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Neural correlates of action attribution in schizophrenia

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Abstract

Patients with first-rank symptoms (FRS) of schizophrenia do not experience all of their actions and personal states as their own. FRS may be associated with an impaired ability to correctly attribute an action to its origin. In the present study, we examined regional cerebral blood flow (rCBF) with positron emission tomography during an action-attribution task in a group of patients with FRS. We used a device previously used with healthy subjects that allows the experimenter to modulate the subject's degree of movement control (and thus action attribution) of a virtual hand presented on a screen. In healthy subjects, the activity of the right angular gyrus and the insula cortex appeared to be modulated by the subject's degree of movement control of the virtual hand. In the present study, the schizophrenic patients did not show this pattern. We found an aberrant relationship between the subject's degree of control of the movements and rCBF in the right angular gyrus and no modulation in the insular cortex. The implications of these results for understanding pathological conditions such as schizophrenia are discussed.

Keywords: Agency; Schneiderian symptomatology; Positron emission tomography; Volition

1. Introduction

One of the most disconcerting sensations encountered by patients with schizophrenia is the feeling that their actions and personal states are no longer under their own control. Symptoms such as auditory hallucinations, thought insertion, thought broadcasting and the influence of others on the patient's thoughts, actions or emotions are very frequent in schizophrenia. Kurt Schneider (1959) classified these experiences as first-rank symptoms (FRS) and considered them as the consequences of a loss of boundaries between the self and others. Indeed, he stated that major FRS had to be interpreted as the consequence of an impaired selfness, leading to the sensation of being controlled by the others. It has been proposed that these symptoms may reflect a problem with the recognition of the person's own actions or thoughts and to a perturbed sense of agency (the sense that I am the one who is causing an action; Gallagher,

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2000), leading patients to misattribute their own actions to another agent. Experimental evidence for this hypothesis comes from studies that tested source monitoring (i.e. the ability to attribute an action or an event to its correct agent) (Bentall et al., 1991; Daprati et al., 1997; Morrison and Haddock, 1997; Baker and Morrison, 1998; Johns and McGuire, 1999; Brébion et al., 2000; Johns et al., 2001) and other studies that distorted the feedback of patients' actions to evaluate their capacity to detect the distortion (Cahill et al., 1996; Johns and McGuire, 1999; Blakemore et al., 2000; Franck et al., 2001). The results from these studies showed that patients currently experiencing hallucinations and/or delusions of control were not only impaired at detecting the distortion of their own movements, but also tended to misattribute their own actions to another agent.

The presence of FRS is associated with abnormal over-activation in specific brain regions. Some studies have found an association between hallucinatory phenomenon and activation in primary sensory areas of the auditory cortex and in brain areas involved in the generation and understanding of speech (McGuire et al., 1993; Silbersweig et al., 1995; David et al., 1996; Woodruff et al., 1997 Dierks et al., 1999; Bentaleb et al., 2002). It has been proposed that the hyperactivation that occurs during hallucinations arises from a failure in the neural processes subserving self-generated action (Frith, 1996; Frith and Dolan, 1996). Studies on willed action in normal subjects have shown that self-generated movements involved an inhibitory process (from prefrontal and cingular cortices), in the areas involved in the processing of the sensory consequences of the action (Müller-Preuss and Jürgens, 1976; Müller-Preuss and Ploog, 1981; Frith et al., 1991a,b; Blakemore et al., 1998). Auditory hallucinations may be explained by a deficit in inhibitory processes leading to an over-activation of those areas normally involved in the reception of verbal messages (Silbersweig et al., 1995). Increased activity in those regions might lead to incorrect agency judgments. The same explanation can be applied to delusions of control. Patients experiencing this symptom feel that some outside force is creating their own actions. Spence et al. (1997) found hyperactivity in the right inferior parietal lobule when patients with schizophrenia experienced alien control during a movement selection task. Delusions of control may arise because of a disconnection between frontal brain regions, where actions are initiated, and parietal regions, where the current and predicted states of limbs are represented (Frith, 1996; Frith et al., 2000).

