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Subcortical modulation of attentional control by second-generation antipsychotics in first-episode psychosis ☆

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ABSTRACT

Psychotic disorders are characterized by significant deficits in attentional control, but the neurobiological mechanisms underlying these deficits early in the course of illness prior to extensive pharmacotherapy are not well understood. Moreover, little is known regarding the symptom and brain changes associated with amelioration of attentional impairments through antipsychotic pharmacotherapy. In this study 14 male patients experiencing a first-episode of psychosis with minimal prior antipsychotic treatment completed an attentional control task while undergoing functional magnetic resonance imaging at the onset of treatment with a second generation antipsychotic (risperidone or aripiprazole) in a double blind randomized clinical trial and then again following approximately 12 weeks of treatment. In addition, 14 age-, and performance-matched healthy male volunteers who were not treated completed the same task at a baseline timepoint and then again following 12 weeks. Patients showed significantly greater activation than healthy volunteers in the right globus pallidus, left thalamus, and right thalamus at the time of the baseline scan. Among patients there was a significant reduction in right globus pallidus blood-oxygen level dependent (BOLD) response following antipsychotic treatment that correlated significantly with improvement in response accuracy and reductions in thought disturbance. No changes in globus pallidus activation were observed in healthy volunteers over this time period. These preliminary findings suggest that improvement in attentional control and concomitant reductions in thought disturbance in first-episode psychosis may be associated with reductions in subcortical activity following administration of second-generation antipsychotics early in the course of illness. These findings have implications for understanding how changes in basal ganglia activity may be linked to improvements in attentional control through antipsychotics.

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1. Introduction

Given their strong dopaminergic inneveration, the basal ganglia have strong relevance to neurobiological models of schizophrenia (Perez-Costas et al., 2010) and may play a role in successful treatment intervention (Molina et al., 2011). Furthermore, both mitochondrial and receptor density abnormalities within the basal ganglia have been reported in schizophrenia (Kung and Roberts, 1999; Meisenzahl et al., 2007; Murray et al., 1995), further supporting their relationship to mechanisms underlying antipsychotic medications. Magnetic resonance (MR) imaging studies have demonstrated structural alterations involving the caudate nucleus, globus pallidus and putamen in patients with schizophrenia (Bilder, 1992; Brandt and Bonelli, 2008; Corson et al., 1999; Hokama et al., 1995) and unaffected siblings (Mamah et al., 2008). Several literature reviews suggest that administration of typical (in contrast to atypical) antipsychotics may be associated with volumetric increases in the basal ganglia (Navari and Dazzan, 2009; Smieskova et al., 2009). Thus, examination of regions comprising the basal ganglia early in the course of illness and prior to extensive pharmaocologic intervention may best address

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questions regarding their role in the neurobiology of schizophrenia and how antipsychotics may mediate associated changes in neuropsychological functioning.

Attentional control is the ability for an individual to decide what should be acknowledged in the environment compared to what can be ignored. Deficits in attentional control are considered one of the hallmark features of schizophrenia and related psychotic disorders (Carter et al., 1992; Lalanne et al., 2012; Reilly et al., 2008). Successful attentional control (or executive attention) is related to the ability to conduct top-down processing and is mainly under the individual's control (in contrast to bottom-up processing). Aside from frontal regions, empirical work indicates that attentional control is mediated by structures comprising the basal ganglia, including the globus pallidus (Bočková et al., 2011; Muir et al., 1993; Scott et al., 2002), caudate nucleus (Canavero and Fontanella, 1998) and putamen (Max et al., 2002). Moreover, hyperactivation in basal ganglia regions has been reported in rats during attention related tasks (Sotoyama et al., 2011) and lesions to the basal ganglia yield attention deficits both in rats (Muir et al., 1993; Thompson et al., 1985) and humans (Max et al., 2002; Scott et al., 2002). Also, involvement of the globus pallidus and caudate nucleus in attentional control has been demonstrated using electrophysiological recording in Parkinson's disease (Bočková et al., 2011; Kropotov et al., 1997) as well as in healthy human positron emission tomography studies (Corbetta et al., 1991).

There is increasing data that basal ganglia dysfunction may be associated with attentional control deficits in schizophrenia (Manoach et al., 2000). For example, measures of attention/vigilance have been linked to volumetric alterations within the caudate nucleus and putamen (Mamah et al., 2008). Additional data suggest that attentional control in schizophrenia may improve with antipsychotics (McGurk et al., 2004) and that this could be related to their significant D2 dopaminergic antagonism efficacy. In this regard Cohen et al. (1998) reported that the basal ganglia play a role in sustained attention, likely contribute to psychotic symptoms and mediate antipsychotic response. More specifically, these authors reported that patients had greater regional cerebral metabolic rates in the posterior putamen during an attention task, which was associated with worse antipsychotic treatment response.

