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ORIGINAL PAPER

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Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation

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Abstract *Background* Working memory as a part of higher-order executive functions is defined by the parallel storage and processing of information. Recent functional fMRI studies have revealed a functional, interregional disintegration of a neuronal network connecting cortical, subcortical and cerebellar regions in schizophrenic patients (SZ). Cognitive impairment in working memory is a core psychopathological correlate of schizophrenic symptoms. Atypical neuroleptics such as quetiapine have shown good efficacy in treating positive and negative symptoms. The presented study evaluated the impact of a neuroleptic steady state treatment with quetiapine on the altered working memory activation patterns in schizophrenia. *Methods* Patients were examined by fMRI at baseline and after 12 weeks of steady state treatment with quetiapine. Matched healthy controls (HC) underwent baseline examination. In the scanner, stimuli were presented in a 2-back and 0-back condition of a working memory (wm) paradigm, whereby a degraded and a non-degraded version were used each time. Additionally, behavioural responses (reaction time to target stimuli and error ratio) were measured. *Results* At baseline, healthy controls revealed increased activity in the frontal lobe, especially in regions of the prefrontal cortex. Compared to HC, SZ showed hypoactivation in the right dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC) bilaterally for the 2-back condition. In the 2-back degraded condition there was a hypoactivation in both, the right DLPFC and the VLPFC. Additionally, patients showed bilaterally decreased activation in the basalganglia in the 2-back and in the right caudatus in the 2-back degraded condition compared to healthy controls. After treatment with quetiapine, patients activations patterns were increased. The pre–post comparison of the 2-back condition revealed a significant increase of activation in the left VLPFC at a significance level of 0.001 (uncorrected). The 2-back degraded condition led to a significant activation pattern in the lingual gyrus and the right precuneus. In both wm conditions, at baseline there were no differences in reaction time but only a worse performance in SZ. After treatment, behavioural measurement of responses, including reaction time and performance, showed slight improvements in SZ, although these did not reach statistical significance. *Conclusions* The neuronal networks underlying working memory are clearly altered in schizophrenia. After 12 weeks of treatment with quetiapine monotherapy, patients showed significant clinical improvement and revealed increased BOLD activity in the VLPFC during a working memory task, although there was no improvement of cognitive performance.

Key words working memory · schizophrenia · neuroleptic treatment · quetiapine · functional magnetic resonance imaging

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Introduction

Working memory (wm) as a part of executive function enables the contemporaneus storage and

manipulation of information and is therefore important for intentional action control and behaviour inhibition. Previous neuropsychological investigations found a diversity of cognitive impairments in schizophrenic patients, especially of working memory. The prefrontal cortex seems to play a crucial role in working memory and can be divided into the ventrolateral prefrontal cortex (VLPFC, BA 44,45,47 in the inferior frontal gyrus) and the dorsolateral prefrontal cortex (DLPFC, regions superior to the inferior frontal gyrus, i.e. BA 46,9). For a better understanding of memory functions Petrides [29] has proposed the following network model: incoming information is first processed in the parietal cortex, posterior associations build connections to VLPFC and the VLPFC is connected to DLPFC.

The interaction of DLPFC and VLPFC allows higher-order control like monitoring and manipulating information. Previous fMRI studies found altered activation patterns in schizophrenic patients (SZ) in DLPFC compared to healthy controls (HC). Whereas some found hypoactivation [23, 4], other researchers detected the converse effects during wm performance [9, 22]. Therefore it seems to be also important to evaluate wm capacity load. In healthy subjects the activity of the DLPFC increases with the difficulty of the task. When wm capacity is exceeded, BOLD signal decreases.

Hypofrontality can be regarded as a diminished wm capacity in schizophrenic patients, an interpretation which is supported by lower wm task performance of schizophrenic patients. Additionally Callicott et al. [10] found that schizophrenic patients only showed hypofrontality when they performed poorly and that high performance was correlated with hyperactivity. These results could reflect different neural strategies in schizophrenic patients compared to healthy controls.

Potential subgroups of SZ or different motivational states represent another possible explanation for the heterogeneous findings. Poor performance can either be the result of a true cognitive deficit or the incapability to exert the necessary effort for optimal task performance. There are some studies [21, 22] which try to control motivational influences by monetary rewards. These studies results show hyperfrontality in patients, so that a possible influence of motivational aspects should not be forgotten when interpreting fMRI data. Finally, an important aspect is that most of the studies presented to date investigated the working memory functioning with medically treated patients.

Using a functional MRI working memory task, Callicott investigated three untreated patients and seven patients treated with mixed typical and atypical neuroleptics. However, no differences in activation pattern emerged between the subgroups. In contrast, Barch showed a prefrontal hypoactivation in 14 drug-naïve patients [4]. Finally, Schlosser et al. detected by use of a structural equation modelling a decreased connectivity in cerebellar-thalamic and cerebellar-frontal pathways [35]. Our own results in a large sample of 20 drug-naïve and three unmedicated schizophrenic patients prove the concept of a hypoactivation in the prefrontal cortex with hypoactivation of the right VLPFC compared to healthy control subjects [34].

