

Cortical Effects of Quetiapine in First-Episode Schizophrenia: A Preliminary Functional Magnetic Resonance Imaging Study

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Background: Quetiapine improves both psychotic symptoms and cognitive function in schizophrenia. The neural basis of these actions is poorly understood.

Methods: Three subject groups underwent a single functional magnetic resonance imaging (fMRI) session: drug-naïve ($n = 7$) and quetiapine-treated samples of patients with schizophrenia ($n = 8$) and a healthy control group ($n = 8$). The fMRI session included an overt verbal fluency task and a passive auditory stimulation task.

Results: In the verbal fluency task, there was significantly increased activation in the left inferior frontal cortex in the quetiapine-treated patients and the healthy control sample compared with the drug-naïve sample. During auditory stimulation, the healthy control group and stably treated group produced significantly greater activation in the superior temporal gyrus than the drug-naïve sample.

Conclusions: Quetiapine treatment is associated with altered blood oxygen level-dependent responses in both the prefrontal and temporal cortex that cannot be accounted for by improved task performance subsequent to drug treatment.

Key Words: Antipsychotic, first episode, fMRI, schizophrenia, verbal fluency

Quetiapine is a novel, atypical antipsychotic drug, with a broad spectrum of in vitro receptor affinity similar to that of clozapine, although with lower absolute affinities for most important receptor subtypes (Goldstein 1995). Preclinical animal studies show that quetiapine has a greater effect on tests associated with limbic function, such as conditioned avoidance, and a greater physiologic effect on ventral tegmental area dopamine neurons. It also has a low potential to produce extrapyramidal side effects (Goldstein 1995). The functional consequences of this neuropharmacologic profile at the neuronal level are unclear. Functional magnetic resonance imaging (fMRI) techniques now permit assessment of brain activity in living subjects by mapping the blood oxygen level-dependent (BOLD) effect consequent on oxygen extraction from hemoglobin by active neurons.

In addition to its antipsychotic effect, quetiapine appears to improve cognitive functions including verbal fluency (Velligan et al 2003). The neural basis for these actions has not been determined. Because cognitive function is an important predictor of overall functional outcome in schizophrenia (Green 1996), mapping the neuronal response to the drug may help provide a neurobiological basis for these effects and an important surrogate marker of the effectiveness of antipsychotic drugs.

Verbal fluency is robustly impaired in schizophrenia. Functional imaging studies have reported reduced left prefrontal cortex activation in unmedicated and medicated schizophrenic patients compared with healthy control subjects (Curtis et al 1998; Yurgelen-Todd et al 1996). Quetiapine, in contrast to other

antipsychotic drugs, may improve this aspect of cognition (Purdon et al 2000; Velligan et al 2003).

We have used fMRI to test the hypothesis that treatment with the atypical antipsychotic drug quetiapine results in a normalization of the BOLD response to a verbal fluency paradigm in frontal cortical areas previously linked to this task (Curtis et al 1998; Yurgelen-Todd et al 1996).

Functional imaging studies of prefrontal cortex function are greatly dependent on task performance (Manoach 2003). For this reason, we decided to use an additional task, auditory stimulation, that is less reliant on task performance and for which deficits in activation are well documented in schizophrenia (Braus et al 2002; Woodruff et al 1997).

Methods and Materials

Ethical approval for the study from the ethical committee of the South London and Maudsley NHS Trust, London, was obtained before the start of the investigation. Subjects were recruited from patients and staff within the South London and Maudsley NHS Trust. After a full explanation of the aims of the study and before inclusion in it, all subjects provided written informed consent.

The patients were selected from a cohort of subjects recruited by a specialist service dealing with first-episode psychosis. All patients recruited to this service were offered treatment with quetiapine as a first-line antipsychotic. None of the patients scanned when drug-naïve was included in the quetiapine-treated sample. Initial clinical diagnosis was made using DSM-IV and a diagnosis of schizophrenia confirmed 6 months later. The quetiapine-treated patients exhibited no significant motor side effects at the time of scanning as measured by standard rating scales for extrapyramidal side effects and akathisia (Barnes 1989; Simpson and Angus 1970).

The following inclusion and exclusion criteria were set for the study subjects.

General (for All Groups)

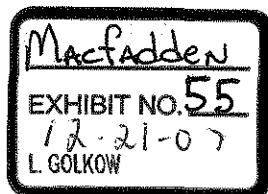
Inclusion Criteria. Capacity to give written informed consent, cooperate with the scanning procedure and perform the

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study tasks; right-handedness as measured by the Annett handedness scale (Annett 1970).