In normal subjects, attribution of action judgment has been shown to involve different brain areas. When subjects feel in control of an action and thus attribute it to themselves, activation in the insular cortex is observed (Farrer and Frith, 2002). However, when they do not feel in control and attribute the action to another agent, the right inferior parietal lobule is activated (Ruby and Decety 2001; Decety et al., 2002; Farrer and Frith, 2002). Furthermore, a study by Farrer et al. (2003) suggests that the feeling of being in control of an action is not an all or none state. It varies continuously on the basis of the various action-related signals concerned with sensation (kinesthetic, visual) and motor control (motor commands). In this study visual feedback was distorted by varying degrees up to the point where the movements seen were completely unrelated to those executed. The results showed that the level of activity in the areas known to be activated during attribution judgments (e.g. posterior parietal cortex and insula) co-varied continuously with the feeling of being in control of the action.

The studies reviewed above indicate that patients with FRS are impaired in attributing actions to their respective authors and that these symptoms are associated with neurofunctional abnormalities. Studies with normal subjects have associated attribution of action judgments with activations in the right inferior parietal cortex and the insula. In the present study we went one step further and examined the neural correlates of the same attribution judgments in a group of patients suffering from FRS. We aimed at determining whether the attribution deficit observed in such patients is linked to abnormal neurofunctional processes. We considered FRS as a whole and patients were included according to the presence of at least one such symptom. Each of them was considered equivalent in the present study, since

our hypothesis was that all of them would be related to the same impairment of action attribution. We did not attempt to evaluate the neural correlates of these symptoms while they occurred, but rather mechanisms that favor their production. We expected that the weakening of action attribution processes could produce conditions necessary for FRS production. Thus we sought to find evidence of trait markers rather than state markers. We selected patients who experienced FRS frequently, but we did not try to record cerebral blood flow during the presence of FRS.

We used a device previously used in a group of normal subjects (Farrer et al., 2003) that allows modulation of the feeling of being in control of the movements (and thus action attribution) of a virtual hand presented on a screen. This feeling was modulated across the different experimental conditions by introducing a distortion between the executed movements and their indirect visualization. The higher the distortion, the more the subjects felt that they were not controlling the movements on the screen. The maximal distortion was obtained when they executed movements and saw the movements of another agent (the experimenter). In normal subjects the activity of two main brain areas (the right angular gyrus and the insula cortex) appeared to be modulated by the subject's degree of control of the movements of the virtual hand (Farrer et al., 2003). The present study aimed at evaluating whether the feeling of being in control of one's action was correlated with activation in the angular and insular areas in a group of patients with Schneiderian symptoms.

2. Methods

We studied eight healthy right-handed male subjects (mean age 34 ± 6.71 years, mean years of education 12 ± 3.26) and eight right-handed male medicated patients with DSM-IV diagnoses (established according to clinical consensus) of schizophrenia (mean age 36.25 ± 9.57 years; mean years education 10.25 ± 2.96). Exclusion criteria were visual and auditory disorders, history of neurological illness or trauma, alcohol and drug dependence according to the DSM-IV criteria, and age above 70 and below 18. The two groups were demographically similar in terms of age and level of education. None of the patients had localized cerebral lesions on magnetic resonance imaging (MRI) scans. The patients underwent clinical assessment with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Mean scores were: 40.88 ± 16.14 for the SAPS and 27.63 ± 16.16 for the SANS. The mean duration of illness was 10.12 ± 11.87 years. Patients were selected, for the presence of FRS in the weeks before the experiment (i.e. verbal hallucinations, impressions that another agent was controlling actions and thoughts, that thoughts have been stolen or introduced in the patient's mind or that someone else knows his thoughts). However, the patients did not manifest these symptoms during the scanning sessions. A Schneiderian score was calculated for each patient according to seven items from the SAPS (item 2: voices commenting; item 3: voices conversing; item 15: delusions of control; item 16: delusions of mind reading; item 17: thought broadcasting; item 18: though insertion; item 19: thought withdrawal). The mean Schneiderian score was 6.88 ± 5.67. All patients were under antipsychotic treatment (risperidone, olanzapine, clozapine, haloperidol or levomepromazine), but one of them also received prazepam (benzodiazepine) and another one valproate (mood stabilizer). All were clinically stable at the time of testing and gave written informed consent to participate in the study, which had been approved by the local Ethics Committee (CCPPRB, Centre Léon Bérard, Lyon).

