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Task-evoked substantia nigra hyperactivity associated with prefrontal hypofunction, prefrontonigral disconnectivity and nigrostriatal connectivity predicting psychosis severity in medication naïve first episode schizophrenia

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Abstract

The widely cited prefrontal dysfunction – excess subcortical dopamine model of schizophrenia posits that prefrontal deficits give rise to cognitive impairments and the disinhibition of subcortical dopamine release underlying psychosis. While this has been one of the most influential schizophrenia models, only a handful of studies have provided evidence supporting it directly in patients with schizophrenia. We previously demonstrated task-evoked substantia nigra hyperactivity in the context of prefrontal hypofunction and prefrontonigral functional disconnectivity. In addition, nigrostriatal functional connectivity was identified as a potential marker of psychosis. Because patients in this prior study had chronic schizophrenia and were treated with antipsychotics, in the present study we tested whether these findings were confounded by illness chronicity and medication effects by seeking to reproduce these findings in an independent sample of antipsychotic naïve, first episode (FE) patients. We compared event-related fMRI activations from12 FE patients with 15 demographically matched healthy control subjects during cognitive testing. We found substantia nigra hyperactivity associated with prefrontal hypofunction and prefrontonigral functional disconnectivity, as well as the magnitude of

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The authors declare no conflicts of interests, financial or otherwise.

nigrostriatal functional connectivity positively correlating with severity of psychosis. This study adds to the body of evidence supporting the prefrontal – dopamine model of schizophrenia and further validates nigrostriatal functional connectivity as a marker of psychosis.

1. Introduction

Schizophrenia is a complex condition manifesting with diverse symptoms affecting multiple domains of mental function. Psychosis (delusions and hallucinations), along with negative symptoms and cognitive deficits, is a hallmark of the illness and its appearance usually marks the formal onset of illness. Thus, a neural systems account of the altered neural circuitry underlying psychosis in schizophrenia may offer unique insights into its pathophysiology.

One of the strongest lines of evidence for the neural mechanisms of psychosis implicates excess function of the subcortical dopamine (DA) system. Psychostimulants, such as cocaine and amphetamine, can induce psychotic states resembling schizophrenic psychosis by promoting increased release of striatal DA, reviewed by Lieberman (Lieberman et al., 1990). Excess subcortical DA has been consistently demonstrated in schizophrenic psychosis with increased presynaptic metabolism of dopamine precursors in the striatum (Hietala et al., 1999; Hietala et al., 1995; Lindstrom et al., 1999; Meyer-Lindenberg et al., 2002; Reith et al., 1994) and excess amphetamine induced release of striatal DA (Abi-Dargham et al., 1998; Breier et al., 1997; Kegeles et al., 2010; Laruelle et al., 1996). In addition, correlations between antipsychotic efficacy with the magnitude of striatal D2 receptor blockade by antipsychotic agents have been demonstrated (Agid et al., 2007; Kapur et al., 2000).

While this convergent evidence has made the DA theory one of the most compelling models of schizophrenia, DA dysfunction alone may not be a sufficient explanation for the pathogenesis of this condition. Schizophrenia entails other major symptom domains, such as cognitive deficits, which are likely the direct result of dysfunction of neural systems other than DA. A number of investigators have proposed that schizophrenia results from a combination of impairments in the prefrontal cortex and the DA system (Davis et al., 1991; Weinberger, 1987). According to this model, the prefrontal cortex normally provides descending inhibitory modulation of subcortical DA function. Prefrontal dysfunction in schizophrenia results not only in cognitive deficits but also the loss of this descending modulation, setting the stage for the emergence of excess subcortical DA and psychosis. As compelling as this model may be in offering a plausible and parsimonious systems level account for the coexistence of two of the core features of schizophrenia, there have been a limited number of empirical studies that have directly supported this model.

Our prior event-related fMRI findings (Yoon et al., 2013) are consistent with the predictions of the PFC-DA model of schizophrenia. We found hyperactivity of the substantia nigra (SN), one of the main structures responsible for synthesis, storage and release of DA in the brain (Björklund and Dunnett, 2007; Haber, 2003), in the context of PFC hypofrontality and functional disconnectivity between these structures during the response phase of a cognitive task. We undertook the current study to confirm these findings and to provide further validation of the PFC - DA model for schizophrenia by addressing some of the major

previous limitations. In the prior study, we studied a sample of patients with chronic schizophrenia receiving treatment with antipsychotics. In this study, to rule out the possibility that previous findings were confounded by illness chronicity and/or treatment with antipsychotics, we tested antipsychotic naïve subjects with first episode (FE) schizophrenia. A secondary goal was to confirm SN to caudate functional connectivity (i.e., nigrostriatal connectivity) may be a marker for psychosis. We previously discovered that the magnitude of task-evoked nigrostriatal functional connectivity was strongly correlated with psychosis severity, i.e. patients with higher functional connectivity demonstrated greater severity of psychosis. This finding is consistent with theories (Carlsson et al., 2000) and empirical studies cited above proposing that a key site of psychotogenic action of dopamine is the striatum. Thus, we set out to demonstrate this association between nigrostriatal functional connectivity and psychosis severity in a medication naïve, FE sample.