Exclusion Criteria. A history of organic neurologic illness or clinically significant substance abuse; any general contraindications for MRI examination.

Drug-Naive Sample

Inclusion Criteria. Diagnosis of schizophrenia by DSM-IV criteria reconfirmed after 6 months.

Exclusion Criteria. Previous exposure to antipsychotic treatment at any time before initial presentation.

Drug-Treated Sample

Inclusion Criteria. Diagnosis of schizophrenia by DSM-IV criteria; score on the Positive and Negative Syndrome Scale (PANSS) less than 50 to indicate low level of active symptoms; no significant change in symptoms (i.e., <10% difference) for at least 1 month before scan procedure (assessed by trained raters using a well-validated measure of schizophrenic symptomatology; Kay et al 1987); on quetiapine monotherapy for at least 3 months with no change in dose for at least 6 weeks.

After application of these criteria, seven drug-naive subjects, eight stably treated patients on quetiapine, and seven healthy control subjects participated in the study.

Cognitive Tasks

Verbal Fluency. The task was a phonemically cued word generation task, designed for use in functional imaging studies (Abrahams et al 2003). This task has a slow rate of word presentation that appears to be important in patients likely to perform poorly in standard tests of verbal fluency (Abrahams et al 1996). The paradigm used a blocked periodic design. Written and verbal instructions were given to each subject before entering the scanner, and the instructions were repeated when each individual was inside the scanner. Subjects were asked to respond to visual cues presented on a computer screen. The active task involved the overt articulation of a word in response to a single letter. Ten presentations of each letter were given, after each of which the subject was asked to speak a single word aloud. A compressed image sequence was employed to avoid confounds due to head motion during speech production (Amaro et al 2002). The control task involved repetition of the word "REST" displayed on the screen. Subjects were given 5 cycles of 10 presentations of the word REST followed by 10 presentations of a given letter (in this study, the letters used were T, S, L, C, and P). Letters were presented every 6 sec and appeared on the screen for 2 sec. The total experimental run time was 10 min.

Passive Auditory Stimulation. This task involved a blocked periodic AB design. Subjects were presented with passive auditory stimulation that consisted of a list of neutral words spoken through headphones (A) alternated with silence (B). In this auditory task, there were 8 cycles with each lasting 16 sec. Subjects were instructed to remain alert with eyes open but to make no response to either task. This auditory task has previously been well described (Brammer et al 1997; Bullmore et al 1996).

fMRI Scanning

Imaging Parameters. Gradient echo echoplanar MRI data were acquired with a 1.5-T General Electric MR system using a standard quadrature head coil. Head movement was minimized by positioning the subject's head between cushioned supports. T₂*-weighted images depicting BOLD contrast were acquired at each of 16 near-axial 7-mm-thick planes parallel to the anterior–

posterior commissural (AC-PC) line (.7 mm interslice gap, echo time [TE] = 40 msec, flip angle 90°). In the verbal fluency task, 100 images were collected (repetition time [TR] = 2 sec). In the auditory–visual stimulation task 144 images were collected (TR = 2 seconds).

An inversion recovery echoplanar imaging (EPI) data set was also acquired to facilitate registration of each individual's fMRI data set to Talairach space (Talairach and Tournoux 1988). This comprised 43 near-axial 3-mm slices (.3-mm gap), which were acquired parallel to the AC-PC line (TE = 73 msec, inversion time [TI] = 180 msec, TR = 12 sec).

Data Analysis

Individual and Group Functional MRI Analysis. Three-dimensional realignment of each image volume was first carried out to correct for head movement during the course of the experiment using a well-validated methodology (Bullmore et al 1999).

The data at each intracerebral voxel were analyzed to detect significant correlations between and the experimental paradigm. This was achieved by convolving the experimental paradigm with two gamma variate functions chosen to model hemodynamic delays of 4 and 8 sec. A weighted sum of these two convolutions will encompass delays in the likely physiologic range of 4- to 8-sec design (Friston et al 1998). Following computation of the best (least-squares) fit of the weighted sum of the two convolutions to the time series at each voxel, a goodness-of-fit statistic was computed (the ratio of the sums of squares due to the model fit and the residuals, or SSQ ratio). Significant values of this statistic were identified by comparison of observed values of SSQ ratio with a null distribution computed by repeating the fitting procedure 10 times at each voxel after wavelet resampling of the data to destroy the relationship between the experimental stimuli and responses (Bullmore et al 2001). Combining the resulting data across all voxels to produce a large distribution (typically 150,000–200,000 values) of the SSQ ratio under the null hypothesis. The critical value of SSQ ratio for any desired type I error level can easily be obtained from this null distribution and used to identify activated voxels at that level of significance.

