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Evidence of altered cortical and amygdala activation during social decision-making in schizophrenia

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Impaired social cognition is a frequently observed and disabling characteristic of schizophrenia. An important aspect of social cognition involves making social decisions about others. The present study investigates whether brain activity related to social decision-making differs between patients with schizophrenia and healthy controls. Twelve patients with schizophrenia and 21 control subjects participated in the study. Behavioral performance and brain activity were assessed during a task that involved judging the trustworthiness of faces. We performed region-of-interest-based analyses, which revealed that patients with schizophrenia display specific increases and reductions in activation of the medial orbitofrontal cortex, amygdala and the right insula during social decision-making, areas that play key roles in the network that underlies social decisions. These findings suggest that the impairments in social cognition that are often observed in schizophrenia are, at least in part, related to altered brain activity in these areas.

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Introduction

Impaired social cognition is a frequently observed feature in schizophrenia. Numerous studies have reported specific abnormalities in the ability of patients to interpret the beliefs and intentions of others in order to explain and predict their behavior (Pinkham et al., 2003). Other studies have found impairments in the ability to identify facial and prosodic expressions of emotion (Edwards et al.,

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2001; Habel et al., 2000; Kohler et al., 2003; Penn et al., 2000; Pinkham et al., 2003). As a result of these social cognitive impairments, patients with schizophrenia often display poor social skills and frequently misinterpret social cues, making it one of the most disabling clinical features of the disease (A.P.A., 1994).

An important aspect of social cognition involves making decisions based on the appearance of others. Even though the exact neural mechanisms of social decision-making in healthy subjects are not fully understood, considerable progress has been made during recent years. It has become clear that a network of both cortical and subcortical brain areas is required to make accurate social decisions (Adolphs et al., 1998; Druzgal and D'Eposito, 2001). Neuropsychological and imaging research provides evidence for the involvement of several key areas that make up this network. The amygdala (Adolphs et al., 1998; Winston et al., 2002) is engaged during vigilance and attention to emotionally salient information, and the (ventromedial) prefrontal cortex (PFC) (Damasio, 1994; Eslinger and Damasio, 1985) is implicated in emotional and attentional processes. The insula (Sprengelmeyer et al., 1996; Winston et al., 2002) is involved in the perception and representation of affective/emotional states, most notably disgust. The fusiform gyrus (Iidaka et al., 2001; Kanwisher et al., 1997; Winston et al., 2002) is important for processing face stimuli. It has been suggested that the anterior cingulate cortex (ACC) is involved in monitoring the performance of systems evaluating the behavioral relevance of target stimuli (Druzgal and D'Eposito, 2001) and that the superior temporal sulcus (STS) acts as an association area that processes behavior of others (Brothers, 1990).

The main goal of the present study was to examine whether brain activity within this network differs between patients with schizophrenia and healthy controls during social decision-making. To accomplish this, we used an event-related functional magnetic resonance imaging (fMRI) paradigm to measure brain responses during evaluative social information processing. We employed a psychological task that requires subjects to make trustworthiness

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and age judgments about faces with a neutral emotional expression (Winston et al., 2002). Age judgments were included in the task to establish whether trustworthiness of faces is being processed implicitly, when subjects make an unrelated age assessment. Given that trustworthiness judgments require processing of subtle emotional cues, and thus place relatively high demands on social information processing, we expected this trustworthiness judgment task to be sensitive to subtle differences in social information processing between patients and controls. Based on the prior functional neuroimaging findings described above, we hypothesized that differences in brain activation between schizophrenia patients and controls would be observed in a network containing the amygdala, PFC, insula, fusiform gyrus, ACC and STS. Given earlier findings of reduced amygdala activation in schizophrenia patients (Fahim et al., 2005; Schneider et al., 1998) and the rich interconnections between the amygdala and prefrontal areas (Bechara and Van der Linden, 2005), we mainly expected to find reduced reactivity of the amygdala and prefrontal areas in patients relative to controls.

