Neural Effects of Ziprasidone Monotherapy in First-Episode Schizophrenia: A Longitudinal Study using fMRI and a Procedural Learning Paradigm

Veena Kumari [1], Anantha P. P. Anilkumar [2], Dominic H. ffytche [3], Ravi Mehrotra [2], Martina T. Mitterschiffthaler [3], Tonmoy Sharma [4]

Abstract

Introduction: Deficient procedural learning (PL) and lack of striato-thalamic-cortical activity in chronic schizophrenia patients on typical antipsychotics, compared to healthy people, has been previously demonstrated. There is also evidence of striatal dysfunctioning with normal or near-normal performance in schizophrenia patients treated mostly or predominantly with atypical antipsychotics. The purpose of this study was to examine procedural learning and its neural correlates, as well as the effect of ziprasidone monotherapy on neural responses using functional magnetic resonance imaging (fMRI) and a relatively simple non-verbal, sequence-learning task in a longitudinal design in first-episode patients with schizophrenia. **Methods:** A cohort of patients who were experiencing their first psychotic episode and had no or minimum exposure to antipsychotic medication underwent blood oxygenation level-dependent fMRI during a blocked, periodic procedural learning task at baseline (pretreatment) and again after six-week ziprasidone monotherapy. Behavioral data were recorded online. **Results:** We found 1) procedural learning in patients, but with a different pattern to that normally seen in healthy people, and abnormal, rather than absent, activity in the striatal region in patients at baseline; and 2) changes towards normalization of the procedural learning pattern and increased neural activity in a number of regions, including cingulate gyrus, caudate nucleus, thalamus and temporal lobe, following ziprasidone monotherapy. **Conclusions:** First-episode schizophrenia patients are characterized by aberrant, rather than absent, procedural learning and brain activity, which change towards normalization with six-week ziprasidone monotherapy.

Key Words: Psychosis, Striatum, Thalamus, Temporal Lobe, Brain Activity, Antipsychotics

[1]Department of Psychology, Institute of Psychiatry, King's College London
[2]Department of Psychological Medicine, Institute of Psychiatry, King's College London
[3]Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London
[4]The Cognition Group, Newark, Delaware

Address for correspondence: Veena Kumari, PhD, Department of Psychology, P078, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, U.K.
Phone: +44 207 848 0233; Fax: +44 207 848 0860;
E-mail: v.kumari@iop.kcl.ac.uk

Submitted: October 8, 2007; Revised: November 13, 2007; Accepted: November 15, 2007

Introduction

Schizophrenia is associated with functional abnormalities of the cortical, as well as sub-cortical regions (1), even at illness onset (review, 2). Antipsychotic medication may impact on some brain structures and functions. Studies investigating the effects of antipsychotic medication on brain functions in patients, relative to healthy people, have generally shown a change with medication towards normalization (reviews, 3, 4; 5-7), though occasionally studies have failed to detect any effect of medication (8), or have found that treatment with haloperidol, a typical antipsychotic, may have led to the basal ganglia dysfunction (9). Studies of chronic as well as first-episode patients indicate that atypical antipsychotics may have greater normalizing effects on brain functions than typical antipsychotics (3, 10).

In this study we examined the neural effects of six-week ziprasidone monotherapy using functional magnetic resonance imaging (fMRI), a within-subjects design, and an established procedural learning (PL) paradigm in a group of first-episode schizophrenia patients. Ziprasidone is an atypical antipsychotic. It is a potent antagonist at the serotonergic 5HT1D, 5HT2A, 5HT2C and the dopaminergic D2 receptors and an agonist at the 5HT1A receptor. Its affinity for the noradrenergic alpha-1 and the histaminergic H1 receptors is moderate, with negligible affinity for the muscarinic acetylcholine M1 receptor (11). Positron emission tomography (PET) studies have shown considerably greater 5HT2 than D2 occupancy with ziprasidone at therapeutic doses (85% and 65%, respectively [12]; 76% and 56%, respectively [13]). Ziprasidone has shown therapeutic efficacy and a favorable safety, tolerability, and toxicity profile in schizophrenia (14). Recent studies suggest improvement of similar magnitude with ziprasidone to that of olanzapine on a range of cognitive functions in acutely ill patients with schizophrenia or schizoaffective disorder (15, 16). A very recent study (17) has shown that a switch from previous treatment with risperidone, olanzapine, or conventional antipsychotics to open-level ziprasidone produces clinical remission in 50%, and cognitive improvement by 0.05 standard deviation (SD) in 20% of patients with schizophrenia.

Procedural learning (PL) is a form of skill acquisition in which improvement occurs as a function of practice on task, without the need for conscious awareness of the learned skill or routine (18, 19). The brain structures known to have important roles to play in PL are the basal ganglia, in particular the striatum, cerebellum and the frontal lobes (20-29).

There have been previous investigations of antipsychotic effects on PL in schizophrenia. Chronic patients medicated with olanzapine are reported to show preserved PL on the Tower of Toronto test, while those treated with haloperidol or risperidone show deteriorated PL after six months of sustained treatment (30). Six-week clozapine treatment is found to improve PL on the Tower of Toronto test in patients previously treated with typical antipsychotics (31). Haloperidol-treated but not olanzapine-treated patients have been found to show reduced PL on a visual tracking task, which in turn correlates with striatal D2-receptor occupancy (32). Procedural learning on the sequence learning task (serial reaction task [SRT]) has also been found to be impaired in chronic, mostly treated with typical antipsychotics, schizophrenia patients (e.g., 27, 33, 34). Procedural learning, indexed by mirror drawing performance, has been found to be relatively intact in drug-naive and clozapine-treated patients, compared to those treated with typical antipsychotics (35, 36). In another study (37), neuroleptic-naive patients showed comparable mean PL on the mirror drawing task to that shown by healthy people, but with lower learning smoothness (i.e., performance improvement over trials). These previous findings, together with findings of impaired PL after the administration of dopamine-D2 blocking agents in healthy people (38), suggest that typical antipsychotics may contribute to impaired PL in schizophrenia patients, most likely via their strong dopamine-D2 blocking actions in the striatum. However, basal ganglia abnormalities have been reported in patients with no prior exposure to antipsychotics (39-42), which may also contribute to disturbances in striatal-based PL (43, 44). Very recently, an acute symptomatic state has been linked to PL deficit in schizophrenia (45).

