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Salience network-midbrain dysconnectivity and blunted reward signals in schizophrenia

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ABSTRACT

Theories of schizophrenia propose that abnormal functioning of the neural reward system is linked to negative and psychotic symptoms, by disruption of reward processing and promotion of context-independent false associations. Recently it has been argued that an insula–anterior cingulate cortex (ACC) salience network system enables switching of brain states from the default mode to a task-related activity mode. Abnormal interaction between the insula–ACC system and reward processing regions may help explain abnormal reinforcer processing and symptoms. Here we use fMRI to assess the neural correlates of reward processing in schizophrenia. Furthermore we investigated functional connectivity between the dopaminergic midbrain, a key region for the processing of reinforcers, and other brain regions. In response to rewards, controls activated task related regions (striatum, amygdala/hippocampus and midbrain) and the insula–ACC salience network. Patients similarly activated the insula–ACC salience network system but failed to activate task related regions. Reduced functional connectivity between the midbrain and the insula was found in schizophrenia, with the extent of this abnormality correlating with increased psychotic symptoms. The findings support the notion that reward processing is abnormal in schizophrenia and highlight the potential role of abnormal interactions between the insula–ACC salience network and reward regions.

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1. Introduction

Efficient processing of reward and punishment information is essential for achieving optimal behavior and interacting successfully with the environment. Some studies suggest this important ability may be impaired in schizophrenia, with patients exhibiting difficulties in learning from incentive feedback (Koch et al., 2010). Abnormalities in reinforcement learning processes may be linked to negative symptoms (e.g., anhedonia and social apathy) by disrupting the processing of rewarding events and to psychotic symptoms by promoting abnormal associations (Corlett et al., 2007; Juckel et al., 2006a). This is consistent with long standing evidence that the dopamine system (which is known to be important for processing reinforcement events (Berridge, 2007; Montague et al., 1996) has altered function in schizophrenia (Guillin et al., 2007).

Neuroimaging studies of healthy subjects have linked the processing of reinforcers with the activation of a network that includes the dopaminergic midbrain and projection regions, such as the striatum and medial frontal cortex, the amygdala–hippocampal complex and insula (Cohen et al., 2008; Kahnt et al., 2009; O'Doherty et al., 2003). Some fMRI studies have investigated the processing of reinforcers in schizophrenia, reporting abnormalities in some of these regions such as the striatum, midbrain, amygdala and insula (Corlett et al., 2007; Juckel et al., 2006b; Romaniuk et al., 2010; Waltz et al., 2009). Consistent with the hypothesis that abnormal functioning of the reward system could be linked to negative symptoms, reduced ventral striatal activation during anticipation of rewards was found to correlate with the severity of negative symptoms in unmedicated (Juckel et al., 2006b) and medicated (Juckel et al., 2006a) schizophrenia. It has been proposed that psychotic symptoms (hallucinations and delusions) may also be linked to abnormal processing of reinforcers, with patients attributing

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abnormally increased motivational salience to otherwise neutral/irrelevant stimuli, leading to false context independent associations (Kapur, 2003). Consistent with this hypothesis, attenuated and augmented responses to reward and neutral stimuli respectively, were observed in the midbrain of patients with schizophrenia (Murray et al., 2008).

Based on a body of evidence, it has been hypothesized that a brain system including the insula and anterior cingulate (ACC) may function abnormally in schizophrenia (Palaniyappan and Liddle, 2011). The insula and ACC tend to co-activate across a variety of cognitive tasks (Taylor et al., 2009). This brain system has been characterized as a cognitive task control network and as part of a salience network (Dosenbach et al., 2007; Seeley et al., 2007). During the processing of stimuli, the insula–ACC system is thought to play a key role in facilitating engagement of task-related brain networks while disengaging the "default mode network" (a network typically active during rest and decreased in activation during cognitively demanding tasks) (Menon and Uddin, 2010). Abnormal interactions between the insula–ACC salience network system, and regions specialized for the processing of rewards, may account for abnormalities reported in reward processing studies of schizophrenia.

The hypothesis of an abnormal interaction between brain systems is consistent with a long standing view that schizophrenia cannot be fully explained by focal brain abnormalities, but results from abnormal integration between brain regions (Pettersson-Yeo et al., 2011; Stephan et al., 2009). Consistent with this "dysconnectivity hypothesis", studies have reported abnormal functional connectivity between widespread regions during the 'resting state' (Zhou et al., 2007) and during tasks (Calhoun et al., 2009; Kim et al., 2003; Lawrie et al., 2002; Spence et al., 2000).

