-second delay period, and making a match discrimination with a probe face shown for 1 second, with a right index or middle finger button press when a match or nonmatch occurred, respectively. Cue-probe match probability was 50%. The intertrial interval was 13 seconds. A total of 50 trials were presented, evenly divided across five blocks. A total of 750 fMRI volumes were obtained for each subject.

fMRI

Whole-brain functional scans (T2* echo planar images, repetition time 2000 msec, echo time 40 msec, flip angle 90°, field of view 22 cm, 4.0 mm axial slices with 3.4 mm2 in-plane resolution) were acquired on a 1.5T GE scanner (Milwaukee, Wisconsin). Preprocessing with SPM5 (http://www.fil.ion.ucl.ac.uk/spm5; The Wellcome Trust for Neuroimaging, University College London, London, United Kingdom) included temporal and spatial realignment, normalization to the echo planar images template, .001 Hz high-pass filtering, and spatial smoothing (8 mm full width at half maximum Gaussian kernel for whole-brain analysis; 2 mm kernel for subcortical analysis). In Supplement 1, we present data demonstrating the necessity of the smaller smoothing scale for detecting midbrain activity (Figure S1 in Supplement 1).

Controlling for Movement and On-Task Performance. We excluded two SZ and one C subject for exhibiting greater than 4 mm within run movement. A multivariate analysis of variance of the mean scan-to-scan head movement for the six movement parameters (linear movement in x, y, z axes and rotational movement of roll, pitch, yaw) indicated no significant group difference among the 18 patients and 19 control subjects included in the study, F(6,30) = 1.15, p = .359; Wilks’ λ = .813. Summary statistics for these measures along with details of additional methods controlling for movement can be found in Supplement 1. To ensure that all subjects included in this study were engaged with the task, we excluded subjects whose task performance was below 60% accuracy. There was one patient who displayed substandard task performance but this subject was already excluded due to excessive movement.

Table 1. Subject Demographics, Clinical Profile, and Behavioral Performance on the Cognitive Task

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 18)</th>
<th>Control Subjects (n = 19)</th>
<th>t/Chi-Square</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>33.1 ± 10.7</td>
<td>28.8 ± 7.3</td>
<td>1.30</td>
<td>.202</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>66.7</td>
<td>57.9</td>
<td>.30</td>
<td>.582</td>
</tr>
<tr>
<td>Education (Years)</td>
<td>12.9 ± 2.1</td>
<td>15.8 ± 2.4</td>
<td>3.99</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Parental Education (Years)</td>
<td>13.9 ± 3.1</td>
<td>14.1 ± 3.6</td>
<td>.37</td>
<td>.721</td>
</tr>
<tr>
<td>IQ</td>
<td>100.6 ± 9.9</td>
<td>109.1 ± 8.0</td>
<td>2.94</td>
<td>.006</td>
</tr>
<tr>
<td>Handedness (% Right)</td>
<td>94.4</td>
<td>100</td>
<td>1.09</td>
<td>.298</td>
</tr>
<tr>
<td>GAS</td>
<td>33.1 ± 10.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorganization</td>
<td>6.50 ± 2.64</td>
<td>8.05 ± 4.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANS Total</td>
<td>8.05 ± 4.65</td>
<td>4.61 ± 3.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS Total</td>
<td>30.56 ± 9.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS Total</td>
<td>18</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On Antipsychotics</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ Equivalents</td>
<td>365 ± 294</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>.75 ± .11</td>
<td>.86 ± .09</td>
<td>3.47</td>
<td>.001</td>
</tr>
<tr>
<td>RT (msec)</td>
<td>1129 ± 228</td>
<td>953 ± 207</td>
<td>2.45</td>
<td>.020</td>
</tr>
</tbody>
</table>

BPRS, Brief Psychiatric Rating Scale; CPZ, chlorpromazine; GAS, Global Assessment of Symptoms; RT, reaction time; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

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fMRI Analysis. We conducted a slow event-related analysis with covariates for encoding, maintenance, and response for correct trials and a separate set of covariates for incorrect trials. The three task phases were modeled in the following manner: encoding—a single covariate during cue presentation at the beginning of the trial \( t = 0 \) sec; maintenance—a single covariate in the middle of the delay period \( t = 8 \) sec; and response—a single covariate during probe presentation \( t = 16 \) sec. We included the first temporal derivative of covariates in the regression matrix to account for potential confound differences in blood oxygen level–dependent (BOLD) signal temporal dynamics resulting from reaction time differences or other variables. A random-effects second-level comparison between groups on the contrast between WM phases and implicit baseline was conducted.

