Neural correlates of reward processing in schizophrenia – relationship to apathy and depression

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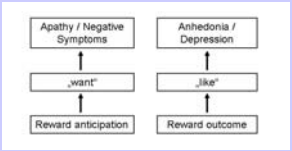
Background

A dysfunction of the reward system has been proposed as a core deficit in schizophrenia (Juckel et al, 2006). A reduced activation of the ventral striatum during reward anticipation has been observed in unmedicated patients and those treated with typical neuroleptics (Juckel et al, 2006; Kirsch et al, 2007; Schlagenhauf et al, 2008). Group differences in brain activation during outcome evaluation have received less attention. One study showed no difference between patients treated with typical and atypical antipsychotics (Kirsch et al, 2007).

One previous study has shown a negative correlation between negative symptoms and reward anticipation (Juckel 2006). A further differentiation of the relationship between symptoms of schizophrenia and dysfunctions of the reward system can be based on the differentiation of neural activation related to „wanting" and „liking" (Berridge & Robinson, 1998).



Therefore, the study had two aims:

(1) to investigate group differences between healthy controls and schizophrenic patients treated with atypical neuroleptics during both reward anticipation and outcome.

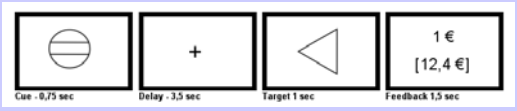
(2) to differentially relate apathy to brain activation during reward anticipation and anhedonia/depression to reward outcome

Methods

Subjects: 15 healthy control subjects and 15 patients with schizophrenia or schizoaffective disorder were included in the study. All patients were treated with atypical antipsychotic drugs.

	Healthy Controls	Schizophrenic Patients
Age	25.2 ± 3.2 (20-32)	26.3 ± 5.4 (18-38)
Gender	5 females, 10 males	5 females, 10 males
Reaction Time	486 ± 54.5	498 ± 70.1
Win total (Euros)	34.3 ± 2.97	34.7 ± 1.71

Paradigm: We employed a monetary incentive delay task (Knutson et al, 2001; Abler et al, 2005). Subjects were presented a cue indicatin the possibility of winning either 1 Euro, 20 Cent or 0 Euro. After a delay period they had to perform a left or right button press within 1 s. After correct performance they would win the cued amount of money with 60% probability.



fMRI acquisition: Scanning was performed on a Siemens Trio 3T scanner with an EPI sequence adapted for imaging of the orbitofrontal cortex. 32 Slices oblique to the AC-PC axis were obtained with the following parameters: 3mm slice thickness, 3x3 mm in-plane resolution, TR = 2000ms, TE = 30ms, flip angle 80°. In addition a high resolution sagittal T1 weighted image was acquired.

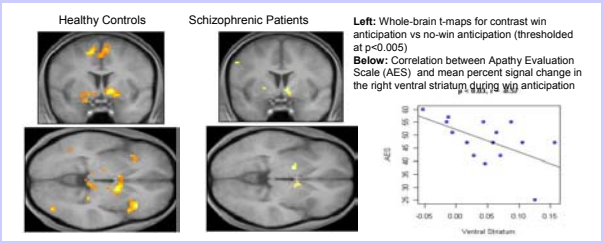
fMRI analysis: Data analysis was performed with SPM5. After standard preprocessing procedures images were normalized to the MNI templated and smoothed with a kernel of 8mm FWHM. A general linear model was computed for each individual subjects with the following regressors of interest. Anticipation (Cue + Delay): Anticipation 1 Euro, Anticipation 20 cent, No Anticipation. Outcome (Feeback): Win Outcome 1 Euro, No-Win Outcome 1 Euro, Win Outcome 20 cent, No-Win Outcome 20 cent, Outcome after No Anticipation.

For statistical analysis ROIs were defined for the ventral striatum based on the BrainMap database and for the medial orbitofrontal cortex based on the data of a large group of control subjects previously studied with this paradigm. Mean percent signal change was extracted from these ROIs for each individual subject. One sample t-tests were performed to assess for significant within group activation. Two sample t-tests were performed for between group comparisons. Simple correlations were performed between psychopathological rating scales and mean percent signal change.

Results

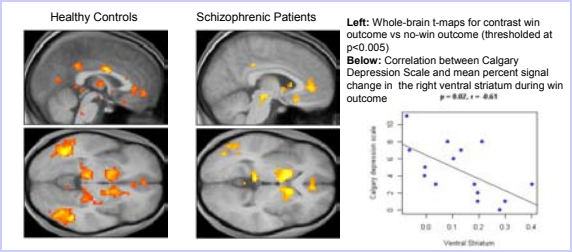
Behavioral data: Groups did not differ significantly in reaction time or total win (see table).

fMRI data: During anticipation both groups showed signficant activation in the ventral striatum in the contrast *win anticipation vs no-win anticipation*. There was no significant difference between groups.



Left: Whole-brain t-maps for contrast win anticipation vs no-win anticipation (thresholded at p<0.005)
Below: Correlation between Apathy Evaluation Scale (AES) and mean percent signal change in the right ventral striatum during win anticipation

During feedback both groups showed significant activation in the ventral striatum and the medial orbitofrontal cortex in the contrast *win outcome vs no-win outcome*. There was no signficant difference between groups.



Left: Whole-brain t-maps for contrast win outcome vs no-win outcome (thresholded at p<0.005)
Below: Correlation between Calgary Depression Scale and mean percent signal change in the right ventral striatum during win outcome

Correlations psychopathological ratings – signal change ventral striatum: There was no significant correlation between ventral striatal activation during win anticipation and PANSS negative subscale. However, the Apathy Evaluation Scale was negatively correlated with ventral striatal signal change.

There was a significant negative correlation between the Calgary Depression Scale and ventral striatal signal change during outcome evaluation. There was no significant correlation between the Chapman anhedonia scales and brain activation during outcome evaluation.

Discussion

Our findings provide additional evidence that on a group level schizophrenic patients treated with atypical antipsychotic drugs do not show dysfunctional activation of brain regions involved in reward processing. In addition to the existing literature our data also show intact processing of rewarding outcomes in the ventral striatum and the medial orbitofrontal cortex.

Regarding the relationship between brain activation patterns and psychopathological ratings we did not find a relationship between PANSS negative symptoms and ventral striatal activation during reward anticipation. Since our patients were treated with atypical antipsychotics, this is consistent with one other study that failed to find this relationship in patients treated with olanzapine (Schlagenhauf et al, 2008). However, patients with higher apathy scores showed lower activation of the ventral striatum during reward anticipation, which suggests that the putative link between negative symptoms and reward anticipation might more specifically relate to a lack of motivation and drive.

The most important finding regarding processing of reward outcomes is a negative relationship of depressive symptomatology with ventral striatal activation. This is consistent with a decreased striatal response to positive feedback in patients with major depression (Steele et al, 2007). We have not found a relationship of outcome processing with anhedonia as assessed by the Chapman scale, which might be related to the self-rating procedure.

Overall, although the present study is limited by sample size and medicated status of the patients it shows that a differentiation of common negative and depressive symptoms of the schizophrenic illness might be important to understand the role of the reward system in the pathogenesis of these symptoms.

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