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ORIGINAL INVESTIGATION

Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine

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Abstract
Rationale High blockade of dopamine D2 receptors in the ventral striatum including the nucleus accumbens may interfere with reward anticipation and cause secondary negative symptoms such as apathy or anhedonia. This may not be the case with newer neuroleptics such as olanzapine, which show less dopamine D2 receptor blockade and a faster off-rate from the receptor.
Objectives We used functional magnetic resonance imaging to assess the blood oxygenation level dependent response in the ventral striatum of schizophrenics medicated with typical neuroleptics (T1) and after switching them to olanzapine (T2) and of healthy control subjects at corresponding time points during reward anticipation.
Materials and methods Ten schizophrenics, while medicated with typical neuroleptics (T1) and after having been switched to olanzapine (T2), and ten matched healthy volunteers participated in a monetary incentive delay task, in which visual cues predicted that a rapid response to a subsequent target stimulus would either result in monetary gain or have no consequence.
Results During reward anticipation, healthy volunteers showed significantly higher ventral striatal activation compared to schizophrenic patients treated with typical neuroleptics but not olanzapine, which was reflected in a significant interaction between group and session. In patients treated with typical neuroleptics, but not with olanzapine, decreased left ventral striatal activation was correlated with negative symptoms.
Conclusions Failure to activate the ventral striatum during reward anticipation was pharmacologically state-dependent and observed only in patients treated with typical neuroleptics but not with olanzapine, which may indicate that this drug did not induce secondary negative symptoms via interference with reward anticipation.

Keywords Accumbens · Basal ganglia · Reward · Schizophrenia · Motivation · Functional magnetic resonance imaging · Antipsychotic agents

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Introduction

Schizophrenic patients suffer from negative symptoms such as affective flattening, anhedonia and apathy, which can precede the onset of psychotic symptoms and may not improve with typical neuroleptic treatment (Akhondzadeh 2001; Andreasen 1990; Glick et al. 2001). In schizophrenic patients, chaotic or stress-induced dopamine release in the ventral striatum including the nucleus accumbens may interfere with signaling of a prediction error, i.e., the occurrence of unexpected reward or reward-indicating

stimuli (Heinz 2002; Kapur 2003; Menon et al. 2007; Pessiglione et al. 2006; Schultz 1998). Indeed, unmedicated schizophrenic patients confronted with reward-indicating stimuli displayed a reduced activation of the ventral striatum, which was associated with the severity of negative symptoms (Juckel et al. 2006b), and a disrupted prediction error signal was observed in the ventral striatum and prefrontal cortex of schizophrenic patients (Corlett et al. 2007; Jensen et al. 2007; Murray et al. 2007). However, a high degree of dopamine D2 receptor blockade during medication with typical neuroleptics may also contribute to negative symptoms, which are supposed to be secondary to the medication and caused by its interference with striatal dopaminergic neurotransmission (de Haan et al. 2004; Heinz et al. 1998; Kapur et al. 2000). In accordance with this hypothesis, Heinz et al. (1998) observed a linear correlation between the degree of striatal dopamine D2 receptor blockade and the severity of the negative symptom "apathy", and Juckel et al. (2006a) observed that the severity of negative symptoms was linearly correlated with reduced ventral striatal activation during reward anticipation in patients treated with typical neuroleptics. Decreased activation of the ventral striatum was also observed in schizophrenic patients who experienced odors and was associated with the severity of negative symptoms (Crespo-Facorro et al. 2001). Dopamine D2 receptor blockade may also exacerbate dopamine deficits in the prefrontal cortex and thus contribute to cognitive negative symptoms (Bertolino et al. 2004; Heinz et al. 1998; Heinz 2002; Honey et al. 1999).

Unlike traditional neuroleptics such as haloperidol, newer antipsychotics such as olanzapine induce a lower degree of striatal D2 receptor blockade, show faster dissociation from the receptor, and interact with several other neurotransmitter systems including the serotonin 5-HT_{2A} receptor, which may reduce anti-dopaminergic effects of D2 receptor blockade (Farde et al. 1992; Kapur and Seeman 2001; Sawa and Snyder 2003). Therefore, atypical neuroleptics may reduce secondary negative symptoms due to high blockade of striatal D2 receptors, while they may or may not be able to restore phasic dopaminergic neurotransmission in response to reward-indicating stimuli. Using the same paradigm that is applied in the current study (Knutson et al. 2001), we previously observed that patients treated with typical neuroleptics (e.g., haloperidol) failed to activate the ventral striatum during reward anticipation, while no significant difference to healthy control subjects was found in a group of patients treated with newer, second-generation neuroleptics (e.g., olanzapine; Juckel et al. 2006a). Moreover, reduced activation of the ventral striatum during reward anticipation was associated with the severity of negative symptoms in patients treated with typical but not atypical antipsychotics (Juckel et al. 2006a). However, in this previous study, heterogeneity of schizophrenic patients may limit comparability between groups treated with typical vs different atypical neuroleptics. Therefore, we examined schizophrenics treated with typical neuroleptics (at time point T1) and then, after they had been switched to treatment with the atypical neuroleptic olanzapine for 2 weeks (at time point T2), compared them with healthy controls measured at two time points separated by a similar interval. We hypothesized that schizophrenic patients would show reduced ventral striatal activation during reward anticipation when treated with typical neuroleptics but not olanzapine and that reductions in ventral striatal activation would be associated with the severity of negative symptoms.

Materials and methods

Subjects and instruments

The local ethics committee approved the study, and written informed consent was obtained from all participants after the experimenter explained the procedures. Twenty subjects were included (ten schizophrenic patients and ten healthy volunteers matched for age, gender, and handedness). Schizophrenic patients (nine men and one woman; mean age, 30.5±10.6 years) fulfilled Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria for schizophrenia, had no other psychiatric axis I disorder [Structured Clinical Interview for DSM-IV (SCID) interview; First et al. 2001], and no current drug abuse or past history of drug dependence (SCID interview and random urine drug testing). Patients were recruited at the Department of Psychiatry and Psychotherapy of the Charité-Universitätsmedizin Berlin (Campus Charité Mitte). Before inclusion into the study, four first-episode patients were drug-naïve, and six patients had received neuroleptic medication before (risperidone, amisulpride, quetiapine, and perazine) for a mean duration of 4.6 years (range 0.3–15 years).