Materials and methods

Subjects

Twelve right-handed patients with schizophrenia (10 males, two females; mean age 28.7, SD=5.7) participated in the study. Presence of schizophrenia in these patients was established using the Comprehensive Assessment of Symptoms and History Scale (Andreasen et al., 1992). Current symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (Table 1). At the time of the study, all patients were outpatients on stable doses (chlorpromazine equivalent doses, range: 200 to 500 mg, mean: 335.4 mg, SD=110.0 mg) of atypical antipsychotic medication (including clozapine, olanzapine, quetapine and risperidone). Mean duration of illness was 6.7 years, SD=5.1 years. None of the patients experienced paranoid symptoms (PANSS suspiciousness/persecution mean score was 1.8, SD=1.1).

Twenty-one right-handed healthy (17 males, four females; mean age 31.2, SD=9.7) control subjects were recruited from community advertisements, and selected from the same age range (no significant group difference; t(1,31.7)=0.948, p=0.350). Control subjects had a mean education score comparable to the patients (mean education score for controls was 16.1, SD=1.8, mean education score for patients was 15.1, SD=2.1, with no significant group difference; t(1,19.8)=1.529, p=0.142). Control subjects were not taking any medication and were free of all psychiatric disorders according to the Mini International Neuropsychiatric interview (MINI) (Sheehan et al., 1998). Further exclusion criteria for both groups included significant medical or neurological illness at the time of participation, past major head injury and history of alcohol or drug abuse.

The present study was carried out in accordance with the Declaration of Helsinki and the study design was reviewed and

Table 1 Results of PANSS assessment

	Mean total (SD)
PANSS positive symptoms	10.8 (3.2)
PANSS negative symptoms	12.7 (4.2)
PANSS general symptoms	21.7 (4.1)
PANSS total	45 (9.3)

approved by the local human ethics committee. Informed written consent was obtained from all participants after the nature of the procedures had been fully explained.

Stimuli

120 frontal grayscale images of faces with a neutral emotional expression were used as stimuli. More than 80% of the photos were of Caucasian persons. These images were selected from a larger set of images on the basis of trustworthiness and emotional valence ratings given by 36 healthy subjects in a separate pilot study (9 men, 27 women; mean age 21.6, SD=3.3). We discarded images of which trustworthiness ratings correlated strongly with emotional valence ratings. Of the images used in the present study, 75 were from the set that Adolphs et al. used in their study of social cognition in patients with bilateral amygdala damage (Adolphs et al., 1998). In order to obtain a sufficient number of images from the psychological image collection of the psychology department of Stirling University (PICS). All images were rated in the pilot study.

Experimental paradigm

The psychological task used in the present study was an adapted version of a task used by Winston et al. (2002). A scanning session lasted for 25 min and consisted of 16 task blocks with a duration of 45 s, 16 rest blocks with a duration of 45 s and 16 instruction trials with a duration of 3 s. There were two types of task blocks and these types of task blocks were presented in random order for each subject. At the start of each task block, the word "age" or "trustworthiness" appeared on screen during an instruction trial to inform the subject of the task requirement. During eight task blocks, which were preceded by the word "age", subjects had to decide whether the faces that were presented in the subsequent task block were older or younger than 30 years. In the other eight task blocks, which were preceded by the word "trustworthiness", subjects had to judge whether the faces were trustworthy or untrustworthy. Task blocks consisted of 15 trials that were presented sequentially, and each trial consisted of a stimulus that was presented for 1 s followed by a fixation cross that was presented for 2 s. The stimulus that was presented in each trial could either be a face or fixation cross, in which case the trial served as a null event trial. These null event trials were included to enhance the estimation efficiency of our event-related fMRI analyses and were randomly interspersed among face trials. All stimuli, fixation crosses and instructions were presented on a gray (50% white) background. Face stimuli were presented once to each subject, randomized to the different task blocks and presented in random order across subjects. In total there were 120 face stimuli and 120 null event trials. Every task block was followed by a rest block, during which a fixation-cross remained on screen.