2. Methods

2.1 Participants

Participants were selected from an on-going fMRI study of FE schizophrenia at the University of California Davis School of Medicine. FE status was defined as the onset of psychosis within 12 months of testing. Patients were recruited primarily from the Early Diagnosis and Preventive Treatment clinic at UC Davis and healthy controls were recruited from the surrounding Sacramento community. From this cohort, 12 patients who were neuroleptic naïve at time of scanning and15 demographically matched healthy control subjects were included in this study.

Diagnostic evaluations with the Structured Clinical Interview for DSM-IV-TR were conducted to confirm the diagnosis of schizophrenia in patients and exclude major psychiatric illness in controls. Controls with a first-degree relative with a psychotic disorder were also excluded. Diagnoses were confirmed by consensus conference. Symptoms were quantified with the Brief Psychiatric Rating Scale (BPRS) (Overall, 1974), Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) and Scales for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Sub-scores from the BPRS, SANS, and SAPS were used to derive an index of disorganization (Barch et al., 2003). Exclusion criteria for all subjects were: IQ < 70, drug/alcohol dependence history or abuse in the previous three months or a positive urine drug screen on the day of testing, significant head trauma, or any known contraindication to MRI. After complete description of the study, written informed consent was obtained. This study was approved by the Institutional Review Board of the University of California Davis School of Medicine.

2.2 fMRI Paradigm

AX-Continuous Performance Task (AX-CPT)—Subjects completed the AX-CPT during scanning (Barch et al., 2003; Cohen et al., 1999). This is an alternative forced choice delayed response task in which the correct response to the probe letter is contingent upon encoding and maintaining the cue letter and cue dependent task rules. This task is well suited for this study because it is one of the best-validated fMRI tasks for uncovering PFC hypofunction in schizophrenia (Barch et al., 2001; Barch et al., 2003; MacDonald et al.,

2005; Yoon et al., 2008). It has also recently been shown to be a driver of activity within midbrain dopaminergic regions (D'Ardenne et al., 2012), consistent with lines of evidence implicating the involvement of dopamine in cognitive control (Braver et al., 1999; Kudlicka et al., 2011; Montague et al., 2004). The trial begins with the presentation of the cue letter for 500 msec. Following a 3500 msec delay period, a probe letter is shown for 500 msec. Subjects are required to make a target response (using a right-index-finger button press) to the probe letter X only when it follows the cue letter A. All other stimuli require a nontarget response (using a right-middle-finger button press), including trials in which the letter X is preceded by any letter other than A (collectively referred to as B). The AX cue-probe pair, which constitutes 70% of all trials, establishes the pre-potent stimulus-response mapping to the X probe. The comparison that best tests for impairments in PFC function in schizophrenia, while controlling for generalized deficits on this task, is between the BX and AX conditions (Yoon et al., 2008). We limited our analyses to the contrast of BX probe – AX probe since the relevant findings in the prior study was limited to the probe phase. Thus, this contrast was used for all between group comparisons.

2.3 fMRI Acquisition and Processing

Data were collected at the UC Davis Imaging Research Center. Functional scans (T2* EPI, TR 2000 ms, TE 40 ms, flip angle 90 degrees, FOV 22 cm, 4.0 mm axial slices with 3.4 mm^2 in-plane resolution) were acquired on a 1.5T GE scanner. Preprocessing, implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm5), included: temporal and spatial realignment, normalization to the EPI MNI template using a nonlinear warping algorithm, and spatial smoothing. A Gaussian 8 mm FWHM kernel was applied to images for the PFC analysis while a 2mm kernel was applied to images for the subcortical analysis. The use of the smaller smoothing kernel for the SN analysis is supported by the matched filter theorem, the substantially smaller volume of the SN and expected activity within this structure. The matched filter theorem proposes that greatest sensitivity to detecting activations occurs when the spatial scale of smoothing matches that of the expected spatial extent of activity. We previously demonstrated that a 2mm smoothing kernel is necessary to detect SN hyperactivity in schizophrenia (Yoon et al., 2013).

To reduce likelihood of spurious estimates of univariate activity and functional connectivity, the groups were well matched for movement during scanning. Scan-to-scan movement quantified by summing the absolute difference in spatial realignment generated movement parameters between sequential fMRI volumes were similar across groups for both linear and rotational movement, $p > .70$. We also included movement parameters in all our GLM based fMRI analyses.