There have been three previous fMRI studies of PL in schizophrenia (27-29). All of these studies used variants of the SRT, and examined brain activity during random (control) and pattern (experimental) blocks, relative to each other, with participants required to follow as quickly as possible a target which moved randomly during the random blocks and in a predetermined sequence during the pattern blocks. The first study (27) revealed lack of PL and striato-thalamic-cortico-cerebellar dysfunction in chronic patients (n=6), all of whom were treated with typical antipsychotics, relative to healthy people (n=6). The second study (28) examined mostly chronic patients on atypical antipsychotics (n=10) relative to healthy controls (n=10) and observed less striatal activity in association with normal PL in the patient group. The patients also showed an idiosyncratic pattern of activity in that they activated the frontal cortex more during the random than pattern blocks. The third study (29) also examined chronic patients medicated mostly with atypical antipsychotics (n=10; 4 clozapine, 1 risperidone, 2 quetiapine, 2 quetiapine and typical antipsychotics, 1 olanzapine and typical antipsychotics) relative to healthy controls. This study observed near-normal PL, but reduced activity bilaterally in the frontal cortex, left parietal cortex and bilateral caudate regions, and greater activity in the right temporal cortex, right anterior cingulate and left globus pallidus; hypoactivations were considered to reflect disease-related effects and hyperactivations as compensatory mechanisms facilitating near-normal performance in patients. Interestingly, this study also noted increased frontal activity in patients during the random, relative to pattern, blocks. Very recently, an fMRI study by Woodward and colleagues (46) has reported less activity in the frontal, parietal and basal ganglia regions with normal performance in unaffected siblings of patients with schizophrenia; this study suggests that some neural abnormalities detected during procedural learning performance in the patient groups may be genetically mediated. Importantly, siblings like the patients in two previous studies (28, 29) also showed increased frontal activity during the random, relative to pattern, blocks.

There is no previous imaging investigation of the effects of ziprasidone using an activation paradigm in first-episode

or chronic schizophrenia patients. Based on separate strands of previous literature on PL, functional imaging of antipsychotic treatments (3-7, 10), and efficacy of ziprasidone treatment in schizophrenia (15-17), our initial hypotheses were that: 1) antipsychotic-naive, first-episode patients would show at least some, if not significant, PL at baseline; and 2) neural activity in relevant regions would remain unchanged or would improve with ziprasidone monotherapy.

Method and Materials

Subjects and Design

Twelve patients meeting the criteria for a diagnosis of schizophrenia using the Structured Clinical Interview for the DSM-IV (SCID) (47) and consenting to participate in a longitudinal study involving neuroimaging and clinical investigations before (baseline) and after six-week ziprasidone monotherapy were recruited from the inpatient and outpatient services within and around London, U.K. All patients were in their first psychotic episode and unmedicated at the time of their participation. There were no pregnant or lactating women.

Eight of the initial twelve patients provided usable behavioral and fMRI data at baseline. The final patient sample consisted of six patients (2 men, 4 women; mean age=29.33 years, SD=12.89) who remained in the study with continued consent, agreed to be rescanned after they had received ziprasidone for six weeks, provided usable data on both occasions, and retained the diagnosis of schizophrenia at one year since the initial diagnosis. The behavioral data in a group of six healthy subjects (mean age=31.83 years, SD=4.88) from a previous study (27) were utilized in patient-versus-healthy people baseline comparison. The fMRI data from this healthy group could not be utilized because of an unavoidable difference between the imaging protocols of the two studies.

The study procedures were approved by the Ethics Committee of the Institute of Psychiatry and the South London and Maudsley NHS Trust. All patients gave their written informed consent after the study procedures had been fully explained to them.

Clinical Assessments

Symptoms were rated within four days of scanning using the Positive and Negative Syndrome Scale (PANSS) (48) on both occasions. Side effects were also recorded within four days of scanning using the Barnes Akathisia Scale (49).

Drug Dose and Administration

All patients were first placed on a 20 mg bd dose, and those responding clinically remained on this dose throughout the study. Patients were seen by a psychiatrist on a weekly basis and, for those not responding to 20 mg bd dose, the dose was increased to 40 mg bd and 60 mg bd, and then 80 mg bd depending on their clinical response. Patients remained on the dose to which they responded clinically. For six patients in the final sample, the final doses were: one patient 40 mg/day, one patient 60 mg/day, two patients 80 mg/day, one patient 100 mg/day, and one patient 160 mg/day. None of the patients displayed significant side effects at the final dose, thus no need was felt to put them back to a relatively lower dose.

Experimental Design and Procedure

All subjects performed a five-minute sequence learning task in a blocked periodic AB design, which was exactly the same as used previously (27) while undergoing fMRI. The task consisted of two 30-second (s) alternating conditions: blocks of random trials (control condition) and blocks of pattern trials (experimental condition). In total, there were five blocks of random trials and five blocks of pattern trials. Patients were presented with a white target stimulus (an asterisk) on a black screen, viewed via a prismatic mirror fitted in the radio frequency head coil, as they lay in the scanner. This target moved between four locations on the screen, which was divided into four equal quadrants by two intersecting white lines. The target movements during the pattern trials were predictable for 75% of cases, i.e., determined following three specific rules: 1) a horizontal target movement was followed by a vertical target movement; 2) a vertical target movement was followed by a diagonal target movement; 3) a diagonal target movement was followed by a horizontal movement. The fourth movement of the target during the pattern trials was unpredictable, which then was followed by these three specific rules.