Debriefing

After the scanning session, subjects were required to perform a self-paced task in which they rated all the faces that were presented during scanning on a scale of trustworthiness that ranged from 1 (highly untrustworthy) to 7 (highly trustworthy), with 4 being neutral. This task was intended to obtain ratings of subjectively experienced trustworthiness of all faces, including those that were presented during the age judgment task.

fMRI image acquisition

Brain imaging data were acquired using a 1.5 T Philips ACS-NT scanner (Philips Medical Systems, Best, The Netherlands). For functional scans, 2D-EPI with BOLD (blood oxygenation level dependent) contrast was used, with the following parameters: echo time 40 ms; repetition time 2500 ms; flip angle 90°; field of view 192×192 mm. Each volume comprised 33 axial scans with 2.2 mm slice thickness (and a gap of 0.8 mm). Thus, voxel size was 3 mm isotropic, and volumes were continuously acquired every 2.5 s in an interleaved fashion (bottom slice first). In total 600 volumes were acquired. In the scanner, the head was held in place with a strap and padding. Each run was preceded by 6 'dummy' scans (which were not used in further analyses) to allow for T1 equilibration effects. Finally, a T1 weighted structural image was acquired.

fMRI image pre-processing

Image pre-processing was done using SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom). All functional volumes were corrected for slice timing (Henson et al., 1999) using the central slice in time as a reference, realigned to the first volume acquired and normalized to the Montreal Neurological Institute (MNI) standard brain (Friston et al., 1995). All volumes were then smoothed with a 6 mm full-width at half-maximum isotropic Gaussian kernel.

fMRI data analysis: whole-brain activation maps

We analyzed the data with an event-related model (Josephs et al., 1997) using SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom). Our whole-brain analyses were geared towards detecting brain activations in controls and patients as well as differences in brain activations between schizophrenia patients and healthy controls during explicit and implicit processing of social information. To this aim, we performed a general linear model (GLM) analysis with one factor modeling task condition (two levels: explicit and implicit social information processing) and a parametric factor modeling trustworthiness (ratings ranging from 1 to 7). Trustworthiness of faces was determined based on the judgments given by the individual subject after scanning. To create the regressors of interest, we modeled the presentation of each face by convolving a delta function at the onset of each stimulus with the standard SPM2 canonical hemodynamic response function (HRF) and its temporal derivative (Josephs et al., 1997). These regressors were parametrically modulated to model subject-specific trustworthiness judgments. A high-pass filter with a cut-off of 128 s was included to model out low-frequency scanner drifts. No global scaling was applied in any of the analyses (Desjardins et al., 2001). Next, parameter estimates pertaining to each regressor were calculated for each voxel and contrast images were calculated by applying linear contrasts to these parameter estimates. The contrast images were then entered into one-sample t-tests to test for significant activations related to the main effect of task, the main effect of trustworthiness and the effect of trustworthiness in the explicit and implicit task conditions within each group. We performed a two-sample t-test to compare groups regarding the main effect of task, the main effect of trustworthiness and the effect of trustworthiness in the explicit and implicit task conditions. All group maps were thresholded at p=0.05 (family wise error (FWE) corrected). We report descriptively activations surviving a threshold of 0.001 uncorrected with an extent threshold of 5 contiguous voxels.

