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Dysfunction of ventral striatal reward prediction in schizophrenia

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Background: **Negative symptoms may be associated with dysfunction of the brain reward system in schizophrenia. We used functional magnetic resonance imaging (fMRI) to assess the BOLD response in the ventral striatum of unmedicated schizophrenics during presentation of reward-indicating and loss-indicating stimuli.**
Methods: **A total of 10 schizophrenic men (7 never medicated, 3 unmedicated for at least 2 years) and 10 age-matched healthy male volunteers participated in an incentive monetary delay task, in which visual cues predicted that a rapid response to a subsequent target stimulus would result either in monetary gain or loss or would have no consequence.**
Results: **Compared to healthy controls, unmedicated schizophrenics showed reduced ventral striatal activation during the presentation of reward-indicating cues. Decreased activation of the left ventral striatum was inversely correlated with the severity of negative (and trendwise positive) symptoms.**
Discussion: **Reduced activation in one of the central areas of the brain reward system, the ventral striatum, was correlated with the severity of negative symptoms in medication-free schizophrenics. In unmedicated schizophrenic patients, a high striatal dopamine turnover may increase the "noise" in the reward system, thus interfering with the neuronal processing of reward-predicting cues by phasic dopamine release. This, in turn, may contribute to negative symptoms as such as anhedonia, apathy, and loss of drive and motivation.**

Introduction

Negative symptoms figure prominently in the prodromal and early phase of schizophrenia, adversely affecting patients' well-being and compliance with treatment (Andreasen, 1990; Harrow et al., 1994; Ruhrmann et al., 2003; Strous et al., 2004). While brain imaging research has long focused on the neurobiological correlates of cognitive dysfunction in prefrontal–striatal–thalamic neurocircuits (Andreasen et al., 1996; Callicott et al., 2000; Meyer-Lindenberg et al., 2002, 2005; Abi-Dargham et al., 2002; Molina et al., 2003), only a few imaging studies have examined the central correlates of negative symptoms associated with affective dysfunction in schizophrenia, such as affective flattening or anhedonia (Breiter et al., 1997; Crespo-Facorro et al., 2001; Heinz et al., 1998). Anhedonia and other predominantly affective negative symptoms may be caused by a dysfunction of dopaminergic neurons in the ventral striatum, including the nucleus accumbens—a core region of the brain reward system (Breiter et al., 1997). This condition may be the result of a primary disconnection between the prefrontal and temporolimbic cortices (Carlsson et al., 1999; Sesack and Carr, 2002; Weinberger and Lipska, 1995). The ventral striatum, including the nucleus accumbens, is activated by events essential to the survival of the species, such as those related to food, sexuality, or important social interactions (Berridge and Robinson, 1998; Robbins and Everitt, 1996; Wise, 1982). Ventral striatal activity has been associated with pleasant emotions of anticipation (Berridge and Robinson, 1998), and ventral striatal dysfunction has long been associated with reduced motivation or anhedonia (Goldstein and Volkow, 2002; Wise, 1982). Because brain imaging techniques can be used to observe activation in the ventral striatum, impairments in this area of the brain can now be visualized in humans (Breiter et al., 1997; Knutson et al., 2001).

To date, brain imaging studies investigating the central correlates of negative symptoms in schizophrenia have primarily examined patients who are on neuroleptic medication (Crespo-Facorro et al., 2001; Heinz et al., 1998). In these patients, reduced activation resulting from the presentation of affective pictures and human faces was observed in limbic and paralimbic brain areas such as the amygdala, hippocampus, prefrontal (PFC) and insular cortex, nucleus accumbens, and parahippocampal gyrus (Schneider et al., 1998; Gur et al., 2002; Taylor et al., 2002; Takahashi et al., 2004). In paradigms using event-related potentials, negative

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symptoms were associated with a reduction in P300 amplitude (Mathalon et al., 2000). However, in these studies, neuroleptic blockage of dopamine D2 receptors in the ventral striatum may interfere with the processing of reward-indicating cues (Berridge and Robinson, 1998; Robbins and Everitt, 1996; Wise, 1982) and may cause secondary negative symptoms that mimic primary negative symptoms associated with schizophrenia (Heinz et al., 1998; Schmidt et al., 2001). Therefore, we examined unmedicated schizophrenics and healthy controls subjects by measuring ventral striatal activation during the presentation of stimuli that predicted monetary gain or loss (Knutson et al., 2001). We hypothesized that unmedicated schizophrenics would show reduced ventral striatal activation during reward anticipation and that reductions in ventral striatal activation would, in turn, be associated with the severity of negative symptoms.

