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An fMRI study of visual attention and sensorimotor function before and after antipsychotic treatment in first-episode schizophrenia

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ABSTRACT

While much is known about receptor affinity profiles of antipsychotic medications, less is known about their impact on functional brain systems in patients with schizophrenia. We conducted functional magnetic resonance imaging (fMRI) studies with first-episode schizophrenia patients as they made saccades to unpredictable visual targets before and after 4–6 weeks of antipsychotic treatment. Matched healthy individuals were scanned at similar time intervals. Pretreatment, patients had less activation in frontal and parietal eye fields and cerebellum. After treatment these disturbances were not present, suggesting improved function in attentional and sensorimotor systems. Other pretreatment abnormalities were noted in sensory and ventromedial prefrontal cortex, but after treatment these abnormalities were absent or less prominent, in line with improved function in attentional systems. In addition, although not abnormal at baseline, there was reduced activity after treatment in dorsal prefrontal cortex, dorsal striatum, and dorsomedial thalamus, suggesting a potential adverse effect of treatment on frontostriatal systems, perhaps related to dopamine blockade in the caudate. These findings provide evidence for a complex impact of antipsychotic medication on functional brain systems in schizophrenia and illustrate the potential of neuroimaging biomarkers for both adverse and beneficial drug effects on functional brain systems.

1. Introduction

Studies of brain physiology after antipsychotic treatment in schizophrenia patients have primarily investigated effects on resting metabolism and blood flow (Miller et al., 2001; Ngan et al., 2002; Lahti et al., 2005). This work has been paralleled by short duration drug administration studies in healthy individuals (Honey et al., 2003; Lane et al., 2004). In contrast to studies of resting state physiology, functional magnetic resonance imaging (fMRI) provides an approach for examining drug effects on the functional brain systems that support cognitive and perceptual abilities in which change is the target for drug treatment. Two prior studies investigated treatment effects on task-related brain activation in initially medication-free first-episode schizophrenia patients and compared them with healthy participants. Each utilized behavioral flexibility tasks to target prefrontal function (Snitz et al., 2005; Brewer et al., 2007). While such work has helped characterize the impact of antipsychotics on prefrontally mediated executive cognitive functions, more work is needed to improve understanding of medication effects throughout the brain and on more basic neurocognitive systems such as simple attention, sensory, and sensorimotor processing. Such work will help broaden understanding of the clinical effects of antipsychotic treatment, and provide more direct translational linkage to a wider range of animal model systems.

Examining automatic attention systems with simple saccadic eye movement tasks is one such approach. Visually guided saccades are rapid shifts in gaze from one location to another in the visual field. Studies of nonhuman primates have mapped the neurophysiology and biochemistry of the oculomotor system, defining the unique contributions of different brain regions to sensorimotor and attentional aspects of eye movement control. The generation of visually guided saccades is tightly linked with exogenous visual attention via processes mediated by neocortical areas that include and overlap with the frontal and parietal eye fields (Corbetta, 1998; Merriam et al., 2001). These cortical eye fields as well as striatum, thalamus, cerebellum, and brainstem contribute to sensorimotor aspects of eye movement control and their regulation by automatic attentional processes. Thus, oculomotor tasks provide a useful strategy for assessing the effects of drug treatment on attentional and sensorimotor brain systems. Of note, antipsychotic drugs have high affinity for dopamine

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receptors in the caudate nucleus of the striatum, and dopaminergic modulation in the caudate is important for saccade control (Hikosaka et al., 2000; Goldman-Rakic et al., 2004).

Studies of medicated patients performing visually guided saccades during fMRI have found either slightly reduced activation in frontal, parietal, and supplementary eye fields, visual cortex, and anterior cingulate (Raemaekers et al., 2002) or no differences (McDowell et al., 2002) compared to healthy controls. In an fMRI study of saccadic eye movements in unmedicated first-episode patients in a subject cohort different from the one recruited for this study, significantly reduced activation was observed in frontal, supplemental, and parietal eye fields (Keedy et al., 2006). This is consistent with findings from a laboratory study of never medicated first-episode schizophrenia patients showing speeded saccade latencies prior to treatment (Reilly et al., 2005). Reduced attentional regulation from neocortical eye fields to brainstem oculomotor nuclei, suggested by the findings of Keedy et al. (2006), represent one potential cause of these speeded pretreatment saccade latencies (Everling and Munoz, 2000). Reilly et al. (2005) also found a slowing of the initially speeded responses after atypical antipsychotic treatment. This may be related to a normalization in saccade-related cortical eye field function after treatment, but this has not yet been directly examined.

To assess the effect of antipsychotic treatment on attentional and sensorimotor circuitry supporting visually guided saccades, we performed fMRI studies with first-episode schizophrenia patients with no or limited prior antipsychotic treatment. They were unmedicated at the time of the first scan and were scanned again after 4–6 weeks of antipsychotic treatment. Matched healthy individuals were studied over a similar time interval. Our first aim was to characterize pretreatment group differences to assess illness-related abnormalities in oculomotor and attentional systems. For this aim, we anticipated reduced activation in frontal eye fields as reported previously by Keedy et al. (2006). Our second aim, which reflects the most novel aspect of the study, was to characterize brain function in oculomotor and attentional systems after treatment. Based on prior longitudinal laboratory studies, and previous fMRI studies where treated or untreated patients were studied separately, we predicted less abnormality in attentional and sensorimotor circuitry after treatment.