2.3.1 PFC Analysis—This analysis was undertaken to confirm the presence of PFC deficits during the execution of the AX-CPT and analyses were limited to the PFC using anatomic masks (comprising the union of the superior, middle and inferior frontal gyrii) from the Wake Forest University Pickatlas (http://www.fmri.wfubmc.edu/download.htm) to test for the presence of PFC dysfunction in patients. fMRI analysis followed previously published procedures (Yoon et al., 2008). In short, analyses in SPM5 were conducted using a general linear model within an event related framework. Incorrect trials were modelled

separately and excluded. In addition to experiment specific covariates of interest, the regression matrix contained the first temporal derivative to account for potential group differences in the temporal dynamics of the BOLD signal and movement parameters to minimize the effects of in-scanner movement. We modelled correct trials with covariates for A cue, B cue, AX probe, AY probe, BX probe and BY probe. The contrast of BX probe and AX probe was used for all inferential testing. One control subject displayed SN activity greater than three standard deviations away from the group mean. Rather than exclude this subject, the data were winsorized (Dixon and Yuen, 2010). One patient had too few trials to produce meaningful functional connectivity values and this subject's data were excluded from functional connectivity analyses. The statistical significance of the reported correlations with symptoms did not, however, depend on excluding this subject. Contrast maps were rendered using MRIcroGL (http://www.cabiatl.com/mricrogl). We relied on a voxel-wise analysis for the PFC, as opposed to an ROI analysis using ROI's identified in the prior study because of the likelihood that different PFC regions would be engaged by the cognitive paradigm utilized in the present study compared to the cognitive paradigm employed in the previous study.

2.3.2 Subcortical Analysis—Given the relatively limited sample size of this difficult to obtain sample of FE, antipsychotic naïve patients, and the much lower signal that is recoverable from small subcortical structures, we relied on an a priori identified ROI approach, rather than a voxel-wise mapping approach, to evaluate SN and striatal activity. This method is well-recognized as a powerful and unbiased means of hypothesis testing in fMRI research (Saxe et al., 2006; Vul and Kanwisher, 2010). We employed an inclusive mask of a cluster within the SN (Fig. 1) identified on the basis of a significant group difference in activity in our prior study (Yoon et al., 2013) to sample univariate activity in the FE and matched control samples in the SN. For the nigrostriatal functional connectivity analysis (described below) we utilized the same caudate ROI utilized in our prior study for this purpose (Yoon et al., 2013). Note that the fMRI data from which these ROIs were derived and fMRI data from the present study were obtained and processed in an identical manner. Both experiments were conducted on the same scanner, with identical EPI sequences and data processing methods, including spatial normalization to the same EPI MNI template in SPM5. This ensured that the a priori identified ROIs localized the same regions in the functional volumes from this study as in the prior study.

2.3.3 Functional Connectivity—We utilized the beta series correlation method and the contrast of BX probe and AX probe to measure task component specific functional connectivity. Details of this method can be found elsewhere (Rissman et al., 2004; Yoon et al., 2008). In summary HRF-convolved trial and event-specific covariates estimated the trial-to-trial magnitude of activity within a voxel, e.g. SN BX trial response period beta series. Paralleling the univariate analyses outlined above, we employed different strategies for testing SN connectivity with the PFC and the striatum. For the former, we conducted what is referred to as a seeded, voxel-wise connectivity analysis, which entailed generating voxel-wise maps of connectivity values with a SN seed. In line with the goals of this study, we focused our analyses on the PFC by using PFC masks described above. The same functional ROI, which was identified in our prior study and used in the univariate analysis served as the

seed. To assess nigrostriatal functional connectivity, we used what is referred to as a paired-ROI functional connectivity analysis. In this analysis the connectivity between two ROIs are examined by first generating vectors of beta series values for the probe phase of the task that have been averaged across voxels within each ROI and then calculating the trial-to-trial covariance between these vectors. As mentioned above, we used the SN and head of caudate ROIs from our original study to quantify functional connectivity between these structures. The use of these ROIs represents a strong test of the robustness of a potential marker of psychosis. The magnitude of functional connectivity was quantified with the means of a Pearson's correlation of their beta series. To mitigate right skew, the arc hyperbolic tangent of the Pearson's correlations were used for group comparisons with *t*-tests (Fisher, 1921). All correlation analyses were conducted in SPM5 with custom Matlab (MathWorks, Natick, MA) scripts.

2.3.4 Statistical testing—For all fMRI contrasts, activation significance controlling for multiple comparisons was determined at the cluster level of $p < .05$, FWE, using an initial threshold of $t=2.5$ (p=0.01) (Friston et al., 1996). To test for the presence of PFC hypofunction and SN-PFC functional disconnectivity, we used small volume correction (SVC) statistics for the PFC as defined by the Pickatlas masks. One-tailed significance levels were applied only in instances with clear directional hypotheses, e.g. same direction as prior results, and these have been clearly indicated. Otherwise, two-tailed significant levels were used.

