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Impaired prefrontostriatonigral functional connectivity and substantia nigra hyperactivity in schizophrenia

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Abstract

Background—The theory that prefrontal cortex (PFC) dysfunction in schizophrenia leads to excess subcortical dopamine (DA) 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 fMRI study to test the hypothesis that PFC dysfunction is associated with altered function of and connectivity with DA regulating regions of the basal ganglia.

Methods—18 individuals with schizophrenia or schizoaffective disorder and 19 healthy control participants completed event-related fMRI 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 prefrontostriatonigral circuit may be a common pathway linking the pathogenesis of cognitive deficits and psychosis in schizophrenia.

Keywords

schizophrenia; psychosis; fMRI; substantia nigra; prefrontal cortex; basal ganglia

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INTRODUCTION

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 GABAergic 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 WM 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 controls (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 confirmed the diagnosis of schizophrenia or schizoaffective disorder in patients and excluded the presence of Axis-I conditions in controls. Negative symptoms and

psychosis severity were quantified using the SANS and SAPS total scores respectively. We derived a disorganization index from BPRS, SANS, and SAPS sub-scores (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 three months, a positive urine drug screen on test day, significant head trauma, or any MRI contraindication. Controls with psychotic first-degree relatives were excluded. We obtained written informed consent after providing a complete study description. University of California Davis IRB 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 sec at the beginning of each trial, maintaining its mental image throughout the 15 sec delay period and making a match discrimination with a probe face shown for 1 sec; a right index or middle finger button press when a match or non-match occurred respectively. Cue-probe match probability was 50%. The inter-trial interval was 13 sec. 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* 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 with SPM5 (http://www.fil.ion.ucl.ac.uk/spm5) included: temporal and spatial realignment, normalization to the EPI template, .001 Hz high-pass filtering and spatial smoothing (8 mm FWHM 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).

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 MANOVA 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 controls included in the study, $F(6, 30)=1.15$, $p=.359$; Wilk's $\lambda=0.813$. 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 sub-standard task performance but this subject was already excluded due to excessive movement.

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 group differences in BOLD signal temporal dynamics resulting from RT 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 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) (22). This atlas is based on the Talairach Daemon, 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 (Fig. 1). For this analysis, we identified a PFC 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

SZ responses were slower $p=.020$ and less accurately $p=.001$ compared to controls (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 (RIFG), $p<.05$, corrected (Fig. 1A). In the BG, we found clusters in the left and right head of caudate, $p<.05$, SVC (Fig. 1B). Given the crossed anatomical connections and functional interactions at multiple levels within the prefrontostriatonigral 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 120mm^3 cluster, coordinates [-8 -16 -12], met corrected threshold for significance, p<.05, SVC (Fig. 1C). Although a few voxels within the right cluster met voxel-wise FWE 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 10–14 (Fig. 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, which showed between-group differences in activity in the univariate analyses. As explained above in the Methods section and in Supplement 1, we conducted this analysis using PFC ROIs identified from independent fMRI data, denoted as LocPFC (Figure S2). 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) but was not hypothesized to play a regulatory role on BG function. We compared BG functional connectivity with the LocFFA to 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 non-interest in an 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 (Fig. 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 non-significant 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 towards 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, (Fig. 2B).

The group difference in connectivity for both the PFC-SN and PFC-caudate circuits was significant after Bonferoni correction for multiple comparisons. The Bonferoni 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 significant univariate and functional connectivity results reported above. In all cases, the number of trials was a non-significant covariate (for all p>.585), and group differences in the fMRI measures remained significant with the inclusion of this covariate.

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, (Fig. 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 (GAS), with the prediction that they would be non-significant. SN-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 anti-psychotics as quantified by chlorpramazine (CPZ) equivalents, p>.2.

DISCUSSION

We observed functional abnormalities within the prefrontostriatonigral circuit during WM in schizophrenia. Along with the frequently reported PFC hypoactivity, patients exhibited striatal hypoactivity and nigral hyperactivity. We examined the possibility that the BG abnormalities could be due to prefrontal disconnectivity 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 prefrontostriatonigral 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 pathogensis 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 towards increased DA neurotransmission in schizophrenia.