It is assumed that different neuroleptic treatments have a strong impact on cognitive patterns in schizophrenia. Atypical neuroleptics seem to have more positive effects on cognitive functions than typical ones. This is important in regard to the correlation of positive outcome and cognitive improvement [16]. Additionally, atypical antipsychotics are believed to be more efficient than conventional ones in treating negative symptoms [24, 25].

The atypical neuroleptic quetiapine is an effective 5HT2a and D2 receptor antagonist and has been reported to be a 5HT1a receptor partial agonist, increasing dopamine and achetylcholine release in the prefrontal cortex [37]. The quetiapine 5HT2a antagonism not only reverses D2 antagonism but causes a net increase in dopaminergic activity in the mesocortical dopamine pathway. It has been shown that quetiapine has very limited side effects, with sedation and somnolence being most frequently reported. Extrapyramidal disturbances occur rarely and only at high doses [26]. Quetiapine has been shown to have a placebo-like incidence of EPS including akathisia across its full dose range [2]. Due to its better side effects profile in contrast to classical neuroleptics and its good antipsychotic effects quetiapine has become a commonly used drug in clinical practice, especially as it leads to better functioning and quality life [32].

Furthermore, quetiapine seems to improve impaired cognitive functions in schizophrenia. For example, the positive effects of quetiapine on cognitive functions like verbal fluency, memory and executive functions were superior to those of the typical neuroleptic haloperidol [40, 31]. The double blind, long-term study by Purdon et al. [31] included 23 acutely exacerbated schizophrenic patients who received either haloperidol or quetiapine for 6 months. Whereas, the quetiapine group showed clear cognitive improvement in all investigated areas (especially in verbal tests of reasoning/fluency and immediate recall) haloperidol-treated patients showed no specific improvement in their objective test performance. Furthermore, some studies [30, 11] suggest that cognitive enhancement is not correlated to symptomatic change or general clinical improvement.

Only recently, two follow-up fMRI studies investigated the effect of quetiapine, at a mean dosage of 529 mg daily, on schizophrenic patients before treatment and after 6 months. In a task involving emotional stimuli, an increased prefrontal activity after neuroleptic treatment with quetiapine in was demonstrated schizophrenic patients [39, 15]. A recent study by Jones compared fMRI measurement of healthy control subjects at one fixed point to the results of

seven drug-naïve and eight quetiapine-treated patients using a verbal fluency task [19]. Both quetiapine-treated patients and healthy control subjects showed a significantly increased activation in the left inferior frontal cortex compared to the drug-naïve group.

Up to now, the possible cognitive improvement of working memory under treatment with quetiapine has not been investigated by means of functional MRI in a longitudinal design.

In the study presented here, we investigated the hypothesis of an improved performance in wm functioning and an approximation of patients' activation patterns to healthy controls of cerebral activity, after treatment with quetiapine for 12 weeks.

Methods and materials

Subjects

Sixteen untreated inpatients with a diagnosis of schizophrenia according to DSM-IV were recruited from the Department of Psychiatry of the Ludwig-Maximilians-University, Munich and 12 gender- and age-matched healthy control subjects were recruited from the general population. All participants were right handed. Exclusion criteria were as follows: age under 18 or over 65, current neurological disorder, history of head injury resulting in loss of consciousness, alcohol or substance abuse, suicidal tendencies, laboratory or ECG/EEG abnormalities (blood or urine values outside standard range by more than 20%), pregnancy or lactation, relevant medical history, brain surgery, unstable somatic conditions including HIV, metallic objects in their body and cortisol or tranquilizer medication in the last 3 months. Patients were also excluded if they had any comorbidity DSM-IV axis I disorder, or had undergone previous electroconvulsive therapy and control subjects if they had first-degree relatives with psychiatric disorders. Patients characteristics are shown in Table 1.

Four of the patients dropped out because of incompliance with the second fMRI scan. Thus, we investigated 12 healthy controls and 12 schizophrenic patients. Schizophrenic symptomatology was characterized using the Positive and Negative Symptom Scale (PANNS) and the Scale of Negative Symptoms (SANS) [1]. Additionally, the Clinical Global Impression (CGI) and the Brief Psychiatric Rating Scale (BPRS) were assessed. Upon entering the study, a thorough psychiatric investigation was performed, complemented by a chart review. Each patient also received a medical check-up including physical examination, electrocardiogram (ECG), electroencephalogram (EEG), laboratory tests, urine drug screen and pregnancy test. The same check-up procedure was performed on all patients at endpoint.