BOLD Time Series. We generated time series by trial-averaging the BOLD signal across all voxels within a functional region of interest (ROI) for all correct trials for each subject. Signal change was calculated by normalizing each value in the time series by the mean fMRI signal across the entire scan. The percent change at time zero was then subtracted from every point in the time series. We then averaged the time series across all subjects within a group.

Basal Ganglia Analysis. We localized activations with the Wake Forest University Pickatlas (http://www.fmri.wfubmc.edu; Advanced NeuroImaging Research Lab, Wake Forest University School of Medicine, Winston-Salem, North Carolina) (22). This atlas is based on the Talairach Daemon (University of Texas, Austin, Texas), one of the most commonly used databases of anatomic regions (23). We overlaid anatomic masks to confirm that an activation cluster was located within a particular region. For midbrain activations, we confirmed SN localization by verifying that voxels were situated within the anatomic SN mask and excluded from the red nucleus mask.

Functional Connectivity. We utilized the beta series correlation method (7,24) to quantify task epoch-specific, e.g., WM response, functional connectivity between brain regions. Detailed descriptions of this method can be found in Supplement 1.

Localization of Cortical ROIs from Independent Scans for Functional Connectivity Analyses. We compared between groups the level of prefrontal functional connectivity with the dysfunctional BG regions identified in the univariate analysis (Figure 1). For this analysis, we identified a PFC (LocPFC) ROI from a separate 1-back face WM fMRI experiment completed by all our subjects. We did this to avoid ROI localization biasing the functional connectivity analyses. We refer to these as the LocPFC ROIs to distinguish them from the PFC region identified from the delayed-response WM data and to emphasize their independent localization. We also identified the fusiform face area (LocFFA), a visual area specialized for face processing, from the 1-back face WM scan. The LocFFA served as a control region with which we tested the specificity of the prefrontal connectivity results. See Supplement 1 for a detailed explanation of our methods and the rationale for the localization of ROIs from independent data.

Statistical Testing. Significance controlling for multiple comparisons was determined at the cluster level of \( p < .05 \), using an initial threshold of \( t = 2.5 \) (25). For analyses of the BG, small volume corrected (SVC) statistics for the volumes of interest were applied, e.g., SN and head of caudate. Two-tailed statistical tests were used for all analyses.

Results

Behavioral Results

Responses of subjects with schizophrenia or schizoaffective disorder were slower \( p = .020 \) and less accurate \( p = .001 \) compared with control subjects (Table 1).

fMRI Results: PFC and Caudate Hypofunction in Schizophrenia

Across the three WM task phases, we observed significant C > SZ activity only during response. In the cortex, we found one cluster in the left parahippocampal gyrus and another in the right inferior frontal gyrus, \( p < .05 \), corrected (Figure 1A). In the BG, we found clusters in the left and right head of caudate, \( p < .05 \), SVC (Figure 1B). Given the crossed anatomical connections and functional interactions at multiple levels within the prefrontal striatonigral circuit (26,27) and the more prominent between-group difference in the right caudate, we focused on this region in the analyses presented below. Additional analyses using data combined from left and right caudate yielded essentially identical results (data not shown).

fMRI Results: SN Hyperactivity in Schizophrenia

We observed significant SZ > C activity only during WM response. There were bilateral SN clusters just dorsal to the cerebral peduncles and superolateral to the midline interpeduncular notch. The left 120 mm^3 cluster, coordinates \( (–8 –16 –12) \), met corrected threshold for significance, \( p < .05 \), SVC (Figure 1C). Although a few voxels within the right cluster met voxel-wise family-wise error corrected significance, the entire cluster did not meet the a priori specified cluster-level standard for significance (Table 2). Consequently, all subsequent analyses were restricted to the left SN cluster. The trial-averaged BOLD time series of the left SN cluster confirmed that both groups exhibited transient peaks during scans 10 to 14 (Figure 1G), reflecting response-related activity, and greater SZ > C signal. No cortical region showed significant SZ hyperactivity.

fMRI Results: Diminished PFC-Basal Ganglia Functional Connectivity

Although the co-occurrence of the BG functional abnormalities with PFC hypoactivity is consistent with a pathophysiologic link between PFC and BG dysfunction in schizophrenia, a stronger support for this link would be the demonstration of diminished functional connectivity between these regions. To directly address this issue, we tested whether there was diminished connectivity between the PFC and (in parallel) those caudate and SN regions that showed between-group differences in activity in the univariate analyses. As explained above in Methods and Materials and in Supplement 1, we conducted this analysis using PFC ROIs identified from independent fMRI data, denoted as LocPFC (Figure S2 in Supplement 1). Furthermore, we tested the prefrontal specificity of our prediction with a control region from the visual cortex (LocFFA) that was also localized from independent data. This region was involved in processing faces (Figure S2 in Supplement 1) but was not hypothesized to play a regulatory role on BG function. We compared BG functional connectivity with the LocFFA with that of the LocPFC.