Whether enhanced nigral activity and DAergic drive translates into increased post-synaptic 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. demonstrated an inverse relationship between task-evoked PFC hypoperfusion and metabolic markers of midbrain DA function in schizophrenia (12).

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 GABAergic medium spinal neurons, which project to and may inhibit the firing of DA neurons (14, 15). Seen in this context, the striatal hypoactivity and decreased PFC-striatal functional connectivity in schizophrenia observed in this study supports 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 striatonigral 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 pre-clinical 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 8mm would have literally smoothed out the nigral hyperactivity (Figure S1). 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 anti-psychotics and other psychiatric medications. Although we did not detect an association with anti-psychotics, 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 rewarding 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); pre-morbid 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). DA 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 finding for the VTA can be uncovered using paradigms that engage limbic system circuitry.

In summary, our demonstration of prefrontostriatonigral 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry. 1998; 155:761–767. [PubMed: 9619147]
2. Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A. 1997; 94:2569–2574. [PubMed: 9122236]
3. Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry. 2010; 67:231–239. [PubMed: 20194823]
4. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A. 1996; 93:9235–9240. [PubMed: 8799184]
5. Berman KF, Zec RF, Weinberger DR. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. Arch Gen Psychiatry. 1986; 43:126–135. [PubMed: 2868701]
6. Ingvar DH, Franzen G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand. 1974; 50:425–462. [PubMed: 4423855]
7. Yoon JH, Minzenberg MJ, Ursu S, Ryan Walter BS, Wendelken C, Ragland JD, et al. 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. 2008; 165:1006–1014. [PubMed: 18519527]
8. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987; 44:660–669. [PubMed: 3606332]
9. Pycock CJ, Kerwin RW, Carter CJ. Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature. 1980; 286:74–76. [PubMed: 7393327]
10. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: mechanisms and meaning. Neuropsychopharmacology. 2011; 36:316–338. [PubMed: 20844478]
11. Bertolino A, Knable MB, Saunders RC, Callicott JH, Kolachana B, Mattay VS, et al. The relationship between dorsolateral prefrontal N-acetylaspartate measures and striatal dopamine activity in schizophrenia. Biol Psychiatry. 1999; 45:660–667. [PubMed: 10187995]
12. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, et al. Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci. 2002; 5:267–271. [PubMed: 11865311]
13. Björklund A, Dunnett S. Dopamine neuron systems in the brain: an update. Trends in neurosciences. 2007; 30:194–202. [PubMed: 17408759]
14. Grace AA, Bunney BS. Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. Brain Res. 1985; 333:271–284. [PubMed: 2986775]
15. Paladini CA, Celada P, Tepper JM. Striatal, pallidal, and pars reticulata evoked inhibition of nigrostriatal dopaminergic neurons is mediated by GABA(A) receptors in vivo. Neuroscience. 1999; 89:799–812. [PubMed: 10199614]
16. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry. 2008; 13:239, 267–276. [PubMed: 17684497]
17. Romaniuk L, Honey GD, King JR, Whalley HC, McIntosh AM, Levita L, et al. Midbrain activation during pavlovian conditioning and delusional symptoms in schizophrenia. Arch Gen Psychiatry. 2010; 67:1246–1254. [PubMed: 21135324]
18. Landau SM, Lal R, O'Neil JP, Baker S, Jagust WJ. Striatal dopamine and working memory. Cereb Cortex. 2009; 19:445–454. [PubMed: 18550595]
19. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. Eur J Neurosci. 2004; 19:755–760. [PubMed: 14984425]

20. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 2009; 66:811–822. [PubMed: 19652121]
21. Barch DM, Carter CS, MacDonald AW 3rd, Braver TS, Cohen JD. Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. J Abnorm Psychol. 2003; 112:132–143. [PubMed: 12653421]
22. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 2003; 19:1233–1239. [PubMed: 12880848]
23. Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp. 2000; 10:120–131. [PubMed: 10912591]
24. Rissman J, Gazzaley A, D'Esposito M. Measuring functional connectivity during distinct stages of a cognitive task. Neuroimage. 2004; 23:752–763. [PubMed: 15488425]
25. Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD. Detecting activations in PET and fMRI: levels of inference and power. Neuroimage. 1996; 4:223–235. [PubMed: 9345513]
26. Gerfen CR, Staines WA, Arbuthnott GW, Fibiger HC. Crossed connections of the substantia nigra in the rat. J Comp Neurol. 1982; 207:283–303. [PubMed: 7107988]
27. Kelly PA, Graham DI, McCulloch J. Specific alterations in local cerebral glucose utilization following striatal lesions. Brain Res. 1982; 233:157–172. [PubMed: 7059797]
28. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012; 59:2142–2154. [PubMed: 22019881]
29. Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage. 2012; 60:623–632. [PubMed: 22233733]
30. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage. 2011; 59:431–438. [PubMed: 21810475]
31. Schott BH, Minuzzi L, Krebs RM, Elmenhorst D, Lang M, Winz OH, et al. Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J Neurosci. 2008; 28:14311–14319. [PubMed: 19109512]
32. Devor A, Tian P, Nishimura N, Teng IC, Hillman EM, Narayanan SN, et al. Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. J Neurosci. 2007; 27:4452–4459. [PubMed: 17442830]
33. Schafer K, Blankenburg F, Kupers R, Gruner JM, Law I, Lauritzen M, et al. Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. Neuroimage. 2012; 59:3119–3127. [PubMed: 22155327]
34. Lee JH, Durand R, Gradinaru V, Zhang F, Goshen I, Kim DS, et al. Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. Nature. 2010; 465:788–792. [PubMed: 20473285]
35. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001; 412:150–157. [PubMed: 11449264]
36. Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R. Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. Science. 2005; 309:951–954. [PubMed: 16081741]
37. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci. 2000; 20:2369–2382. [PubMed: 10704511]
38. Lappin JM, Reeves SJ, Mehta MA, Egerton A, Coulson M, Grasby PM. Dopamine release in the human striatum: motor and cognitive tasks revisited. J Cereb Blood Flow Metab. 2009; 29:554–564. [PubMed: 19088741]

39. Bertolino A, Breier A, Callicott JH, Adler C, Mattay VS, Shapiro M, et al. The relationship between dorsolateral prefrontal neuronal N-acetylaspartate and evoked release of striatal dopamine in schizophrenia. Neuropsychopharmacology. 2000; 22:125–132. [PubMed: 10649825]
40. Frankle W, Laruelle M, Haber S. Prefrontal cortical projections to the midbrain in primates: evidence for a sparse connection. Neuropsychopharmacology. 2006; 31:1627–1636. [PubMed: 16395309]
41. Chuhma N, Tanaka KF, Hen R, Rayport S. Functional connectome of the striatal medium spiny neuron. J Neurosci. 2011; 31:1183–1192. [PubMed: 21273403]
42. Carlsson A, Lindqvist M. Effect of Chlorpromazine or Haloperidol on Formation of 3methoxytyramine and Normetanephrine in Mouse Brain. Acta Pharmacol Toxicol (Copenh). 1963; 20:140–144. [PubMed: 14060771]
43. Seeman P, Chau-Wong M, Tedesco J, Wong K. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc Natl Acad Sci U S A. 1975; 72:4376–4380. [PubMed: 1060115]
44. Farde L, Wiesel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry. 1988; 45:71–76. [PubMed: 2892477]
45. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000; 157:514–520. [PubMed: 10739409]
46. Nordstrom AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatry. 1993; 33:227–235. [PubMed: 8097114]
47. Gold JM, Waltz JA, Matveeva TM, Kasanova Z, Strauss GP, Herbener ES, et al. Negative symptoms and the failure to represent the expected reward value of actions: behavioral and computational modeling evidence. Arch Gen Psychiatry. 2012; 69:129–138. [PubMed: 22310503]
48. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 1982; 17:319–334. [PubMed: 7187776]
49. Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, et al. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron. 2006; 49:603–615. [PubMed: 16476668]
50. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, et al. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci. 2002; 22:3708–3719. [PubMed: 11978847]
51. Durstewitz D, Seamans JK. The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. Biol Psychiatry. 2008; 64:739–749. [PubMed: 18620336]
52. Winterer G, Weinberger DR. Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends Neurosci. 2004; 27:683–690. [PubMed: 15474169]
53. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry. 1991; 148:1474–1486. [PubMed: 1681750]
54. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci. 2000; 20:2369–2382. [PubMed: 10704511]
55. Williams SM, Goldman-Rakic PS. Widespread origin of the primate mesofrontal dopamine system. Cereb Cortex. 1998; 8:321–345. [PubMed: 9651129]