The present study used fMRI and a reward learning paradigm to investigate the possible role of altered reward processing in schizophrenia. We hypothesized that patients would exhibit abnormalities in the processing of rewards in regions of the brain often associated with reward information processing, i.e., ventral striatum, midbrain, medial pre-frontal cortex (mPFC), amygdala–hippocampus and insula. To further investigate reward processing in schizophrenia we conducted a functional connectivity analysis at the whole brain level using the dopamine rich midbrain, a critical region for the processing of reinforcers (Schultz et al., 1998), as a seed region.

2. Methods

2.1. Participants

The study was approved by the local research ethics committee and written informed consent was obtained from all participants. Data was acquired from two groups of subjects: a group of 15 patients with DSM IV schizophrenia and a group of 20 healthy controls. Exclusion criteria were any neurological disorder, claustrophobia, and any other DSM IV Axis I or II diagnosis. Two control and one patient data set were excluded because of structural brain abnormalities, failure to understand the task or scanner hardware failure. Eighteen controls and fourteen schizophrenia patients were included in the analysis. The two groups did not differ significantly on a between groups *t*-test with respect to age ($t_{(30)}=0.543$, $p=0.591$) and National Adult Reading Test estimated pre-morbid IQ (Nelson and Wilson, 1991) ($t_{(26)}=1.96$, $p=0.061$). Given the smaller proportion of females in the schizophrenia group compared to the control group, gender was used as a covariate for the image analyses. Details of subjects included in the analysis are presented in Table 1 and Supplementary Table S1 describes patient's antipsychotic medication at the time of the study.

Immediately before scanning, all subjects completed the Beck Depression Inventory (BDI, Beck et al., 1961) and Spielberger State Anxiety Scale (Spielberger, 1983). Positive, negative and general symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987).

Table 1
Participant details.

	Controls	Schizophrenia	Significance
Age (years)	40.39 ± 11.57	42.71 ± 12.60	NS
Gender (M/F)	8/10	12/2	
NART	113.00 ± 8.18	105.58 ± 11.84	NS
BDI	3.00 ± 2.93	18.50 ± 13.01	$p=0.001$
SP	30.06 ± 10.57	45.07 ± 12.18	$p=0.001$
PANSS_positive		13.85 ± 3.28	
PANSS_negative		13.29 ± 6.73	
PANSS_general		22.86 ± 6.99	
PANSS_total		50.00 ± 15.11	
WP	76.22 ± 23.91	85.21 ± 14.95	NS
First	83	71	NS
Last	67	29	$p=0.033$

Values are mean ± DS; NART, National Adult Reading Test; BDI, Beck depression inventory; SP, Spielberg anxiety scale; PANSS, Positive and Negative Syndrome Scale; WP, water pleasantness rating as percentage; 'First, Last' = average percentage of correctly reported picture–water associations for first and last blocks; NS, no significant difference between groups.

2.2. Experimental task

The fMRI task consisted of a Pavlovian reward learning task. On each trial, one of two fractal pictures was presented. Two seconds after picture presentation, 0.1 ml of water (reward) was delivered or not according to a probabilistic pattern. This volume was chosen empirically so that subjects could perceive the water delivery but minimised the need for swallowing, so reduced the risk of movement artifacts. Subjects were asked to abstain from drinking fluids from the night before the scan (this is a routine requirement for many types of medical procedure and does not cause detectable biochemical alteration) to ensure they were thirsty at the time of the scan and that would perceive the water as rewarding. Water delivery was via a polythene tube attached to an electronic syringe pump (World Precision Instruments Ltd, Stevenage, UK) positioned in the scanner room and interfaced to the image presentation and log file generating computer.

The task consisted of 100 trials of 6 s duration acquired asynchronously with blood oxygen level-dependent (BOLD) brain volume acquisition (TR 2.5 s). The task was divided into blocks of 20 trials. In each block one of the fractal pictures had a higher probability of water delivery. The fractal picture associated with the high-probability stimulus changed throughout the task. The high-probability stimulus was associated with a range of probabilities of water delivery from 50% to 90%. The low probability stimulus was associated with a range of probabilities from 0% to 20%. This evolving pattern was used to help maintain participant engagement in the task. Before scanning subjects were told that the object of the task was to notice which picture was most associated with the water and that this association may change slowly. The task lasted for ~10 min.

Immediately after scanning, subjects completed a linear analogue rating scale of perceived pleasantness of the delivered water. To test engagement and attention to the task, participants were asked which picture was more associated with water delivery at the beginning and at the end of the task (first and last block).

2.3. Image acquisition and analysis

For blood oxygen level dependent (BOLD) response imaging, T2* weighted gradient echo planar images were obtained using a GE Medical Systems Signa 1.5 T MRI scanner. A total of 30 axially orientated 5mm thick contiguous sequential slices were obtained for each volume, 246 volumes being obtained with a TR of 2.5 s, TE 30 ms, flip 90°, FOV 240 mm and matrix 64 × 64. The first four volumes were discarded to allow for transient effects. A T1 weighted image was obtained to exclude gross structural brain abnormality.