Nine patients were drug naïve and three had been washed out over a period of 3 days, ending 2 days before the beginning of the trial Prior to the wash-out period, one patient had been receiving haloperidol (10 mg/day), one risperidone (6 mg/day) and 1 amisulpride (200 mg/day). Clinical assessments were carried out at regular weekly intervals.

All patients gave their written informed consent according to procedures approved by the ethics committee of the University of Munich medical faculty prior to study inclusion. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Treatment

Treatment with quetiapine was initiated as follows: 50 mg on day 1, 100 mg on day 2 and then daily increase of 100 mg to 600 mg/day on day 7. After day 7 the dose of medication was adjusted according to the investigatorś clinical judgement. Doses of quetiapine ranged from 200 mg to 1000 mg/day with a mean of 566.7 mg ± 242.5. Lorazepam (≤4 mg/day) and zopiclone (≥15 mg/day) were allowed for agitation and insomnia. Biperiden hydrochloride (≤8 mg/day) was used to treat EPS. No additional psychotherapy or cognitive training was performed. Plasma levels of quetiapine were measured after 12 weeks to ensure compliance with treatment.

Table 1 Clinical and behavioural data of patients and healthy controls (mean and standard deviation)

	Schizophrenic patients before treatment	Schizophrenic patients after treatment	Healthy controls at baseline
Gender	11 male, 1 female	11 male, 1 female	11 male, 1 female
Age	33.50 (9.39)		33.58 (9.27)
Range	20–48		22–48
Age of onset	29.08 (11.12)		
Years of education	10.83 (1.50)		13.0 (0)
Dose of quetiapine		566.7 mg (242,5)	
PANNS	54.60 (15.57)	23.80 (7.41)	
SANS	63.9 (19.60)	24.30 (15.06)	
BPRS	56.6 (21.08)	23.90 (5.195)	
CGI	5.42 (0.52)	2.42 (0.99)	
% of correct answers			
0-back	96.53 (1.41)	98.96 (0.61)	99.6 (0.20)
0-back degraded	97.92 (1.03)	98.96 (0.61)	99.6 (0.20)
2-back	90.97 (1.76)	92.36 (1.21)	97.57 (0.69)
2-back degraded	81.25 (3.5)	92.01 (0.81)	95.84 (0.66)
Reaction times (in ms)			
0-back	702 (78)	698 (75)	678 (39)
0-back degraded	728 (89)	726 (84)	714 (49)
2-back	777 (130)	746 (115)	752 (100)
2-back degraded	804 (105)	801 (115)	800 (102)

Cognitive tasks

Experimental tasks were programmed by the ERTS software package (Experimental Run Time System, Beri Soft Cooperation, Frankfurt, Germany). Reactions were registered by an MRI-compatible fiber response device with connection to an IBM TP 600 E (type 2645) personal computer. Before measurements were made, subjects practiced until they understood the task procedure. They were instructed to respond to the target stimuli as accurately as possible. Subjects did not receive any monetary reward for the investigation. Stimuli were presented via MRI-compatible video-glasses (Resonance Technology Inc., Northridge, CA) and were in white arial font on a black background (visual field: 30° in the horizontal and 20° in the vertical dimension).

Participants responded by pressing a key (LUMItouch, Photon Control Inc, Burnaby, Canada) with their right index finger.

We used a modified version of the Continuous Performance Test (CPT) with four different conditions

0-back: single letters (A–Z) presented in a random order centered in the visual field; subjects were instructed to press the key for the target letter "X".

0-back degraded: equivalent to 0-back, but presentation not on a black, but a blurred background, which requires more attention.

2-back: single letters (A–Z) presented in a random order centered in the visual field, subjects were instructed to press the key if the last but one letter was the same.

2-back degraded: equivalent to 2-back, but presentation not on a black, but a blurred background, which requires more attention.

Two runs were performed, each of which included the four conditions in the described order. During each activation block baseline phases (fixation of a centered cross without key pressing)

were implemented. Stimulus presentation time was 1300 ms with an interstimulus interval of 700 ms with 30% of targets. Each condition was preceded by a short written instruction of 500 ms. Baseline crosses took 20 s and each condition lasted 40, resulting in a total length of 8 min and 16 s for each run. The subsequent MPrage (see below) lasted for 14 min and 13 s.

Image acquisition

We used a 1,5 T Siemens Scanner (Siemens, Erlangen), Echo Planar Imaging (EPI), BOLD contrast. All participants were given headphones for noise protection within the headcoil. After the two functional runs, a structural MPrage dataset for anatomical localization and coregistration of the functional data was performed. The transaxial functional images (EPI, 64 × 64, 32 slices, 4 mm thickness, FOV 256 mm, voxelsize 4 × 4 × 4 mm , TR 60 ms, TE 0.6 ms, alpha 90°) covered the whole brain and were positioned to the intercommissural line (AC-PC). The two runs with 140 scans were completed by scanning synchronized with stimulus presentation, so that a set of 32 slices was acquired every 3 s. The 3D-dataset compromised of 160 slices ((256 × 256 sagittal, FOV 256 mm, voxelsize 1 × 1 × 1 mm, TE 4.4 ms, TR 11.4 ms, alpha 15°).