PFC-SN Connectivity. We first examined group differences in PFC-SN functional connectivity. Although the groups did not exhibit significant differences in movement, studies suggest that head movement may significantly affect estimates of functional connectivity (28–30) and confound group comparisons of this...
measure. Therefore, to control for movement in a manner analogous to what was done in the univariate analysis, we included each subject’s six total scan-to-scan movement parameters as covariates of noninterest in an analysis of covariance (ANCOVA) of the functional connectivity measures, along with the factors of group (SZ and C) and circuit (LocPFC-SN and LocFFA-SN). This analysis revealed that connectivity differed between groups in a circuit-specific manner (Figure 2A), with a significant group ×
circuit interaction [$F(1,29) = 5.01, p = .033$]. Follow-up ANCOVAs revealed a significant effect of group on LocPFC-SN connectivity [$F(1,29) = 7.04, p = .013$] with C > SZ but a nonsignificant effect of group in LocFFA-SN connectivity [$F(1,29) = .76, p = .389$].

**PFC-Caudate Connectivity.** We then assessed group differences in functional connectivity between the PFC and caudate using the same approach described above. This analysis revealed a significant effect of group [$F(1,29) = 16.04, p < .001$] and a trend toward a significant group × circuit interaction [$F(1,29) = 3.186, p = .083$]. There was a significant effect of group for both the LocPFC-caudate [$F(1,29) = 15.565, p < .001$] and LocFFA-caudate [$F(1,29) = 8.692, p = .006$] circuits with C > SZ (Figure 2B).

The group difference in connectivity for the PFC-SN and PFC-caudate circuits was significant after Bonferroni correction for multiple comparisons. The Bonferroni-corrected critical $p$ value was .05/2 or .025. Because we excluded incorrect trials, we examined the effect of lower number of trials in the SZ group by including this variable as a covariate in an ANCOVA of the functional connectivity results reported above. In all cases, the number of trials was a nonsignificant covariate (for all $p > .58$), and group differences in the fMRI measures remained significant with the inclusion of this covariate.

### Table 2. List of fMRI Activation Peaks During the Response Phase of the Face WM Task

<table>
<thead>
<tr>
<th>Region</th>
<th>Size ($\text{mm}^3$)</th>
<th>Peak t</th>
<th>$p$, Corrected</th>
<th>Coordinates [x y z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C &gt; SZ</td>
<td>L Parahippocampal Gyrus 29120</td>
<td>5.36</td>
<td>&lt;.001$^a$</td>
<td>–20 –50 –4</td>
</tr>
<tr>
<td></td>
<td>R Inferior Frontal Gyrus 7976</td>
<td>4.20</td>
<td>.035$^a$</td>
<td>52 42 –8</td>
</tr>
<tr>
<td></td>
<td>L Caudate Head        424</td>
<td>3.55</td>
<td>.022</td>
<td>–12  4  4</td>
</tr>
<tr>
<td></td>
<td>R Caudate Head        776</td>
<td>4.05</td>
<td>.005</td>
<td>6 12 –2</td>
</tr>
<tr>
<td>SZ &gt; C</td>
<td>L SN                  120</td>
<td>4.33</td>
<td>.048</td>
<td>–8 –16 –12</td>
</tr>
<tr>
<td></td>
<td>R SN                  48</td>
<td>3.72</td>
<td>.102</td>
<td>8 –16 –14</td>
</tr>
</tbody>
</table>

Coordinates are given in the MNI coordinate system.

*C, healthy control subjects; fMRI, functional magnetic resonance imaging; L, left; MNI, Montreal Neurological Institute; R, right; SN, substantia nigra; SVC, small volume corrected; SZ, subjects with chronic schizophrenia or schizoaffective disorder; WM, working memory.

$^a$These $p$ values are corrected for whole-brain multiple comparisons. All others are SVC $p$ values.