fMRI data analysis: region-of-interest analysis

In order to examine task-related activation in more detail, a region-of-interest (ROI)-based analysis was performed using areas that displayed task-related activation across groups. Analyzing the data in this fashion allows for the detection and examination of small differences between task factors, without the need to correct for statistical testing in brain areas that are not involved in any of the task conditions (Nieto-Castanon et al., 2003). For these ROI analyses, we performed a second GLM analysis, modeling the data slightly differently than during the whole-brain analysis, by using a model with six factors that modeled onsets of trustworthy, neutral and untrustworthy faces during both the explicit and implicit task conditions. Trustworthiness of faces was again determined based on the judgments given by the individual subject after scanning. However, in this model faces with trustworthiness ratings of 1-3 were labeled untrustworthy, those with rating 4 were labeled neutral and those with ratings 5-7 were labeled trustworthy. Factors were convolved with the standard SPM2 canonical HRF and its temporal derivative (Josephs et al., 1997). A high-pass filter with a cut-off of 128 s was included to model out low-frequency scanner drifts and no global scaling was applied (Desjardins et al., 2001).

The ROIs were obtained by selecting clusters that displayed task-related activation across groups (one-sample *t*-test; p < .0001 not corrected for multiple comparisons). As the prefrontal cortex is a functionally heterogeneous brain area that is involved in both emotional and attentional processes (Amodio and Frith, 2006; Elliott et al., 2000; Kringelbach and Rolls, 2004; Yamasaki et al., 2002), groups of clusters within the frontal cortex were separated based on functional divisions suggested in the literature (Amodio and Frith, 2006; Kringelbach and Rolls, 2004). This resulted in four sections; lateral (X > -20 & X > 20, MNI) and medial (-20 < X < 20, MNI) prefrontal (2 < Z < 84, MNI) sections, and lateral and medial orbitofrontal (-51 < Z < 2, MNI) sections.

After identifying the ROIs, the averages of the regression coefficients (obtained from the single subject level analyses) over all voxels for each ROI were calculated for each individual subject. These data were entered into a repeated-measures GLM in SPSS (SPSS inc.) to test for the effect of task condition (two levels: explicit and implicit social information processing), for the effect of trustworthiness (three levels: trustworthy, neutral and untrustworthy) and for the effect of ROI (16 levels, see Table 3).

Results

Behavioral results

On average, patients did not make significantly different trustworthiness judgments than controls after scanning (F(1,31)= 0.71, p=0.79). Mean trust ratings for patients were 3.88 (SD=0.173) and mean ratings for controls were 3.94 (SD=0.13). Regarding the variability of the ratings however, an independent-samples *t*-test of the variances of trustworthiness ratings for each face showed that the patients' trustworthiness judgments were more variable than those of controls (t(238)=9.95, p<.001), indicating that the patient group had a lower inter-rater agreement than the controls. Behavioral data are illustrated in Fig. 1, which shows the



Fig. 1. (A) Distribution of trustworthiness judgements (1=)very untrustworthy, 7=very trustworthy. (B) Trustworthiness judgements given by subjects during scanning.

frequencies of trustworthiness scores after scanning and frequencies of trustworthiness judgments during scanning.

fMRI results: whole-brain activation

The whole-brain analyses were aimed at detecting brain activation in controls and patients as well as differences in brain activations between schizophrenia patients and healthy controls during explicit and implicit processing of social information. We did not find activations that survived an FWE corrected threshold of 0.05. However, using a more liberal threshold of 0.001 uncorrected with an extent threshold of 5 contiguous voxels we found several foci of activation. Activations related to the main effect of task, the main effect of trustworthiness and the effect of trustworthiness in the explicit and implicit task conditions in controls and patients are displayed in Table 2.

fMRI results: region-of-interest analysis

Regions of interest were defined as those areas showing overall task-related activation, combining data of controls and patients (one-sample t-test; p < .0001 not corrected for multiple comparisons). These criteria resulted in a comprehensive network of brain areas showing overall task-related activation. Across groups, performing the task was associated with activity in areas that have been previously shown to be involved during processing of social information: amygdala, prefrontal cortex, insula, anterior cingulate cortex, occipital cortex, right superior temporal sulcus (see Table 3), as well as activity in the thalamus, motor areas and cerebellum.