Analysis of behavioural measures

Participants' responses were analyzed for reaction quality (error ratio) and reaction time to the target stimuli. Reaction times to incorrect responses were excluded. Paired *t*-tests for intergroup and two-sample *t*-tests for intergroup comparisons were used.

fMRI data analysis

Statistical Parametric Mapping (SPM99) was used for data analysis with the following preprocessing steps: realigning to correct subject motion (exclusion criteria: more than 3 mm), coregistration of the functional and structural data sets, spatial normalizing into a standard stereotactic space, using a template of the Montreal Neurological Institute (MNI) and smoothing the data with an 8 mm Gaussian Kernel.

Statistical parametric maps calculation was based on voxel-by-voxel method, using a general linear model and Gaussian Random Field Theory [7]. Contrast images for each condition and each subject were created contrasting the 2-back with the 0-back, the 2-back degraded with the 0-back degraded and all 4 *n*-back conditions in summary with baseline condition. The results for activation increases were chosen in accordance with results of previous studies. Therefore uncorrected *P*-values ($P < 0.001$) were used, two-sample *t*-tests for intergroup and paired *t*-tests for intragroup (before and after treatment) comparisons for the patients' data. We examined all possible main effects and interactions in this design.

Results

Clinical symptomatology

Improvement could be detected on all clinical rating scales. The pre- versus post-treatment difference reached a significant level of improvement for all psychopathological scales (SANS: $P < 0.000$; PANNS: $P < 0.000$; CGI: $P < 0.000$, BPRS: $P < 0.001$). Medication dosage reached a mean of 566.7 mg/day ± 242.5 and the dosages were distributed as following: 200 mg ($N = 2$), 400 mg ($N = 2$) , 500 mg ($N = 1$), 600 mg ($N = 3$), 700 mg ($N = 1$), 800 mg ($N = 2$), 1000 mg ($N = 1$). After 12 weeks the plasma levels of quetiapine were 186.9 ± 171.5 (Table 1). None of the patients required biperidon as concomitant medication, but four patients needed lorazepam during the first 5 weeks, after which lorazepam treatment was discontinued. Finally, ximovan treatment was given intermittently when necessary in six patients.

Task performance

No significant differences in reaction times could be observed, either for intergroup (baseline HC versus SZ) or intragroup (SZ baseline versus SZ after treatment) comparisons. Patients' showed a tendency to improve after treatment. An improvement in reaction times of 20 ms could be detected, which did not reach significance (Tables 1 and 2).

Significant differences in the quality of reactions could be observed for the 2-back conditions, but not for 0-back. Patient's responses were significantly worse before ($P = 0.05$, $t = 2.044$, df = 29.858) and also after treatment ($P = 0.035$, $t = 2.19$, df = 36.484) compared to healthy controls. Analogous results were found for 2-back degraded conditions before ($P = 0.24$, $t = 2{,}404$, df 24.626) and after medication treatment ($P = 0.37$; $t = 2.155$; df = 44.253) (Table 1).

BOLD fMRI responses

Healthy controls

During 2-back conditions signal maxima occurred bilaterally in the DLPFC, VLPFC, parietal areas, limbic system (BA32) and thalamus and in left striatum. For 2-back degraded conditions activations were

Table 2 Significance levels of reaction times in all four working memory conditions

	Healthy controls (a) versus patients at baseline (b) versus patients after treatment*		
	T	df	*P*
0-back	−0.93/−0.78*	22/22*	0.37/0.44*
0-back degraded	−0.45/−0.39*	22/22*	0.65/0.70*
2-back	−0.53/0.15*	22/22*	0.60/0.88*
2-back degraded	−0.11/−0.28*	22/22*	0.92/0.98*
	Patients at baseline versus after treatment		
	T	df	*P*
0-back	0.16	11	0.88
0-back degraded	0.08	11	0.91
2-back	1.12	11	0.28
2-back degraded	−0.56	11	0.59

Table 3 Increased BOLD activations in healthy controls (Talairach coordinates *xyz*, *T*-value, cluster size *K*, $P < 0.001$ uncorrected)