The subjects underwent 12 perfusion scans with positron emission tomography (PET) in a single session. Subjects lay in the scanner with head movements minimised by a mask. Radioactivity was administered as an intravenous injection of H_2O^{15} by a plastic canula placed in the left cubital vein. The subjects held a joystick with their right hand and were instructed to execute random movements at a constant rate throughout the 70-s block. This task is very similar to that used by Spence et al. (1997) to demonstrate parietal overactivity in patients with delusions of control. They were requested to move the joystick back to the center

after each excursion in the chosen direction. This procedure ensured that the movements were similar across conditions and subjects. The movements of the joystick controlled an image of a virtual hand holding a joystick. This system provided a dynamic representation of the movements of the joystick held by the subjects with an intrinsic delay of less than 30 ms (Franck et al., 2001).

The joystick was attached to a table above the bed of the scanner. The image of the virtual hand holding the joystick was projected onto a mirror placed in front of the subject. The angle of visualisation of the image in the mirror was adjusted so as to coincide with the real position of the joystick actually held by the subjects. The position of the subject's forearm was adjusted so as to coincide with the direction of the virtual forearm seen in the mirror. A black cloth was then hung above the subject's forearm so as to prevent him from seeing his forearm and the device controlled by the experimenter.

Angular distortions could be introduced into this system, modifying the direction of the movement actually performed by the subjects with respect to the movement displayed on the computer screen. The experiment involved four experimental conditions. In the first condition ('0°' condition) the subjects could see the movements of the virtual hand in perfect concordance with their movements made with the joystick. In the second condition ('25°' condition), they saw the movements of the virtual hand deviating by 25° from their hand's actual trajectory. In the third condition ('50°' condition) the value of the deviation was 50°. In the latter two conditions, the deviation was to the right on half of the sessions and to the left on the other half. In the fourth condition ('Other' condition), the subjects saw the movements of the joystick controlled by another agent (the experimenter).

During each session subjects were asked to direct their attention to the origin of the movement they saw. They had to give a verbal response to indicate whether it was their own movement ('Self' response), their own movement distorted ('Distorted' response) or the movement of another agent ('Other' response).

Two low-level control conditions ('C1' and 'C2') were also included. In condition 'C1' the subjects had to execute random movements without seeing anything on the screen. In condition 'C2' they had to watch the virtual hand moving by itself without doing anything.

At the beginning of the experiment subjects undertook a practice session in order to get acquainted with the device and to experience generating random movements. They sat in front of the monitor and executed random movements in three different conditions: '0°' condition, 'Distorted' condition (the deviation was 35°) and 'Other' condition. When the subjects were lying in the scanner, they had a second practice session so that they could familiarize themselves with the new angle of visualization caused by their supine position. Only the '0°' and the 'Distorted' conditions were performed in this final practice session.

The PET scanning comprised two blocks of each of the six conditions of 70 s each. The interval between each start time was 8 min. The order of the conditions was randomised and reversed within and between subjects. Each trial was initiated by an auditory stimulus.