SPM8 (http://www.fil.ion.ucl.ac.uk/spm) was used for analysis. Images were slice-time corrected and realigned to the first image in each time series. No scans had head movements greater than the voxel dimensions. The average realigned image was used to derive parameters for spatial normalization to the SPM8 Montreal Neurological Institute (MNI) template with the parameters applied to each image of the time-series. The resultant time-series realigned and spatially normalized images were smoothed with an 8 mm Gaussian kernel.

For first level analysis, an event related design was implemented with the two feedback conditions (reward vs. no-reward) modeled as explanatory variables convolved with the hemodynamic response function. Six head motion realignment terms where included as further covariates of no interest, to allow for residual movement artifacts not removed by pre-processing realignment. Individual contrast images were computed for the contrast [reward vs. no-reward] and taken to second-level random effects analyses.

Second level analyses tested for within group activations for reward vs. no-reward using one-group *t*-tests and for between group differences using a two-sample *t*-test with gender as a covariate. For all analyses, regions are reported as significant at a whole brain $p<0.05$ cluster level. This was achieved by a simultaneous requirement for a voxel threshold of $p<0.005$ plus a minimum cluster size of 106 continuous voxels. Voxel and cluster size parameters were identified using standard Monte Carlo simulations (Slotnick et al., 2003) with code available at http://www2.bc.edu/~slotnics/scripts.html. As described by the authors, assuming a voxel type I error, this method allows estimating a probability for each cluster extent (number of contiguous voxels). In this way, the desired correction for multiple comparisons can be enforced by using as a threshold, the corresponding cluster extent.

We investigated functional connectivity during the task between the dopaminergic midbrain (which was taken as the seed region for the analysis) and every other voxel in the brain. The midbrain seed region was defined based on combined anatomical and functional constrains (Fig. 2D). Specifically, the dopaminergic midbrain was anatomically defined as the union between the Wake Forest University Pickatlas toolbox (Maldjian et al., 2003) substantia nigra defined region and a 10 mm diameter sphere located at MNI coordinates (0, −20, −10) (Talairach coordinates (0, −20, −7)) as described in a previous study (Romaniuk et al., 2010). We included in our midbrain seed region all the voxels in the anatomical mask that were active above the significance threshold for the contrast [reward > no-reward] at a group level including both controls and patients in the calculation. The time course of activity of each individual subject from the seed region was extracted using the Mars-Bar (Brett et al., 2002) SPM toolbox. The seed region time-series was used as a regressor in a further multiple linear regression analysis that included as covariates the reward and no-reward events (convolved with the SPM hemodynamic response function) to account for feedback related activity. To remove sources of spurious or regionally nonspecific variance (Vincent et al., 2006) the following regressors were also included: a whole brain BOLD time series, a white matter BOLD time series taken as the average of a number of voxels in a region centered in the deep cerebral white matter, a CSF (cerebrospinal fluid) BOLD time-series averaged over a region centered in the left lateral ventricle, the six movement parameters created during the pre-processing realignment and the first temporal derivatives of the movement parameters.

The parameter estimates for the midbrain seed region regressor, which represents the extent to which activity on each voxel correlates with activity in the seed region, were taken to the second level of a random effects analysis and entered in one group *t*-tests for the within group analysis, and into a two-sample *t*-test with gender as a covariate for the between groups analysis. The former tested the null hypothesis of no correlation of any brain region with the midbrain seed region, the latter the null hypothesis of no difference between schizophrenia and control groups. As above, within group and between group maps were thresholded at $p<0.05$ whole brain corrected at the cluster level.

Next, we investigated whether brain abnormalities observed in the patient group, both in the reward vs. no-reward contrast, and in the connectivity analyses, correlated with illness severity measures. This analysis was limited to *a priori* regions of interest which usually activate during reward processing (Cohen et al., 2008; Kahnt et al., 2009; O'Doherty et al., 2003)) – ventral striatum, amygdala–hippocampus, medial prefrontal cortex and insula – and which exhibited abnormalities on the between groups analysis. The dependent variable in this analysis was the mean value of the parameter estimates across voxels within a 10 mm diameter sphere, centered at the maximum peak coordinates of the regions that showed between group differences. Pearson correlations between mean parameter estimates were tested against the negative symptom scale of the PANSS and a psychotic (positive) symptom subscore (delusions plus hallucinations subscores) given the hypothesized link between these symptoms and reinforcement learning abnormalities.

To investigate whether abnormalities observed in the schizophrenia group were secondary to antipsychotic medication, we tested for correlations between the relevant parameter estimates (of fMRI reward vs. no-reward and connectivity analyses) and medication dose in chlorpromazine equivalents at a less stringent (to be sensitive to detecting a confound) threshold of $p<0.01$ uncorrected voxel level significance.

