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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, fourteen 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

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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.

Keywords

functional magnetic resonance imaging; second generation antipsychotics; attentional control; first episode psychosis; schizophrenia; basal ganglia

1. Introduction

Given their strong dopaminergic innervation, 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 pharmacologic intervention may best address 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 (Bošković 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 (Bošković 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 and colleagues

(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 ($SD = 3.6$). The mean number of weeks between the baseline and followup MR imaging exams for patients treated with either risperidone or aripiprazole was 12.5 ($SD = 1.0$) weeks. Patients had, on average, 5.57 days ($SD = 7.87$) 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 (SD = 10.9) and 4.0 (SD = 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.

2.4 Functional Magnetic Resonance Imaging Task

All participants completed the Multi Source Interference Task (MSIT) to assess attentional control (Bush and Shin, 2006). Details of the MSIT have been reported previously (Bush et al., 2000; Bush and Shin, 2006; Bush et al., 2003). Briefly, a block design was used to present two conditions: Interference and Control. In both conditions, three digits (0, 1, 2, or 3) were presented at once in a horizontal row in the center of the screen, in which two of the three digits were identical. Participants were instructed to press the button that corresponded to the non-identical (i.e. different) number. The different number was either 1, 2, or 3, and participants learned to press a specific button that corresponded to each number (index finger for 1, middle finger for 2, and ring finger for 3). In the Control condition, the two identical numbers were always 0, and the different number was either 1, 2 or 3 and corresponded to the positions of the fingers. That is, the sequences of three digits were 100, 020, and 003, whose corresponding correct responses were 1, 2, and 3. In the Interference condition, the position of the different number did not correspond to the value of the number. Zeros were not included in these sequences. That is, the sequences of three digits were 212, 221, 313, 331 (correct response = 1), 211, 112, 233, 332 (correct response = 2), and 311, 131, 322, 232 (correct response = 3). All subjects used their right hand.

2.5 Image Acquisition and Processing

A total of 536 EPI volumes were acquired on a General Electric 3T HDx MR imaging system (TR=1500ms, TE=27ms, matrix=64*64, FOV=220mm, slice-thickness=5mm, 26 continuous slices) axially aligned along the anterior and posterior commissures. Imaging data were analyzed using FMRI Expert Analysis Tool (<http://www.fmrib.ox.ac.uk/analysis/research/feat>) in the FMRI Software Library (FSL: <http://www.fmrib.ox.ac.uk/fsl/>). Images were slice time and motion corrected, linearly registered to the 3D spoiled gradient echo (SPGR) structural volume (TR = 7.5 ms, TE = 3 ms, matrix = 256×256, FOV = 240 mm, 216 contiguous 1mm thick images), normalized to the standard MNI template via the coregistered structural volume and smoothed using an 8mm FWHM Gaussian Kernel. Subcortical regions-of-interest included the caudate nucleus, putamen, globus pallidus and thalamus.

2.6 Statistical Analysis

Given our a priori hypothesis that patients would have abnormal baseline BOLD activation in the basal ganglia compared to healthy volunteers, a Z statistic image was estimated where clusters were determined by voxel $Z > 3.719$ ($p < .0001$) with a family wise error corrected cluster significance threshold of $p=0.05$ assuming a Gaussian random field for the Z-statistics.

Voxelwise paired t-tests were conducted between baseline and 12 week scans, to assess longitudinal changes in the whole-brain, separately for patients and controls. Likewise, Z statistic images were estimated where clusters were determined by voxel $Z > 3.719$ with a family wise error corrected cluster significance threshold of $p=0.05$ assuming a Gaussian random field for the Z-statistics.