2.1. Image acquisition

The PET images were acquired using a Siemens CTI HR+ (63 slices, 15.2-cm axial field of view) PET tomograph with collimating septa retracted operating in 3D mode. Relative rCBF was measured by recording the regional distribution of cerebral radioactivity using H_2O^{15} as a tracer. After a 9-mCi bolus injection of H_2O^{15}, scanning started when the brain radioactive count rate reached a threshold value and continued for 60 s. Integrated radioactivity accumulated in 60 s of scanning was used as an index of rCBF. A transmission scan collected before the first emission scan permitted correcting for radiation attenuation.

2.2. Data analysis

2.2.1. Image analysis: pre-processing

The data were analysed with SPM99 (Wellcome Department of Cognitive Neurology, London, UK).

Each subject's PET data were realigned to the first scan of the time series. The estimates extracted from the rigid body transformation (described as three translations (x, y, z) and three rotations about the axes) were used to realign the images and to perform a mathematical adjustment (minimising the sum of the squares of differences in intensity between each image and the reference) to remove movement-related components. The images were then spatially normalised into the system of reference of Talairach and Tournoux (1988) using as the template a representative brain from the Montreal Neurological Institute (MNI) series (Evans et al., 1994). The first step of spatial normalisation was to determine the optimal affine transformation (correction for variation in position and size) that mapped the brain image onto the template (minimisation of first the sum of the squares of the differences between those two images and also the squared distance between the parameters and their known expectation). Residual differences between each pair of images were corrected using nonlinear basis functions (Friston et al., 1995). The normalization parameters were subsequently applied to the PET images. Finally, PET images were filtered with the use of a low-pass Gaussian filter (FWHM = 11.1, 13.2, and 14.5 mm) to reduce noise and maximise signal. The smoothness was achieved by forcing the deformations to consist of a linear combination of predefined smooth spatial basis functions.

2.2.2. Statistical model and inference

The data were modeled so as to partition the rCBF of each voxel into components of interest, confounds of no interest and an error term. The data were first adjusted for the effect of global image signal with the proportional scaling method. The fraction of mean signal over the whole brain was specified for thresholding signal intensities above the grey matter value. Since the subjects were requested to move the joystick freely, there were some differences in the amount of movement between subjects and between conditions. To eliminate this bias, the co-ordinates of the position of the joystick were recorded so as to obtain a measure of the distance covered by the joystick. This reflected the amount of movement made by each subject in each condition. These measures were modeled as confounds in the analysis so as to remove variations in blood flow that were related to the amount of movement.

The analysis of regionally specific effects was realized using the general linear model. We specified the following six effects of interest: '0°', '25°', '50°', 'Other', 'C1' and 'C2'. The '25°' and '50°' effects of interest grouped together the trials in the two directions of deviation (to the left and to the right). We were interested in finding brain areas showing significant variations (i.e, increased or decreased rCBF) as a function of the discrepancy between the movements made by the subjects and the movements of the virtual hand on the screen. To achieve this aim, the four experimental conditions ('0°', '25°', '50°' and 'Other') were modeled as independent covariates and two conjunction analyses (Price and Friston, 1997) of three contrasts each were performed. The first one was designed to identify brain areas showing increased rCBF with increasing distortion from the '0°' condition to the 'Other' condition (('25°'–'0°') in conjunction with ('50°'–'25°') and ('Other'–50°)). The second analysis allowed us to determine brain areas showing decreased rCBF with increasing distortion from the '0°' condition to the 'Other' condition (('0°'–'25°') in conjunction with ('25°'–'50°') and ('50°'–'Other')). An exclusive masking procedure with the contrast (('0°' + '25°' + '50°' + 'Other') – 'C1') was applied to each conjunction analysis to eliminate hemodynamic activity related to visual feedback and eye movements. In the 'C1' condition the patients were requested to move the joystick while fixating the center of the blank screen. Thus the contrast (('0°' + '25°' + '50°' + 'Other') – 'C1') allowed us to obtain brain activity related to visual feedback and eye movements.

Complementary simple contrast analyses within the patient group and comparisons between the patients and the normal subjects were realized to assess, respectively, differences in brain activation between the effects of interest and differences in the magnitude of activation effects between groups.