Patients were not told of the existence of specific rules governing the target movements during the pattern blocks, and the beginning of random and pattern blocks was not marked in any way. They were asked to follow each target movement with their right hand as fast as possible using a magnetic resonance (MR) compatible key pad with four keys, each key corresponding to one of the four quadrants. The movement of the target was initiated by the subjects touching the target key. Reaction times were recorded online.

Prior to scanning, all patients underwent a practice session during which they practiced on five 30-s blocks of random trials and five 30-s blocks of pattern trials, both alternated with 30-s rest periods. It was felt that patients would require exposure to the task and the button pad prior to being exposed to them in the scanner.

Image Acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Sigma system (General Electric, Milwaukee WI, U.S.) at the Maudsley Hospital, London. Daily quality assurance was carried out to ensure high signal to ghost ratio, consis-

tent high signal to noise ratio and excellent temporal stability using an automated quality control procedure (50). A quadrature birdcage head coil was used for radio frequency (RF) transmission and reception. In each of 16 near-axial, noncontiguous planes parallel to the intercommissural (AC-PC) plane, 100 T2*-weighted MR images depicting blood oxygenation level-dependent (BOLD) contrast (51) were acquired over the 5-minute experiment with echo time (TE)=40 milliseconds (ms), repetition time (TR)=3 s, inplane resolution=3.1 mm, slice thickness=7.0 mm, and interslice gap=0.7 mm. Head movement was limited by foam padding within the head coil and a restraining band across the forehead. At the same session, a high resolution 3-D inversion recovery prepared spoiled GRASS volume dataset was acquired in the AC-PC plane with TE=5.3 ms, inversion time (TI)=300 ms, TR=12.2 s, inplane resolution=0.94 mm, and slice thickness=1.5 mm.

Data Analysis

Behavioral and Clinical Measures

The difference between the mean reaction times to random and pattern trials reflects PL. Procedural learning in patients at baseline relative to healthy people was examined using a three-way Group (patients, healthy subjects) x Trial Type (random, pattern) x Block (five 30-s blocks of random and pattern trials) analysis of variance (ANOVA).

The focus of our study was on the neural effects of ziprasidone; the study was not powered to detect a significant effect of ziprasidone at the behavioral level. Nonetheless, we explored possible effects of ziprasidone monotherapy on PL using a repeated-measure ANOVA involving the Time (baseline, following ziprasidone monotherapy) x Trial Type x Block factors.

The clinical data on positive symptoms, negative symptoms, general psychopathology, total PANSS scores and side effects measures (separately) were examined using paired t-tests.

All analyses were performed by SPSS (Windows version 15.0). Effects sizes, where reported, are partial eta squared (i.e., the proportion of variance associated with a factor). Alpha level for testing significance of effects was p=0.05 unless stated otherwise.

Functional MRI

Image Pre-Processing

For each subject, the one-hundred volume functional time series was motion corrected (52), transformed into stereotactic space, spatially smoothed with a 10 mm FWHM Gaussian filter and band pass filtered using statistical parametric mapping software. (SPM99; http://www.fil.ion.ucl.ac.uk/spm).

Models and Statistical Inferences

Data were analyzed using a two-stage random effect procedure (53). The first stage identified subject-specific activations. This analysis consisted of a 30-s boxcar (convolved with the hemodynamic response function) modeling the experimental condition (pattern trials). The control condition (random trials) formed the model's implicit baseline. The second stage of the random effect model tested for generic activations across subject-specific images using a one-sample t-test for baseline and follow-up activations. Finally, the neural effects of six-week ziprasidone monotherapy were examined using paired-sample t-tests. Significance was assessed using a correction for multiple comparisons at the cluster level ($p<0.05$; maps thresholded at $p=0.005$).

We also extracted subject-specific values representing the degree of change in peak voxel of the regions showing an increase from baseline to follow-up scans and explored (within SPSS) their associations with the degree of PL (% advantage in random trials [RT]) using Pearson's r.

Results

Patients showed reduced symptoms after ziprasidone therapy, relative to baseline, but no significant change occurred in side-effect ratings (see Table 1).

Table 1 Symptoms and Side Effects at Baseline and Following Six Weeks of Ziprasidone Therapy

	Baseline (SD)	Following Ziprasidone Therapy (SD)	*t*	*p*
PANSS: Positive symptoms	25.00 (3.03)	16.50 (4.13)	6.62	**0.001**
PANSS: Negative symptoms	20.83 (5.04)	19.00 (6.39)	0.99	0.37
PANSS: General psychopathology	52.83 (8.70)	43.67 (8.70)	3.04	**0.03**
PANSS: Total	97.00 (13.64)	79.33 (17.66)	5.01	**0.004**
BAS: Objective	0.00 (0.00)	0.33 (0.52)	1.58	0.18
BAS: Subjective awareness of restlessness	0.17 (0.41)	0.17 (0.41)	0.00	1.00
BAS: Subjective distress relates to restlessness	0.17 (0.41)	0.17 (0.41)	0.00	1.00
BAS: Global clinical assessment of akathisia	0.00 (0.00)	0.33 (0.52)	1.58	0.18
BAS: Total	0.33 (0.82)	1.00 (1.67)	0.79	0.47

SD=standard deviation; PANSS=Positive and Negative Syndrome Scale; BAS=Barnes Akathisia Scale

Procedural Learning: Behavioral Measures

Baseline Comparisons

The results revealed comparable PL, on average, in both healthy and patient groups (Trial Type: F=5.42, df=1,40; p=0.04, eta^2=0.352). There was no effect of Group (F=0.15) or a Group x Trial Type interaction (F=0.69). The pattern of learning over the experiment, however, appeared different in patients. While healthy people showed increased and stable PL over successive blocks of trials on this task (27, 38), first-episode patients showed decreased PL over the experiment due to increasing reaction times over successive blocks of pattern trials. This effect was apparent (see Figure 1) although the Group x Trial Type x Block interaction failed to attain formal statistical significance (F [4, 40]=1.79, df=1,40; p=0.15) due to a small sample size (effect size, eta^2=0.15).