Methods

Subjects and instruments

The local ethics committee approved the study, and written informed consent was obtained from all participants after the procedures had been fully explained. A total of 10 unmedicated schizophrenic male patients (mean age: 26.8 ± 7.8, range 19–34) who fulfilled DSM-IV and ICD-10 criteria for schizophrenia and had no other psychiatric axis I disorders (SCID interview) (First et al., 2001) and no current drug abuse or past history of drug dependence (SCID interview and random urine drug testing) were recruited at the Charity University Medical Center's Department of Psychiatry and Psychotherapy (Campus Charité Mitte). Of these participants, 7 were completely drug naive, and 3 had been drug-free for at least 2 years (2 had been treated with olanzapine 10 mg for 12 weeks 2 years prior to the study and 1 with quetiapine 300 mg for 3 weeks 3 years prior to the study). The duration of illness was 1.9 ± 1.5 years, and the age of onset was 25 ± 4.6 years. Psychopathological symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

The control group included 10 healthy males (mean age: 31.7 ± 8.4, range: 18–41) with no psychiatric axis I or II disorders (SCID interview) (First et al., 2001) and without any family history of psychiatric disorders. Control subjects were matched with schizophrenic subjects with regard to age and task performance (i.e. the total amount of money a patient won during the task, or "total gain") (Table 1). All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) (Table 1).

None of the patients or healthy control subjects had a current drug abuse or had a past history of drug dependence other than nicotine consumption (SCID interview and random urine drug testing). In total, 6 controls and 5 schizophrenics were identified as smokers (controls 8.0 ± 8.5 vs. schizophrenics 12.8 ± 15.1 cigarettes per day; t value −0.8, $P > 0.4$). These participants smoked their last cigarette on the average 117 ± 235 min before scanning (range: 10 to 780 min, no significant group difference t value 1.1, $P > 0.3$).

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, reaction time, effort for gain and to avoid loss (visual analogue scales, VAS), and positive emotions elicited by monetary gain (VAS) (Table 1). Patients and control subjects did not differ significantly with respect to attention or concentration as assessed with the d2 test (Zillmer and Kennedy, 1999), for verbal IQ (Word Sorting Test; Schmidt and Metzler, 1992), and executive function measured with the Wisconsin Card Sorting Test (WCST) (Heaton, 1981). Sample characteristics of patients and controls are given in Table 1. There were no significant group differences for any of the variables assessed (Student's t test; t value 0.2 to 1.2, $P > 0.1$, Table 1).

Table 1
Group description

	Schizophrenic patients	Healthy controls
Age (years)	26.8 ± 7.8 (19–34)	31.7 ± 8.4 (18–41)
Gender	10 males	10 males
Edinburgh Handedness Inventory	34.0 ± 1.9 (30–36)	34.7 ± 1.9 (30–36)
Reaction time (ms)	276.7 ± 99.8	266.6 ± 138.0
Total gain (in euro)	19.4 ± 8.2	16.4 ± 7.2
VAS effort for gain	8.2 ± 1.4	7.4 ± 1.6
VAS effort to avoid loss	9.5 ± 3.9	6.7 ± 2.3
VAS positive emotions elicited by monetary gain	197.5 ± 52.85	241.1 ± 47.6
Verbal IQ (WST)	106.0 ± 11.9	106.9 ± 9.3
Executive function (WCST)	80.5 ± 9.7	83.1 ± 11.7
Attention (d2)	97.0 ± 16.9	105.1 ± 11.2
Duration of illness (years)	1.9 ± 1.5 (0.2–5)	
Age of onset (years)	25 ± 4.6 (19–32)	
Medication	7 drug naive 3 received neuroleptics in the past at least 2 years ago	
PANSS total	92.8 ± 23.7 (56–129)	
PANSS positive	26.3 ± 7.6 (13–39)	
PANSS negative	23.1 ± 7.0 (12–31)	
CGI severity	5.5 ± 1.1 (4–7)	