Ten healthy volunteers (nine men and one woman; mean age, 31.8±8.7 years) were included; they had no Axis I or II psychiatric disorder (SCID interview; First et al. 1997, 2001), no family history of psychiatric disorders in first-degree relatives, current drug abuse, or a past history of drug dependence other than nicotine consumption (SCID interview and random urine drug testing). In all subjects, handedness was assessed with the Edinburgh Handedness Inventory (Oldfield 1971), executive function with the Wisconsin Card-Sorting Test (WCST; Heaton 1981) and verbal IQ with Word-Sorting Task (WST; Schmidt and Metzler 1992; Table 1).

Table 1 Group description and performance in monetary incentive delay task

	Schizophrenic patients	Healthy controls	Significance
Age (years)	30.5±10.6 (18–52)	31.8±8.7 (18–45)	n.s.[a]
Gender	9 men, 1 woman	9 men, 1 woman	
Edinburgh Handedness Inventory	27.5±81.7 (−100–100)	25.8±91.2 (−100–100)	n.s.[a]
	6 right-, 3 left-, 1 mixed-handed	6 right-, 3 left-, 1 mixed-handed	
Verbal IQ (WST)	95.3±16.4 (77–122)	106.8±9.3 (90–118)	n.s.[a]
Executive function (WCST): Perseveration error (%)	13.6±12.0 (1.4–36.5)	4.2±6.6 (0.0–21.9)	$p<0.05$[a]
Interval T2-T1 (days)	31.7±17.3 (17–67)	32.7±15.5 (18–63)	n.s.[a]
Reaction time T1 (ms)	391.9±147.1 (224–689)	255.1±95.0 (180–479)	
Reaction time T2 (ms)	297.5±94.6 (205–443)	243.5±91.3 (182–451)	
Total gain T1 (in euro)	22.5±12.6 (−3.7–34.6)	24.2±8.2 (8.0–32.9)	
Total gain T2 (in euro)	25.1±8.3 (2.3–32.6)	28.9±5.4 (4.9–38.2)	
VAS effort for gain T1	7.3±1.9 (4.3–10.0)	8.0±1.6 (5.3–10.0)	
VAS effort for gain T2	7.6±1.9 (4.3–10.0)	7.7±2.9 (0.0–10.0)	
Medication T1, dose (mg)	4 haloperidol, 10.8±4.3 (5–15)		
	5 flupenthixol, 7.0±5.1 (1–15)		
	1 fluphenazine (15)		
Duration of treatment with typical neuroleptics (days)	17.8±15.0 (7–54)		
Medication T2, dose (mg)	Olanzapine, 18.5±7.5 (10–35)		
Duration of treatment with olanzapine (days)	20.2±6.7 (13–33)		
Duration of illness (years)	5.2±7.3 (0.1–20)		
Age of onset (years)	25.4±8.2 (15–41)		
CGI Severity T1	4.5±1.0 (3–6)		$p<0.05$[b]
CGI Severity T2	3.4±0.7 (3–5)		
PANSS total T1	74.0±18.0 (38–104)		n.s.[b]
PANSS total T2	63.6±14.5 (42–81)		
PANSS positive T1	15.2±4.3 (8–20)		n.s.[b]
PANSS positive T2	13.7±4.0 (8–19)		
PANSS negative T1	22.8±9.3 (9–36)		n.s.[b]
PANSS negative T2	19.9±6.4 (11–33)		

[a] *t* Test for independent samples
[b] Paired *t* tests

Patients and healthy controls were investigated with functional magnetic resonance imaging (fMRI) at two time points (T1 and T2). Schizophrenic patients were scanned for the first time (T1) after having received typical neuroleptic medication (i.e., flupenthixol, haloperidol, or fluphenazine; see Table 1) for 2 weeks. The second scan (T2) was performed after they were switched to olanzapine, with an interval of 4 weeks from the first scan and after at least 2 weeks of treatment with olanzapine (18.5±7.5 mg; Table 1). Switching from conventional antipsychotics to olanzapine was conducted according to clinical demands. Psychopathological symptoms were assessed at both time points with the Positive and Negative Syndrome Scale (Kay et al. 1987; Table 1). Healthy volunteers were also scanned twice, with the second scan (T2) being performed approximately 4 weeks after the first one. There were no differences between the schizophrenic and the control group in age (t=0.301, p>0.7), handedness (t=−0.043, p>0.9), IQ (t=1.845, p=0.082) or interval between scan 1 (T1) and scan 2 (T2; t=0.136, p>0.8; Table 1). Patients showed significantly poorer performance than controls in the WCST (perseveration error; t=−2.129, p=0.049).

A total of six controls and six schizophrenic patients were identified as smokers. There were no significant group differences in number of cigarettes per day (patients, 9.2± 9.2 and controls, 7.1±7.7 cigarettes per day; t=−0.547, p>0.5). Participants smoked their last cigarette on average 63±92 min before scanning (range, 5 to 360 min), and there were no significant differences between group (F=2.049, p=0.190) and session (F=2.026, p=0.192) and no group × session interaction (F=1.599, p=0.242) using an analysis of variance (ANOVA) with repeated measures.

It is known that performance differences between patients and controls can confound interpretation of imaging data (Callicott et al. 2003). Therefore, groups were matched for total monetary gain (Table 1).