Effects of Ziprasidone Monotherapy

There was significant PL over the two sessions (Trial Type: F=6.44, df=1,20; p=0.05). However, unlike the pattern of learning shown by patients at baseline, the pattern following ziprasidone monotherapy closely resembled that in healthy people. This effect was apparent (see Figure 1) with a moderate effect size (eta^2=0.28) though not formally significant due to a small number of participants (Time x Trial Type x Block: F=1.96, df=4,20; p=0.14).

Procedural Learning: fMRI

Baseline Activations

At baseline, patients showed increased activity in association with PL (pattern>random) in only one cluster that was located in the occipital lobe (Brodmann area [BA] 18, peak 2, -90, -2 [x, y, z]; t=20.15; number of contiguous voxels=745; uncorrected p=0.014), but even this failed to survive correction for multiple comparisons (see Figure 2, top panel).

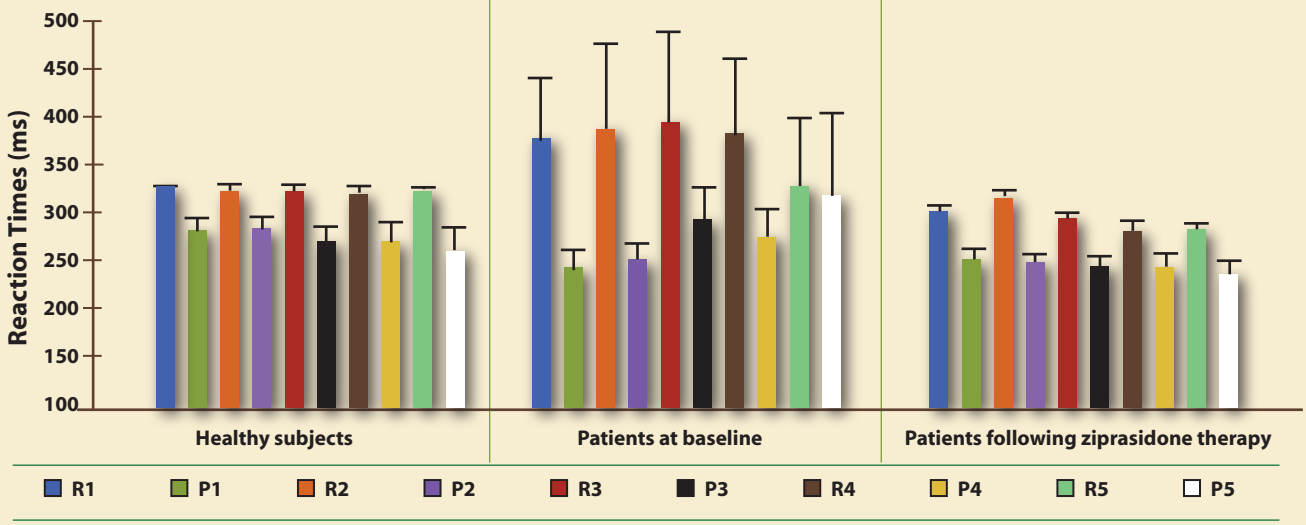
Patients, however, showed significant activations in the striatum, including parts of both the caudate nucleus and putamen (peak 10, 18, 2; t=13.64; number of contiguous voxels=378; corrected p<0.001), middle temporal gyrus (BA21, peak -58, -34, 0; t=11.84; number of contiguous voxels=184; corrected p=0.04), and anterior cingulate (BA24, peak -12, 44, 6; t=8.62; number of contiguous voxels=391; corrected p<0.001) in association with random (relative to pattern) trials (see Figure 2, top panel).

Activations after Six-Week Ziprasidone Monotherapy

On the second occasion, patients showed significant activity in association with PL (pattern>random) in a very large cluster with peak in the anterior-middle cingulate (BA24, -28, -18, 38; t=24.44; number of contiguous voxels= 11,772; corrected p<0.001), and subpeaks in the middle temporal gyrus (BA21, 44, -46, -4; t=22.64) and putamen (28, -14, 6; t=22.17). This cluster extended to further areas including parts of the insula and the inferior frontal cortex (see Figure 2, bottom panel).