Monetary incentive delay (MID) task

We used a "monetary incentive delay" (MID) task as described by Knutson et al. (2001) to invoke anticipation of reward (gain) and punishment (loss) in schizophrenic patients and normal volunteers. Subjects were examined using functional magnetic resonance imaging (fMRI) 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. Task details are given in Fig. 1. Before entering the scanner, 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 were able to earn for performing the task successfully in the scanner, and the money was shown in cash to them. Once in the scanner, anatomical and functional scans were collected. An MID task session consisted of two runs with 72 trials each. One trail took 8 s, and the inter-trial interval was 4 s (for details, see legend in Fig. 1). After the

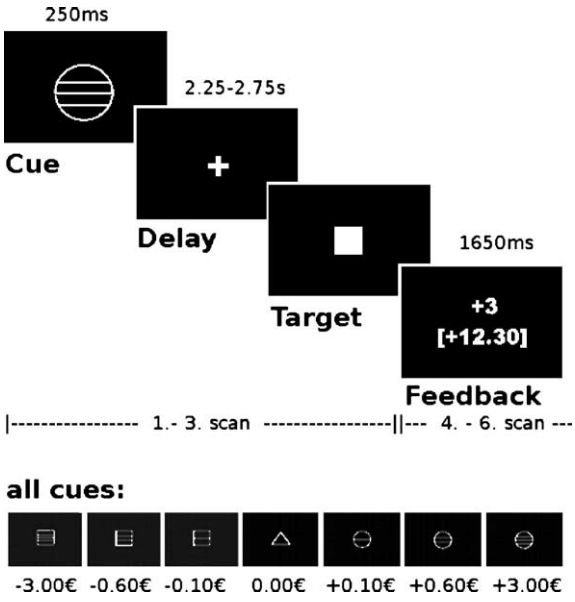

Fig. 1. Task structure for a representative trial. In each trial, volunteers saw one of seven shapes ("cue"; 250 ms), which indicated that they would, in a few moment, be able to respond and either win or avoid losing different amounts of money (3.00 euros, 0.60 euros, or 0.10 euros) or that they should 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 euro, two horizontal lines for 0.60 euro, and three horizontal lines for 3.00 euro. Similarly, loss cues signaled the possibility of losing the same amounts of money. After the cue, volunteers waited a variable interval (delay; 2000–2500 ms) and then responded to a white target square that appeared for a variable length of time (target; 200–400 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. Change 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 4000 ms. Trial types were randomly ordered within each session.

scanning, subjects retrospectively rated their own exertion in response to each of the 7 cues on a visual analogue scale (VAS effort, no significant group difference, Student t test; t value -1.1 and -1.9, $P > 0.05$ respectively, Table 1).

Functional magnetic resonance imaging

fMRI was performed on a 1.5 T 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 mm × 4 mm × 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. fMRI volume acquisitions were time-locked to the offset of each cue and were thus acquired during anticipatory delay periods. Six fMRI volumes were acquired per trial, resulting in 450 volumes per run. For anatomical reference, a 3D MPRAGE (*M*agnetization *P*repared *R*apid *G*radient *E*cho, TR = 9.7 ms; TE = 4 ms; flip angle 12°; matrix = 256 × 256, voxel size 1 mm × 1 mm × 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 in order to avoid non-steady state effects caused by T1 saturation. Sinc interpolation was used to realign all volumes to the remaining first volume to correct for between-scan movements and to remove signals correlated with head motion. Motion correction confirmed that no subjects showed more than 4 mm head movement during the run and less that 1 mm translation and 1° rotation in any dimension from one volume acquisition to the next. The structural 3D data set was coregistered with the first T2* image. The coregistered structural image was spatially normalized to the standard template provided by the Montreal Neurological Institute (MNI template) using an automated spatial transformation (12-parameter affine transformation followed by non-linear iterations using 7 × 8 × 7 basis functions). This transformation was subsequently applied to the T2* data, and a downsampling to a resolution of 3 × 3 × 3 mm voxel size was performed. The normalized images were smoothed with a Gaussian kernel (full width at half maximum = 8 mm) to create a locally weighted average of the surrounding pixels (Knutson et al., 2001).