3. Results

3.1 Behavioral Results

The behavioral results, as well as the groups' demographics and level of symptoms in patients, are displayed in Table 1. ANOVA of in-scanner behavioral results showed that patients exhibited a differential deficit in the performance of the BX compared to the AX condition, as indicated by a significant Group x Condition interaction on accuracy and RT, $p < .01$, with patients displaying lower accuracy and slower RTs (see Table 1 for details).

3.2 Task-evoked SN hyperactivity in association with PFC hypofunction and functional disconnectivity

A between-group comparison of the fMRI data in the contrast of BX-AX trials during the response phase of the AX-CPT revealed a cluster of patient hypoactivity within the right inferior frontal cortex, $p < .05$, SVC. In the same contrast, patients displayed greater activity compared to controls in the SN ROI, one-tailed $p = .02$ (Fig. 2A). In patients, SN activity significantly correlated with positive symptoms (SAPS), $r = .74$, $p = .006$. After controlling for its relationship with positive symptoms, SN activity was not significantly associated with other symptom domains or general levels of psychopathology, $r < .42$ and $p > .22$. A between-group comparison of the SN seeded functional connectivity maps showed that the SN displayed decreased connectivity with an area within the left inferior frontal cortex, $p < .05$, SVC.

3.3 Nigrostriatal connectivity predicts psychosis severity in first episode sample

The level of SN-caudate functional connectivity was highly positively correlated with positive symptoms (SAPS), $r = .62$, $p = .02$, one-tailed (Fig. 2B), but not with other symptom domains or general psychopathology, for all correlations, $r < .38$ and $p > .26$.

4. Discussion

This study expands upon previously reported findings of cognition-evoked SN hyperactivity, prefrontal hypofunction and disconnectivity by demonstrating their presence in an antipsychotic naïve sample with FE schizophrenia. This demonstration indicates that the findings of the previous study were not the result of illness chronicity or antipsychotic medications and provides important empirical support for the PFC hypofunction – excess subcortical DA function model of schizophrenia. In addition, the present study also confirmed previously reported correlation between the magnitude of SN-caudate functional connectivity and psychosis severity, suggesting that task-evoked nigrostriatal functional connectivity is a neural circuitry based marker of psychosis.

Our findings expand the empirical evidence for the PFC - DA model of schizophrenia. While it is one of the most widely cited models, only a small handful of studies have shown an association between PFC deficits and markers of excess subcortical DA function directly in schizophrenia (Bertolino et al., 1999; Meyer-Lindenberg et al., 2002; Yoon et al., 2013). Not only have we obtained evidence of prefrontal hypofunction and hyperactivity of a midbrain dopaminergic region in an independent sample of patients, we have done so with a sample that effectively addresses the important confounds of medication effects and illness chronicity. Within this limited literature, one report studied an unmedicated sample of patients (Meyer-Lindenberg et al., 2002) and the present study is the first to have examined a medication naïve FE sample.

The identification of the SN as a site of pathology in schizophrenia is worthy of discussion. While there are limitations in the inferences that can be drawn on the cellular source for the heighted SN BOLD signal, this finding, nonetheless, suggests the possibility that it is reflecting excess activity of dopaminergic neurons in schizophrenia. This possibility is supported by the fact that the SN is highly enriched with dopaminergic neurons and a recent PET/fMRI study showed strong association between fMRI SN signal and markers of DA release in the striatum (Schott et al., 2006). Excess evoked dopaminergic activity would be consistent with the demonstration of heightened pharmacologically evoked DA release (Abi-Dargham et al., 1998; Breier et al., 1997; Kegeles et al., 2010; Laruelle et al., 1996), as well as increased availability of the pool of DA that may be released as indicated by the heightened metabolic turnover of DA precursors in the striatum in schizophrenia (Hietala et al., 1999; Hietala et al., 1995; Lindstrom et al., 1999; Meyer-Lindenberg et al., 2002; Reith et al., 1994). The identification of the SN as a site of pathology may motivate future investigations to leverage the relatively well-known neurobiological features of this structure to uncover the details of the cellular and neurophysiological mechanisms of how impairments in PFC function results in the hypothesized disinhibition of subcortical DA function.

A cautionary note, however, is warranted regarding the confidence with which we can conclude that the enhanced midbrain BOLD signal in patients is truly from the SN. Since this study utilized an fMRI sequence with standard spatial resolution, we cannot definitively rule out the possibility that other nearby structures in the ventral midbrain did not contribute to this signal. A consideration of the function and anatomical position relative to the SN of these structures reveals that if any region is to be confounding the present results, it may be the subthalamic nucleus (STN). The STN abuts and lies dorsal to the SN and its purported function is to inhibit motor responses (Frank, 2006). Consequently, it is possible that the higher BOLD signal observed in patients could, in part, reflects STN activity. Future studies employing specialized methods, including high-resolution fMRI, will be required to more definitively evaluate this possibility. However, a consideration of the convergent lines of evidence supporting a model of PFC dysfunction and hyperactivity of ventral midbrain dopaminergic regions in schizophrenia, in conjunction with the paucity of established models or empirical evidence pointing to dysfunction of the STN in schizophrenia, would suggest that the most reasonable interpretation of the elevated midbrain signal observed in this study reflects hyperactivity of the SN and not the STN.