Brodman area	Area	*x*	*y*	*z*	*T*	*K*
	2-back					
BA 47	l inferior frontale gyrus	−49	21	−9	6.02	428
BA 40	l supramarginal gyrus	−46	−42	38	8.98	594
BA 40	l inferior parietal lobe	−42	−44	48	5.65	594
BA 9	r inferior frontal gyrus	48	11	23	8.34	269
BA 45	r inferior frontal gyrus	51	22	15	4.09	269
	l thalamus/sub-lobar	−12	−11	10	8.15	826
	l nucleus caudate/sub-lobar	−10	2	9	7.52	826
	r thalamus/ sublobär	6	−19	3	6.91	826
BA 6	l precentral gyrus	−40	1	29	7.74	55
BA 47	r inferior frontal gyrus	34	21	−16	7.20	164
BA 46	l middle frontal gyrus	−46	23	26	7.00	82
BA 40	r inferior parietal lobe	46	−41	41	5.96	44
BA 40	l inferior parietal lobe	−63	−40	24	5.67	21
BA 7	r superior parietal lobe	32	−60	49	5.63	34
BA 10	l middle frontal lobe	−36	47	7	5.54	103
BA 10	l middle frontal gyrus	−34	42	15	5.09	103
BA 8	l middle frontal gyrus	−42	10	40	4.58	18
BA 32	anterior cingulum	−2	36	18	4.50	19
BA 47	l extra-nuclear /frontal lobe	−26	21	−6	14.19	428
BA 32	r gyrus cinguli	2	32	28	7.89	82
	2-back degraded					
BA 40	l superior parietal lobe	−34	−52	49	14.49	1516
BA 40	l inferior parietal lobe	−46	−42	46	10.45	1516
BA 47	l inferior frontal gyrus	−30	25	−6	12.37	460
BA 47	l inferior frontal gyrus	−48	23	−11	6.92	460
BA 8	l middle frontal gyrus	−28	16	43	11.10	900
BA 9	l middle frontal gyrus	−42	10	36	8.52	900
BA 46	r middle frontal gyrus	46	22	21	9.52	893
BA 7	r superior parietal lobe	30	−58	42	9.16	389
BA 40	r inferior parietal lobe	38	−52	39	5.49	389
BA 32	l anterior cingulum	−6	32	19	7.69	85
BA 33	l anterior cingulum	−4	20	21	4.98	85
BA 23	r posterior cingulum	6	−28	25	7.23	60
BA 47	r inferior frontal gyrus	36	19	−9	7.08	168
BA 32	r gyrus cinguli	8	27	28	6.61	72
	l thalamus	−12	−5	8	6.44	237
	r thalamus	6	−13	4	5.19	237
BA 13	l insula	−42	16	5	5.72	11
BA 11	r middle frontal gyrus	30	46	−9	5.58	13
BA 6	l superior frontal gyrus	−4	14	49	5.50	13
BA 7	l precuneus	−12	−68	44	5.26	27
-	r inferior frontal gyrus	53	16	1	5.08	30
BA 44	l precentrale gyrus	−53	16	7	4.95	41
BA 32	l cingulate gyrus	−4	23	39	4.87	11

especially seen bilaterally in the VLPFC, DLPFC, parietal regions, thalamus and cingulate gyrus (BA 23, 32, 33). All comparisons were made for an uncorrected threshold of $P < 0.001$, with an extent of at least 10 voxels (Table 3).

Patients versus healthy controls before treatment

A second step analysis revealed that patients showed no hyperactivations compared to healthy controls, whereas hyperactivation could be detected in healthy participants in the left thalamus, in the basalganglia (right putamen, left claustrum) (Fig. 1), in the right DLPFC and in the VLPFC bilaterally during both 2-back conditions (Table 4).

During 2-back degraded conditions hyperactivation in the prefrontal (right DLPFC and VLPFC), the parietal cortex (BA 40), the basal ganglia (right caudate) and insula (BA13) of healthy controls compared to schizophrenic patients were found (Table 4).

In contrast to the 2-back conditions, the 2-back degraded condition showed in patients increased activations in both temporal lobes and in the left parietal lobe (gyrus postcentralis) (Table 5, Fig. 2).

Patients before versus after treatment

Paired *t*-tests resulted in increased activation after treatment compared to baseline data. There was a significant increase in activation of the left VLPFC for 2-