Finally, to examine whether brain activations were related to symptomatology, we computed the

correlations between effects of interest and the Schneiderian score and between these effects and the SANS score.

The different models were framed in terms of a statistical parametric map of a t value SPM $\{T^3\}$ for the conjunction analysis and of a SPM $\{t\}$ transformed into SPM (Z) for the simple contrasts. Since we were interested in brain activity in the right inferior parietal cortex and in the insula and we had strong a priori hypotheses, we first defined search volume corrections in a region involving the inferior parietal lobule and the intraparietal sulcus and in a second region involving the insula and the circular insular sulcus. These regions were delimited with MRICRO, a software package. To look for other brain activations that were not predicted, we analyzed the SPMs thresholded at $P<0.0001$ uncorrected for multiple comparisons at the voxel level or thresholded at $P<0.05$ corrected at the cluster level. Only activations with a $Z\geq 3.70$ were taken into account. Finally, brain activity localization was identified using the atlas of neuroanatomy by Duvernoy (1992).

3. Results

3.1. Behavioural results

After each experimental condition the patients were first requested to indicate whether the movements they saw on the screen exactly corresponded to their executed movements ('Self' response), whether they had deviated ('Distorted' response) or whether they were controlled by the experimenter ('Other' response). Secondly patients were questioned about their impressions and feelings during the trial.

This debriefing showed that patients did not manifest any passivity phenomena, such as feeling that they were being controlled by another agent, or hallucinating. One patient reported during a '0°' trial that another person was controlling the movements of the virtual hand at the end of the session. This same patient also reported during a '25°' trial that another person was controlling, but that he was able to get back the control very rapidly. Another patient reported during a '0°' trial that he was controlling the movements, but at the same time, another person was doing exactly the same movement. Further questioning of the patients revealed that these impressions only occurred once and were very brief. Indeed these patients reported that they knew they controlled the virtual hand. These patients were included in the analyses.

Analyses of the behavioral responses showed that patients tended to perform well; a t-test for independent comparisons on the percentage of correct responses for each condition did not reveal any significant differences between the patients and the controls. There was, however, a trend for the patients to perform worse on the '25°' and on the '50°' trials. Patients gave 100% correct responses for the '0°' and the 'Other' trials. However, errors were observed in the Distortion conditions. Errors were found in 31% of cases ('Self' response) for the '25°' trials and in 9% of cases ('Self' response) and 6% of cases ('Other' response) for the '50°' trials. T-tests for pairwise comparisons revealed significant differences between the different types of responses for the '0°', '50°' and 'Other' trials. However, there were no significant differences between 'Self' and 'Distorted' responses for the '25°' trials. This result indicates that patients did not easily recognize a perturbation of 25°.

3.2. Functional imaging data

3.2.1. All experimental conditions vs. observation control condition ('C2')

Contrasting all experimental conditions with the observation control condition ('C2') revealed significant activation ($P<0.001$ corrected for multiple comparisons at the voxel level) in the right ventral premotor cortex (PMv) and the left posterior insula. At the cluster level, significant activations were observed in the left sensorimotor cortex. Additional activations that did not survive correction for multiple comparisons were found in the left PMv, the right sensorimotor cortex, the right dorsolateral prefrontal cortex and the left cerebellum. The co-ordinates of these areas, the Z-values and the probability scores are shown in Table 1.

Table 1
Brain areas activated during all the experimental conditions contrasted to the 'Observation' control condition ('C2')

Area	*x*	*y*	*z*	*Z*	*P*
R ventral premotor cortex*	56	8	8	4.79	0.031
L posterior insula*	−32	16	8	4.71	0.044
L sensorimotor cortex**	−38	−32	52	4.57	<0.0001
L ventral premotor cortex	−42	6	24	4.24	<0.0001
R dorsolateral prefrontal cortex	44	34	28	4.18	<0.0001
R sensorimotor cortex	52	−28	52	3.78	<0.0001
L cerebellum	−30	−54	−34	3.73	<0.0001

*$P<0.05$ corrected at the voxel level.
**$P<0.05$ corrected at the cluster level.
All other areas are reported for a $P<0.0001$ uncorrected at the voxel level; voxel extent threshold 10, $Z\geq3.70$.