The possibility that SN hyperactivity merely reflects performance related factors and not psychosis per se was assessed in the following manner. Within controls subjects, a median split based on BX-AX accuracy did not reveal a significant difference in BX-AX SN signal between the better and worse performing subjects, $p = 0.31$.

We employed a delayed response working memory task in the prior study and a cognitive control task in the present and this difference raises questions as to whether the results of the present study should be considered a replication. While the AX-CPT requires working memory to encode and maintain task rules and cue stimuli to guide behaviour, the contrast employed in this study, BX-AX, should have primarily identified cognitive control specific brain regions. Despite the different cognitive operations engaged by these paradigms, they can be viewed as being equivalent for the purposes of testing the PFC–DA model of schizophrenia. They are both prototypical PFC dependent tasks, with a large number of studies having demonstrated robust PFC engagement with both paradigms in healthy subjects. Furthermore, working memory and cognitive control are among the best-studied paradigms for revealing PFC dysfunction in schizophrenia.

As for the SN findings implicating the dopamine system, several lines of evidence support the notion that cognitive control involves dopamine. A number of investigators have proposed, based on computational models, that dopamine signaling is critical for gating task relevant information in PFC and basal ganglia circuits and that this gating facilitates adaptive representations necessary for cognitive control (as well as for working memory) (Braver et al., 1999; Montague et al., 2004). Further evidence for the critical involvement of dopamine in cognitive control can be found in the Parkinson's literature. Since Parkinson's involves the loss of dopaminergic SN neurons, then individuals with this condition should exhibit poor performance on tasks requiring cognitive control if DA were involved in this process. A recent meta-analysis has documented that the magnitude of the effect size for performance decrements in subjects with Parkinson's compared to control subjects was greatest for the Stroop effect among executive function tasks surveyed (Kudlicka et al., 2011). The Stroop

task is a protypical cognitive control paradigm. Seen in this light, the replication of our prior findings with a different cognitive paradigm, we believe, strengthens the evidence supporting the PFC-DA model by demonstrating that the findings generalize across different cognitive paradigms.

If cognitive control involves dopamine signaling, reflected in SN activity, then a reasonable question would be why healthy control subjects did not show appreciable SN BX-AX activity. One explanation may be that the SN ROI we used in this study limited our ability to do so. The SN ROI was generated in our prior study from a between group contrast of SZ > C during the response phase of a task. In other words, this ROI, by design, selected a subregion within the SN that could be more sensitive to detecting greater task evoked activity in patients compared to controls. Thus, this ROI could have biased against our ability to detect evoked activity in the control sample. Another explanation could be understood in relation to the likelihood that complex non-linear functions govern the relationship between cognitive load or performance and physiologic processes (Yerkes and Dodson, 1908), particularly those involving DA (Cools and D'Esposito, 2011) and the possibility that schizophrenia involves a shift of these functions compared to controls (Callicott et al., 2003; Manoach, 2003). It could be that the task conditions under consideration (AX and BX) specifies a flat region within the control group specific function, while these conditions falls within a relative steep region of this function for patients such that the BX elicits higher SN activity compared to the AX condition.

The finding of a strong association between task-evoked nigrostriatal functional connectivity and psychosis across divergent paradigms also suggests that it is a robust marker of psychosis. This assertion is further supported by these results being achieved with the use of functional ROIs of the SN and caudate ROIs from the original study. The use of functional ROIs derived from independent data is one of the most unbiased ways to conduct functional connectivity analyses (Saxe et al., 2006; Vul and Kanwisher, 2010). The demonstration of nigrostriatal functional connectivity correlating with psychosis severity across independent samples and divergent cognitive paradigms suggest that these ROIs could be applied to additional data sets to further test the association between nigrostriatal functional connectivity and psychosis. That the nigrostriatal circuit would be indexing psychosis is consistent with the convergent literature indicating that the dopaminergic neurotransmission in the striatum is one of the most critical psychotogenic pathways (Abi-Dargham et al., 1998; Agid et al., 2007; Carlsson et al., 2000; Kapur et al., 2000). A marker of psychosis could have significant impact on future psychosis research. Psychosis is a key feature of schizophrenia and other neuropsychiatric conditions but it is a notoriously difficult symptom to model in animals (Nestler and Hyman, 2010) since it is subjectively experienced and reported and entails complex and seemingly human-specific constructs such as beliefs. Consequently, brain markers of psychosis could be useful for reverse translation into preclinical animal models.