Coordinates were transformed from MNI to Talairach space using the tool provided in http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach.

3. Results

3.1. Clinical and behavioral ratings

Mean clinical rating scale scores for each group are shown in Table 1. Between group *t*-tests identified significant differences in mood and anxiety as measured by the BDI ($t_{(14.03)}=4.37$, $p=0.001$) and the Spielberger state anxiety scale ($t_{(28)}=3.62$, $p=0.001$) with schizophrenia patients rating themselves lower in mood and higher in anxiety than controls.

After taking part in the scan, participants indicated on a linear analogue scale (ranging from unpleasant to neutral to pleasant) how much they liked receiving the water during the task. *T*-tests indicated that subjects perceived the water pleasantness significantly above neutral ($t_{(31)}=8.25$, $p<0.001$) and there were no significant differences in water pleasantness ratings between schizophrenia and control groups ($t_{(30)}=1.23$, $p=0.23$). There was no significant difference between patients and controls in accuracy of reporting picture–water associations for the first block ($\chi^2=0.653$, $p=0.42$). However, patients and controls did differ in reports for the last block ($\chi^2=4.57$, $p=0.033$) with controls reporting accurately more often than patients.

3.2. fMRI reward vs. no-reward results

Consistent with previous findings (Cohen et al., 2008; Juckel et al., 2006b; Kahnt et al., 2009; O'Doherty et al., 2003; Waltz et al., 2009), healthy controls demonstrated an increased neural response during reward vs. no-reward delivery in the gustatory cortex, striatum, amygdala–hippocampus complex, insula, dorsal anterior cingulate and midbrain (Fig. 1A). During reward vs. no-reward, schizophrenia patients also activated the gustatory cortex, the insula and dorsal anterior cingulate, but in contrast they failed to significantly activate the midbrain, striatal and medial temporal lobe regions (Fig. 1B). For the opposite contrast [no-reward > reward] controls exhibited activations in the medial prefrontal cortex and posterior cingulate cortex (Supplementary Fig. S1) while in the schizophrenia group no activations were significant (Table 2). These activations can also be interpreted as de-activations for the reward vs. no-reward contrast.

Between groups comparison revealed a significant difference for the contrast [reward > no-reward] in one region of interest: the left ventral striatum (Talairach coordinates (−28, 4, −7), $z=3.20$, $p<0.05$ whole brain corrected at the cluster level) (Fig. 1C, Table 2). This difference was driven by an attenuated response to rewards in schizophrenia (Fig. 1D). At a lower level of significance (voxel $p<0.005$ uncorrected) patients also differed from controls in brain activity in the left ventral striatum when only the males of each group were included in the analysis (Supplementary Fig. S3).

Within the schizophrenia group, the neural response for the contrast [reward > no-reward] in the left ventral striatum correlated negatively with the score from the PANSS negative symptoms scale ($r_{(14)}=-0.662$, $p=0.01$) (Fig. 1E). This indicates that reduced ventral striatal activation during reward vs. no-reward conditions were associated with increased severity of negative symptoms. The correlation analysis with the psychotic (delusions plus hallucinations) symptom subscore form the PANSS was not significant. Exploratory correlation analyses with other non-core schizophrenia illness measures such as the BDI mood rating and Spielberg anxiety were not significant for this brain region. No correlation was found between ventral striatal activity and antipsychotic dose calculated as chlorpromazine equivalents. The left ventral striatum was the only region investigated with regard to a correlational analysis with illness severity measures, as this region was the only a priori region of interest which also exhibited differential activation in the fMRI (reward vs. no-reward) between group analysis.

3.3. fMRI functional connectivity results

The dopamine rich midbrain was used as seed region for a whole brain functional connectivity analysis. In controls, significant positive (increased activity in midbrain associated with increased activity in other regions) functional connectivity was found between the midbrain and a cluster of activation that