### Nigrostriatal Connectivity Predicts Psychosis Severity

Given the well-recognized role of DA in the pathogenesis of psychosis and the central role of the SN in regulating DA, we tested the association between the functional properties of this structure or circuits involving this structure (SN univariate activity, SN-caudate, and PFC-SN functional connectivity) with the level of psychosis. We did not find a significant association between psychosis and SN univariate activity or PFC-SN functional connectivity. However, the magnitude of SN-caudate functional connectivity was highly correlated with the level of psychosis, $r = .61, p = .007$ (Figure 3). The correlation with psychotic symptoms was significant after correcting for multiple comparisons (critical $p$ value was .05/3 = .017). To determine the specificity of this finding with psychosis, we examined the correlation between SN-caudate connectivity with the two other symptom domains (negative symptoms and disorganization) and general psychopathology (Global Assessment Scale), with the prediction that they would be nonsignificant. Substantia nigra-caudate connectivity was not significantly correlated with other symptom domains or general psychopathology; for all correlations, $r < .36$ and $p > .15$.

None of our major fMRI findings (SN activity, PFC-caudate, PFC-SN, and SN-caudate functional connectivity) were significantly associated with the use of antipsychotics, as quantified by chlorpromazine equivalents, $p > .2$.

### Discussion

We observed functional abnormalities within the prefrontal striatonigral circuit during WM in schizophrenia. Along with the frequently reported PFC hypoactivity, patients exhibited striatal hypometabolism and nigral hyperactivity. We examined the possibility that...
that the BG abnormalities could be due to prefrontal disconnection by measuring prefrontal functional connectivity with these regions and observed it to be decreased in schizophrenia. We found a strong association between the strength of nigrostriatal functional connectivity and psychosis severity. Taken together, our results are consistent with the theory that prefrontal dysfunction in schizophrenia leads to disrupted PFC-BG circuits, nigral disinhibition, and psychosis. In the context of the emerging recognition of the prefrontal striatonigral circuit’s important role in cognition (18,19), our results suggest that this circuit may be a common pathway for the expression of cognitive deficits and psychosis in schizophrenia. Therefore, this circuit may play a central role in the pathogenesis of this condition.

Our SN findings deserve special consideration because of its central role in regulating DA. An obvious limitation of this study is that, although the nigra is highly enriched with DAergic neurons, its BOLD signal reflects total activity of and inputs into all the different cell types found within this structure. Nonetheless, the following lines of evidence suggest the plausibility that nigral hyperactivity, as measured by fMRI, may reflect enhanced DAergic tone in schizophrenia. A recent PET/fMRI study showed that task-evoked ventral midbrain BOLD signal can strongly correlate with the magnitude of striatal DA release (31). It could be argued that the enhanced nigral BOLD signal reflects greater inhibitory inputs to this region. This interpretation, however, is at odds with emerging evidence that synaptic inhibition leads to decreased BOLD signal (32–34). Thus, increased nigral activity would represent greater net excitatory signaling onto (35) and/or spiking activity (36) of this region. Either interpretation points to the possibility of enhanced DAergic drive biasing the system toward increased DA neurotransmission in schizophrenia.

Whether enhanced nigral activity and DAergic drive translate into increased postsynaptic striatal DA levels and psychosis will have to be clarified by future studies. For now, we can point to several lines of indirect evidence consistent with such a link. These include the well-documented dense nigrostriatal DAergic connectivity (37), the demonstration of increased striatal DA release during responses executed during a cognitive task (38), and, as stated above, the tight correlation between task-evoked midbrain fMRI signal with striatal DA release magnitude (31). The possibility that the nigral hyperactivity associated with prefrontal dysfunction in schizophrenia could lead to enhanced striatal DA is supported by the following evidence. Among the several schizophrenia PET studies that have reported increased pharmacologically evoked striatal DA release (1–4), one study showed an inverse relationship between release magnitude and spectroscopic markers of PFC pathology (39). Another study by Meyer-Lindenberg et al. (12) demonstrated an inverse relationship between task-evoked PFC hyperperfusion and metabolic markers of midbrain DA function in schizophrenia.

Our findings, interpreted in light of the following neuroanatomical evidence, suggest that the striatum may be involved in mediating the effects of PFC dysfunction on midbrain function in schizophrenia. The PFC has sparse direct connections with DAergic midbrain in primates (40), but it has dense connections with the striatum. Excitatory prefrontal efferents synapse onto gamma-aminobutyric acidergic medium spinal neurons, which project to and may inhibit the firing of DA neurons (14,15). Seen in this context, the striatal hypofunction and decreased PFC–striatal functional connectivity in schizophrenia observed in this study support the possibility that PFC dysfunction and its failure to drive inhibitory striatonigral cells may be contributing to nigral hyperactivity. This possibility, however, should be considered in light of evidence suggesting that direct striatoniigral inhibition may be weak (41).