To test the hypothesis that the baseline and 12 week scans differed in BOLD activation within the basal ganglia, a region-of-interest (ROIs) approach was adopted in which baseline and 12 week activation Z-scores were taken from masks of the caudate nucleus, globus pallidus and putamen using the Harvard-Oxford subcortical structural atlas (Desikan et al., 2006). These subcortical ROIs were examined in relationship to accuracy in the interference condition using two tailed Pearson product-moment correlations. In addition, the difference in the activation Z-score within these ROIs in patients between the baseline and 12 week scan was calculated. The R Partial Correlation package (<http://www.yilab.gatech.edu/pcor.html>) was used to assess the partial correlation coefficient between the difference in Z-score and difference in response accuracy after controlling for baseline accuracy, and the partial correlation coefficient between the difference in Z-score and differences in the four BPRS factors after adjusting for baseline Z-score.

Mediation analysis was used to determine whether the relationship between changes in BPRS ratings and activation was mediated by response accuracy using tests of causal steps (MacKinnon et al., 2002). In this approach, the following four steps were conducted to determine whether mediation was present: (Judd and Kenny, 1981a, b) (a) the effect of activation on BPRS rating is significant, (b) the effect of activation on response accuracy, α , is significant, (c) the effect of response accuracy on the BPRS rating controlled for activation, β , is significant, and (d) the direct effect of activation on the BPRS rating adjusted for response accuracy is non-significant. If each of the four steps was satisfied the model was determined to be fully mediated; if only step 4 is relaxed, we conclude that the resulting model is partially mediated (Baron and Kenny, 1986). The mediation effect was calculated using a product-of-coefficients approach (MacKinnon et al., 2007) using the *lavaan* package (<http://lavaan.ugent.be/>) in the R statistical language. In this approach the product estimates of α and β , are considered an estimate of the indirect effect of response accuracy on the causal relationship between activation and BPRS ratings.

3. Results

3.1 Clinical Improvement

There was significant improvement after 12 weeks in overall BPRS score (*mean change* = -19.14 , *range* = -3 to -38 , $t = 6.39$, $df = 22.89$, $p < 0.001$). Among the four clinical domains, thought disturbance (*mean change* = -6.14 , *range* = -1 to -11 , $t = 7.33$, $df = 22.75$, $p < 0.001$), hostility-suspiciousness (*mean change* = -4.57 , *range* = 0 to -9 , $t = 6.11$, $df = 25.28$, $p < 0.001$) and anxiety-depression (*mean change* = -4.07 , *range* = 0 to -10 , $t = 3.42$, $df = 18.80$, $p = 0.029$) showed significant improvement (Table 2).

3.2 Behavioral Results

As control subjects were selected based on their baseline accuracy as well as their age and gender there was no significant difference between groups in baseline accuracy. There was no significant group difference in baseline reaction time or followup reaction time. There was, however, a significant difference between the two groups at the time of the follow up scan for response accuracy ($t = 2.60$, $df = 20.88$, $p = 0.016$; Figure 1A) with healthy volunteers performing better than patients. Among patients there was an improvement in response accuracy ($t = 2.35$, $df = 13$, $p = 0.035$; Figure 1A), but not in reaction time (Figure

1B) following 12 weeks of antipsychotic treatment (Table 3). Healthy volunteers demonstrated an improvement in response accuracy ($t = 3.55$, $df = 13$, $p = 0.0036$, Figure 1A) and reaction time ($t = 3.32$, $df = 13$, $p = 0.0056$, Figure 1B) across the 2 timepoints.

3.3 fMRI Results

At the baseline scan, patients showed significantly greater activation than healthy volunteers in the basal ganglia (Figure 2A), including the right globus pallidus ($t = 3.24$, $df = 25.30$, $p = 0.0034$; Figure 2B), left thalamus ($t = 2.65$, $df = 25.96$, $p = 0.014$; Figure 2C), and right thalamus ($t = 3.56$, $df = 25.98$, $p = 0.0015$; Figure 2D).

The whole brain voxelwise revealed significant changes in patients from the baseline to the 12 week scans. Patients demonstrated significantly decreased activation in the globus pallidus, putamen, and thalamus, as well as several other cortical regions (Figure 3 and Table 4). Healthy volunteers did not show significant decreases in any of these regions (Figure 3).