Monetary incentive delay task

We used a "monetary incentive delay" (MID) task, which is an event-related design, as described by Knutson et al. (2001) to invoke anticipation of reward (gain) and punishment (loss) in schizophrenic patients and normal

volunteers. Subjects were scanned using functional magnetic resonance imaging during trials in which they anticipated potential monetary gain, loss, or no consequences. Participants' monetary gain depended on their performance on a simple reaction-time task at the end of each trial, which involved pressing a button during the brief presentation of a visual target. Trial structure is depicted in Fig. 1. An adaptive algorithm for target duration ensured in an online manner that subjects succeeded on an average of 67% of trials. Before the experiment, participants completed a practice version of the task, for which they did not receive monetary payment, to minimize later-learning effects in the scanner. Subjects were also informed about the amount of money that they could earn for performing the task successfully in the scanner, and cash was shown to them. Once in the scanner, anatomical and functional scans were collected. A MID task session consisted of two runs including 72 trials each. The mean trial duration was approximately 8 s (7.69 s), and the mean inter-trial interval was 3.53 s (for details, see the legend of Fig. 1). After scanning, subjects retrospectively rated their own exertion in response to each of the seven cues on a visual analogue scale (VAS effort).

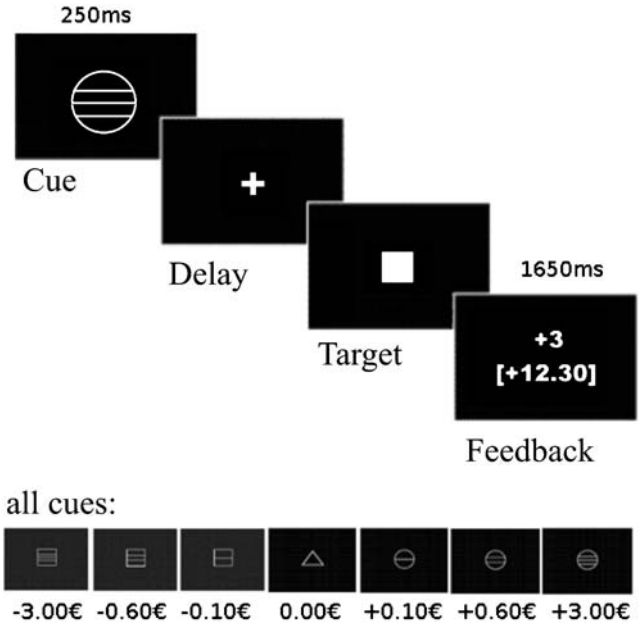

Fig. 1 Task structure for a representative trial. During each trial, volunteers saw one of seven shapes ("cue"; 250 ms), which indicated that they would, in a few moments, be able to respond and either win or avoid losing different amounts of money (3.00 €, 0.60 €, or 0.10 €), or that they should respond for no monetary outcome. The different cues are shown at the *bottom* of the figure. Cues signaling potential gain were denoted by *circles*, potential loss was denoted by *squares*, and no monetary outcome was denoted by *triangles*; the possible amount of money that subjects were able to win was indicated by *one horizontal line* for 0.10 €, *two horizontal lines* for 0.60 € and *three horizontal lines* for 3.00 €. Similarly, loss cues signaled the possibility of losing the same amounts of money. After the cue, volunteers waited a variable interval (delay; 3,740–4,240 ms) and then responded to a white target square that appeared for a variable length of time (target; 200–1,000 ms) by pressing a button. To succeed in a given trial, volunteers had to press the button during which the target was visible. During incentive trials, volunteers could win or avoid losing money by pressing the button during target presentation. Chance of winning was 66%. Immediately after target presentation, feedback appeared ("feedback"; 1,650 ms), notifying volunteers that they had won or lost money and indicating their cumulative total at that point. The inter-trial interval was between 3,280 and 3,780 ms. Trial types were randomly ordered within each session

Behavioral data

Group and time differences in behavioral data (reaction time and VAS effort) were computed with SPSS™ (version 12.0) using a 2×7×2 ANOVA design with repeated measures with session and cue as intrasubject factors and group as intersubject factor. Differences in other measures (age, IQ, etc.) between schizophrenic patients and healthy controls were assessed with two-sample *t* tests, and differences in psychopathological symptoms [Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI)] between the first and second scans were assessed with paired *t* tests in the patient group (significance level $p<0.05$).

Functional magnetic resonance imaging

fMRI was performed with a 1.5 Tesla scanner (Magnetom VISION Siemens®) equipped with a standard circularly polarized head coil (CP-Headcoil) using gradient-echo echo-planar imaging (GE-EPI, TR = 1.9 s, TE = 40 ms, flip angle = 90°, matrix = 64 × 64, voxel size = 4 × 4 × 3.3 mm). Eighteen slices approximately parallel to the bicommissural plane (ac–pc plane) were collected, covering the inferior part of the frontal lobe (superior border above the caudate nucleus), the entire temporal lobe, and large parts of the occipital region. Six fMRI volumes were acquired per trial, resulting in 450 volumes per run. For anatomical reference, a three-dimensional (3D) Magnetization Prepared Rapid Gradient Echo (MPRAGE, TR=9.7 ms; TE=4 ms; flip angle 12°; matrix = 256 × 256, voxel size=1×1×1 mm) image data set was acquired. Head movement was minimized using a vacuum pad.

fMRI data analysis

Functional MRI data were analyzed with SPM2 (http://www.fil.ion.ucl.ac.uk/spm). The first three volumes of each functional time series were discarded to remove non-steady-state effects caused by T1 saturation. Slice time correction was conducted to adjust for time differences due to multislice imaging acquisition. To correct for between-scan movements, all volumes were realigned to the first volume. Motion correction showed a mean maximal head movement of 1.5±0.86 mm (range, 0.53–4.00 mm) during

the entire experiment. There were no significant effects of group (F=0.003, p=0.958), session (F=0.759, p=0.395), or group × session interaction (F=2.187, p=0.156) in a repeated-measure ANOVA. The structural 3D data set was co-registered with the first functional image. The functional images were spatially normalized to the EPI standard template provided by the Montreal Neurological Institute (MNI template) using the algorithm implemented in SPM2 (12-parameter affine transformation followed by a non-linear algorithm using 7×8×7 harmonic basis functions to compensate local anatomical differences). Finally, the normalized images, with a voxel size of 3×3×3 mm, were smoothed with a Gaussian kernel (full width at half maximum=8 mm) to create a locally weighted average of the surrounding voxels. The pre-processed functional MRI data were then analyzed in the context of the general linear model (GLM) approach (Friston et al. 1995), using a two-level procedure.