To facilitate group analysis, the voxelwise SSQ ratios calculated for each subject from the observed data and following wavelet resampling were transformed into the standard space of Talairach and Tournoux (1988) as described previously (Brammer et al 1997). Group activation maps at any desired type I error level were once again obtained by comparing observed median SSQ ratio values at each voxel with the null distribution of median SSQ ratio values computed from the Talairach transformed wavelet resampled SSQ ratio data. Signal-to-noise ratio was improved by smoothing both the observed and wavelet resampled SSQ ratio with a Gaussian filter (full width at half maximum, 7.2 mm).

Group Contrast Analyses

Differences between group responses (F) were inferred at each voxel by regression of the general linear model (GLM), $F = a_0 + a_1H + a_2X + e$, where H codes the individuals for group, X is a covariate (when included), and e is the residual error. Maps of the standardized coefficient (effect size), a_1^* , were tested for significance against a two-tailed distribution generated by repeated randomization of H , representing the null hypothesis of no difference between groups. To improve sensitivity, spatial information was introduced by thresholding the maps of a_1^* such

Table 1. Demographic Data on Schizophrenic Subjects Included in Study

	Age	Gender	PANSS Rating	Quetiapine Dose	Treatment Duration (months)
Drug-Naive					
1	18	m	114		
2	22	m	76		
3	27	m	81		
4	21	m	45		
5	53	f	81		
6	33	m	63		
7	25	m	94		
Quetiapine Treated					
1	21	m	30	450	5
2	23	f	36	200	4
3	38	m	43	400	3
4	22	f	36	300	4
5	21	m	47	500	6
6	38	m	30	300	12
7	24	m	46	400	6

PANSS, Positive and Negative Syndrome Scale.

that only voxels passing a set voxelwise *p* value (see Results) were retained and contiguous suprathreshold voxels aggregated into three-dimensional clusters. The sum of *a_i** for each cluster was then tested for significance against the identically derived randomization distribution (Bullmore et al 1999). The voxel- and clusterwise type I error rates were set to .05 and .01, respectively. At these levels, the expectation of false positive clusters is <1.

Results

Subject Sample

The drug-naive schizophrenic patients (6 men, 1 woman) had a mean age of 28.4 years (± SD 11.9; Table 1). The quetiapine-treated schizophrenic patients (5 men, 2 women) had a mean age of 26.7 years (SD .8). There was no significant age difference between the patient groups. The treated patients had received quetiapine for an average of 5.7 months (± SD 3 months) at a mean daily dose of 364 mg (± SD 103 mg). Patients were receiving no other antipsychotic treatment. Four of the patients had never received any previous antipsychotic treatment. Two patients had received short courses (less than 3 months) of a single antipsychotic. One patient had previously received a depot antipsychotic (haloperidol, 50 mg, 4 times/week) for 2 years. This patient had been on quetiapine monotherapy for more than 2 years at time of study.

Clinical ratings were performed (HMJ) using the PANSS. The drug-naive sample had a mean score of 79.1 (± SD 22, range 45-114). Only one patient did not exhibit clear positive symptomatology at the time of fMRI scanning; however, this individual

was subsequently hospitalized for 8 months during which time it emerged that he had been experiencing positive symptoms throughout his illness. This information was not offered at the initial interview. The stably treated group were chosen to have a low level of current symptoms. They had a mean PANSS total score of 38.2 (± SD 7.1, range 30-47). An independent *t* test analysis demonstrated the difference in mean PANSS ratings between the patient groups to be significantly different (*p* < .001).

The control group comprised 6 men and 2 women, with a mean age of 27.2 years (± SD 3.7 years).

Verbal Fluency

Each subject group was able to perform the task to an adequate standard. During the task, subjects were asked to produce a maximum of 48 words. The mean number of missed words in drug-naive (3.87) and the quetiapine-treated (4.0) groups was not significantly different (*p* = .91). The mean number of errors in the normal control group was .87 errors which was significantly less than either the two patient samples (*p* < .05).

For each subject group, a group activation map was computed. These maps showed activation during the active task in similar brain regions. These included the left inferior frontal cortex (Brodmann area 44), the left and right premotor cortex/supplementary area (Brodmann area 6), left dorsolateral prefrontal cortex (Brodmann area 9), and left medial frontal lobe (Brodmann area 32). These regions are highly consistent with previous findings (Abrahams et al 2003; Curtis et al 1998).