Functional MRI data were then analyzed in the context of the general linear model (GLM) (Friston et al., 1995) as time series, modeled using the gamma-variate function described by Cohen (1997) and similar to Knutson et al. (2001) and Breiter et al. (2001). Data analysis was performed by modeling the different conditions ("gain", "loss" and "no [monetary] outcome" indicating cues) as explanatory variables convolved with Cohen's gamma-function. Changes in the BOLD response can be assessed using linear combinations of the estimated GLM parameters (beta values) and are contained in the individual contrast images (equivalent to percent signal change) for the anticipation of potential monetary gain versus anticipation of no monetary outcome ("gain vs. no outcome") and the anticipation of potential monetary loss versus anticipation of no monetary outcome ("loss vs. no outcome"), resulting in a t statistic for each voxel. To detect group activations in schizophrenic patients and in healthy controls, individual contrast images (i.e. the BOLD response differences) of all subjects in each group were included in a second-level random effects analysis, which compared within-group activation ("gain vs. no outcome", "loss vs. no outcome") with a one-sample t test and between-group differences with a two-sample t test ($P < 0.001$ uncorrected). To test the hypothesis of activation in the ventral striatum during reward anticipation, SPM's small volume correction (S.V.C.) was performed for the ventral striatal volume of interest (VOI) (3592 mm^3, 130 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 0.5 probability (please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date December 1, 2004). The significance level for the

group contrasts was $P < 0.05$ FWR-corrected for the ventral striatal VOI. Transformation from MNI to Talairach coordinates was performed with the tool provided by Matthew Brett (http://www.fil.ion.ucl.ac.uk/spm).

Correlation analysis between ventral striatal activation and psychopathology

In the confirmatory part of the analysis, we tested the hypothesis that the BOLD response in the ventral striatum during reward anticipation is inversely correlated with negative symptoms. Therefore, we correlated the individual maximal fMRI BOLD contrast (beta values) for the contrast "gain vs. no outcome" within the ventral striatal VOI with the negative scale of the PANSS using Spearman's linear correlation coefficient.

In the exploratory analysis, we assessed correlations between cue-induced activation of the ventral striatum and (1) the positive symptom scale of the PANSS as well as (2) the effects of potentially confounding variables such as smoking, age, and age of onset of schizophrenia. In these exploratory analyses, all P values reported are given for illustrative purposes only.

Results

Confirmatory analysis of group differences during anticipation of reward

In accordance with previous studies (Knutson et al., 2001), healthy control subjects showed a significant increase in BOLD

Table 2
Activations anticipation of potential gain and loss in comparison to the neutral condition for healthy controls, unmedicated schizophrenics, and group comparisons

	Anticipation of potential monetary gain > no outcome						Anticipation of potential monetary loss > no outcome					
		t	Talairach			BA			*t*	Talairach			BA
			x	*y*	*z*					*x*	*y*	*z*	
Healthy controls													
Ventral striatum incl. NAcc	L	5.63*	−21	6	−3		Ventral striatum incl. NAcc	L	6.86*	−15	11	−6	
	R	4.26*	9	6	−5			R	5.06*	9	6	−5	
Putamen	L	6.55	−24	6	0		Putamen	L	6.86	−15	11	−6	
Caudate	L	5.39	−12	9	0		Caudate	R	4.85	18	18	2	
	R	4.99	9	9	2								
							Inferior frontal gyrus	L	6.26	−42	20	2	BA 47
							Superior temporal gyrus	L	7.48	−48	0	3	BA 22
									7.26	−50	−32	10	BA 41
							Middle temporal gyrus	L	7.12	−48	−52	3	BA 37
								R	6.2	48	−58	0	BA 37
Insula	L	4.62	−39	−3	6	BA 13	Insula	L	6.4	−42	−17	6	BA 13
							Parahippocampal gyrus	L	6.13	−24	−24	−6	BA 28/30
								R	5.65	27	−47	−3	BA 19
Angular gyrus	L	5.61	−33	−56	36	BA 39							
							Hippocampus	R	4.48	33	−44	2	
							Posterior cingulate	L	6.77	−15	−61	6	BA 30
								R	8.13	21	−64	6	BA 30
Cuneus	L	5.91	−27	−75	9	BA 30	Cuneus	L	8.38	−18	−84	10	BA 17
							Thalamus	L	6.42	−18	−26	12	
Midbrain	R	4.76	6	−24	−9		Substania nigra	R	7.59	6	−15	−7	
Schizophrenics													
No significant activation							–						
Healthy controls > schizophrenics													
Ventral striatum incl. NAcc	L	3.29*	−15	9	−3		Ventral striatum incl. NAcc	L	3.24*	−18	6	−5	
Schizophrenics > healthy controls													
No significant activation													