3.2.2. All experimental conditions vs. execution control condition ('C1')

Contrasting all experimental conditions with the execution control condition revealed significant activation ($P<0.001$ corrected for multiple comparisons) in brain areas associated with visual perception. Activation was observed with a peak in the right striate cortex extending into the precuneus, the inferior occipital cortex, the medial occipital cortex and the superior occipital cortex bilaterally.

3.2.3. Brain areas increasing their activity as a function of the degree of discordance between the executed and the seen movements in controls subjects and patients

The main interest of the present study was to test whether patients with FRS present a modulation of brain activation as a function of the degree of the discordance and thus of the sense of agency. Increased brain activity as a function of the increased discordance was tested with a conjunction analysis between the contrasts (('25°'–'0°'); ('50°'–'25°') and ('Other'–'50°')). In the normal subjects, increased discordance was associated with increased brain activity in the right angular gyrus (Farrer et al., 2003). However, in schizophrenic patients, we did not find any co-variation between the subject's degree of control of the movements and rCBF, in either the right angular gyrus or in other brain areas.

Although we did not find any co-variation between brain activity and the degree of discordance between executed and seen movements, contrasting the two extreme experimental conditions ('Other'–'0°') revealed significant activation in the right inferior parietal lobe (see Fig. 1), with a peak activation in the right angular gyrus ($P<0.001$ corrected for multiple comparisons at the voxel level). This angular activation was also

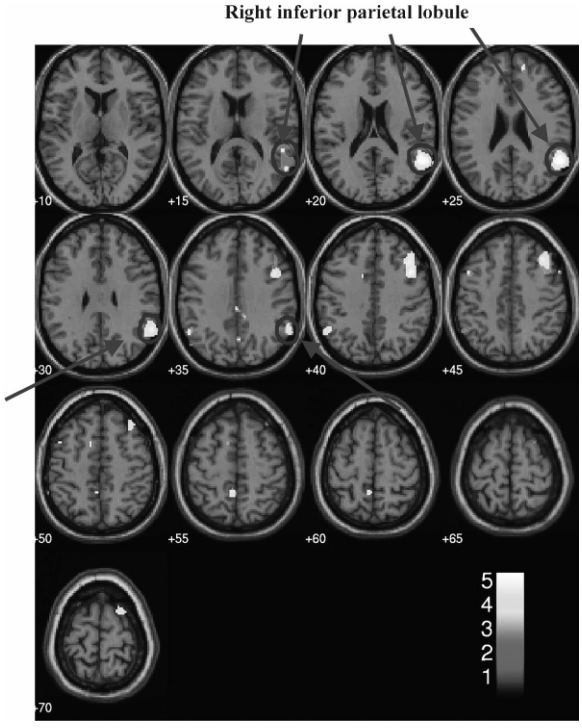

Fig. 1. Brain activations for the contrast ('Other'–'0°'). The SPM is thresholded at $P<0.0001$ (uncorrected) and superimposed on axial sections (from $z=10$ to 70).

