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

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**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-evoked, 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 hypoactivity 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) (1–4) and prefrontal cortex (PFC) dysfunction (5–7) 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

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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 $mm^2$ 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' $\lambda = .813$. 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

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

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.