A limitation of this study is that it was underpowered to support exploratory analyses that could have identified other brain regions involved in the hypothesized PFC-DA dysfunction in schizophrenia. Because of the modest sample size of this difficult to study population, we limited the scope of this study to specifically address reproducibility of our prior findings.

Thus, we relied on a priori identified functional ROIs to conduct this study. However, this approach is indeed limited in assaying brain regions outside of these ROIs. Therefore, this study should not be interpreted as negating the possibility of other structures contributing to the pathophysiology of schizophrenia, such as the VTA, and it is left for future studies to identify additional regions. Another important limitation, as mentioned earlier, is the relatively small sample size of patients. Future studies with FE, neuroleptic naïve individuals will be required to confirm the present findings.

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6. References

Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M, 1998 Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry 155(6), 761–767. [PubMed: 9619147]

Agid O, Mamo D, Ginovart N, Vitcu I, Wilson AA, Zipursky RB, Kapur S, 2007 Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response--a double-blind PET study in schizophrenia. Neuropsychopharmacology 32(6), 1209–1215. [PubMed: 17077809]

Andreasen NC, 1982 Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry 39(7), 784–788. [PubMed: 7165477]

Andreasen NC, 1984 The Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City, Iowa.

Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald A 3rd, Noll DC, Cohen JD, 2001 Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. Arch Gen Psychiatry 58(3), 280–288. [PubMed: 11231835]

Barch DM, Carter CS, MacDonald AW 3rd, Braver TS, Cohen JD, 2003 Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. J Abnorm Psychol 112(1), 132–143. [PubMed: 12653421]

Bertolino A, Knable MB, Saunders RC, Callicott JH, Kolachana B, Mattay VS, Bachevalier J, Frank JA, Egan M, Weinberger DR, 1999 The relationship between dorsolateral prefrontal N-acetylaspartate measures and striatal dopamine activity in schizophrenia. Biol Psychiatry 45(6), 660–667. [PubMed: 10187995]

Björklund A, Dunnett S, 2007 Dopamine neuron systems in the brain: an update. Trends in neurosciences 30(5), 194–202. [PubMed: 17408759]

Braver TS, Barch DM, Cohen JD, 1999 Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol Psychiatry 46(3), 312–328. [PubMed: 10435197]

Breier A, Su T, Saunders R, Carson R, Kolachana B, De Bartolomeis A, Weinberger D, Weisenfeld N, Malhotra A, Eckelman W, 1997 Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proceedings of the National Academy of Sciences 94(6), 2569.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR, 2003 Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down, Am J Psychiatry, pp. 2209–2215. [PubMed: 14638592]

Carlsson A, Waters N, Waters S, Carlsson ML, 2000 Network interactions in schizophrenia - therapeutic implications. Brain Res Brain Res Rev 31(2–3), 342–349. [PubMed: 10719161]

Cohen JD, Barch DM, Carter C, Servan-Schreiber D, 1999 Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. J Abnorm Psychol 108(1), 120–133. [PubMed: 10066998]

Cools R, D'Esposito M, 2011 Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69(12), e113–125. [PubMed: 21531388]

D'Ardenne K, Eshel N, Luka J, Lenartowicz A, Nystrom LE, Cohen JD, 2012 Role of prefrontal cortex and the midbrain dopamine system in working memory updating. Proc Natl Acad Sci U S A 109(49), 19900–19909. [PubMed: 23086162]

Davis KL, Kahn RS, Ko G, Davidson M, 1991 Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148(11), 1474–1486. [PubMed: 1681750]

Dixon WJ, Yuen KK, 2010 Trimmin and Winsorization: A Review. Stastical Papers, 1–14.

Fisher RA, 1921 On the "probable error" of a coefficient of correlation deduced from a small sample. Metron 1, 3–32.

Frank MJ, 2006 Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 19(8), 1120–1136. [PubMed: 16945502]

Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD, 1996 Detecting activations in PET and fMRI: levels of inference and power. Neuroimage 4(3 Pt 1), 223–235. [PubMed: 9345513]

Haber SN, 2003 The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat 26(4), 317–330. [PubMed: 14729134]

Hietala J, Syvalahti E, Vilkman H, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Eronen E, Ruotsalainen U, Salokangas RK, 1999 Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. Schizophrenia research 35(1), 41–50. [PubMed: 9988840]

Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Kirvela O, Ruotsalainen U, et al., 1995 Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346(8983), 1130–1131. [PubMed: 7475604]

Kapur S, Zipursky R, Jones C, Remington G, Houle S, 2000 Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 157(4), 514–520. [PubMed: 10739409]

Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, Hwang DR, Huang Y, Haber SN, Laruelle M, 2010 Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry 67(3), 231–239. [PubMed: 20194823]