All other results $P < 0.001$ uncorrected plus cluster level 20.
* $P < 0.05$ FWE-corrected for ventral striatal VOI.

response during anticipation of potential monetary gain versus no outcome in the bilateral ventral striatum including the nucleus accumbens (Talairach coordinates (x, y, z) left: (−21, 6, −3), t = 5.63; right: (9, 6, −5), t = 4.26, P < 0.05 FWR-corrected for ventral striatal VOI). We also observed bilateral ventral striatal activation during anticipation of potential monetary loss versus no outcome (left: (−15, 11, −6), t = 6.86; right: (9, 6, −5), t = 5.06, P < 0.05 FWR-corrected for ventral striatal VOI). Other activated areas during these contrasts such as the putamen, caudate, insula, and midbrain, in addition to the frontal, temporal, and occipital areas, are given in Table 2 (P < 0.001 uncorrected, 20 voxel cluster size).

In contrast, unmedicated schizophrenic patients did not show significant increases in BOLD response in the ventral striatum or any of the other brain areas activated in healthy control subjects during anticipation of gain or loss versus no outcome (Fig. 2 and Table 2).

Group comparison revealed a significantly greater increase in BOLD response in the left ventral striatum during gain anticipation in healthy controls compared with unmedicated schizophrenics (−15, 9, −3; t = 3.29, P < 0.05 FWE-corrected for ventral striatal VOI; Fig. 3 and Table 2). Healthy controls also showed a significantly higher activation in the left ventral striatum during the anticipation of monetary loss compared to the neutral condition (−18, 6, −5; t = 3.24, P < 0.05 FWE-corrected for ventral striatal VOI; Table 2).

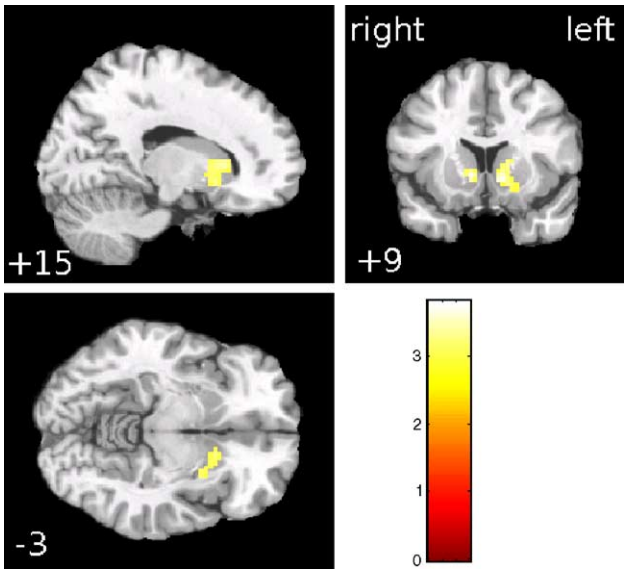

Fig. 3. Group difference. Group difference in ventral striatal activation between healthy controls and unmedicated schizophrenics during anticipation of gain compared with the neutral condition (for illustrative purpose, P < 0.005 uncorrected, cluster level 20).

Correlations between ventral striatal BOLD response and symptom severity

Among schizophrenic patients, left ventral striatal BOLD response during reward anticipation was inversely correlated with the overall score of the PANSS negative symptom scale (Spearman's R = −0.66, P = 0.04; Fig. 2), meaning that reduced ventral striatal activation during reward anticipation was associated with an increase in severity of the negative symptom. Correlations with the positive scale (R = −0.61, P = 0.06) and the total score (R = −0.53, P = 0.12) of the PANSS failed to reach statistical significance. The PANSS subscale scores for positive and negative