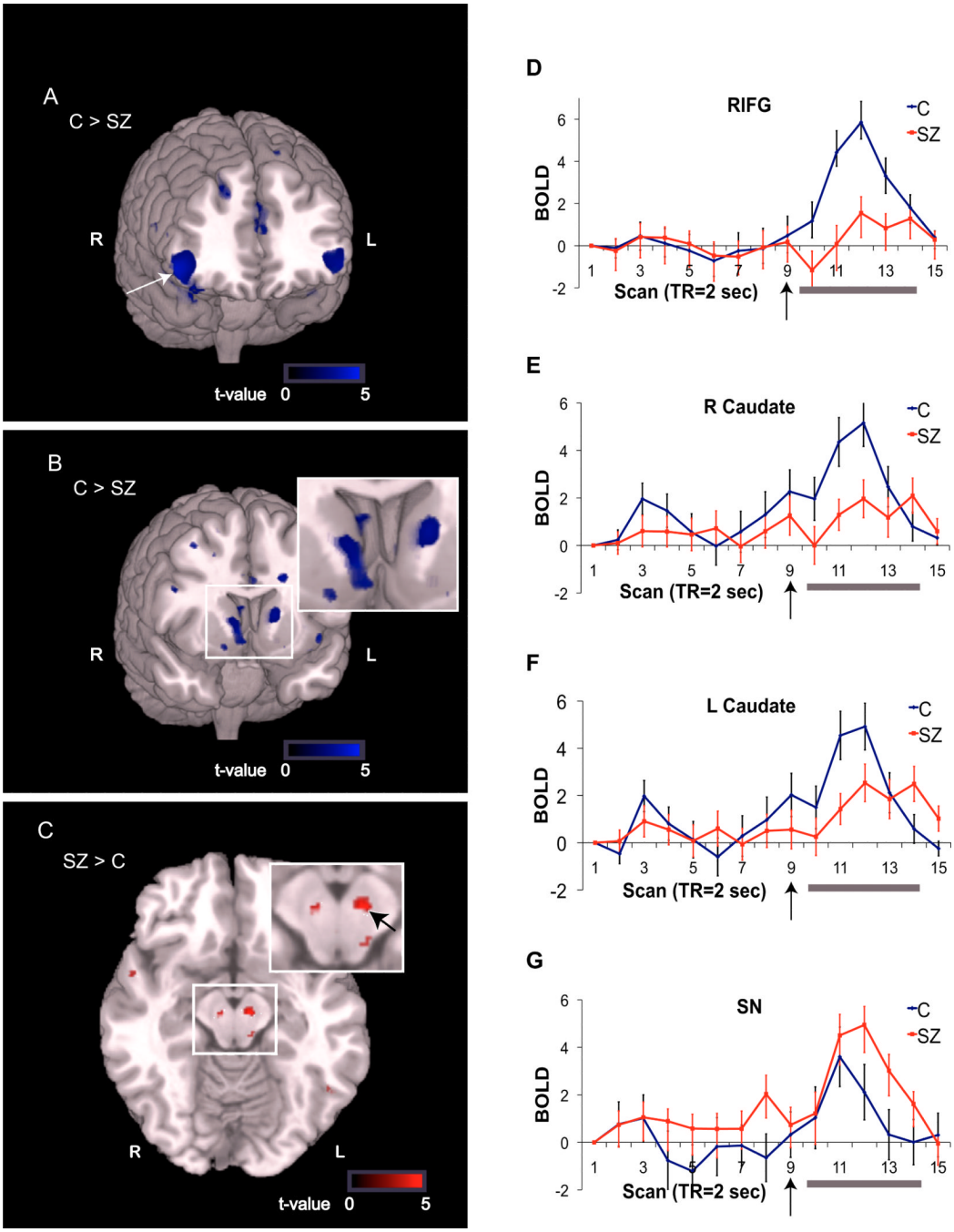

Figure 1. SN hyperactivity in the context of PFC and caudate hypoactivity in schizophrenia