Kudlicka A, Clare L, Hindle JV, 2011 Executive functions in Parkinson's disease: systematic review and meta-analysis. Movement disorders : official journal of the Movement Disorder Society 26(13), 2305–2315. [PubMed: 21971697]

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB, 1996 Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A 93(17), 9235–9240. [PubMed: 8799184]

Lieberman JA, Kinon BJ, Loebel AD, 1990 Dopaminergic mechanisms in idiopathic and drug-induced psychoses. Schizophr Bull 16(1), 97–110. [PubMed: 2185538]

Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P, Langstrom B, 1999 Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 46(5), 681–688. [PubMed: 10472420]

MacDonald AW 3rd, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, Stenger VA, Cohen JD, 2005 Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. Am J Psychiatry 162(3), 475–484. [PubMed: 15741464]

Manoach DS, 2003 Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings, Schizophrenia research, pp. 285–298.

Meyer-Lindenberg A, Miletich R, Kohn P, Esposito G, Carson R, Quarantelli M, Weinberger D, Berman K, 2002 Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nature Neuroscience 5(3), 267–271. [PubMed: 11865311]

Montague PR, Hyman SE, Cohen JD, 2004 Computational roles for dopamine in behavioural control. Nature 431(7010), 760–767. [PubMed: 15483596]

Nestler EJ, Hyman SE, 2010 Animal models of neuropsychiatric disorders. Nat Neurosci 13(10), 1161–1169. [PubMed: 20877280]

Overall J, 1974 Psychological measurements in psychopharmacology. Volume editor: Pichot P; co-editor: R. Olivier-Martin. Karger, Basel, New York,.

Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, Bachneff S, Cumming P, Diksic M, Dyve SE, Etienne P, Evans AC, Lal S, Shevell M, Savard G, Wong DF, Chouinard G, Gjedde A, 1994 Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc Natl Acad Sci U S A 91(24), 11651–11654. [PubMed: 7972118]

Rissman J, Gazzaley A, D'Esposito M, 2004 Measuring functional connectivity during distinct stages of a cognitive task. Neuroimage 23(2), 752–763. [PubMed: 15488425]

Saxe R, Brett M, Kanwisher N, 2006 Divide and conquer: a defense of functional localizers. Neuroimage 30(4), 1088–1096; discussion 1097–1089. [PubMed: 16635578]

Schott BH, Seidenbecher CI, Fenker DB, Lauer CJ, Bunzeck N, Bernstein HG, Tischmeyer W, Gundelfinger ED, Heinze HJ, Duzel E, 2006 The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J Neurosci 26(5), 1407–1417. [PubMed: 16452664]

Vul E, Kanwisher N, 2010 Begging the Question: The Nonindependence Error in fMRI Data Analysis. MIT Press.

Weinberger D, 1987 Implications of normal brain development for the pathogenesis of schizophrenia. Archives of general psychiatry 44, 660. [PubMed: 3606332]

Yerkes R, Dodson J, 1908 The relation of strength of stimulus to rapidity of habit formation, Journal of comparative neurology and psychology, pp. 459–482.

Yoon JH, Minzenberg MJ, Raouf S, D'Esposito M, Carter CS, 2013 Impaired prefrontal-basal ganglia functional connectivity and substantia nigra hyperactivity in schizophrenia. Biol Psychiatry 74(2), 122–129. [PubMed: 23290498]

Yoon JH, Minzenberg MJ, Ursu S, Ryan Walter BS, Wendelken C, Ragland JD, Carter CS, 2008 Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: relationship with impaired cognition, behavioral disorganization, and global function. Am J Psychiatry 165(8), 1006–1014. [PubMed: 18519527]

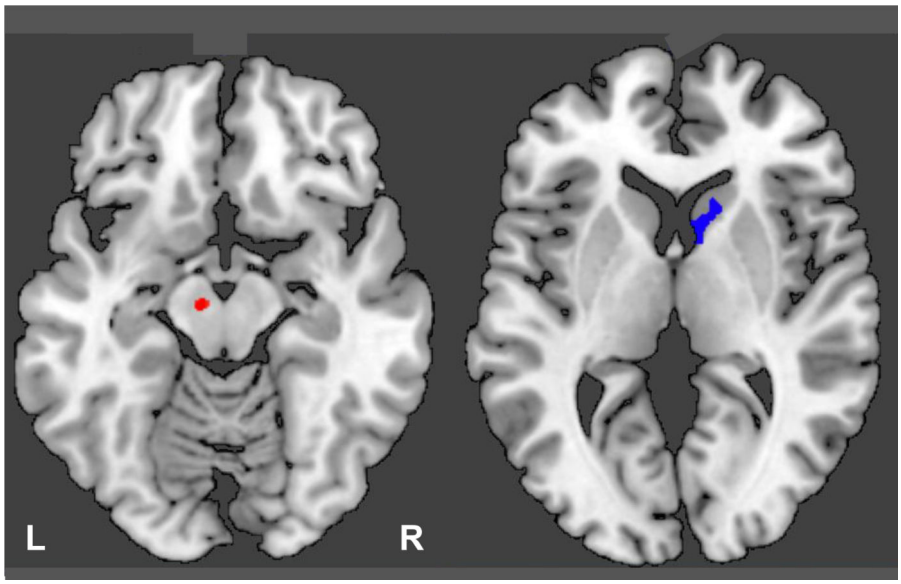

Figure 1. Substantia nigra and caudate functional ROIs.