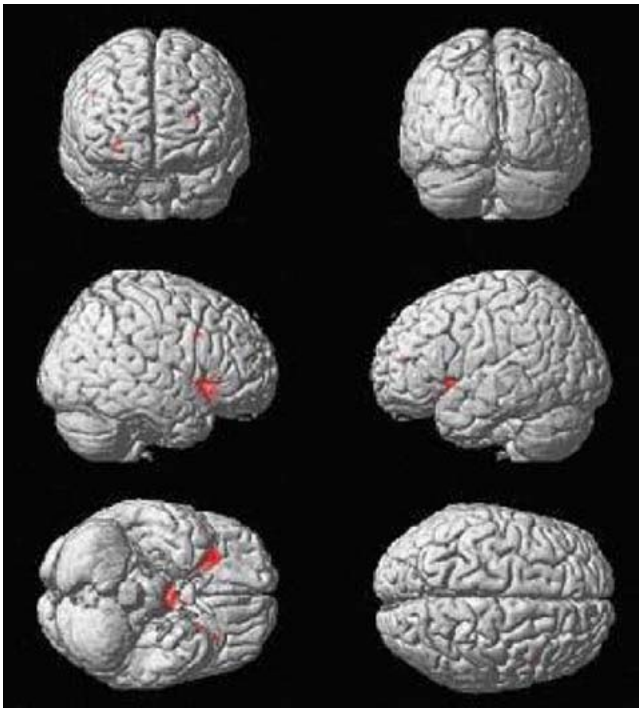

Fig. 1 Increased BOLD activations in healthy controls compared to untreated patients during 2-back conditions, $P < 0.001$ uncorrected

back conditions. For the 2-back degraded task increased activations after treatment occurred in the lingual gyrus bilaterally and the right precuneus in the parietal lobe.

All comparisons were made for an uncorrected threshold of $P < 0.001$, with an extent of at least 10 voxels (Table 6, Fig. 3).

Discussion

This study investigated the hypothesis of an improved performance in working memory functioning and an approximation of patients' activation patterns to healthy controls' cerebral activity after treatment with quetiapine for a duration of 12 weeks. To our knowledge this is the first study to date to investigate working memory functions in schizophrenic patients in a follow-up design with quetiapine and fMRI.

Table 5 Increased BOLD activations in schizophrenic patients compared to healthy controls during 2-back degraded conditions before treatment (Talairach coordinates *xyz*, *T*-value, cluster size *K*, $P < 0.001$ uncorrected

Brodman area	Area	*x*	*y*	*z*	*T*	*K*
BA 22	l superior temporal gyrus	−59	−7	6	6.05	66
BA 40	l postcentral gyrus	−61	−21	16	4.10	21
BA 41	l transverse temporal gyrus	−51	−25	12	4.01	19
BA 22	r superior temporal gyrus	51	−11	4	3.83	10

Healthy controls

Traditionally [17] especially prefrontal region are regarded as essential for such cognitive tasks. We detected bilateral activity in the VLPFC and DLPFC in healthy controls. Our data from healthy controls data confirmed previous findings of the regions involved in wm processes.

The model of Petrides [29], which suggests a parietal attendance—in the sense of primary processing of information—can be affirmed by our results. Healthy participants also showed bilateral hyperactivations in the parietal cortex during both 2-back and 2-back degraded conditions. The DLPFC, connected to VLPFC, is necessary for higher-order functions in 2-back conditions in contrast to simple 0-back conditions, such as monitoring and contemporaneous manipulation of information [13, 38]. Further investigations revealed additional subcortical participation [36], which can also be confirmed by our results. In summary, normal activation in healthy

Table 4 Increased BOLD activations in healthy controls compared to patients before treatment (Talairach coordinates *xyz*, *T*-value, cluster size *K*, $P < 0.001$ uncorrected)

Brodman area	Area	*x*	*y*	*z*	*T*	*K*
	2-back					
–	l thalamus	−10	−12	2	5.94	519
Putamen	r lentiform nucleus	22	10	1	5.53	355
BA 47	r inferior frontal gyrus	28	23	−6	5.97	355
BA 47	l inferior frontal gyrus	−30	25	−8	4.65	23
Putamen	r lentiform nucleus	24	0	9	4.27	39
BA 9	r middle frontal gyrus	46	15	31	4.13	17
BA 10	l middle frontal gyrus	−30	49	12	3.98	12
–	l claustrum	−26	13	−4	5.86	519
	2-back degraded					
BA 40	r inferior parietal lobe	40	−37	41	4.78	26
BA 9	r middle frontal gyrus	44	17	29	4.63	30
BA 45	r inferior frontal gyrus	51	18	12	4.47	42
BA 13	r insula	44	−38	20	4.07	14
BA 47	r inferior frontal lobe	36	15	−11	3.98	13
	r caudate	12	−26	23	3.77	11