At a first level, changes in the blood-oxygenation-level dependent (BOLD) response for each subject can be assessed by linear combinations of the estimated GLM parameters (beta values), which are contained in the individual contrast images (equivalent to percent signal change or effect size). This analysis was performed by modeling the seven cue conditions separately as explanatory variables convolved with the gamma-variate function described by Cohen (1997) and similar to Knutson et al. (2001) and Breiter et al. (2001). To remove low-frequency signal drifts and high-frequency physiological artifacts caused by respiration and cardiologic effects, the voxel time series were filtered with a high pass (cut off frequency= 1/128 Hz) and temporally smoothed with a moving Gaussian kernel [full width at half maximum or (FWHM)=4 s]. After this procedure, the GLM was fitted into the pre-processed data set.

At the second level of analysis, brain activations in the group of schizophrenics and in the healthy controls were determined with one-sample t tests using the individual contrast images "anticipation of gain > neutral condition" comparison at both time points. This contrast compared cues which indicated potential monetary gain with cues which indicated that the motor response will have no monetary consequences, i.e., the neutral condition. At the confirmatory level, we tested the a priori hypotheses of activation differences in the ventral striatum during reward anticipation. We used statistical parametric mapping (SPM)'s small-volume correction using a ventral striatal volume of interest (VOI; right and left, 1,377 mm^3, 51 voxels). This was specified by a voxel mask from a publication-based probabilistic MNI atlas (Fox and Lancaster 2002; Nielsen and Hansen 2002) used as a binary mask at the threshold of 0.75 probability (please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date Aug. 1, 2006). The significance level for the group contrasts was p<0.05 family-wise error (FWE)-corrected for the ventral striatal VOI. All other activations are reported on p<0.05 corrected for cluster level (threshold for inclusion into clusters was p<0.001 uncorrected). Transformation from MNI to Talairach coordinates was performed with the tool provided by Matthew Brett (http://www.fil.ion.ucl.ac.uk/spm). As in our previous studies (Juckel et al. 2006a, b), we correlated the individual maximum fMRI BOLD contrast (beta values) in the ventral striatal region of interest (ROI) for the contrast "anticipation of gain vs no outcome" with the psychopathology (i.e., the negative scale of the PANSS) using Spearman's linear correlation coefficient. Differences in ventral striatal activations of patients vs controls at time point T1 vs T2 were assessed by computing the interaction between group (schizophrenics and controls) and session (time points 1 and 2) with a VOI analysis by extracting the maximum beta value from the ventral striatal VOI and by conducting an ANOVA with repeated measures in SPSS™ with group and session as fixed factors.

Results

Performance

Hit rate (i.e., proportion of successful button presses during target presentation) did not differ between healthy controls (67.9%±15.3%) and schizophrenic patients (68.5%± 13.0%). The overall gain did not differ between healthy controls and schizophrenic patients (F=0.935, p=0.340) nor between the sessions (F=1.620, p=0.211), and there was no significant group × session interaction (F=0.129, p=0.722).

Reaction times

The reaction times (Fig. 2) showed a significant difference between the incentive value cues (F=5.146, p=0.006) and groups (F=5.962, p=0.025). There was a statistical trend for the session factor (F=3.726, p=0.069), reflecting a faster reaction time at T2. There were no significant interactions for group × session (F=2.110, p=0.164) or cue × group (F= 1.110, p=0.408) or group × session × cue (F=1.008, p= 0.461). In post hoc t tests, the schizophrenic patients were slower than the healthy controls at T1 (t=-2.513, p=0.022), but not at T2 (t=-1.351, p=0.194). Post hoc paired comparisons revealed that the reaction time between the neutral condition and all incentive cues (except −0.1 €) was significantly slower but did not differ between the different (gain and loss) incentive cues (except between −0.1 € and +3.0 €). The absence of a cue by group interaction