We found a strong association between task-evoked nigrostriatal functional connectivity and psychosis severity. This association is consistent with the body of literature pointing to the striatum as a major mediator of DA psychosis (42–46). While psychosis is a cardinal symptom of schizophrenia, it is difficult to model in animals. Psychosis is subjectively experienced and entails complex and seemingly human-specific constructs such as beliefs. Consequently, task-evoked nigrostriatal functional connectivity could be useful for reverse translation into preclinical animal models as a brain-based psychosis marker.

It is reasonable to question why ventral midbrain hyperactivity in schizophrenia has not been reported previously among the abundant published fMRI studies employing WM or related paradigms. We believe that two methods we employed could explain this. First, we minimally smoothed our images. We show in Supplement 1 how smoothing with the commonly applied kernel of 8 mm would have literally smoothed out the nigral hyperactivity (Figure S1 in Supplement 1). Second, the apparent response phase-specificity of nigral hyperactivity suggests that event-related analysis may be necessary for its detection. Past fMRI studies of schizophrenia have predominantly utilized blocked designs (20), which may lack sensitivity to detect task-phase-specific abnormalities.

The fact that our significant fMRI findings were restricted to the response phase of WM and not found in other phases thought to reflect essential WM component processes, e.g., delay, raises questions about cognitive mechanisms and specificity to WM. The present study cannot directly address these questions because of design limitations. We utilized a WM paradigm not to address issues related to WM specificity or cognitive mechanisms, but rather as a means of testing the hypothesis of an association between PFC and BG dysfunction in SZ. Consequently, our paradigm did not include additional conditions that would be needed to address these issues, which are left for future studies to resolve. While we did not predict that SN hyperactivity would be restricted to the response phase, this finding is not surprising, given the prevailing thought that response or action selection is one of the primary functions of the BG and the well-documented nigral involvement in motor-related processes.

Another limitation of this study is that we studied subjects taking antipsychotics and other psychiatric medications. Although we did not detect an association with antipsychotics, future studies with unmedicated subjects will be required to more rigorously examine a medication confound.

Two recent fMRI studies have reported excess midbrain responses during neutral conditions and blunted responses during reward or affectively salient conditions in schizophrenia (16,17). It is not surprising that midbrain hyperactivity is not universally present in schizophrenia because simple up or down models of dysfunction are likely inadequate to characterize the complex regulation and response properties of the midbrain in schizophrenia. Our results suggest that the PFC may be an important factor determining the directionality of midbrain dysfunction in schizophrenia. During WM, PFC deficits could result in the failure to dampen task-evoked nigral activity. In reward processing, recent work suggesting that PFC dysfunction contributes to suboptimal action value representations in schizophrenia (47) leaves open the possibility of impaired PFC-mediated up-regulation of reward prediction error-related DAergic activity in this condition. Future research will be needed.
to clarify possible impairments in process-specific PFC modulation of midbrain function.

The primacy of PFC dysfunction in our model is consistent with previously elaborated developmental theories of schizophrenia (8,48) and symptom chronology (10): premorbid cognitive deficits usually precede positive symptoms. However, the possibility of a primary BG pathology leading to PFC dysfunction, as suggested by a recent rodent model (49) and findings of cortical DA deficits in schizophrenia (50–53), cannot be excluded by the present results. This alternative hypothesis should be addressed in future studies.

It may seem surprising that our results implicate the SN and the nigrostriatal circuit and not the VTA and mesolimbic circuits in psychosis. It is now recognized that the previously held view of a strict anatomic segregation between the VTA and SN systems does not hold, particularly in primates. Dopamine neurons that innervate the ventral striatum are found in both the VTA and nigra (54), while DA neurons projecting to the cortex and limbic structures are found not only in the VTA, but also in the SN (37). These findings are consistent with the emerging view that the SN plays an important role in cognition, in addition to its well-recognized role in supporting motor processes (55). Nonetheless, our results should not be interpreted to suggest the unimportance of the VTA and associated limbic systems in psychosis. We speculate that our paradigm may have been more sensitive to detecting abnormalities of the cognitive regions of the BG. It remains to be clarified whether similar findings for the VTA can be uncovered using paradigms that engage limbic system circuitry.

In summary, our demonstration of prefrontal striatonigral abnormalities in schizophrenia supports the proposition that this circuit may be a pathway linking cognitive deficits and psychosis in schizophrenia. Furthermore, our work has identified in vivo brain correlates of psychosis that may be useful to future pathophysiologic studies of schizophrenia.

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Supplementary material cited in this article is available online.

5. Berman KF, Zec RF, Weinberger DR (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. Arch Gen Psychiatry 43: 126–135.