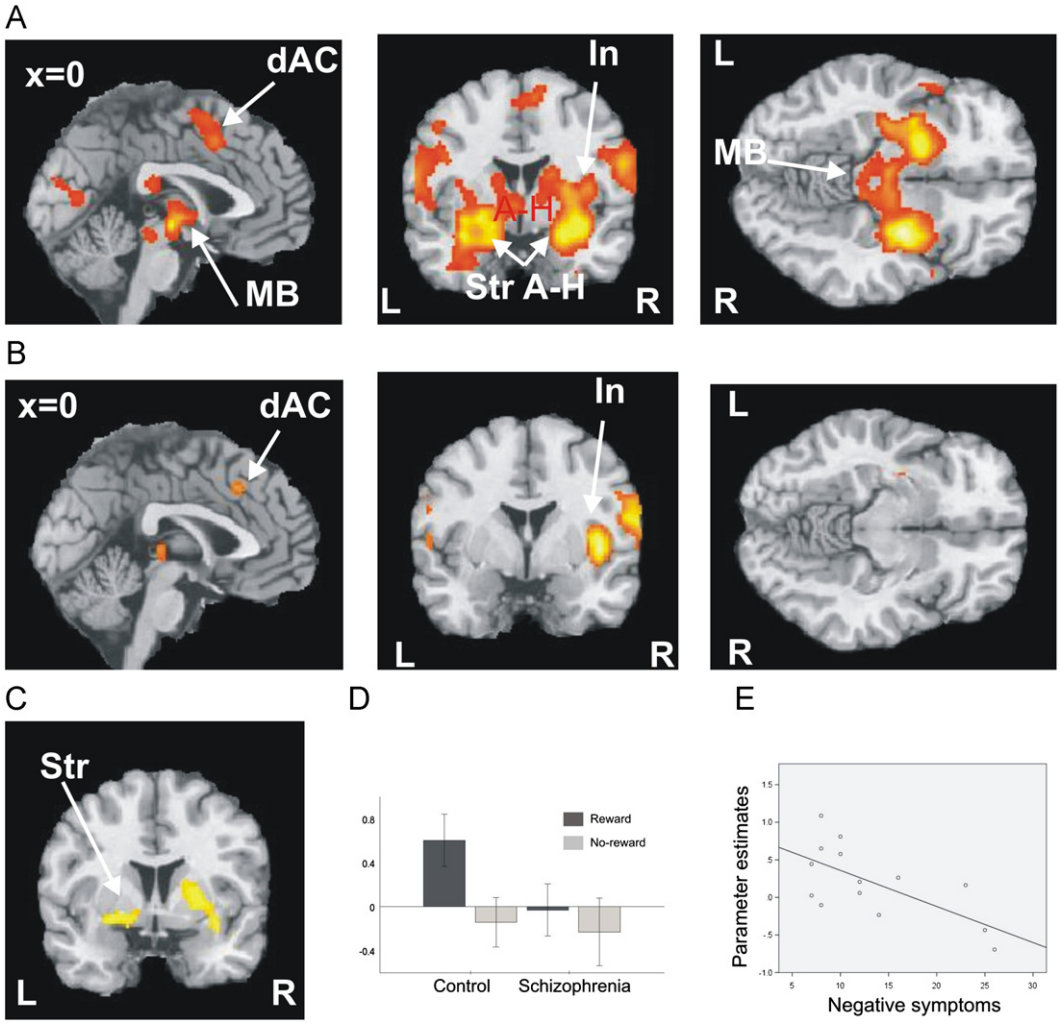

Fig. 1. fMRI analysis. Brain regions active in (A) controls and in (B) patients with schizophrenia during reward vs. no-reward. (C) Regions where controls exhibited greater activation than patients for the contrast reward vs. no-reward (D) Mean value of parameter estimates across voxels within a 10 mm diameter sphere, centred at peak coordinates (−28, 4, −7) of the left ventral striatum region where patients differed significantly from controls. (E) Correlation with negative symptoms for the left ventral striatum of patients (again, the dependent variable is the mean value of parameter estimates across voxels within a 10 mm diameter sphere, centred at peak coordinates (−28, 4, −7)). Regions significant at $p<0.05$ whole brain corrected at the cluster level as described in the methods. dAC=dorsal anterior cingulate; MB=midbrain; Str. A–H=striatum amygdala–hippocampus; In=right insula. L=left; R=right.

extended through several brain regions including medial temporal lobe structures such as the amygdala–hippocampus complex and para-hippocampal gyrus, and in addition the bilateral putamen and insula (cluster peak (−6, −16, −4), $z=7.17$, $k_E=16369$, $p<0.05$ whole brain corrected at the cluster level) (Fig. 2A). In schizophrenia, positive functional connectivity was observed across similar regions as in controls but less strongly and with a more limited spatial extent (cluster peak (6, −20, −9), $z=5.31$, $k_E=8622$, $p<0.05$ whole brain corrected at the cluster level) (Fig. 2B). In controls negative functional connectivity with the midbrain was observed across the ventral anterior cingulate, medial prefrontal cortex and retrosplenial cortex (Supplementary Fig. S2 A). In schizophrenia patients, a similar pattern of negative connectivity was observed, but again with weaker activations than in controls (Supplementary Fig. S2 B).

The between groups analysis revealed a region in the right insula, where patients differentiated significantly from controls in functional connectivity with the dopaminergic midbrain (Talairach coordinates (38, 0, 7), $z=3.52$, $p<0.05$ whole brain corrected at the cluster level) (Fig. 2C). This difference was driven by controls exhibiting positive functional connectivity between the midbrain and the insula and patients showing negative connectivity between these regions (Fig. 2E). This difference between patients and controls was also significant when only comparing the males of each group (Supplementary Fig. S4), indicating that gender imbalance was not a cause of the results.