Among subcortical ROIs, the change in right globus pallidus activation was significantly correlated with response accuracy improvement ($r = -0.50$, $df = 14$, $p = 0.047$) in patients.

The reduction in right globus pallidus activation was also significantly correlated with decreases in the BPRS thought disturbance factor ($r = 0.54$, $df = 11$, $p = 0.032$, Figure 4B). Specifically, the post-hoc analysis revealed that the reduction in right pallidal activity was significantly correlated with the unusual thought content item ($r = 0.52$, $df = 11$, $p = 0.042$, Figure 4C). No other BPRS composite or individual scores were significantly correlated with reductions in right pallidal activity. There was a significant correlation between improvements in response accuracy and decreases in thought disturbance ($r = -0.64$, $df = 12$, $p = 0.013$, Figure 4D).

The causal steps approach showed a trend towards significance for the fully mediated model in which the effect of right globus pallidus activation on thought disturbance was mediated by accuracy in attention. Using the production-of-coefficients approach, the mediation effect size was calculated to be 1.58.

A post-hoc voxelwise analysis did not detect any differences between two medications. Moreover, an ROI analysis of the right globus pallidus comparing the two groups was not statistically significant ($t = 0.43$, $df = 11.64$, $p = 0.67$).

4. Discussion

In this longitudinal study we sought to evaluate the effects of antipsychotic medication on attentional control using fMRI in first episode psychosis patients. Although the sample size is limited, the current results imply that subcortical regions, especially the globus pallidus, appear hyperactivated during the performance of an attentional control task in patients near illness onset. This activation did not differ significantly, however, from healthy volunteers at the time of the 12 week scan (Figure 4A) suggesting that such baseline abnormalities were normalized through pharmacologic intervention. In contrast, healthy volunteers demonstrated no longitudinal changes in BOLD activity within these regions over the 12 week time period. We also observed that reduction in this hyperactivation was associated with improved performance on attentional tasks along with concomitant reductions in thought disturbance. Taken together, these preliminary results are consistent with the possibility that the basal ganglia may mediate aspects of attentional control and concomitant changes in thought disturbance in first-episode psychosis through antipsychotic pharmacotherapy.

Few studies have assessed the potential impact of antipsychotic pharmacotherapy on attentional control in first-episode psychosis early in the course of illness, and thus, it is difficult to compare our results to prior findings. The results of our study are consistent with the hypothesis that the basal ganglia are an important target for second-generation antipsychotics regarding improvement of attentional control and their underlying pharmacokinetic properties (Richtand et al., 2007). Some data suggest that attention deficits are not directly related to symptom severity and could conceivably be at least partially ameliorated by atypical antipsychotic intervention (Harris et al., 2007). Reductions in activity were observed following olanzapine treatment during the performance of a visually paced motor task in the dorsal striatum, suggesting a potential adverse effect of these medications on frontostriatal integrity that may be associated with dopamine blockade (Bertolino et al., 2004). Although multiple regions demonstrated an increase or decrease in activation in patients following 12 weeks of treatment with antipsychotic medication in our study (Table 4), cortical regions failed to show a relationship with behavioral performance in patients, suggesting that these regions may not be directly involved.

Our results are consistent with the hypothesis that antipsychotics improve attentional control by suppressing hyperactivity in the basal ganglia. This reduction in activity may be related to the fact that the basal ganglia are rich in monoaminergic receptors to which second-generation antipsychotics bind as antagonists (Hall et al., 1994; Richtand et al., 2007). It should be noted that one of the two antipsychotics used in the current design was aripiprazole, which is a partial dopamine agonist (Burris et al., 2002). However, the finding that the basal ganglia were hyperactivated in patients at baseline implies elevated availability of dopamine in the basal ganglia. Post-hoc voxelwise analyses failed to detect any significant differences between risperidone and aripiprazole in the study findings, but this should be tempered by the possibility that we did not have adequate statistical power to directly compare these two antipsychotics.