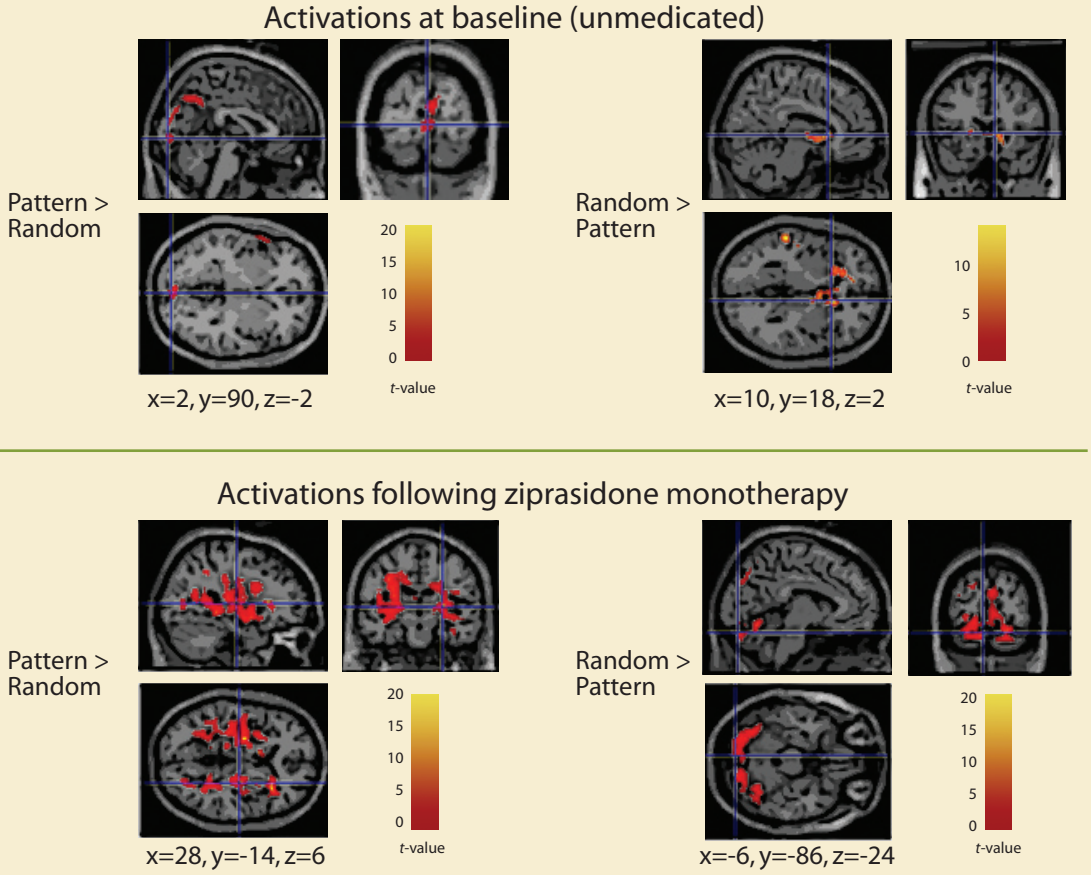
Only one cluster located in the visual cortex (peak: BA19, -8, -78, 40; t=20.18; number of contiguous voxels=3,992; corrected p<0.001; subpeaks: BA19, 18, -72, 32; t=11.45; and cerebellum, -6, -86, -24; t=10.34) showed significant activity in association with random (relative to pattern) trials.

Figure 1 Mean Reaction Times



Mean (+1 SEM) reaction times (ms) over random (R1-R5; Blocks 1 to 5 of random trials) and pattern trials (P1-P5; Blocks 1 to 5 of pattern trials) in healthy subjects and patients with schizophrenia at baseline and after six weeks of ziprasidone monotherapy.

Figure 2 **Activations at Baseline versus Activations following Ziprasidone Monotherapy**



Brain regions showing significant task-related activity at baseline and after six weeks of ziprasidone monotherapy. The colors represent SPM derived *t*-values as shown individually for each image. Left hemisphere is shown on the left of the axial view.

Activation Changes from Baseline to Following Ziprasidone Monotherapy

There was increased activity in several regions, including parts of the caudate nucleus, putamen, thalamus, insula, anterior and posterior cingulate and middle temporal gyrus following ziprasidone monotherapy, relative to baseline, in association with PL (pattern>random contrast) (detailed in Table 2; Figure 3). Of all these regions, increases in the left posterior cingulate (r=0.622), the left anterior cingulate (this cluster extended to the thalamus) (r=0.691) and the right middle temporal gyrus (r=0.732) showed direct positive association with PL advantage; the increase in other regions had weaker relationships (r<0.60). No region showed a significant decrease in activity with ziprasidone therapy.

Discussion

The main findings of this study were: 1) at baseline, first-episode patients were not significantly different from healthy subjects in mean PL, but they seemed to show a reduced rate of learning over the five-minute experiment and did not show significant brain activity in association with PL (i.e., pattern trials>random trials) which, at least in part, was due to greater activity in some of the PL-relevant regions, especially the striatum, during the control (random trials) condition itself; and 2) the pattern of PL over the experiment changed towards normalization, and there was robust evidence of increased neural activity in a number of PL-relevant regions, including the anterior and posterior cingulate, caudate nucleus and thalamus after ziprasidone monotherapy.

Our behavioral results at baseline, although not directly comparable due to procedural differences, appear in line with the observation of reduced learning smoothness with normal mean PL in antipsychotic-naive patients reported by Scherer and colleagues (37). We previously observed faster acquisition of PL on a longer version of the same task as used in the present study in amphetamine-treated healthy subjects compared to those treated with a placebo (38). This, coupled with the well-known hypothesis that positive psychotic symptoms of schizophrenia reflect overactivity in

Table 2 Brain Regions Showing a Significant Increase in Activity following Six Weeks of Ziprasidone Monotherapy Relative to Baseline (no region showed a significant decrease)

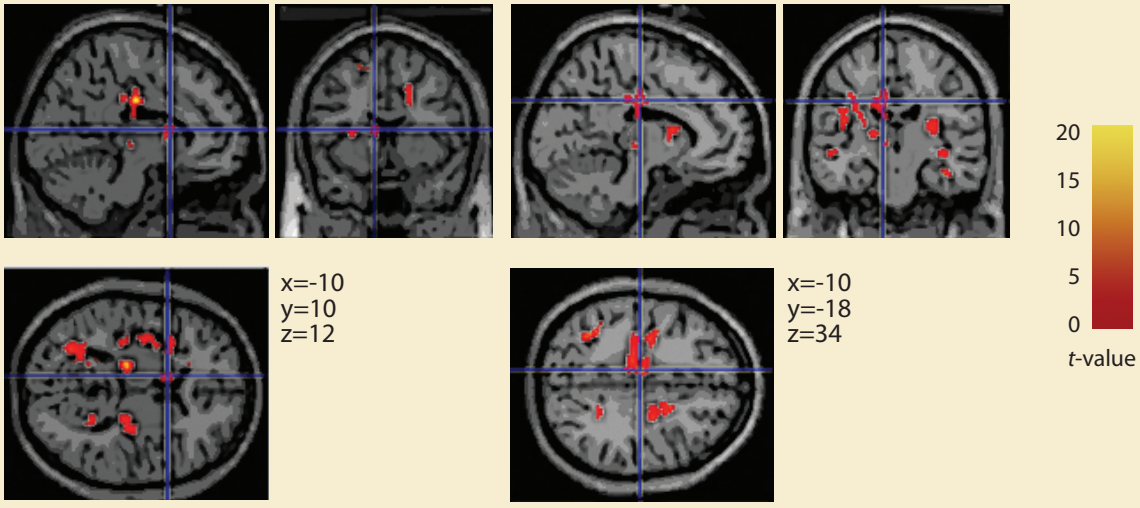
Region (Brodmann Area - BA)	Side	MNI Coordinates of Regional Peak and Subpeaks	t-Value	Number of Contiguous Voxels	Cluster Corrected p
Posterior cingulate (BA23/30) Supramarginal gyrus (BA40) Middle occipital gyrus (BA19)	Left	-22 -52 18 -34 -58 32 -30 -68 14	18.09 9.48 7.32	488	<0.001
Posterior cingulate (BA23/30) Supramarginal gyrus (BA40)	Right	22 -50 18 14 -48 18 36 -48 28	9.40 7.46 6.91	345	<0.001
Cingulate gyrus (BA24) Thalamus Precentral gyrus (BA6)	Left	-10 -18 34 -18 -22 12 -38 -4 36	17.50 12.78 11.87	764	<0.001
Cingulate gyrus (BA24)	Right	20 8 34 26 -6 34	8.11 7.50	179	0.001
Middle temporal gyrus (BA21) Post-central gyrus (BA4)	Left	-58 -30 0 -52 -24 -6 -42 -20 20	13.22 9.23 8.19	492	<0.001
Middle temporal gyrus (BA21)	Right	40 -22 -6 32 -26 6	11.94 9.31	1,012	<0.001
Putamen Insula	Left	-26 14 8 -34 14 12	6.50 5.73	74	0.015
Caudate nucleus	Left	-10 10 12	7.74	68	0.018