C>SZ contrast maps with threshold of t=2.5 applied showing significant group activation differences in A) a cluster in the RIFG and B) left and right head of caudate, p<.05, corrected. C) SZ>C contrast maps with threshold of t=2.5 applied. A close-up of the midbrain showing bilateral regions of greater SN activity in schizophrenia with the black arrow pointing to the left cluster meeting corrected statistical significance, p<.05. D-G) Trial-averaged BOLD time-series of the clusters showing significant group differences in activity depicted to the left. Scans 10-14 correspond to activity evoked during the response phase of WM indicated by gray bars. Black arrows indicate timing of probe face presentation. Error bars are s.e.m.

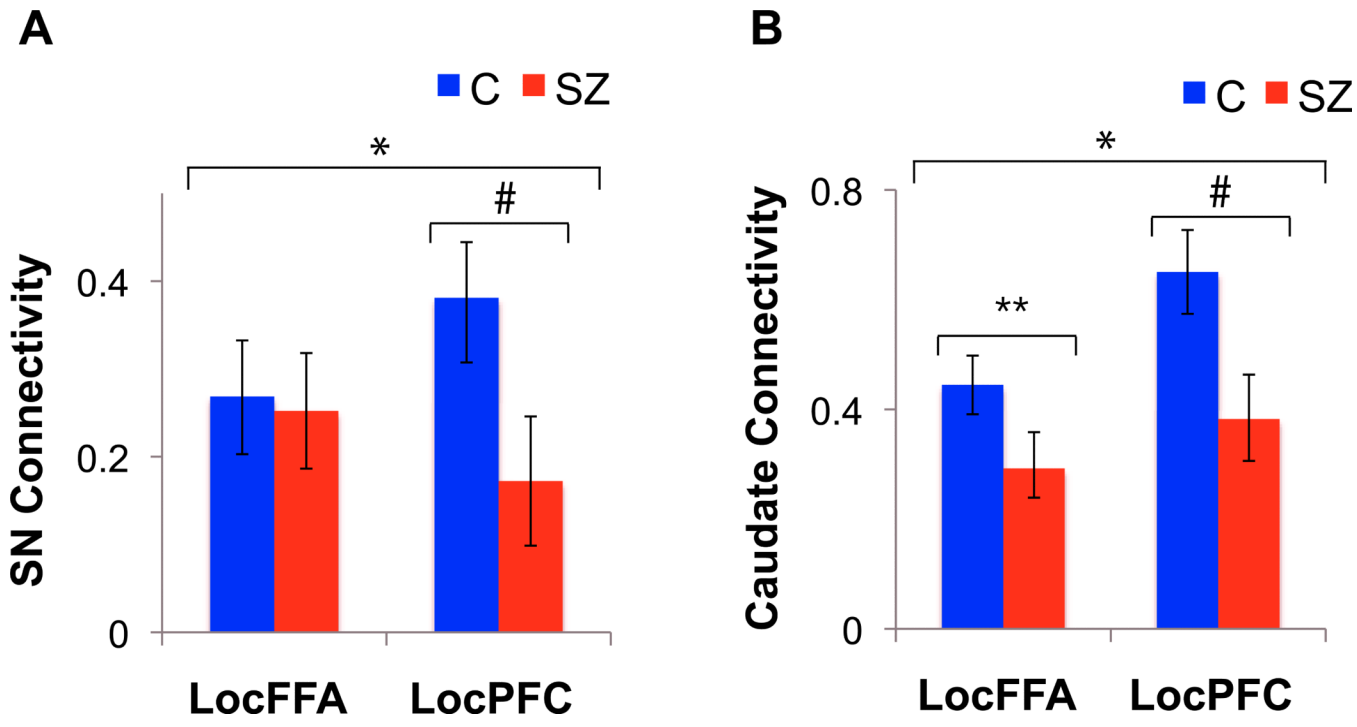

Figure 2. Diminished prefrontal functional connectivity with the SN and caudate in schizophrenia