The association between reduction of pallidal hyperactivation and decreases in thought disturbance may provide a clearer understanding of the therapeutic mechanism of antipsychotics. In conjunction with the association between the reduction of pallidal hyperactivation and accuracy improvement, it could be expected that task accuracy improvement was itself related to clinical improvement. Indeed, improvement in task response accuracy was significantly correlated with reductions in thought disturbance consistent with the literature (Persons and Baron, 1985). Use of mediation analysis suggested the possibility that improvement of thought disturbance by second-generation antipsychotics may be secondary, however, to the improvement of attentional control, although it is acknowledged that the sample size is small to test this effect. However, it is also conceivable that antipsychotics both improves attention and reduces thought disturbance, but greater effects on attention may facilitate the improvement in thought control.

The thalamus bilaterally showed hyperactivation in patients at the baseline timepoint (Figure 2) and significant reduction of activation at week 12 compared to baseline (Figure 3). Although improvement in task accuracy failed to show an association with activation reduction, this may be related to low statistical power. The reduction of thalamic activation by antipsychotic medication has been previously found in a visual attention task (Keedy et al., 2009). The current results replicate the reduction of thalamic activation by antipsychotics during an attention related task.

In the patient group, there were regions that showed hypoactivation at baseline compared to controls and/or increased activation at week 12 compared to baseline. For example, the left frontal pole and occipital regions showed both hypoactivation at baseline (Figure 2A) and

increased activation at week 12 (Figure 3). In a post-hoc analysis, none of these regions demonstrated a significant relationship with performance improvement. However, these regions, especially the prefrontal cortex, has been implicated in attentional control studies in schizophrenia (e.g., Ungar et al., 2010; Weiss et al., 2003).

The current results suggest that healthy individuals (Figure 1) demonstrate a practice effect, whereby their performance improved at week 12 as noted in prior work (Goldberg et al 2007). The concomitant changes in fMRI activation (Figure 3) should therefore be interpreted, at least in part, to reflect practice and/or acclimation to the scanning environment. Interestingly, the control group showed a significant and robust reduction in activation within the occipital cortex and cerebellum. Reduced occipital activation may suggest that healthy volunteers may have employed less visual processing to perform the task, although it should be acknowledged that many factors can reduce posterior activity in the occipital regions, including, for example, repeating stimuli. Reductions in cerebellum activity could be interpreted as a result of acquired motor or cognitive control. The functional connectivity of the cerebellum with cortical cognitive regions has been reported previously (Buckner et al., 2011). More specifically, involvement of the cerebellum in visual attentional control has been reported previously (Kellermann et al., 2012). Interestingly, we did not observe reductions in these regions among patients suggesting that despite improvements in behavioral accuracy, patients did not show the same pattern of brain changes in association with practice effects as healthy volunteers. Accuracy improvement without associated improvements in reaction time are consistent with a previous human study investigating dopamine depletion (Scholes et al., 2006). While the current design did not permit further investigation regarding the group contrast in practice effects, it seems likely that the underlying neurobiology regarding practice effects may differ between patients and healthy volunteers.

There were several study limitations that should be acknowledged. The relatively small sample size ($N=14$) may have limited statistical power, especially when contrasting the two antipsychotics. Moreover, we could not determine whether reductions in basal ganglia activity are acute or reflect a cumulative effect of antipsychotic medication exposure. In addition, as the current design was correlational and did not involve placebo control for ethical reasons, we cannot definitely conclude that BOLD changes observed following 12 weeks were due to antipsychotic treatment. Nonetheless, the fact that the basal ganglia contain a large amount of dopaminergic receptors is consistent with the possibility that normalization of hyperactivation and associated clinical improvements are associated with antipsychotic pharmacotherapy. Also, given that the sample was all male it was not clear whether findings would generalize to females. We also note that given patients were participating in a double blind clinical trial (ClinicalTrials.gov Identifier: NCT00320671) we were unable to investigate our results in relationship to medication dosage separately for each antipsychotic. We also acknowledge that the task utilized in this study could arguably be considered to invoke working memory in which the interference block requires subjects to keep the three maps of the stimulus to the proper button to press "online".