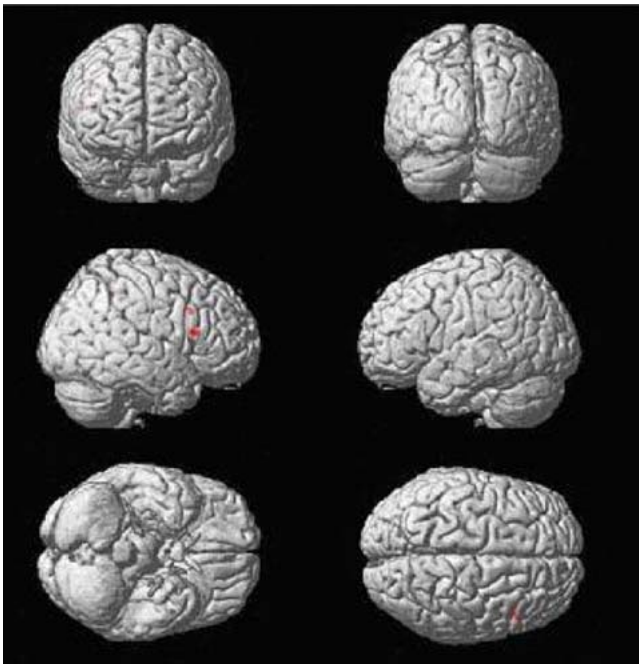

Fig. 2 Increased BOLD activations in healthy controls compared to untreated patients during 2-back degraded conditions, $P < 0.001$ uncorrected

Table 6 Increased BOLD activations in patients after treatment compared to their data before (Talairach coordinates *xyz*, *T*-value, cluster size *K*, $P < 0.001$ uncorrected

Brodman area	Area	*x*	*y*	*z*	*T*	*K*
	2-back					
BA 47	l inferior frontal gyrus	−28	29	2	4.48	10
	2-back degraded					
BA 18	l lingual gyrus	−12	−56	3	5.55	13
BA 19	r lingual gyrus	16	−58	1	5.52	13
BA 7	r precuneus	30	−44	45	4.76	10

controls during a wm paradigm contains parietal regions for first processing steps, prefrontal areas for monitoring, storage and manipulating and subcortical regions like the thalamus [3, 8].

Patients versus healthy controls at baseline

Our data from untreated patients revealed a hypofunction of the prefrontal cortex. Patients showed a signal decrease of the left DLPFC and VLPFC in both 2-back trials, independent of attentional effort. i.e. in both the 2-back and 2-back degraded trials.

Hypofunction in the DLPFC was found by several investigators [4, 9, 28], while other studies demonstrated either hyperfunctions in the DLPFC in patients [9, 10, 21, 22] or no signal differences [20]. Callicott suggests that differences in patients' working memory performance may explain the differing results [10]. The additional effect of antipsychotic medication also has to be taken into account.

However past findings of hypofrontality cannot be solely attributed to medication effects [42]. There is evidence that especially atypical medication leads to an improvement in cognitive functions and numerous studies have demonstrated cognitive improvement in attentional, verbal memory and executive functions after treatment wtih atypical and conventional antipsychotics [41]. It must be emphasized that, although there is a significant cognitive improvement, patients do not reach the same level as healthy controls [12].

Taking into account these neuropsychological findings and the past fMRI results, which confirm hypofrontality in patients performing poorer and hyperfrontality in those performing better, it should be questioned whether prefrontal hypofunction really can be regarded as an artefact of patients' poorer working memory abilities. This because deficits in working memory, which are probably a core symptom of schizophrenia, consequently lead to an poorer performance on average in working memory tasks. Therefore, an fMRI investigation that only includes schizophrenic patients with a performance level comparable to HC would perhaps not reflect a representative sample of patients with a working memory deficit.

As Callicott [10] discussed, it is important to note that high-performance patients show hypo- or hyperactivation in the prefrontal cortex while low-performance patients always show a pattern of less prefrontal activation. Our drug free patients performed significantly worse than HC at baseline, so our results of a decreased prefrontal pattern are in line with Callicott's finding. In our study, psychopharmacological treatment led to a slight increase in activation in the prefrontal cortex.

Additionally, we found that both the 2-back and the 2-back degraded versions of working memory demand reduced the BOLD signals in the basalganglia, which confirms previous assumptions of a basic disturbance in frontostriatal networks [6, 33]

Furthermore, the baseline comparison revealed parietal and temporal hyperactivations within the schizophrenic group. These signal increases were detected only for 2-back degraded, but not for 2-back trials. In accordance with Petrides model, parietal regions receive incoming information during working memory activities. Patients' hyperfunctions during 2-back degraded trials could reflect a compensatory strategy when attentional effort increases. With regard to the worse performance especially in the 2-back degraded condition, this neural mechanism seems to fail.