Comparison of Three Subject Groups

The healthy control group and the stably treated group demonstrated significantly greater activation in the left inferior frontal cortex (Brodmann area 44) than the drug-naive group (see Table 2 and Figure 1). The stably treated patient group demonstrated significantly lower activation in the left orbitofrontal cortex (Brodmann area 11) than either of the other subject groups.

Auditory Stimulation

All subject groups activated a similar group of brain regions, including the right and left superior temporal gyrus (STG; Brodmann area 22) and right and left middle temporal cortex (Brodmann area 21), as would be expected from the task (Table 3). Both the normal volunteer group and quetiapine-treated group demonstrated significantly greater activation in right and left STG compared with the drug-naive subjects. There were also differences between normal volunteers and treated patients in the levels of activation found in other regions of the temporal cortex.

Table 2. Significant Differences in Group Activation During Verbal Fluency Task Across Three Subject Groups

Brain Region (Brodmann Area)	Cluster Size	Talairach Coordinates			Significant Group Difference
		x	y	z	
Left Inferior Frontal Cortex (44)	24	-43	4	26	Stably treated group > drug-naive sample
Left Inferior Frontal Cortex (44)	45	-40	19	31	Normal volunteers > drug-naive sample
Left Dorsolateral Prefrontal Cortex (9)	59	-40	11	42	Normal volunteers > drug-naive sample
Left Orbitofrontal Cortex (11)	63	-14	56	-18	Normal volunteers and drug-naive subjects > quetiapine-treated sample

Table 3. Significant Differences in Group Activation During Auditory Stimulation Across Three Subject Groups

Brain Region (Brodmann area)	Cluster Size	Talarach Coordinates			Significant Group Difference
		y	z	x	
Right Superior Temporal Gyrus (22)	31	51	−33	9	Normal volunteers > drug-naive sample
Right Superior Temporal Gyrus (22)	41	58	−11	4	Quetiapine-treated sample > drug-naive sample
Right Middle Temporal Gyrus (21)	47	54	−7	−2	Normal volunteers > drug-naive sample
Right Middle Temporal Gyrus (21)	41	58	−7	−2	Quetiapine-treated sample > drug-naive subjects

Discussion

To our knowledge this is the first study that has used fMRI to evaluate the effects of quetiapine treatment in vivo in schizophrenia. The use of a drug-naive schizophrenic comparator is rare in the imaging literature and is an important advantage of this study in determining disease- or medication-specific neural responses. Quetiapine-treated patients showed increased left

inferior frontal cortex activation during a verbal fluency task and increased superior temporal gyrus activation during passive auditory stimulation compared with a matched drug-naive schizophrenic patient sample. Task-specific deficits in cortical activation have previously been reported in schizophrenic subjects (Curtis et al 1998; Woodruff et al 1997; Yurgelun-Todd et al 1996), but the extent to which such deficits may be “normalized” by effective antipsychotic treatment is uncertain. Although this study did not demonstrate significant differences in left inferior frontal cortex activation between the drug-treated and control groups, this may reflect reduced statistical power of the relatively small sample sizes in the study. The data presented here are, however, consistent with both the antipsychotic efficacy and the improvement in verbal fluency performance evident during quetiapine treatment (Velligan et al 2003).

Methodological Considerations

This study did not use a prospective design to scan the same schizophrenic subjects before and after quetiapine treatment. We were thus unable to assess the functional consequences of the increased BOLD response associated directly with quetiapine treatment. The patients were, however, closely matched in terms of age and gender. Perhaps more important, the subjects in stably treated patient sample were all relatively newly diagnosed with schizophrenia, providing a good match of the patient groups in terms of illness duration.

The reported reduction in orbitofrontal activation during verbal fluency in quetiapine-treated patients should also be treated with caution as representing altered neuronal activity. It is plausible that this reflects a vascular effect of quetiapine treatment. This change is in the opposite direction from that observed in the healthy control sample, and there is no difference in activation in this region between the drug-naive and healthy control groups.

Effects of Quetiapine on Cortical Activation

Verbal fluency is robustly associated with activation of the left inferior frontal cortex during functional imaging studies (Phelps et al 1997). Although there is some uncertainty about the anatomic location of verbal fluency this region is consistently implicated in letter fluency paradigms such as that examined in the current study (Mumery et al 1996). Reduced left inferior frontal cortex activation has been reported in schizophrenic subjects (Curtis et al 1998; Yurgelun-Todd et al 1996). Our finding of increased left inferior frontal gyrus activation in quetiapine-treated subjects provides a plausible neurobiological explanation for recent clinical data that quetiapine, in contrast to older antipsychotic drugs, improves performance on verbal fluency in schizophrenia (Velligan et al 2003).