ROI activations related to task performance

A repeated-measures general linear model with task condition (two levels: trustworthiness and age), trustworthiness (three levels:

untrustworthy, neutral and trustworthy) and ROI (16 levels: see Table 3) as within-subject factors and group (two levels: patients, controls) as between-subject factor was performed to test for group differences in neural activation during the implicit and explicit social information processing tasks. In cases where Mauchly's test indicated that the assumption of sphericity had been violated, degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity.

There was a significant interaction effect between group and ROI (F(15,17)=3.02, p<.05), indicating that the activation pattern across ROIs differed between groups. Subsequent repeated-measures analyses of activation levels in the individual ROIs were performed to explore this interaction and these revealed a significant overall reduction of right amygdala activation in the patient group, as compared to the controls (F(1,31)=4.36, p<.05). In the left amygdala, trustworthiness had a different effect on activation levels in the patient group than in the control group (F(1.55,48.13)=4.07, p<.05), with left amygdala activation being significantly lower in patients than controls during judgments of trustworthy faces (independent-samples *t*-test, t(31)=2.55, p<.05; see Fig. 2).

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Cerebral foci of activation related to task and trustworthiness in controls and patients

Brain region	No. of voxels	Side	MNI coordinates of peak activation (mm)			Max (<i>Z</i>)
			X	Y	Ζ	
Controls task main effect						
ACC	5	R	3	27	-9	4.22
Middle temporal gyrus	8	L	-54	-33	-3	4.05
Medial OFC	8	L	-18	48	-6	3.85
Medial DFC	11	R	3	63	3	3.57
Controls trustworthiness i	nain effec	t				
Superior temporal gyrus	8	R	36	-33	0	3.67
Postcentral gyrus	6	R	45	-24	45	3.51
Middle temporal gyrus	6	L	-51	-36	-6	-3.85
Controls trustworthiness a	during exp	licit tas	k			
ACC	18	L	-6	39	21	4.31
Cerebellum	5	L	-33	-45	-30	3.45
Cerebellum	6	L	-24	-66	-30	3.45
Controls trustworthiness a	during im	olicit tas	k			
Postcentral gyrus	6	R	45	-24	45	4.36
Patients trustworthiness n	nain effect					
Lateral frontal cortex	6	R	27	18	36	-3.68
Patients trustworthiness d	luring exp	licit tasl	k			
Cerebellum	5	L	-12	-75	-48	-3.84
Superior temporal gyrus	11	R	30	-27	3	-3.76
Patients trustworthiness of	luring imn	licit tas	k			
Supramarginal gyrus	10	R	45	-57	36	4.34
Trustworthiness during in	uplicit task	contro	ls>patie	ents		
Lateral frontal cortex	5	D	20	19	20	2 45

All values, p < .001 uncorrected with an extent threshold of 5 contiguous voxels. Negative Z-values indicate a negative relation between trustworthiness and activation.

Table 3 Details of the regions of interest obtained for the overall task versus baseline contrast, thresholded at p < .001, uncorrected

ROI	Voxels in ROI	Coordi activat	Coordinates of peak activation (mm)		
		X	Y	Ζ	
Left amygdala	114	-20	-2	-17	6.21
Right amygdala	105	17	-8	-14	6.55
Left medial OFC	1	-14	62	-8	3.08
Right medial OFC	15	11	56	-14	3.56
Left lateral OFC	5	-44	53	2	3.56
Right lateral OFC	148	38	59	-5	5.41
Right medial DFC	8	8	68	29	3.78
Left lateral DFC	45	-35	53	26	4.23
Right lateral DFC	493	53	35	20	6.44
Left insula	139	35	17	11	5.60
Right insula	202	38	29	$^{-2}$	6.36
Left occipital	1907	-44	-68	-23	7.24
Right occipital	2417	23	-56	-23	7.12
Left ACC	122	-5	14	44	5.82
Right ACC	93	2	26	41	5.28
Right STS	18	56	-53	8	4.38

DFC refers to the dorsal frontal cortex and OFC refers to the orbitofrontal cortex.