MNI=Montreal Neurological Institute

dopaminergic systems (reviews, 54, 55), may offer possible mechanisms for the present findings of aberrant patterns of PL in patients at baseline. Specifically, the pattern of PL at baseline may be associated with somewhat faster PL initially in first-episode patients than in healthy people resulting from the practice session itself (see Block 1; Figure 1), and then perhaps their consciously or unconsciously searching for/imagining "specific patterns" in the random trials condition driven by the presence of paranoia and other positive symptoms. This, if true, may make the patients rather slow to respond to random trials, rather than allowing a faster response to pattern trials, over the experiment. This possibility also accommodates the finding of increased activity in the striatal and anterior cingulate regions during the random (relative to pattern) trials, and not during the pattern (relative to random) trials, at baseline. However, as mentioned in the introduction, increased anterior cingulate/frontal activity during the random relative to pattern blocks has also been found in medicated patients (28, 29), as well as in unaffected relatives of schizophrenia patients (46) with normal/near-normal performance. The idiosyncratic pattern of increased cortical activity during the random relative to pattern blocks, therefore, as suggested previously by Woodward et al. (46), may be associated with a predisposition to schizophrenia while striatal dysfunction may be state/illness related. The patients in the study by Reiss et al. (28) had also shown nonsignificantly greater activity in the left caudate during the random, relative to the pattern, condition.

Supporting our hypothesis, six-week ziprasidone monotherapy did not disrupt PL. The pattern of learning after ziprasidone monotherapy in patients closely resembled that shown by healthy people (Figure 1). This effect is likely to be related to the clinical improvement with ziprasidone and relatively less dopamine blockade than with typical antipsychotics, especially haloperidol (56). At follow up, there was increased fMRI activity (relative to baseline) in the striatal, thalamic, insular, cingulate, temporal and sensorimotor regions. Importantly, these areas, except the temporal lobe, were activated with this task in healthy people in our previous study (27). Furthermore, fMRI responses in the striatum, thalamus, cingulate gyrus and BA6 were related to the magnitude of PL in healthy people in our previous study (27). Thus, our findings demonstrate, to a large extent, activation changes towards normalization following ziprasidone

Figure 3 **Significant Neural Increases following Ziprasidone Monotherapy in Association with Procedural Learning**



Brain regions showing significant increases in activity in association with PL (pattern>random trials) following six weeks of ziprasidone monotherapy relative to baseline. The colors represent SPM derived *t*-values as shown individually for each image. Left hemisphere is shown on the left of the axial view.

therapy. The observed fMRI changes, however, may reflect clinical improvement (relapsed to more stable state) rather than anything specific to ziprasidone and/or its mechanism of action. Short-term treatment with quetiapine, another second-generation atypical antipsychotic, has also been reported to normalize anterior cingulate activity in medication-naive schizophrenia patients (5). We had not seen temporal lobe activity with this task in healthy people, or in a group of chronic patients who also displayed impaired PL, in our previous study (27). However, Zedkova and colleagues (29) recently reported increased (relative to healthy people) right temporal activity (BA38) in patients who displayed near-normal PL and suggested this effect represented a compensatory mechanism facilitating near-normal performance in the face of disease-related deficits in other PL-relevant brain regions. We speculate that increased temporal activity following ziprasidone therapy and normalized pattern of PL in our study also reflects a compensatory mechanism. Although the peak of activity increases in the temporal lobe in our study was located in BA21, it did extend to BA38 when examined at a slightly lower threshold, and also had the strongest (of all regions showing an increase) positive correlation with PL advantage at follow up.

The findings of (at least partial) normalization of PL and related neural activity with clinical improvement after ziprasidone monotherapy have implications for the management of schizophrenic illness. Procedural learning has been suggested as a facilitator of activities of daily living (57) and very recently was reported to be predictive of social skills in schizophrenia (58).

Our study has some limitations. First, the study sample was not powered enough to detect significant differences between the pre- and post-ziprasidone PL patterns at the behavioral level, and was too small to allow generalization of our findings to the first-episode schizophrenia population on the whole. However, our final sample size was not substantially different from those reported in other imaging studies of drug treatments in schizophrenia, the study employed a within-subjects design, and our fMRI results are very robust. Second, the study did not have a control arm. In an ideal world, it should have included a placebo-treated group of first-episode patients as the control arm, but this would be unethical in a clinical setting over the required time scale. An equal number of healthy controls could have been treated with the same protocol. The effect of drug administration or time on healthy controls, however, may have been completely different, and perhaps not added a much greater understanding of the neural effects of ziprasidone in patients.