A) Functional connectivity between LocPFC and SN was decreased in patients, # p=.013, while the connectivity between LocFFA (a visual cortical region) and SN was similar between groups. *Group × Condition interaction, p=.033. B) Functional connectivity between the caudate and LocPFC in SZ was significantly decreased, # p<.001, but in a non-specific manner because its connectivity with the LocFFA was also significantly decreased in SZ, ** p=.006. *Main effect of Group, p<.001 and a non-significant Group × Circuit interaction, p=.083.

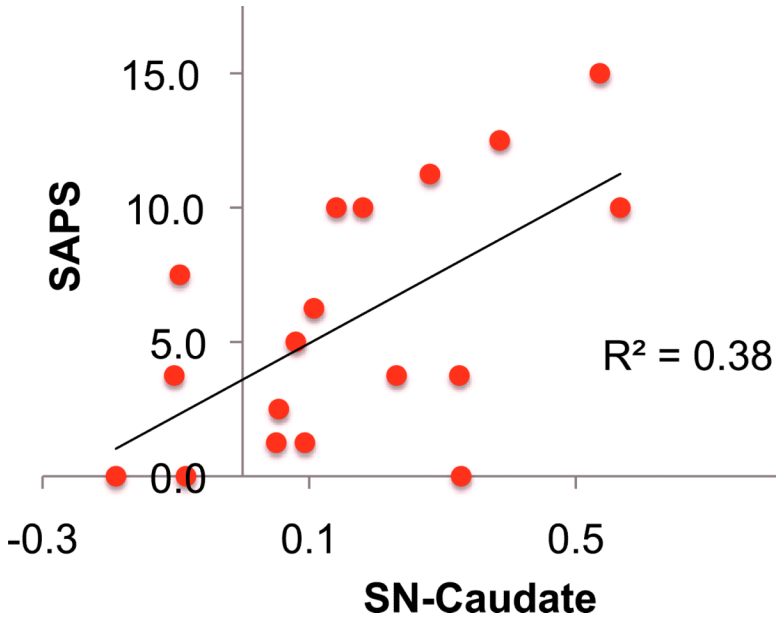

Figure 3. Nigrostriatal functional connectivity predicts severity of psychosis

The magnitude of functional connectivity between the caudate and SN demonstrated a highly significant correlation with psychosis severity, as quantified by the total SAPS score, p=.007.

Table 1

Subject demographics, clinical profile and behavioral performance on the cognitive task.

	Patient (N=18)		Control (N=19)		T/Chi-Squ.	p-value
	Mean	**SD**	**Mean**	**SD**		
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 (% R)	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 Anti-Psychotics	18					
Typical	1					
Atypical	17					
CPZ Equivalents	365	294				
Accuracy	0.75	0.11	0.86	0.09	3.47	.001
RT (msec)	1129	228	953	207	2.45	.020

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).

Table 2

List of fMRI activation peaks during the response phase of the face WM task. Coordinates are given in the MNI coordinate system.

	Region	Size (mm^3)	Peak *t*	*p*, corrected	Coordinates [*x y z*]
C > SZ	L Parahip G	29120	5.36	<.001[a]	-20 -50 -4
	R Inf Front G	7976	4.20	.035[a]	52 42 -8
	L Caud Head	424	3.55	.022	-12 4 4
	R Caud Head	776	4.05	.005	6 12 -2
SZ > C	L SN	120	4.33	.048	-8 -16 -12
	R SN	48	3.72	.102	8 -16 -14

b These statistical values are from the contrasts conducted on the images from the 1-back WM experiment and not from the delayed-response WM experiment (see Supplemental Information).

[a]These *p*-values are corrected for whole brain multiple comparisons. All others are SVC *p*-values.