In the right insula, trustworthiness also had a different effect on activation levels in the patient group than in the control group, with patients displaying an increase and controls displaying a decrease in activation as trustworthiness of the faces decreased (F(2,30)=3.37, p<.05; see Fig. 3). However, no significant group differences were found when testing activation at individual levels of trustworthiness in the right insula ROI using independent-samples *t*-tests.

Furthermore, a trustworthiness by task by group interaction was found in the left medial OFC (F(1.59,49.21)=6.29, p<.01; see Fig. 4). Two subsequent repeated-measures analyses, one for implicit (age) and one for explicit (trustworthiness) task conditions, with trustworthiness as within-subject factor and group as betweensubject factor, revealed a group by trustworthiness interaction in the explicit task condition (F(1.61,46.15)=5.45, p<.05), but not in the implicit condition. Next, independent-samples *t*-tests in the explicit condition showed that left medial OFC activation was reduced in patients as compared to controls during judgments of neutral faces in the explicit task condition (t(31)=2.47, p=0.02).

Discussion

We aimed to examine whether brain activity underlying social decision-making is abnormal in schizophrenia, using a social decision-making paradigm that involves making trustworthiness judgments. In our whole-brain analyses we did not find significant activations that survived an FWE corrected threshold of 0.05. However, when exploring overall task-related activation across groups at a more liberal threshold in order to define ROIs for our ROI analyses, we found a more comprehensive network of activation. Across groups, performing the task engaged a network of brain areas that are commonly reported to be activated during social decision-making. Furthermore, when using ROI based analyses, our results indicate that this network is impaired in patients with schizophrenia. Our main findings are, compared to controls, patients displayed specific reductions in amygdala and left medial OFC activation, as well as a dissimilar effect of

trustworthiness on activation in the right insula. These findings will be discussed below.

Patients displayed decreased amygdala activation compared to controls and this finding replicates the results of several previous studies (Aleman and Kahn, 2005). We hypothesize that this decreased activation is not the result of an inability to activate the amygdala per se because left amygdala activity was found to increase in patients when faces were judged to be neutral or trustworthy (Fig. 2), but rather reflects an inability to recruit the amygdala fully when making judgments of trustworthiness. Notably, left amygdala activity was most strongly decreased in patients compared to controls in response to trustworthy faces. Several studies have demonstrated that amygdala activation during encoding enhances memory retrieval of emotional stimuli (Cahill et al., 1996; Canli et al., 2000; Hamann et al., 1999). Seen in this light, the specific reduction in response to trustworthy faces is consistent with a recent study that demonstrated that patients with schizophrenia fail to display a memory enhancement for positive emotional stimuli which is normally found in healthy subjects, although the patients' memory enhancement for negative images did not differ from that of healthy participants (Herbener et al., 2007).

In addition to reduced amygdala activation, we found that trustworthiness of faces had a different effect on activation levels in the right insula in patients than in controls, with patients displaying an increase and controls displaying a decrease in activation as trustworthiness of the faces decreased. This finding is consistent with a recent finding of increased right insula activity in schizophrenia patients as compared to controls during a visual oddball task (Gur et al., 2007). As activation of the right insula has been linked to risk taking during decision-making (Paulus et al., 2003), we conjecture that the pattern of activation in the right insula of patients is likely to reflect decreased confidence when their judgments concerned less trustworthy faces.