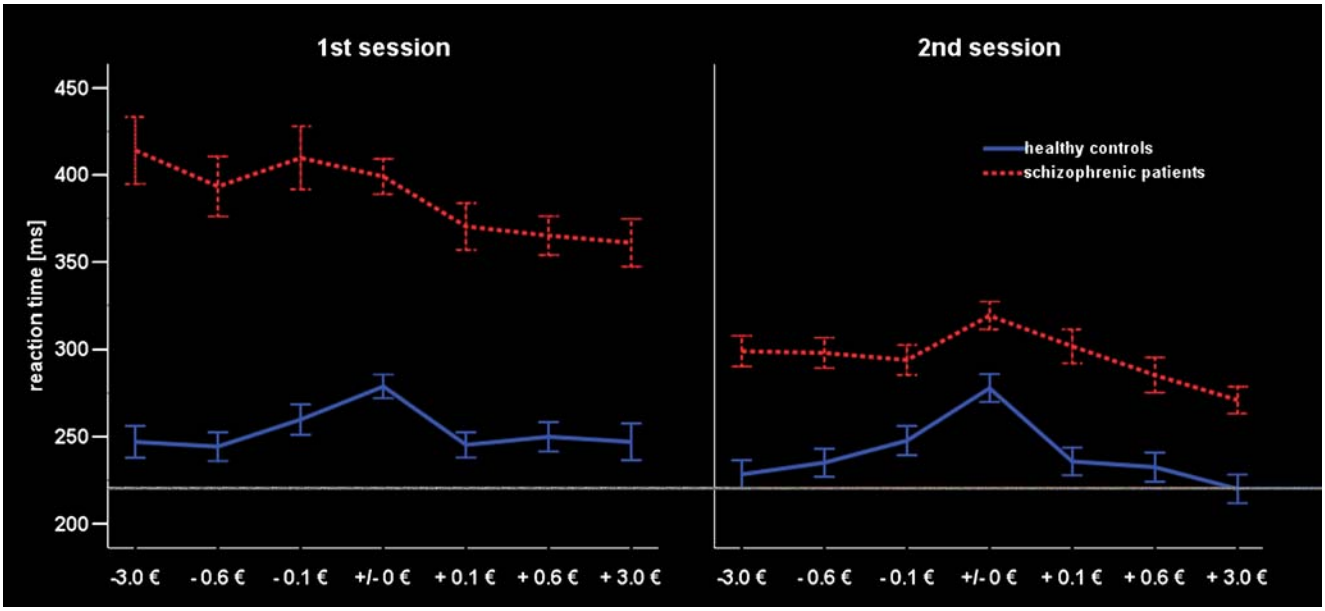

Fig. 2 Reaction times with standard errors of schizophrenic patients (*red dotted line*) and healthy controls (*blue line*) at both time points (first and second sessions) for the different reward value cues

indicated that the participants understood the paradigm and confirmed that the groups were matched for performance (total monetary gain).

Visual analog scale

The incentive value of each cue did alter effort ratings in the visual analog scale. There was a significant effect of the incentive cue value on the VAS effort scale (F=6.054, p=0.003) but no significant group (F=0.245, p=0.626), session (F=0.045, p=0.834) or interaction effects (F=0.432–1.868, p>0.1). Specifically, paired comparisons indicated that all participants reported experiencing more effort when high value (+3.0 € or −3.0 €) cues appeared, relative to neutral or low incentive cues (0.0 €, +0.1 €, or −0.1 €).

Confirmatory analysis of group differences during anticipation of reward

In accordance with previous studies, healthy control subjects showed a significant increase in BOLD response during anticipation of potential monetary gain vs no outcome in the bilateral ventral striatum including the nucleus accumbens at both time points (Table 2 and Fig. 3).

Schizophrenic patients treated with typical neuroleptics did not show a significant BOLD response in the ventral striatum during anticipation of gain vs no outcome (Table 2 and Fig. 3). After having been switched to olanzapine, schizophrenic patients showed a significant activation of the right ventral striatum including the nucleus accumbens during gain anticipation compared to the neutral condition (Table 2 and Fig. 3).

For the contrast anticipation of potential monetary loss vs no outcome, healthy controls displayed a significant BOLD response in the bilateral ventral striatum at T1 and the right ventral striatum at T2. Schizophrenic patient at T1, while receiving typical antipsychotics, revealed a significant BOLD response in the left ventral striatum. After the switch to olanzapine, patients did not show a significant ventral striatal activation (see ESM Table 1).

There were no significant deactivations in both groups at both time points at the chosen threshold for the contrasts “anticipation of monetary gain > neutral condition” nor for the contrast “anticipation of monetary gain > neutral condition”.

Correlation with psychopathology

In schizophrenic patients treated with typical neuroleptics (T1), low left ventral striatal activation during gain anticipation was significantly correlated with high severity of negative symptoms as measured with the PANSS (PANSS negative scale, R=−0.721, p=0.019). After the switch to olanzapine (T2), no significant correlation between BOLD contrast in the ventral striatum and psychopathology was observed. No significant correlation was found between reaction time (cue specific and vs neutral) and BOLD in schizophrenic patients and controls.

VOI analysis

VOI analysis using an ANOVA with repeated measures revealed a significant interaction between group and session for the peak activation in the right ventral striatum (F=

Table 2 Activation during anticipation of monetary gain compared to the neutral condition in the healthy controls at two time points (T1 and T2) and in schizophrenic patients while treated with typical neuroleptics and after switching to olanzapine

	BA		*p* corrected	Cluster size	*t* value	*p* uncorrected	*x*	*y*	*z*
Healthy controls at T1									
Ventral Striatum		L	0.004	34	3.870	0.002	−18	6	−9
		R	0.004	32	4.700	0.001	18	6	−3
Sub-lobar									
Putamen		R	0.002	77	6.376	0.000	18	6	3
Amygdala		R			5.982	0.000	24	−3	−18
Limbic Lobe									
Posterior cingulate	31	L	0.002	77	6.757	0.000	−24	−60	12
Cuneus	30	L			5.549	0.000	0	−72	0
Occipital cortex									
Middle occipital gy.	19	L	0.012	52	6.258	0.000	−27	−90	6
Lingual gy.	17/18	R	0.004	66	5.580	0.000	3	−81	−15
	17	R			5.236	0.000	9	−93	−9
Midbrain			*0.064*	33	6.668	0.000	0	−15	−18
Cerebellum			0.006	61	6.452	0.000	6	−57	−18
					5.906	0.000	−6	−60	−18
Healthy controls at T2									
Ventral striatum		L	0.003	22	6.070	0.000	−15	6	−3
		R	0.024	5	4.440	0.001	15	15	−3
Basal ganglia									
Claustrum		L	0.000	187	6.339	0.000	−33	−6	−6
Putamen		L			6.252	0.000	−21	−3	6
Basal ganglia									
Putamen		R	0.000	72	5.485	0.000	18	15	0
Lateral G. pallidus		R			5.156	0.000	21	−3	0
Temporal lobe									
Sup. temporal gy.	29	L	0.026	23	5.566	0.000	−51	−36	15
Frontal lobe									
Precentral gy.	6	R	*0.084*	17	4.956	0.000	63	0	12
Basal ganglia									
Claustrum		R	*0.084*	17	4.947	0.000	36	0	3
Schizophrenic patients with typical at T1									
Ventral striatum		L	–						
		R	–						
Schizophrenic patients with olanzapine at T2									
Ventral striatum		L	–						
		R	0.018	9	4.360	0.001	15	6	−12

Ventral striatal activations are $p<0.05$ FWE-corrected for ventral striatal VOI. All other results are clusters with $p<0.05$ on the cluster level at $p<0.001$ uncorrected (three clusters with statistical tendency at $p<0.1$ are reported with an italic corrected p value).
Displayed are the corrected p value on the cluster level ($p<0.1$), the cluster size, the t values, uncorrected p values, and coordinates in MNI space of the peak voxels.
– No activation in ventral striatal VOI at $p<0.005$ uncorrected; *gy.* gyrus

6.406; $p=0.021$) but no significant group ($F=3.328$, $p=0.085$) or session ($F=1.507$, $p=0.235$) effect.