2. Method

2.1. Participants

The study was approved by the Institutional Review Board of the University of Illinois at Chicago, and all participants provided written informed consent. Six male and three female patients were recruited who met DSM-IV criteria for schizophrenia using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) and collateral clinical data reviewed at consensus diagnosis meetings. Nine healthy individuals who did not meet criteria for any present or past Axis I disorder according to SCID interviews were recruited from the surrounding community. They matched the patient group on age ($t[df_{16}]=0.36$, *n.s.*), gender ($\chi^2[df_1]=2.0$, *n.s.*), and parental socioeconomic status ($t[df_{14}]=2.1$, *n.s.*; status could not be reliably ascertained for two patients). All participants met the following criteria: no known systemic or neurologic disease; no history of head trauma with loss of consciousness, no lifetime history of substance dependence or substance abuse within 3 months of study participation; and, no coffee, tea or cigarettes at least 2 h prior to testing.

One schizophrenia patient was antipsychotic naïve. The remaining eight had brief prior second generation antipsychotic exposure (average of 2.8 [S.D.=2.3] weeks). One had an additional 2-week exposure to a first generation antipsychotic before admission. Those taking antipsychotics at the time of consenting to the study were withdrawn from their medication under clinical supervision on an inpatient research unit. The minimum was 6 medication-free days prior to baseline fMRI studies (mean=8.1 days). This was done to minimize acute treatment effects on fMRI data such as sedation, and to provide better comparative baseline data for examining medication effects to a degree that was clinically and ethically feasible.

Risperidone was the preferred treatment of choice, unless patients had a prior or emergent adverse reaction, or were inadequately responding to it per clinical judgment. At the time of follow-up scanning, six patients were still on risperidone (mean dose=4.2 mg [2.1]). One was on ziprasidone (200 mg) and two were on haloperidol (4 and 5 mg). Patients were rated on the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) and Simpson–Angus Scale for extrapyramidal signs (SAS) (Simpson and Angus, 1970) at both time points. Mean PANSS scores at baseline were 73.5 (S.D.=18.2) before treatment and 57.1 (S.D.=20.9) after treatment. Although not statistically different, the reduction in PANSS scores show that patients were stabilizing during the interval between scans. Ratings of extrapyramidal side effects were low both before (0.44 [S.D.=.93]) and after (1.33 [S.D.=2.07]) treatment. Healthy individuals were re-scanned after a time interval similar to that of the patients ($t[df_{16}]=2.0$, *n.s.*).

2.2. fMRI task

The behavioral task used in the scanner has been used in previous studies (Berman et al., 1999; Keedy et al., 2006) and was designed to contrast exogenously generated visual attention and visually guided saccades to unpredictable target displacements with central fixation in a block design paradigm. Six 30-second blocks of a visually guided saccade task alternated with seven 30-second blocks of central fixation. During the saccade task, a circular target subtending 0.5° of visual angle moved in 4° steps between 5 possible locations (0±4° and ±8°) along the horizontal plane at a fixed interval of 810 ms. The direction of target movement was unpredictable except after the ±8° locations, when the target always moved back toward center. Participants demonstrated the ability to understand and perform the tasks in a practice session prior to scanning. Task compliance during the scan was visually verified via an infrared video camera (30 Hz sampling, sufficient to verify performance but not to accurately measure saccade latencies or metrics).

2.3. Image acquisition and analysis

The fMRI studies were conducted using a 3.0 Tesla whole body scanner (Signa VHi, General Electric Medical Systems, Waukesha, WI) with a gradient echo, echo-planar sequence (epiRT, 25 axial slices, 5 mm thick, skip 1 mm, TR=2500 ms, TE=25 ms, flip angle=90, matrix=64×64, FOV=20 cm^2, voxel size=3.125×3.125×5 mm; 156 volumes acquired). Anatomic images were also acquired (three-dimensional spoiled gradient recalled, 1.5 mm thick contiguous axial slices) for co-registration with the functional data. Images were reconstructed, autoscaled, and motion-corrected using Functional Image Analysis Software Computational Olio (Eddy et al., 1996). Individual volumes from the time series were excluded from analysis if head displacement was greater than 1.5 mm or rotation was greater than 0.5° from the median volume location. The groups did not significantly differ on number of volumes excluded from analysis (mean [S.D.] number of excluded volumes: schizophrenia=52.7 [24.2]; healthy=55.3 [22.7]) or in head motion measurements in the remaining data used for analyses.

Effect size maps were generated to characterize BOLD signal differences between saccade and fixation blocks for each subject. These were expressed as Fisher z' statistics. The z' maps from each subject were warped into Talairach space and resampled to 3×3×3 mm voxels (in-plane voxel resolution at acquisition). We then conducted between group t tests to assess group differences at baseline and at follow-up, and applied a contiguity threshold to preserve a familywise Type 1 error rate of $P<0.05$. The volume threshold was determined with AFNI's (Analysis of Functional Neuroimages) (Cox, 1996) AlphaSim Monte Carlo simulation program run with a template brain mask for restricting contiguity simulations to in-brain voxels.

Due to the limited sample size, we elected to focus primary hypothesis testing analyses on between group differences at each time point due to insufficient statistical power for evaluating group×time