There were no other regions where controls showed increased functional connectivity compared to patients. Patients exhibited increased functional connectivity in a small cluster in the cerebellum ((0, −41, −1), $z=3.44$).

As the insula was an *a priori* region of interest that exhibited abnormality on the between group analysis we investigated correlations with core schizophrenia illness severity measures. Planned correlations with the negative and psychotic (delusions plus hallucinations) subscales from the PANSS were tested as these symptoms have been linked to abnormal processing of reinforcers (Juckel et al., 2006b; Kapur, 2003). Within the schizophrenia group, decreased functional connectivity between the midbrain and right insula correlated with increased severity of psychotic symptoms ($r_{(14)}=-0.59$, $p=0.026$) (Fig. 2F). The correlation analysis with the negative symptom scale from the PANSS was not significant. Exploratory correlation analyses with other non-core schizophrenia illness measures, such as the BDI mood rating and Spielberg anxiety, were not significant for this region.

Table 2
Within and between group activations during reward processing. Coordinates (*x*, *y*, *z*) reported in Talairach space; R/L=right/left. All results significant at $p<0.05$ cluster extent corrected across the whole-brain (cluster extent=106 resampled voxels).

	BA	*x*	*y*	*z*	*Z* value
Contrast: Reward > no-reward					
Controls					
L putamen, nucleus accumbens and caudate		−24	2	−7	5.10
L amygdala extending into the hippocampus		−22	−3	−17	4.56
L insula		−34	−7	10	4.16
L parietal lobe, postcentral gyrus (gustatory cortex)	43	−63	−11	17	5.51
L cerebellum		−22	−63	−19	3.49
R putamen		30	−2	2	4.55
R amygdala extending into the hippocampus		24	−3	−13	5.17
R insula		36	0	9	3.83
R parietal lobe, postcentral gyrus (gustatory cortex)	43	57	−11	19	4.85
R cerebellum		20	−65	−17	3.13
Dorsal anterior cingulate	32	−2	14	42	3.58
Midbrain extending into thalamus		4	−16	−4	5.4
Occipital lobe, cuneus	18	−6	−89	14	3.82
Schizophrenia					
L parietal lobe, postcentral gyrus	3	−59	−11	21	4.02
L parietal lobe, postcentral gyrus (gustatory cortex)	43	−50	−11	17	3.47
L insula		−44	−5	9	3.67
R frontal lobe, precentral gyrus	4	55	−3	17	4.74
R parietal lobe, postcentral gyrus (gustatory cortex)	43	53	−11	19	4.21
R insula		40	−2	6	4.65
Dorsal anterior cingulate	32	0	23	38	3.35
Thalamus		2	−23	5	3.43
Contrast: No-reward > reward					
Controls					
Medial prefrontal cortex	11	6	44	−16	4.26
Medial prefrontal cortex	10	−2	59	10	3.82
Posterior cingulated cortex	30	−12	−52	10	4.54
L, frontal lobe, middle frontal gyrus	8	−28	25	39	3.68
R, frontal lobe, middle frontal gyrus	8	28	31	41	3.49
R occipital lobe, middle temporal gyrus	19	51	−73	15	4.33
L temporal lobe, angular gyrus	39	−46	−76	30	3.16
Dorsal anterior cingulate	32	12	23	34	3.61
Schizophrenia					
No significant activations					
Contrast: *Reward* > No-*reward*					
Controls > Schizophrenia					
L ventral putamen and nucleus accumbens		−28	4	−7	3.20
R upper putamen		24	0	0	3.37
L parietal lobe	40	−55	−33	42	4.04
Cerebellum		22	−48	−25	3.79
Contrast: *No-reward > reward*					
Controls > Schizophrenia					
R occipital lobe, cuneus	18	24	−79	15	4.11

No correlation was found between right insula connectivity and chlorpromazine equivalent medication doses.

4. Discussion

This study investigated the functioning of the reward circuitry in schizophrenia using a primary reinforcer, water delivery when thirsty. Compared to healthy controls, patients showed reduced ventral striatal responses during reward vs. no-reward conditions. The reduced ventral striatal activation correlated with increased severity of negative symptoms. In addition, patients exhibited reduced functional connectivity between the dopamine rich midbrain and the right insula, the extent of this abnormality correlating with increased severity of psychotic symptoms.

Our finding of reduced ventral striatal activation during reward vs. no-reward conditions is consistent with previous studies (Corlett et al., 2007; Juckel et al., 2006a, 2006b). Juckel and colleagues reported reduced ventral striatal activation during exposure to reward-indicating cues in unmedicated (Juckel et al., 2006b) and medicated (Juckel et al., 2006a) schizophrenia patients. We replicated this finding and found the extent of the abnormality correlated with negative symptom severity. This correlation was also reported in both of Juckel and colleagues studies, indicating that negative symptoms are associated with abnormal processing of reward information in the ventral striatum.