The group × session interaction in the right ventral striatum was further assessed with post hoc tests. At time point T1, there was a significant group difference in the right ventral striatum between healthy controls and schizophrenic patients with reduced BOLD response in schizophrenic patients (two-sample t test, $t=2.662$, $p=0.016$). After the switch to olanzapine (T2) there was no significant group difference (two-sample t test, $t=-0.102$, $p=0.920$).

BOLD response in the right ventral striatum in schizophrenic patients showed no significant increase from T1 (treatment with typical neuroleptics) to T2 (treatment with olanzapine; post hoc paired t test, $t=-0.788$, $p=0.451$), whereas the right ventral striatal activation in the healthy controls showed a significant decrease ($t=3.345$, $p=0.009$; Fig. 4).

We found no such interaction between group and session for the activation in the left ventral striatum (group, $F=2.766$, $p=0.114$; session, $F=3.005$, $p=0.100$; group × session, $F=0.321$, $p=0.578$).

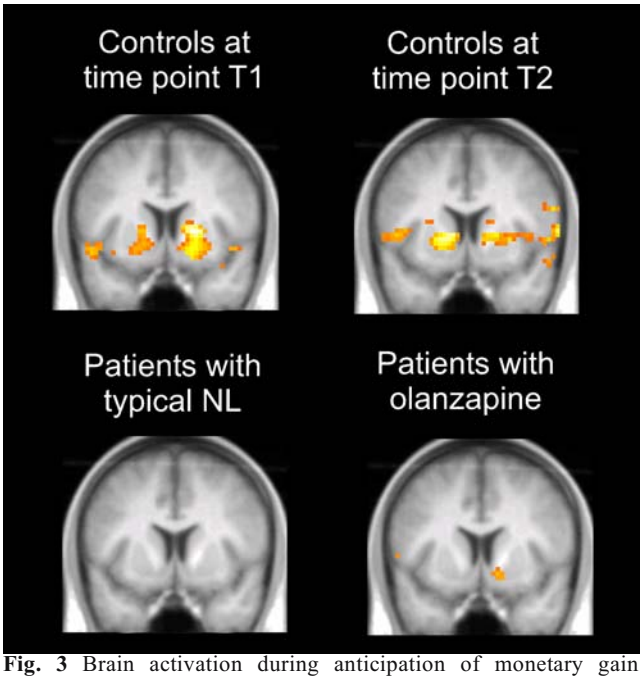

Fig. 3 Brain activation during anticipation of monetary gain compared to the neutral condition. Schizophrenic patients were scanned while medicated with typical neuroleptics (T1) and after switching to olanzapine (T2), unmedicated healthy controls were scanned at equivalent time points [for illustrative purpose $p<0.005$ uncorrected; slices displayed at MNI $y=9$ in neurological convention, displayed on a group template (mean image of individual normalized MPRAGEs smoothed with FWHM=4 mm)]

An ANOVA with repeated measures for the contrast anticipation of loss compared to the neutral condition using the peak activation in the right ventral striatum revealed a significant interaction between group and session ($F=9.185$; $p=0.007$) but no significant group ($F=2.195$, $p=0.156$) or session ($F=3.562$, $p=0.075$) effect, indicating a significant decrease form T1 to T2 in the healthy control group ($t=3.497$, $p=0.007$) and a numeric increase in the patient group ($t=-0.804$, $p=0.442$). We found no such interaction between group and session for the activation in the left ventral striatum (group, $F=1.502$, $p=0.236$; session, $F=3.778$, $p=0.068$; group × session, $F=0.985$, $p=0.334$).

To assess the test–retest reliability of our paradigm, we computed the intra-class coefficient (ICC) of the maximum ventral striatal VOI values for gain anticipation from session T1 and T2 within the healthy control group. We found a significant correlation for activation in the right ($R=0.764$, $p=0.021$) but not left ventral striatum ($R=0.098$, $p=0.440$).

Exploratory analysis

Significant activations during reward anticipation outside the ventral striatum from the whole-brain analysis are reported in Table 2 (only clusters at $p<0.05$ corrected at the cluster level are reported). Healthy controls at time point T1 activated the right putamen and amygdala, the left posterior cingulate, and bilateral occipital areas and showed a statistical trend for a cluster in the midbrain and in the