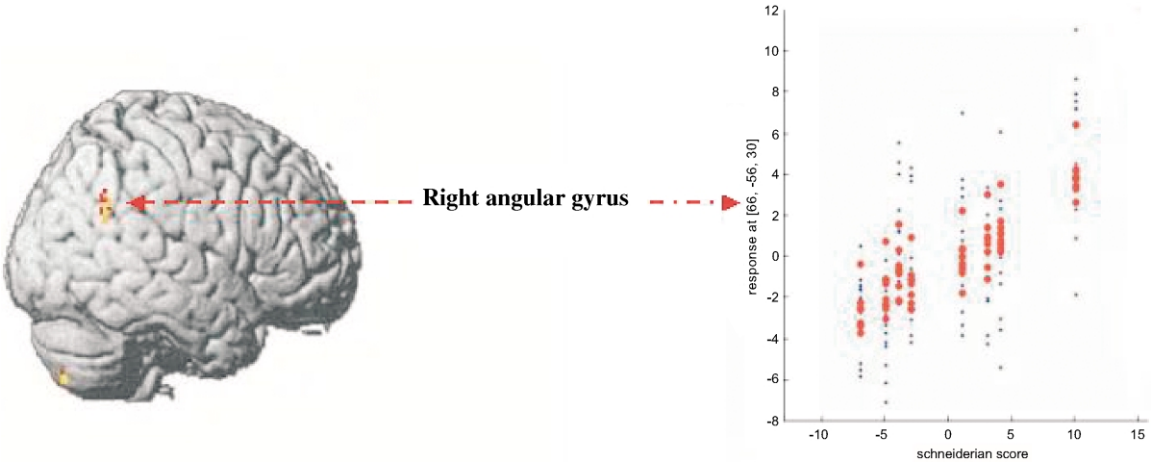

Fig. 2. Interaction between the sense of agency ('Other'–'0'°) and the Schneiderian score revealed peak activation in the right angular gyrus ($x=64$, $y=-56$, $z=24$, $Z=3.67$). When patients attributed the movements of the virtual hand to the experimenter, activity in the right angular gyrus increased as a function of the Schneiderian score.

positively correlated with the Schneiderian score ($P<0.001$ uncorrected for multiple comparisons, $Z=3.67$) but not with the SANS score (see Fig. 2). Additional activations were found in the rostral part of the right dorsal premotor cortex (prePMd) ($P<0.001$ corrected at the cluster level), the left precuneus and the left orbital gyrus ($Z\geq 3.70$; $P<0.001$ uncorrected for multiple comparisons) (see Table 2).

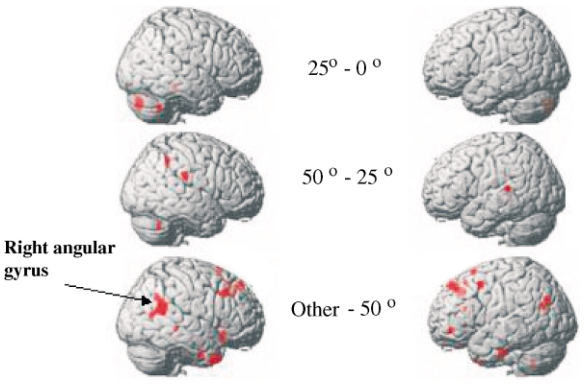

Fig. 3. Brain areas with increased activity in the different contrast: ('25°'–'0°'); ('50°'–'25°') and ('Other'–'50°'). Contrasting the 'Other' condition with the '50°' condition revealed activation in the right angular gyrus, however, this was not the peak activation, which was localized in the left pre-SMA

Contrasting the other condition with the 50° condition also revealed activation in the right angular gyrus; however, this effect was weak ($Z=3.90$, $P<0.001$ uncorrected) and was not the peak activation, which was localized in the left pre-supplementary motor area (pre-SMA). No sufficiently significant activation was found in the two