Compared to controls, patients displayed significantly reduced activation of the left medial OFC in response to neutral faces during the trustworthiness task condition. This finding is consistent with earlier findings of reductions in ventromedial prefrontal cortex activity during rest as well as during implicit and explicit emotion perception tasks (Galeno et al., 2004; Taylor et al., 2002; Williams et al., 2004). Additional imaging studies of social cognition in schizophrenia patients that used theory of mind tasks (Brunet et al., 2003; Russell et al., 2000) and empathy and forgivability tasks (Lee et al., 2006) also report reduced prefrontal cortical activity in patients. By contrast, a study of subjects at enhanced risk of schizophrenia found an increase in prefrontal cortex activity in a subset of the enhanced risk group during theory of mind task (Marjoram et al., 2006). However, to our knowledge, lower medial OFC activation in patients with schizophrenia during social information processing has not been previously reported in the literature. The medial part of the OFC is normally involved in decoding and outcome monitoring of the reward value of reinforcers (Elliott et al., 2000; Kringelbach and Rolls, 2004) and neurological patients with injury to the ventromedial prefrontal cortex, which includes the medial OFC, display abnormalities in emotion, affect, personality and (social) decision-making (Bechara and Van der Linden, 2005; Damasio, 1994). These abnormalities overlap considerably with the abnormalities commonly found in schizophrenia and we therefore interpret the present finding of lower medial OFC activation in patients to be related to the impairments in social cognition that are often seen in schizophrenia. This notion is consistent with previous morphological studies



Left Amygdala

Fig. 2. In the right amygdala ROI, overall activation levels differed significantly between patients and controls. In the left amygdala ROI, trustworthiness had a different effect on activation levels in patients than in controls. The graphs on the right illustrate mean task-related activation levels within these ROIs (in arbitrary units with error bars depicting SEM). * indicates p < .05.

revealing decreases in gray matter density in the medial and lateral OFC in schizophrenia (Hulshoff Pol et al., 2001). Such reductions of the medial OFC have been found to be correlated with loss of white

matter density in the corpus callosum (Pol et al., 2004) and, at the behavioral level, with reduced premorbid and post diagnosis social function as well as more severe negative symptomatology (Baare





Right Insula

Fig. 3. The effect of trustworthiness was different for patients than controls in the right insula. The graph on the right illustrates mean task-related activation levels within the right insula ROI (in arbitrary units with error bars depicting SEM).



Fig. 4. The effect of trustworthiness on activation levels in the left medial OFC ROI was different in patients than in controls. The graphs on the right illustrate mean task-related activation levels within left medial OFC ROI (in arbitrary units with error bars depicting SEM). * indicates p < .05.

et al., 1999; Chemerinski et al., 2002). It should be noted, however, that normal functioning of the medial OFC depends on the integrity of other neural structures, particularly the insula, dorsolateral prefrontal cortex (DLPFC) and amygdala (Bechara and Van der Linden, 2005; Ernst and Paulus, 2005). Importantly, the latter structure also displayed significantly lower activity in patients in the present study.

With these differences in brain activation in mind, one would expect corresponding differences in trustworthiness judgments. Although the average subjective trustworthiness judgments of controls and patients are not different, patients do make more variable judgments (Fig. 1A), which could imply that patients make more random judgments.

It should be noted that the patient group that participated in the present study consisted of patients who were outpatients at the time of the study and who were not very ill (Table 1); this might be a limitation to the extendibility of the present findings to patient groups with strong symptomatology. Also, it is presently unclear which aspects of abnormal social cognition in schizophrenia are more state than trait related. For instance, Drury et al. found that difficulties in interpreting interpretsonal contexts are more state than trait related (Drury et al., 1998). Inoue et al., on the other hand, found that deficits in theory of mind in schizophrenia are trait related (Inoue et al., 2006). Finally, most of our findings were not highly statistically significant. A reason for this could be that the paradigm is relatively insensitive to

schizophrenia. Also, the patient group that participated in the present study was rather small and as a consequence the statistical power of the present study was relatively low.

Taken together, our findings suggest that brain activation during social decision-making in schizophrenia is characterized by specific alterations in the activation of the amygdala, the insula and the medial OFC, areas that play key roles in the network that underlies social decisions. It seems plausible that these abnormalities are related to the impairments in social cognition that are often seen in schizophrenia.

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