Reduced left temporal cortex activation during auditory processing tasks in acutely psychotic subjects is well documented (Braus et al 2002; Woodruff et al 1997). There are, however, few reports of the effects of antipsychotic drug treatment on activation in such a task. Here we show that quetiapine treatment is associated with a partial “normalization” of this reduced activa-

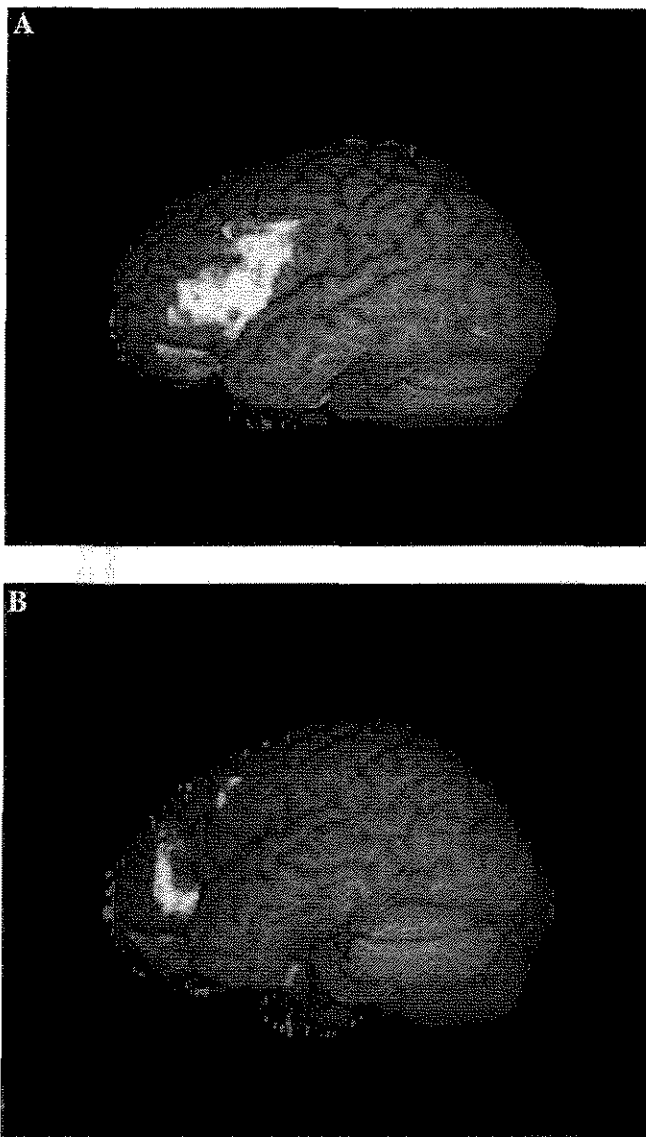


Figure 1. Increased activation in left inferior frontal cortex during verbal task in (A) quetiapine-treated ($n = 7$) compared with (B) drug-naive ($n = 7$) schizophrenic subjects samples.

tion. It has been suggested (Frith et al 1995) that subtle differences in task performance might underlie changes in activation such as that seen in this study; however, the auditory stimulation task appears less susceptible to such an effect. It was designed to require minimal cognitive effort and may be well suited for studies in acutely ill subjects.

Pharmacologic studies are designed primarily to assess drug action rather than to elucidate the neural mechanisms of cognitive function. There is a significant overlap between cognitive and psychotic symptoms in schizophrenia, and antipsychotic drugs appear to improve both. It may thus be more helpful to consider the reported results as possible surrogate markers predicting clinical improvement rather than relating to specific cognitive processes.

It is now fairly well established that there is a neural basis to the BOLD signal in fMRI (Logothetis 2002), although possible neurovascular confounds may occur with some drug treatments. Changes in activation associated with antipsychotic drug treatment may reflect direct effects of these drugs on synaptogenesis and neural plasticity, thought to underlie the longer-lived changes in symptoms consequent on antipsychotic treatment (Konradi and Heckers 2001).

This study demonstrates the feasibility in using fMRI to assess the effects of antipsychotic treatment in vivo. Our results suggest that quetiapine treatment in schizophrenia may provoke significant improvements in prefrontal and temporal cortical neuronal activity. This methodology could be used more generally to assess in vivo effects of existing and novel antipsychotic drugs. If these findings represent a consistent surrogate marker associated with antipsychotic efficacy, the fMRI approach would make a useful tool for assessing preclinical efficacy of promising novel compounds with good antipsychotic potential and few side effects.

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