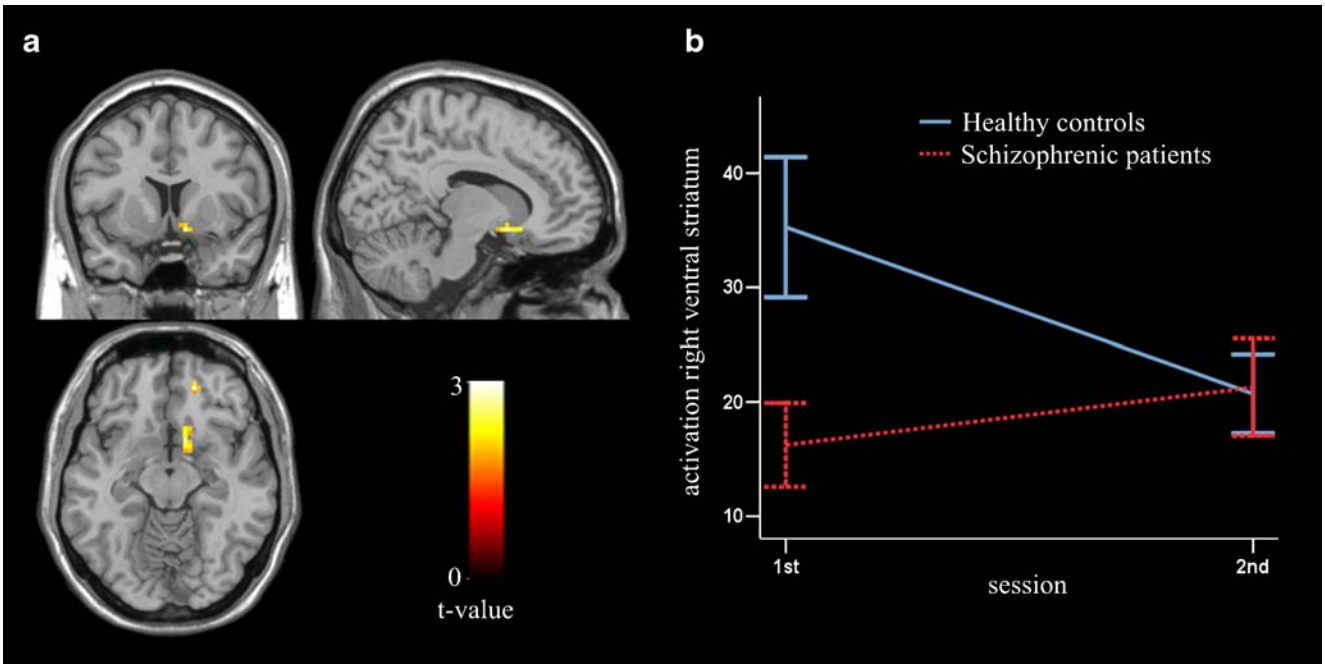

Fig. 4 Schizophrenic patients showed higher increase in the right ventral striatum between T1 and T2 compared to healthy controls during reward anticipation. On the *left*, **a** paired *t* test between schizophrenics while medicated with typical antipsychotics and after switching to olanzapine (displayed at MNI coordinates [*x y z*]=(12 9 −12), for illustrative purpose $p<0.05$ uncorrected). On the *right*, **b** VOI analysis of right ventral striatum with beta values for the contrast anticipation of gain vs neutral condition for both groups and time points (session T1 and T2)

cerebellum. At time point T2, the healthy controls displayed significant clusters in the bilateral basal ganglia, the left superior temporal gyrus (BA 29), and a statistical trend for the precentral gyrus (BA 6) and another cluster in the right basal ganglia. Schizophrenic patients did not show significant clusters outside the ventral striatum. Healthy controls at time point T1 displayed stronger activation than the schizophrenic patients while treated with typical neuroleptics of the cerebellum (cluster size=169, $p_{\text{at the cluster level}}$ <0.001, peak voxel, t=5.617, [x y z]=[−6 −60 −18]). At time point T2, healthy controls displayed a statistical trend towards a stronger activation of the precentral gyrus (cluster size=31, $p_{\text{at the cluster level}}$=0.096, peak voxel, t=4.591, [x y z]=[24 0 27]).

Discussion

These findings support the hypothesis that dysfunction of the ventral striatum/nucleus accumbens during reward anticipation is found in patients treated with typical neuroleptics and that this dysfunction correlates with the severity of negative symptoms. In a previous study of a different group of schizophrenics (Juckel et al. 2006a), patients treated with typical neuroleptics also displayed reduced activation of the ventral striatum during reward anticipation, which was also inversely correlated with the severity of negative symptoms. Moreover, similar to the present study, patients treated with atypical neuroleptics did not differ significantly from healthy controls with respect to ventral striatal, and we observed no significant correlation with the severity of negative symptoms (Juckel et al. 2006a). However, in this previous study, individual differences in schizophrenic patients may have contributed to the observed group differences between patients treated with typical vs atypical neuroleptics. In the current study, the same schizophrenic patients were tested twice, once during treatment with typical neuroleptics and again after having been switched to the newer neuroleptic olanzapine, thus limiting effects of interindividual variance. The absence of a significant difference in the ventral striatal BOLD response between healthy controls and patients switched to olanzapine seems important in the light of our previous study, which showed a significant reduction in ventral striatal activation during reward anticipation in unmedicated schizophrenic patients (Juckel et al. 2006b). Altogether, both unmedicated patients and patients with typical neuroleptics displayed a reduced ventral striatal BOLD response during reward anticipation, which was not found in patients treated with olanzapine.

In healthy controls, test performance remained stable, while the BOLD response in the ventral striatum decreased at time point T2 compared with T1. This observation may indicate learning effects due to repeated testing, which can increase the efficiency of signal processing and decrease the associated BOLD response. Indeed, in the prefrontal cortex, decreases of the BOLD response at a given level of test performance have been interpreted as increased efficiency of task-relevant information processing (Callicott et al. 2003). On the other hand, schizophrenic patients who were switched from typical neuroleptics to the newer neuroleptic olanzapine showed no decrease in the task-associated BOLD response, and individual ventral striatal BOLD responses were no longer associated with the severity of negative symptoms.