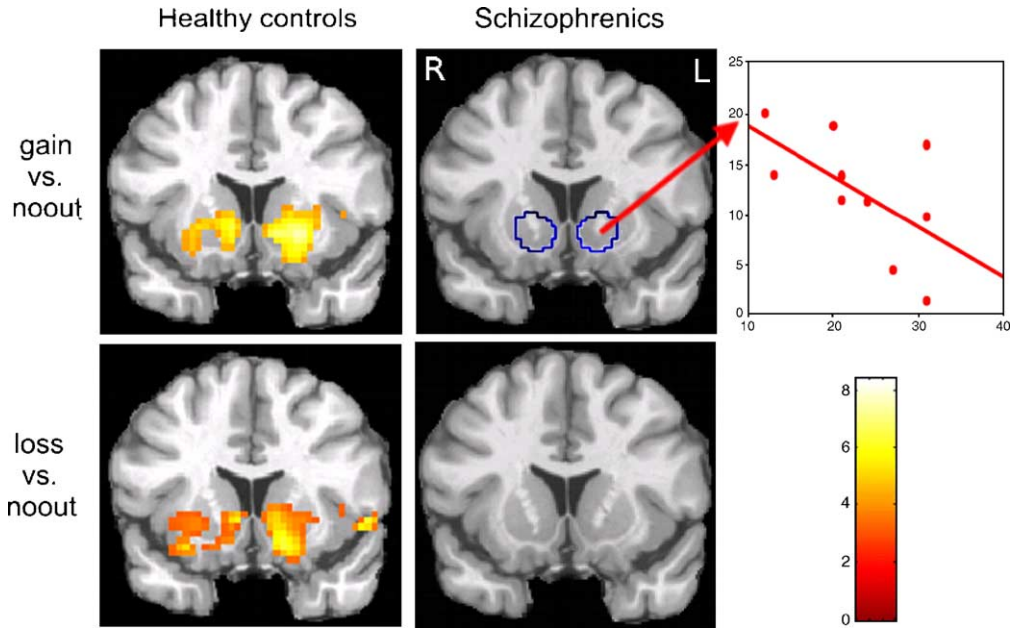

Fig. 2. Activations in the ventral striatum during anticipation of gain and loss in healthy controls and unmedicated schizophrenics; correlation with negative symptoms. Top: healthy control subjects displayed significant activation of the ventral striatum during the presentation of reward-indicating versus neutral cues (top-left). This was not the case in unmedicated schizophrenics (top-center, outline of ventral striatal VOI is shown). In schizophrenics, low activation of the left ventral striatum by reward cues was correlated with increased severity of negative symptoms (Spearman's R = −0.66, P = 0.038; top-right). Bottom: healthy controls showed activation of the ventral striatum bilaterally during the presentation of loss versus neutral cues (bottom-left); this was not observed in unmedicated schizophrenics (bottom-center). (All slices are shown at MNI y coordinate 9, for illustrative purpose, P < 0.005 uncorrected, cluster level 20.)

symptoms were significantly correlated with each other ($R = 0.82$, $P = 0.004$). No significant correlations were observed with potentially confounding variables, such as the number of cigarettes smoked per day, the time of the last cigarette before scanning, total gain in euros, age, age of onset, or duration of schizophrenia (Pearson's R: range −0.45 to 0.32, all $P > 0.2$).

Discussion

This study resulted in two major findings: (1) compared to healthy controls, unmedicated schizophrenics showed reduced ventral striatal activation during the presentation of reward-indicating cues; (2) reduced activation in the ventral striatum during exposure to reward-indicating versus neutral visual cues was inversely correlated with the severity of psychopathology in schizophrenic patients. In previous brain imaging studies, a high blockage of striatal dopamine D2 receptors has been associated with the severity of negative symptoms, such as affective flattening and apathy (Heinz et al., 1998)—a finding that may easily be explained by a neuroleptic-induced dysfunction of the brain reward system (Prosser et al., 1987). However, in the present study, schizophrenics were unmedicated, and, in prior studies, neuroleptic-free schizophrenics displayed increased, rather than decreased, presynaptic dopamine uptake capacity (Hietala et al., 1999; Lindstrom et al., 1999) and dopamine release (Abi-Dargham et al., 2000). With this in mind, one could ask: why should unmedicated schizophrenics with increased ventral striatal dopamine turnover show a dysfunction of reward circuitry, especially in a region as central as the nucleus accumbens?