This figure depicts the two functional ROIs that were derived from a prior study to sample univariate activity from the substantia nigra (red) and functional connectivity between the caudate (blue) and the substantia nigra.

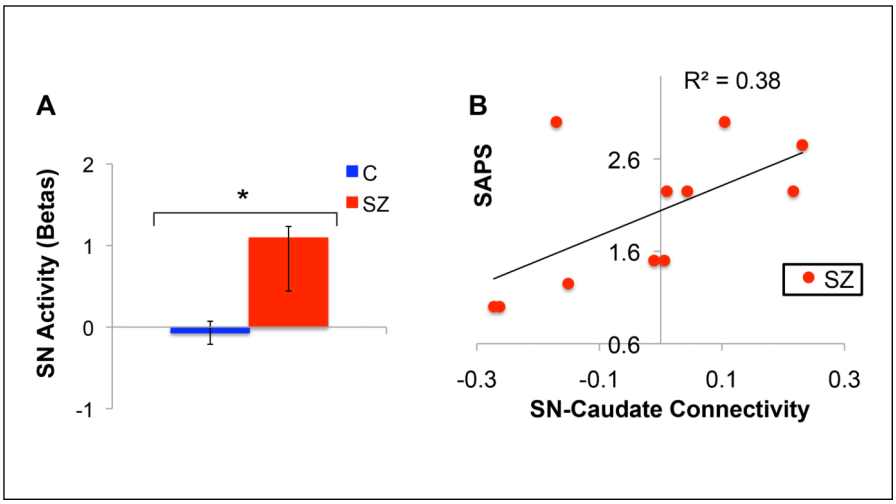

Figure 2. Substantia nigra hyperactivity and associations with psychosis severity in first-episode, neuroleptic-naive subjects with schizophrenia.

A) The SN showed greater activity compared to controls, *one-tailed *p*=.022. B) The magnitude of SN-caudate functional connectivity was correlated with psychosis severity as measured by the SAPS, Scale for the Assessment of Positive Symptoms, p = .021.

Table 1.

First-episode, neuroleptic-naive schizophrenia and healthy control sample demographics, clinical profile and behavioral performance on cognitive task.

	Patient (N=12)		Control (N=15)		T/Chi-Squ.	p-value
	Mean	SD	Mean	SD		
Age (years)	20.9	4.2	21.0	4.8	.05	.959
Gender (% male)	83.3		86.7		.06	.809
Education (years)	13.1	2.9	13.1	3.0	.04	.971
Parental Education (years)	14.6	2.2	14.5	2.3	.11	.913
IQ	103.3	14.7	114.2	10.8	2.14	.045
Handedness (% R)	100		93.3		.83	.362
GAS	45.0	11.8				
Disorganization	0.24	0.16				
SANS	2.05	1.01				
SAPS	2.16	0.97				
BPRS	47.2	14.2				
AX Accuracy	.95	.03	.98	.03	2.78	.011
AY Accuracy	.79	.32	.77	.21	.20	.845
BX Accuracy	.77	.23	.95	.06	2.68	.020
BY Accuracy	.94	.09	.99	.02	1.89	.083
AX RT (msec)	651	199	485	59	2.79	.016
AY RT (msec)	826	201	672	99	2.44	.028
BX RT (msec)	865	348	527	94	3.27	.006
BY RT (msec)	715	225	510	83	3.00	.010

ANOVA of accuracy with factors of Condition (AX and BX) and Group, revealed a main effect of Group [$F(1, 25) = 2712.65$, $p < .001$] and Condition [$F(1, 25) = 15.97$, $p = .001$] and a Group × Condition interaction [$F(1, 25) = 7.57$, $p < .011$]. ANOVA of RT revealed a main effect of Group [$F(1, 25) = 317.09$, $p < .001$] and Condition [$F(1, 25) = 21.34$, $p < .001$] and a Group × Condition interaction [$F(1, 25) = 9.70$, $p < .01$]. Reaction time (RT); Brief Psychiatric Rating Scale (BPRS); Scale for the Assessment of Negative Symptoms (SANS); Scale for the Assessment of Positive Symptoms (SAPS), and Global Assessment of Symptoms (GAS).