It has previously been observed that typical neuroleptics cause a high degree of striatal dopamine D2 receptor blockade (Farde et al. 1992; Kapur and Seeman 2001), which was clinically associated with a high level of negative symptoms such as apathy (Heinz et al. 1998). According to Schultz et al. (1998), phasic dopamine release signals a prediction error in the expectance of reward or conditioned stimuli that indicate upcoming reinforcement. In the paradigm developed by Knutson et al. (2001), the possibility to gain reward or avoid loss is predicted by abstract stimuli, which were not preceded by any other cue, i.e., they were unexpected and thus reflect a prediction error with respect to reward anticipation. In accordance with this hypothesis, the presentation of cues that predict reward (and, to a lesser degree, also of cues that predict the ability to avoid loss) was associated with a phasic increase in the ventral striatal BOLD response of healthy control subjects (Juckel et al. 2006a, b; Knutson et al. 2001). We and others have postulated that in schizophrenia, increased striatal dopamine release may attribute incentive salience to otherwise irrelevant stimuli (Heinz 2002; Kapur 2003; Meisenzahl et al. 2007). Indeed, an increased BOLD response to neutral stimuli was found in the ventral striatum and ventral tegmental area/substatia nigra of schizophrenic patients during processing of a prediction error (Corlett et al. 2007; Jensen et al. 2007; Murray et al. 2007). However, in these studies, as in the current study, central dopaminergic neurotransmission was not directly assessed. When Knutson et al. (2004) applied amphetamine to healthy controls to stimulate dopamine release, reward-indicating cues no longer elicited a phasic BOLD response in the ventral striatum. Similarly, reward-indicating cues did not significantly activate the ventral striatum in unmedicated schizophrenic patients, who presumably suffer from increased striatal dopamine turnover (Abi-Dargham et al. 2000; Kumakura et al. 2007). On the other hand, dopamine D2 blockade caused by haloperidol has also been shown to reduce the prediction-error-related BOLD response in the ventral striatum (Menon et al. 2007). High degrees of striatal dopamine D2 receptor blockade by typical neuroleptics may thus interfere with the attribution of incentive

salience to conditioned stimuli, i.e., incentive learning (Beninger 2006), and Paquet et al. (2004) described a procedural learning deficit in haloperidol treated patients (6 mg), but not in patients receiving olanzapine (14 mg) or healthy controls.

Once patients were switched to olanzapine in the current study, the task-associated BOLD response no longer differed significantly from the response observed in healthy controls and no longer correlated with the severity of negative symptoms. It may be tempting to speculate that olanzapine's pharmacological effects, e.g., lower blockade of and faster dissociation from the dopamine D2 receptor (Kapur and Seeman 2001) or the additional blockade of 5-HT_{2A} receptors (Meltzer et al. 2003), may help to preserve some degree of dopaminergic neurotransmission in the ventral striatum, which then no longer differs significantly from healthy controls and may therefore cause less secondary, neuroleptic-induced negative symptoms. However, neither the increase in ventral striatal activation from T1 to T2 nor the decrease in overall negative symptoms was statistically significant. Moreover, our study only measures the BOLD response, which rather indirectly reflects brain activation, and does not address dopaminergic neurotransmission. Further studies that combine fMRI with a measurement of the degree of dopamine D2 receptor blockade (with positron emission tomography) may help to directly assess effects of typical and atypical neuroleptics on striatal dopaminergic neurotransmission and functional activation during reward anticipation as well as their respective interaction with negative symptoms.

To date, only a few neuroimaging studies have compared the effect of typical antipsychotics with olanzapine on brain function (Muller et al. 2003; Muller and Klein 2000). Important for our study, a single dose of olanzapine (15 mg) but not haloperidol (10 mg) increased resting ventral but not dorsal striatal-regional cerebral blood flow (Lahti et al. 2005). A recent fMRI study showed that acute application of a single dose of olanzapine in healthy subjects altered reduced reward-related brain activity in the ventral striatum in a monetary reward paradigm similar to ours and that this effect was independent of the overall drug effects assessed with a hypercapnic challenge (Abler et al. 2007). Although acute drug effects in healthy controls may substantially differ from chronic drug effects in schizophrenic patients, these findings confirm a modulation of reward-associated activation by olanzapine.

Given reduced BOLD response in schizophrenic patients vs healthy controls at corresponding levels of performance, the question may arise how the patients do the task. We would like to emphasize that schizophrenic patients showed a significant BOLD response to cues indicating potential loss and that their mean reaction time was rather high, so that the threshold for successful responding was indirectly adjusted to ensure similar monetary gain. However, our study was supposed to reflect Pavlovian conditioning and the attribution of incentive salience to reward-indicating cues and does not address the question which brain areas drive behavior adjustment/operant conditioning. This question was addressed in a separate study in healthy controls and showed that different brain areas drive motor adjustment, e.g., the ventral striatum after unexpected gain or the dorsal striatum after expected gain (Wrase et al. 2007).

Several limitations of this study need to be addressed in future research. First, although the test–retest design limited the effect of interindividual variance, the sample size was small, and so the findings require replication in an independent sample. Some patients and controls showed a rather poor performance; however, our sample was too small to address subgroup differences, which should be done in further studies. Furthermore, patients were scanned only once in each treatment condition, preventing independent assessment of temporal effects of schizophrenic patients. However, temporal effects were observed in healthy controls and went in the opposite direction (i.e., a decrease rather than an increase in the ventral striatal BOLD response during reward anticipation).

In summary, these findings demonstrate that schizophrenic patients treated with typical neuroleptics respond with decreased ventral striatal activation during reward anticipation, while this was no longer the case after the patients were switched to olanzapine. Both patients treated with typical neuroleptics and unmedicated schizophrenics tested in previous studies (Juckel et al. 2006a, b) failed to activate the ventral striatum during reward anticipation. Moreover, decreased activation of the brain reward system was associated with increased negative symptoms in both unmedicated schizophrenics and in patients treated with typical neuroleptics. Failure to normalize reward anticipation in the ventral striatum may limit the effectiveness of typical neuroleptics in treating negative symptoms. The combination of positron emission tomography studies that directly assess dopaminergic neurotransmission and fMRI studies that measure task-relevant BOLD response (Siessmeier et al. 2006) may help to further quantify pharmacological drug effects on task-specific brain activation and correlated clinical symptoms.

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