Abnormal neural responses to reward processing in the ventral striatum may be linked to abnormalities of the dopamine system. It has been hypothesized (Corlett et al., 2007; Juckel et al., 2006b; Roiser et al., 2009) that increased 'noise' in the dopamine system, perhaps due to increased dopamine metabolism, causes abnormal striatal responses during reward processing. Reward stimuli as well as reward indicating cues have been associated with a phasic increase in dopamine firing encoding an error in the prediction of reward (Schultz, 1998). Increased noise in the dopamine system

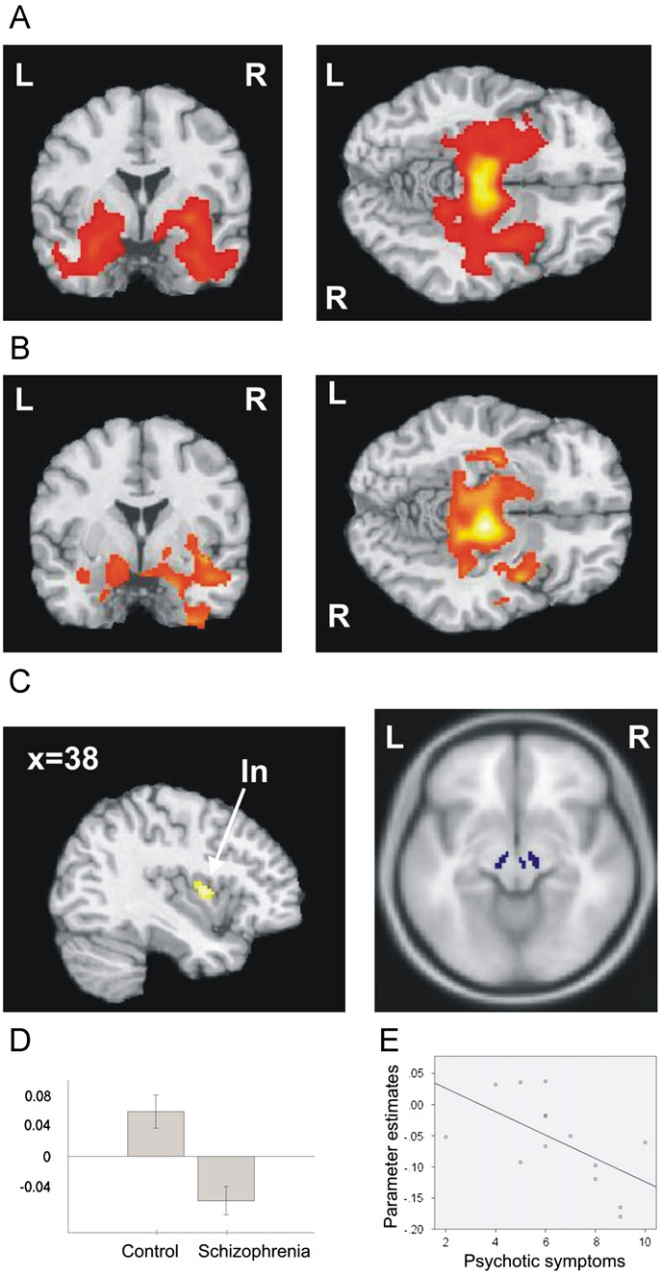

Fig. 2. Functional connectivity analysis. Brain regions in controls (A) and schizophrenia (B) exhibiting significant positive functional connectivity with the midbrain. (C) Between group difference in functional connectivity in the insula. In (D) dopaminergic midbrain seed region, (E) mean value of parameter estimates across voxels within a 10 mm diameter sphere, centred at peak coordinates (38, 0, 7) of the right insula where patients differed significantly from controls. (F) Correlation with psychotic symptoms in the right insula of patients (dependent variable is the mean value of parameter estimates across voxels within a 10 mm diameter sphere, centred at peak coordinates (38, 0, 7)). Regions significant at $p < 0.05$ whole brain corrected at the cluster level as described in the methods. In = right insula; L = left; R = right.

in schizophrenia could interfere with the normal phasic signals that process reward information.

Compared to controls, patients showed reduced functional connectivity between the dopamine rich midbrain and right insula. The insular cortex has emerged in the last few years as a key region in schizophrenia research, with studies reporting consistent structural and functional alterations (Palaniyappan and Liddle, 2011). Across a variety of cognitive tasks, the insula usually activates conjointly with the anterior cingulate cortex (ACC) (Taylor et al., 2009). This system of activation has been described as part of a salience network and is thought to play a role in enabling switching between the default mode network (which includes the ventromedial prefrontal cortex and the posterior cingulate cortex) and task related networks (Menon and Uddin, 2010). Further characterizing the insula–ACC salience network system, Palaniyappan and colleagues introduced the concept of "proximal salience". They argue that an event (sensation or thought) attains "proximal salience" when it generates momentary activity within the salience network, which results in updating expectations and depending on the context, initiates/alters an action. The salience network therefore initiates the recruitment of brain regions relevant for processing currently salient stimuli, decreasing activity in networks engaged in processing previously salient stimuli (Palaniyappan and Liddle, 2011).