In sum, we report reductions in activation of the basal ganglia during attentional control by second-generation antipsychotics, and the association of these activation reductions to improvements in thought disturbance.

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Figure 1.

Accuracy and Reaction Time (with standard error bars) in Patients and Healthy Volunteers at Baseline and 12 Week Followup Timepoints

Note: Asterisks denote the following: blue = significant change in controls, red = significant increase in patients, black = significant difference between patients and controls at 12 week scan).

(A)

(B)

(C)

(D)

Figure 2. Baseline activation at $Z = 0$ slice; (A) Red/Yellow: patients higher than healthy volunteers; Blue: patients lower than healthy volunteers; (B) Right Globus Pallidus ROI; (C) Right Thalamus; (D) Left Thalamus

Figure 3.
Regions demonstrating Significant Changes in BOLD Activation in Patients and Healthy Volunteers

(A)

(B)

(C)

(D)

Figure 4.

(A) Contrast Z score in the Right Globus Pallidus. (B) Association between baseline to 12 week change in the BPRS Thought Disturbance factor (where negative values indicate improvement) and baseline to 12 week change in contrast Z score (where negative values indicate reduced activation) in the Right Globus Pallidus. (C) Association between baseline to 12 week improvement in the BPRS Unusual Thought Content item and baseline to 12 week change in contrast Z score in the Right Globus Pallidus. (D) Association between baseline to 12 week change in the BPRS Thought Disturbance factor and baseline to 12 week change in response accuracy in the Interference condition.

Table 1

Sample Characteristics

	Patients (<i>n</i> =14)		Controls (<i>n</i> =14)		t-test
	Mean	SD	Mean	SD	
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	$t = 0.53, p = 0.60$

Table 2

Brief Psychiatric Rating Scale Clinical Evaluation

	Total	Thought Disturbance	Hostility- Suspiciousness	Anxiety- Depression
Baseline	51.86	11.00	9.71	9.50
(SD)	10.10	2.60	4.01	2.18
12 week	31.00	4.86	5.64	4.86
(SD)	6.86	1.75	1.95	1.83

Table 3

Behavioral Results

	Accuracy (% correct)		Reaction Time (msecs)
Patients	baseline	82.79	882.10 $t(13) = 1.47$ $p = 0.1$
	12 week	89.14	825.71
Controls	baseline	88.57	864.52 $t(13) = 3.32$ $p = 0.0056$
	12 week	94.64	703.32

Table 4

Regions Demonstrating 12 Week Changes in BOLD Activation in Patients

	Number of Voxels	P	Z-MAX	MNI			Region
				Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	
Decrease in 12 weeks	48996	3.64E-15	7.88	27	0	57	Superior Frontal Gyrus
	12049	1.37E-06	7.03	45	-31	51	Post Central Gyrus
	9078	1.26E-05	6.21	-12	-18	1	Left Thalamus
			5.74	11	-20	1	Right Thalamus
			4.83	26	-6	0	Right Globus Pallidus
			4.79	1	-27	-12	Brain Stem
			4.76	-4	-28	-12	Brain Stem
			4.54	15	-12	9	Right Thalamus
	8544	0.0000191	5.91	50	2	35	Right Precentral Gyrus
	7245	0.000055	5.95	15	-52	-19	Cerebellum
	6939	0.0000712	6.7	36	35	24	Right Frontal Pole
	6486	0.000105	6.13	-53	0	-8	Left Central Opercular Cortex
	1205	0.0309	5.53	-36	-53	-31	Cerebellum
Increase in 12 weeks	2887	0.00356	5.32	-49	-63	25	Left Lateral Occipital Cortex
	1932	0.0113	5.57	-10	27	59	Left Superior Frontal
	1729	0.0147	5.05	-14	59	28	Left Frontal Pole