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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

Jong H. Yoon [a,b,*], Andrew J. Westphal [c], Michael J. Minzenberg [d,e], Tara Niendam [c], J. Daniel Ragland [c], Tyler Lesh [c], Marjorie Solomon [c,f], Cameron S. Carter [c,g]

[a] Stanford University, Department of Psychiatry and the Behavioral Sciences, United States
[b] Veterans Affairs Palo Alto Health Care System, United States
[c] University of California Davis, Department of Psychiatry, United States
[d] University of California San Francisco, Department of Psychiatry, United States
[e] San Francisco Veterans Affairs Medical Center, United States
[f] University of California Davis, MIND Institute, United States
[g] University of California Davis, Center for Neuroscience, United States

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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 from 12 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 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.

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1. Introduction

Schizophrenia is a complex condition manifesting 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 system 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 et al. (1990). Excess subcortical DA has been consistently demonstrated in schizophrenic psychosis with increased presynaptic metabolism of dopamine precursors in the striatum (Reith et al., 1994; Hietala et al., 1995, 1999; Lindstrom et al., 1999; Meyer-Lindenberg et al., 2002) and excess amphetamine induced release of striatal DA (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998; Kegeles et al., 2010). In addition, correlations between antipsychotic efficacy with the magnitude of striatal D2 receptor blockade by antipsychotic agents have been demonstrated (Kapur et al., 2000; Agid et al., 2007).

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

* Corresponding author at: VA Palo Alto Health Care System, 3801 Miranda Ave., Building 4, 2nd Floor, Palo Alto, CA 94304, United States.

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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 (Weinberger, 1987; Davis et al., 1991). 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 system 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 (Haber, 2003; Björklund and Dunnett, 2007), 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 that 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 and 15 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

2.2.1. AX-continuous performance task (AX-CPT)

Subjects completed the AX-CPT during scanning (Cohen et al., 1999; Barch et al., 2003). 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, 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; Montague et al., 2004; Kudlicka et al., 2011). 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 were 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°, 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 realignments, 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 2 mm 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 2 mm 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