In our study, the insula activated conjointly with the dorsal ACC during reward vs. no-reward delivery, suggesting activation of the insula–ACC salience network system. Thus, our finding of reduced functional connectivity between the dopaminergic midbrain and insula could indicate reduced inter-regional integration between the insula–ACC salience network and the dopaminergic midbrain in schizophrenia. In the framework of Palaniyappan's theory, this is consistent with a failure of recruitment of reward processing brain regions by the insula–ACC salience network system. One possibility is that this could be due to abnormal functioning of the insula–ACC system in schizophrenia. Supporting this interpretation, several schizophrenia studies have reported gray matter and/or functional abnormalities within the insula–ACC salience network (Glahn et al., 2008; Wylie and Tregellas, 2010). Palaniyappan and colleagues have proposed that abnormal functioning of the insula–ACC salience network system could be linked to schizophrenia psychotic symptoms, by inappropriately allocating proximal salience to irrelevant internal or external stimuli (Palaniyappan and Liddle, 2011). Consistent with this, we found that reduced connectivity between the midbrain and insula correlated with increased severity of psychotic symptoms. This correlation is also consistent with previous findings indicating that abnormal processing of reinforcers is related to psychotic symptoms such as delusions (Corlett et al., 2007; Heinz and Schlagenhauf, 2010; Murray, 2011; Schlagenhauf et al., 2009).

It is also possible that the abnormal coupling observed in the present study may be due to altered functioning of the midbrain (independent of the insula–ACC salience network) or to abnormalities in both the midbrain and insula–ACC system. Our observed correlation between psychotic symptoms and abnormal connectivity supports both possibilities, given the link between psychotic symptoms and dopamine activity (Kapur, 2003). Regarding the second possibility, based on a body of evidence it has been argued that dopamine acts as a modulator of the insula–ACC salience network (Palaniyappan and Liddle, 2011). Thus reduced functional connectivity between the midbrain and the insula could reflect abnormal functioning of the midbrain with consequent abnormal functioning of the insula–ACC salience network. Further work is needed to clarify the mechanisms underlying the abnormal midbrain–insula connectivity in schizophrenia.

It should be noted that whilst a difference in connectivity between patients and controls was found with regard to the insula, this was not observed for the ACC. This could be due to the insula and ACC having different functions (Menon and Uddin, 2010). It is also possible that our connectivity analysis (covarying out global brain activity plus white matter and ventricule signals) was too conservative to allow detection of significant differential connectivity with the ACC. This could be addressed in further work.

Consistent with patients exhibiting abnormalities in the neural processing of rewards at the outcome time of the task, patients were not as accurate as controls in post-scan verbal reports of picture–water associations for the last block of the task. Between group differences in post-scan reports may reflect less attention and learning during scanning, or an impaired ability of patients to correctly report what they did learn during scanning. It might have been possible to incorporate a requirement for a behavioural response into the paradigm, using reaction times as a further measure of learning and engagement; however, this was not done to avoid a possible motor confound with regard to the reward processing signals.

Potential limitations of this study should be noted. The sample size was limited although the numbers of subjects are similar to many clinical imaging studies. Patients were receiving medication which could be an important potential confound. However, there are a number of reasons to believe that the reduction in striatal responses to reward delivery were not a consequence of medication. First, reduced neural responses in the striatum correlated with increased severity of negative symptoms and no correlations were observed between antipsychotic equivalent medication doses and brain activity. Second, reduced ventral striatal responses to reward-predicting cues have been observed in unmedicated patients with schizophrenia (Juckel et al., 2006b). Regarding the reduced connectivity between the midbrain and insula in schizophrenia, no correlations with antipsychotic equivalent medication doses were observed, although this lack of correlation does not rule out medication effects. Another potential limitation is that the schizophrenia group had a higher male to female ratio than the control group, but gender was used as a covariate in all analyses. It should also be noted that we did not use a task related connectivity analysis such as psychophysiological interaction (PPI). This was because, for PPI to be efficient, a multifactorial design with at least two factors is recommended and our design had one factor (reward vs. no-reward).

In summary, our findings support the notion that reward processing is abnormal in schizophrenia. Furthermore, our findings highlight for first time, the potential role of abnormal interactions between the insula–ACC salience network system and reward processing regions, as a putative biological mechanism underlying symptoms and altered reward processing in schizophrenia.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.06.003.

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