Patients before versus after treatment with quetiapine

Patients improved significantly after 12 weeks treatment with quetiapine. All patients were compliant as

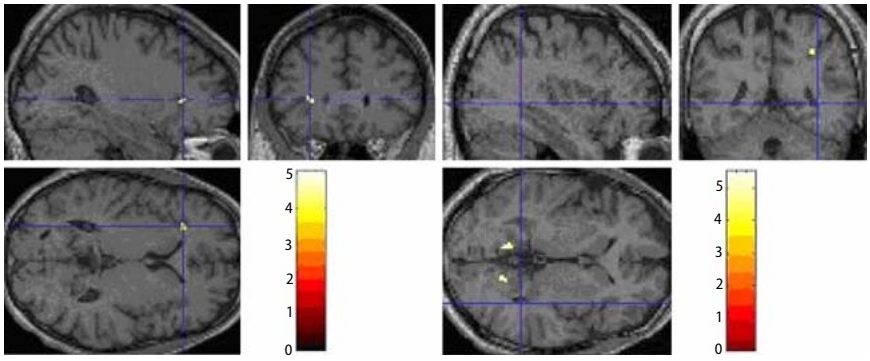

Fig. 3 Increased BOLD activations in patients during 2-back and 2-back degraded conditions, $P < 0.001$ uncorrected, after treatment

plasma level measurements of quetiapine were in a good range and correlated with the last medication intake.

Besides the improvement of positive symptoms measured by PANSS, during the 12 weeks of monotherapeutic treatment, quetiapine showed good efficacy in treating negative syndromes, as measured by SANS. In fact, atypical neuroleptics are believed to be more effective than conventional antipsychotics in treating negative symptoms, due to better tolerability and a broader neurotransmitter action [24, 25]. Only recently, a study performed by Riedel and colleagues demonstrated in a double-blind design that quetiapine has an equivalent efficacy and superior tolerability to risperidone in schizophrenic patients with predominantly negative symptoms [32].

As expected, after treatment there was an approximation of activation patterns of patients to those of healthy controls. Comparing the contrast images of patients before and after treatment, significantly increased signals could be detected in 2-back conditions in the left VLPFC and for 2-back degraded in the parietal precuneus in treated patients. Both regions are core modules of the working memory circuits [14].

There are some studies which confirm signal increases in the prefrontal cortex by atypical antipsychotic medication. Thus, Honey et al. [18] reported a normalisation of decreased frontal activity using an *n*-back paradigm after a change of medication from typical antipsychotics to risperidone. Another study also confirmed, by using a wm task, an enhancement of effective connectivity in patients receiving atypical antipsychotics compared to schizophrenic patients treated with typical antipsychotics [35]. Therefore, our results may confirm an increase of BOLD activation pattern in important modules of wm circuits. Furthermore, there is proof of a genetic influence on the efficacy of the atypical olanzapine with regard to working memory performance and altered cerebral correlates [5].

There are only a few fMRI studies which examine the special efficacy of quetiapine. For example Fahim et al. [15] and Stip et al. [39] investigated the effects of quetiapine on frontal activation. However, as they used emotional stimuli and no working paradigm, results can hardly be compared with our data, but it should be emphasized that these two investigations found an increase in prefrontal activity in schizophrenic patients after treatment with quetiapine. Jones et al. [19], investigated a small sample of drug-naïve patients ($n = 7$) versus quetiapine-treated patients ($n = 8$). Patients had to solve a verbal fluency task, which represents another part of executive functions. Quetiapine-treated patients showed signal increases in the inferior frontal cortex compared to drug-naïve patients. Thus, although care must be applied when comparing different paradigms, there is growing evidence that quetiapine increases prefrontal cerebral activity, in the sense of an approximation of schizophrenic activity patterns to healthy ones. Taking into account the relatively small sample of schizophrenic patients that has been investigated up to now by means of fMRI, further studies with larger samples are needed to clarify different influence factors on neuroleptic treatment.

Our results show that cerebral pattern approximation is accompanied by an improvement in task performance. Additionally, patients' reaction times became shorter. The mean reaction time over all four conditions improved by nearly 20 ms. Although this is a considerable change, the difference between reaction times before and after treatment was not significant because of the high standard deviations. Thus, the question arises whether the study duration of 12 weeks has to be extended. A neuropsychological study investigating treatment with quetiapine over 6 months [31] revealed a highly significant improvement in cognitive functions. For clozapine, another atypical antipsychotic, effects became evident after 1 year of treatment [27].

Therefore, further investigations with a larger sample of schizophrenic patients should be examined over a longer course of time. Despite the tendency to be able to react faster, an analogous change in error ratio could not be observed so clearly. In summary, the data allows the assumption to be made that treatment with quetiapine results in better task performance in the sense of better speed performance and altered cerebral activation patterns in the sense of an approximation to healthy controls' neural signals.

The strength of the study is the strict clinical, prospective design. A limitation is without question the significance level of the detected signal increases after treatment. Although, this is one of the largest studies with a working memory paradigm for quetiapine the number of patients included is still limited.

In summary, by including only untreated schizophrenic patients and investigating baseline and post-treatment fMRI data, the current study confirms the positive effects of quetiapine on cognitive functioning in schizophrenia. Working memory as a cognitive core deficit in this disease can be influenced by psychopharmacological treatment with quetiapine. Effects can be observed in cerebral approximation in activation pattern, based especially on frontal activity increases and the tendency towards improvement in task performance.

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