Conclusions

In conclusion, this study demonstrates that first-episode schizophrenia patients are characterized by aberrant, rather than absent, PL and striatal activity. Six-week ziprasidone monotherapy produced clinical improvement and robust changes in neural activity in a number of regions, including the anterior and posterior cingulate, caudate nucleus and thalamus, all of which are found to be activated with this

task in healthy people. Further studies are required to establish whether a longer (than six weeks) duration of ziprasidone therapy will not cause deterioration in PL, as has been shown to be the case for risperidone (but not olanzapine) with six-month sustained treatment (30). Given the significance of PL in activities of daily living and social skills, it is important to establish the longer term effect of ziprasidone on PL in schizophrenia, and to avoid treating this illness with antipsychotics, which may impair this kind of learning in the long run.

Acknowledgments

The study was supported by an unrestricted grant from Pfizer Inc. VK is supported by the Wellcome Trust Senior Research Fellowship in Basic Biomedical Science (067427/427/Z/02/Z).

References

1. Callicott JH. An expanded role for functional neuroimaging in schizophrenia. Curr Opin Neurobiol 2003;13(2):256-260.
2. Sharma T, Kumari V. Structural and functional brain abnormalities in first episode schizophrenia. In: Sharma T, Harvey P, editors. The early course of schizophrenia. New York: Oxford University Press; 2006. p. 111-130.
3. Davis CE, Jeste DV, Eyler LT. Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. Schizophr Res 2005;78(1):45-60.
4. Kumari V, Cooke M. Use of magnetic resonance imaging in tracking the course and treatment of schizophrenia. Expert Rev Neurother 2006;6(7):1005-1016.
5. Stip E, Fahim C, Mancini-Marie A, Bentaleb LA, Mensour B, Mendrek A, et al. Restoration of frontal activation during a treatment with quetiapine: an fMRI study of blunted affect in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(1):21-26.
6. Snitz BE, MacDonald A 3rd, Cohen JD, Cho RY, Becker T, Carter CS. Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. Am J Psychiatry 2005;162(12):2322-2329.
7. Meisenzahl EM, Scheuerecker J, Zipse M, Ufer S, Wiesmann M, Frodl T, et al. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. Eur Arch Psychiatry Clin Neurosci 2006;256(8):522-531.
8. Gur RE, Resnick SM, Gur RC, Alavi A, Caroff S, Kushner M, et al. Regional brain function in schizophrenia. II. Repeated evaluation with positron emission tomography. Arch Gen Psychiatry 1987;44(2):126-129.
9. Corson PW, O'Leary DS, Miller DD, Andreasen NC. The effects of neuroleptic medications on basal ganglia blood flow in schizophreniform disorders: a comparison between the neuroleptic-naive and medicated states. Biol Psychiatry 2002;52(9):855-862.
10. Kumari V, Antonova E, Geyer MA, Ffytche D, Williams SC, Sharma T. An fMRI investigation of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics. Int J Neuropsychopharmacol 2007;10(4):463-477.
11. Tandon R, Harrigan EP, Zorn SH. Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. J Serotonin Res 1997;4:159-177.
12. Fischman AJ, Bonab AA, Babich JW, Alpert NM, Rauch SL, Elmaleh DR, et al. Positron emission tomographic analysis of central 5-hydroxytryptamine2 receptor occupancy in healthy volunteers treated with the novel antipsychotic agent, ziprasidone. J Pharmacol Exp Ther 1996;279(2):939-947.
13. Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F, et al. A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. Am J Psychiatry 2004;161(5):818-825.
14. Nemeroff CB, Lieberman JA, Weiden PJ, Harvey PD, Newcomer JW, Schatzberg AF, et al. From clinical research to clinical practice: a 4-year review of ziprasidone. CNS Spectr 2005;10(11):s1-20.
15. Harvey PD, Meltzer H, Simpson GM, Potkin SG, Loebel A, Siu C, et al. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. Schizophr Res 2004;66(2-3):101-113.
16. Harvey PD, Siu CO, Romano S. Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Psychopharmacology (Berl) 2004;172(3):324-332.
17. Buckley PF, Harvey PD, Bowie CR, Loebel A. The relationship between symptomatic remission and neuropsychological improvement in schizophrenia patients switched to treatment with ziprasidone. Schizophr Res 2007;94(1-3):99-106.
18. Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science 1980;210(4466):207-210.
19. Squire LR, Zola-Morgan S. Memory: brain systems and behavior. Trends Neurosci 1988;11(4):170-175.
20. Heindel WC, Butters N, Salmon DP. Impaired learning of a motor skill in patients with Huntington's disease. Behav Neurosci 1988;102(1):141-147.
21. Knopman D, Nissen MJ. Procedural learning is impaired in Huntington's disease: evidence from the serial reaction time task. Neuropsychologia 1991;29(3):245-254.
22. Grafton ST, Mazziotta JC, Presty S, Friston KJ, Frackowiak RS, Phelps ME. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J Neurosci 1992;12(7):2542-2548.

23. Pascual-Leone A, Grafman J, Clark K, Stewart M, Massaquoi S, Lou JS, et al. Procedural learning in Parkinson's disease and cerebellar degeneration. Ann Neurol 1993;34(4):594-602.

24. Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science 1996;273(5280):1399-1402.

25. Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur J Neurosci 1996;8(4):637-648.

26. Hikosaka O, Nakahara H, Rand MK, Sakai K, Lu X, Nakamura K, et al. Parallel neural networks for learning sequential procedures. Trends Neurosci 1999;22(10):464-471.

27. Kumari V, Gray JA, Honey GD, Soni W, Bullmore ET, Williams SC, et al. Procedural learning in schizophrenia: a functional magnetic resonance imaging investigation. Schizophr Res 2002;57(1):97-107.