A recent study by Knutson et al. (2004) may help to explain this finding. Using the same paradigm that was employed in this study, the authors showed that amphetamine-induced dopamine release blunted ventral striatal activation elicited by reward-indicating cues in healthy control subjects (Knutson et al., 2004). Reward-indicating stimuli have been associated with a phasic short-term increase in the firing rate of dopaminergic neurons (Grace, 1991; Schultz et al., 1993). In unmedicated schizophrenic patients, a high striatal dopamine turnover may increase the "noise" in the reward system, interfering with neuronal processing of the cue-elicited "signal" mediated by phasic dopamine release in the ventral striatum including the nucleus accumbens. This hypothesis may be tested directly using combined multimodal imaging of functional activation and dopamine uptake capacity of the ventral striatum in unmedicated schizophrenics.

In the exploratory part of our analysis, we observed a trend towards a negative correlation between reduced activation of the left ventral striatum elicited during reward anticipation and the severity of positive symptoms. Altered activation of the ventral striatum during reward anticipation may also contribute to aberrant attribution of salience to environmental stimuli and thus interact with positive symptoms (Kapur, 2003). However, both positive and negative symptoms showed a rather high degree of correlation in this group of unmedicated schizophrenics, meaning that studies in patients with predominantly negative or positive symptoms may help to elucidate further the specific correlations of altered brain activation during reward anticipation in schizophrenia.

Interestingly, healthy volunteers displayed significant activation in their bilateral ventral striatum during the presentation of visual cues that indicated potential monetary loss. It has been suggested that dopamine is released in the ventral striatum including the nucleus accumbens during stressful situations if an unpleasant outcome can be avoided by a motor response (Ikemoto and Panksepp, 1999). In this study, subjects were also able to avoid monetary loss with a fast motor response after being presented with the loss cue. Schizophrenic patients did not show a significant ventral striatal activation during reward anticipation but neither did they do so during the presentation of the loss cue, indicating an altered BOLD response in this core area of the brain reward system during both reward anticipation and the anticipation of potentially being able to avoid a negative outcome. Along these lines, Crespo-Facorro et al. (2001) also observed a lack of activation in the ventral striatum among schizophrenic patients who experienced unpleasant odors.

Reward anticipation has been associated with the activation of a neuronal network that includes, in addition to the nucleus accumbens, other limbic and prefrontal brain areas, such as the orbitofrontal and anterior cingulate cortex, amygdala, hippocampus, insula, thalamus, striatum, and dopaminergic midbrain (O'Doherty et al., 2002; Kirsch et al., 2003; Ernst et al., 2004; Wittmann et al., 2005). In accordance with these studies, we observed that, during reward anticipation, healthy control subjects activated the midbrain, including the substantia nigra, the dorsal striatum, insula, hippocampus, and parahippocampal gyrus, and parts of the prefrontal cortex. Schizophrenics failed to activate this network during the anticipation of a reward. Further studies will need to examine the connectivity between these brain areas and the specific psychopathological correlates of their reduced activation in schizophrenia.

Several limitations of this pilot study should be addressed. The sample size was limited and to avoid potentially confounding gender effects on the processing of emotional stimuli (Canli et al., 2002; Wrase et al., 2003), only men were included in the study. Furthermore, patients were too ill to be maintained and scanned again in a drug-free condition, so we were not able to address the question of whether the observed failure to activate the ventral striatum during reward anticipation was a state or trait marker. Lastly, patients displayed both positive and negative symptoms, and it would be worthwhile to attempt to replicate our results in schizophrenic patients with a longer history of illness and prominent negative symptoms.

In summary, this study shows that schizophrenics respond with decreased ventral striatal activation to reward-indicating stimuli and to stimuli that predict the ability to avoid monetary loss. Paradiso et al. (2003) recently reported that schizophrenics fail to activate the prefrontal cortex when exposed to pleasant cues and fail to activate the amygdala when confronted with unpleasant stimuli and that the patients instead activated subcortical regions such as the thalamus and cerebellum. Our study confirms the presence of abnormal activation patterns in schizophrenics during incentive processing and suggests that dysfunction of one subcortical region, the ventral striatum including the nucleus accumbens, may contribute to the presence of negative symptoms in schizophrenia.

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