Few functional magnetic resonance imaging (fMRI) studies have assessed the potential impact of antipsychotic medications on attentional control early in the course of schizophrenia and prior to extensive pharmacotherapy. In one study Keedy et al. (2009) reported less dorsal striatal activation using fMRI in patients compared to healthy controls during visual tracking and attention following antipsychotic treatment, which the authors interpreted as a possible adverse effect of treatment that could relate to dopamine blockade.

To clarify the role of second-generation antipsychotics in mediating attentional control in patients with psychotic disorders, we conducted a longitudinal fMRI study examining the relationship between antipsychotic pharmacotherapy on basal ganglia activity during performance of the Multisource Interference Test (Bush and Shin, 2006) and its relationship to clinical improvement. We hypothesized that patients would demonstrate functional abnormalities in the basal ganglia at the onset of treatment when performing an attentional task in line with the rich dopaminergic innervations of the basal ganglia (Hall et al., 1994; Richtand et al., 2007), and that there would be significant changes in BOLD activity following antipsychotic treatment. An additional study goal was to investigate whether changes in BOLD response following pharmacotherapy were associated with symptom improvement.

2. Methods

2.1. Participants

Fourteen male patients experiencing a first-episode of psychosis and 14 age, handedness and performance-matched male healthy volunteers participated in the study (Table 1). Patients were enrolled in an NIMH-funded randomized, double-blind treatment study comparing the efficacy and tolerability of risperidone and aripiprazole. Mean age at first psychotic symptoms was 19.8 years (S.D.=3.6). The mean number of weeks between the baseline and followup MR imaging exams for patients treated with either risperidone or aripiprazole was 12.5 (S.D.=1.0) weeks. Patients had, on average, 5.57 days (S.D.=7.87) of antipsychotic exposure in the clinical trial prior to the baseline scan, including five patients who were antipsychotic drug naïve. All patients received a physical exam and laboratory screening to rule out medical causes for their initial psychotic episode. All diagnoses were based on the Structural Clinical Interview for DSM-IV for Axis I DSM-IV Disorders (SCID; First et al., 2002a) supplemented by information from clinicians and, when available, family members. Patients met DSM-IV criteria for schizophrenia ($n=11$), psychosis NOS ($n=2$) or schizophreniform disorder ($n=1$). Healthy volunteers were selected from a larger sample recruited from advertisements posted on websites and by word of mouth, to match the demographic distributions of patients, with respect to age, education, Edinburgh laterality quotient, the number of weeks between scans, and baseline task accuracy. Exclusion criteria for healthy subjects included the presence of any lifetime history of a major mood or psychotic disorder as determined by clinical interview using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-patient Edition (SCID-NP; First et al., 2002b). Exclusion criteria for all study participants included MR imaging contraindications, and serious medical conditions that could affect brain functioning or mental retardation. This study was approved by the North Shore – Long Island Jewish Medical Center Institutional Review Board and written informed consent was obtained from all study participants or their parents in the case of minors. All minors provided written informed assent to participate in the study.

2.2. Antipsychotic titration schedule in treatment trial

The initial daily dose for patients in the treatment trial was 5 mg for aripiprazole and 1 mg for risperidone. After one week, dose increases occurred at intervals of 1–3 weeks until the subject improved or reached a maximum daily dose of 30 mg of aripiprazole or 6 mg of risperidone. Lorazepam was prescribed for anxiety or agitation.

2.3. Clinical assessment

Patients completed the 18-item Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) on average within 3.5 (S.D.=10.9) and 4.0 (S.D.=10.4) days following the baseline and follow-up MR imaging exams, respectively. We derived four clinical domains from the BPRS using previously published work (Hedlund, 1980; Malhotra et al., 1998) including thought disturbance, withdrawal-retardation, hostility-suspiciousness and anxiety-depression.

Table 1
Sample characteristics.

	Patients ($n=14$)		Controls ($n=14$)		t-test
	Mean	S.D.	Mean	S.D.	
Age (range)	22.0 (16 to 38)	5.70	22.4 (15 to 38)	6.16	$t=0.17$, $p=0.85$
Education	12.57	1.70	12.71	2.23	$t=0.19$, $p=0.85$
Edinburgh Laterality Quotient	0.60	0.55	0.56	0.55	$t=0.18$, $p=0.85$
Weeks between Baseline and Followup Scans	12.4	1.0	12.3	0.6	$t=0.53$, $p=0.60$

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