28. Reiss JP, Campbell DW, Leslie WD, Paulus MP, Ryner LN, Polimeni JO, et al. Deficit in schizophrenia to recruit the striatum in implicit learning: a functional magnetic resonance imaging investigation. Schizophr Res 2006;87(1-3):127-137.

29. Zedkova L, Woodward ND, Harding I, Tibbo PG, Purdon SE. Procedural learning in schizophrenia investigated with functional magnetic resonance imaging. Schizophr Res 2006;88(1-3):198-207.

30. Purdon SE, Woodward N, Lindborg SR, Stip E. Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol. Psychopharmacology (Berl) 2003;169(3-4):390-397.

31. Purdon SE, Woodward ND, Mintz A, LaBelle A. Procedural learning improvements after six weeks of clozapine treatment. Schizophr Res 2002;53(1-2):165-166.

32. Paquet F, Soucy JP, Stip E, Levesque M, Elie A, Bedard MA. Comparison between olanzapine and haloperidol on procedural learning and the relationship with striatal D2 receptor occupancy in schizophrenia. J Neuropsychiatry Clin Neurosci 2004;16(1):47-56.

33. Green MF, Kern KS, Williams O, McGurk S, Kee K. Procedural learning in schizophrenia: evidence from serial reaction time. Cognit Neuropsychiatry 1997;2(2):123-134.

34. Kern RS, Green MF, Marshall BD Jr, Wirshing WC, Wirshing D, McGurk S, et al. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenic patients. Biol Psychiatry 1998;44(8):726-732.

35. Bedard MA, Scherer H, Delorimier J, Stip E, Lalonde P. Differential effects of D2- and D4-blocking neuroleptics on the procedural learning of schizophrenic patients. Can J Psychiatry 1996;41(7 Suppl 1):S21-24.

36. Scherer H, Bedard MA, Stip E, Paquet F, Richer F, Beriault M, et al. Procedural learning in schizophrenia can reflect the pharmacologic properties of the antipsychotic treatments. Cogn Behav Neurol 2004;17(1):32-40.

37. Scherer H, Stip E, Paquet F, Bedard MA. Mild procedural learning disturbances in neuroleptic-naive patients with schizophrenia. J Neuropsychiatry Clin Neurosci 2003;15(1):58-63.

38. Kumari V, Corr PJ, Mulligan OF, Cotter PA, Checkley SA, Gray JA. Effects of acute administration of d-amphetamine and haloperidol on procedural learning in man. Psychopharmacology (Berl) 1997;129(3):271-276.

39. Rubin P, Holm S, Friberg L, Videbech P, Andersen HS, Bendsen BB, et al. Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform disorder. A regional cerebral blood flow study. Arch Gen Psychiatry 1991;48(11):987-995.

40. Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch Gen Psychiatry 1992;49(12):921-926.

41. Buchsbaum MS, Haier RJ, Potkin SG, Nuechterlein K, Bracha HS, Katz M, et al. Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch Gen Psychiatry 1992;49(12):935-942.

42. Glenthoj A, Glenthoj BY, Mackeprang T, Pagsberg AK, Hemmingsen RP, Jernigan TL, et al. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. Psychiatry Res 2007;154(3):199-208.

43. Granholm E, Bartzokis G, Asarnow RF, Marder SR. Preliminary associations between motor procedural learning, basal ganglia T2 relaxation times, and tardive dyskinesia in schizophrenia. Psychiatry Res 1993;50(1):33-44.

44. Gimenez M, Junque C, Perez M, Vendrell P, Baeza I, Salamero M, et al. Basal ganglia N-acetylaspartate correlates with the performance in the procedural task 'Tower of Hanoi' of neuroleptic-naive schizophrenic patients. Neurosci Lett 2003;347(2):97-100.

45. Exner C, Boucsein K, Degner D, Irle E. State-dependent implicit learning deficit in schizophrenia: evidence from 20-month follow-up. Psychiatry Res 2006;142(1):39-52.

46. Woodward ND, Tibbo P, Purdon SE. An fMRI investigation of procedural learning in unaffected siblings of individuals with schizophrenia. Schizophr Res 2007;94(1-3):306-316.

47. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for Axis I DSM-IV disorders. Research version-patient edition (SCID-I/P, Ver. 2.0). New York (NY): New York State Psychiatric Institute, Biometrics Research Department; 1996.

48. Kay SR, Fiszbein A, Olper LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-276.

49. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-676.

50. Simmons A, Moore E, Williams SC. Quality control for

functional magnetic resonance imaging using automated data analysis and Shewhart charting. Magn Reson Med 1999;41(6):1274-1278.

51. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 1990;87(24):9868-9872.
52. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med 1996;35(3):346-355.
53. Friston KJ, Holmes AP, Worsley KJ. How many subjects constitute a study? Neuroimage 1999;10(1):1-5.
54. Gray JA, Feldon J, Rawlins JNP, Hemsley DR, Smith AD. The neuropsychology of schizophrenia. Behav Brain Sci 1991;14:1-84.
55. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis--linking biology, pharmacology and phenomenology of psychosis. Schizophr Res 2005;79(1):59-68.
56. Corripio I, Catafau AM, Perez V, Puigdemont D, Mena E, Aguilar Y, et al. Striatal dopaminergic D2 receptor occupancy and clinical efficacy in psychosis exacerbation: a 123I-IBZM study with ziprasidone and haloperidol. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(1):91-96.
57. Liberman RP, Gutkind D, Mintz J, Green M, Marshall BD Jr, Robertson MJ, et al. Impact of risperidone versus haloperidol on activities of daily living in the treatment of refractory schizophrenia. Compr Psychiatry 2002;43(6):469-473.
58. Kawakubo Y, Rogers MA, Kasai K. Procedural memory predicts social skills in persons with schizophrenia. J Nerv Ment Dis 2006;194(8):625-627.