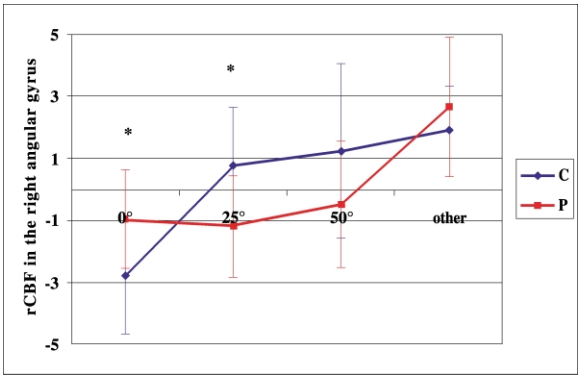

Fig. 4. rCBF in the right angular gyrus ($x=56$; $y=-56$; $z=36$) across the four experimental conditions ('0°', '25°', '50°', 'Other') for schizophrenic patients (P) and normal subjects (C). This graph clearly shows systematically increased rCBF in the right inferior parietal lobe from the '0°' through to the 'Other' conditions in the normal subjects. In the patients, increased activation is only seen for the 'other' condition. Significant differences between the two groups were observed for the '0°' and '25°' conditions. *$P\leq 0.05$.

Table 2
Brain areas activated during 'Other' condition compared with '0°' condition

Area	*x*	*y*	*z*	*Z*	*P*
R angular gyrus*	54	−52	22	4.59	0.02
R rostral dorsal premotor cortex	44	10	38	4.43	<0.0001
L precuneus	−4	−46	56	4.07	<0.0001
L orbital gyrus	−44	42	−2	3.94	<0.0001

*$P<0.05$ corrected at the voxel level.
All other areas are reported for $P<0.0001$ uncorrected at the voxel level; voxel extent threshold 10, $Z\geq3.70$.

other contrasts: ('25°'–'0°') and ('50°'–'25°') (see Fig. 3).

3.2.4. Comparison of schizophrenic patients with controls

Since schizophrenic patients only showed significant activation in the right angular gyrus in contrasts of the two extreme conditions, we compared rCBF in the right angular gyrus for each condition between the two groups. A *t*-test for independent variables revealed significantly greater activity in the patients for the '0°' condition ($t=-2.08$, d.f.$=14$, $P=0.05$). Interestingly, the tendency reversed at '25°' ($t=2.16$, d.f.$=14$, $P=0.05$), with a significantly lower activity in the schizophrenic group. For the '50°' and 'Other' conditions there were no significant differences between the groups (see Fig. 4). This result shows that the patients' lack of increase in activation with increasing distortion was associated with an abnormally high level of activation in the zero distortion condition, with an increase in activity only appearing for the 'Other' condition.

3.2.5. Brain areas decreasing their activity as a function of the degree of discordance between the executed and the seen movements in controls subjects and patients

Decreased brain activity in the right posterior insula (('0°'–'25°') in conjunction with ('25°'–'50°') and ('50°'–'Other')) was observed in the controls (Farrer et al., 2003) but not in schizophrenics, in either the insular cortex or in other brain areas. Furthermore, we did not obtain significant activation in the insular cortex when contrasting the '0°' condition with the 'Other' condition, even when using a search volume correction in a region involving the insula and the circular insular sulcus. Only the right cingulate gyrus was found activated ($Z\geq3.80$, $P<0.001$ uncorrected for multiple comparisons); however, since this activation was not predicted and was not significant at $P<0.001$ corrected, we will not consider it in further discussion. The other contrasts between the different experimental conditions did not reveal activations significant enough to be taken into account.

4. Discussion

This study aimed at evaluating whether the feeling of being in control of one's action was correlated with brain activity in a group of patients with FRS. This feeling was modulated across the different experimental conditions by introducing a distortion between the executed movements and their indirect visualization. The higher the distortion, the more the subjects felt that they were not controlling the movements on the screen. The maximal distortion was obtained when they executed movements and saw the movements of another agent (the experimenter). In this case, they did not feel in control of the movements and attributed them to the experimenter. Our results showed that, contrary to the results of our study in normal subjects (Farrer et al., 2003), we did not find any co-variation between the degree of distortion and rCBF in either of the brain areas that were predicted (right inferior parietal lobule and the insular cortex), nor in other brain areas. However, contrasting the two extreme conditions ('Other' with '0°' condition) revealed activation in the right angular gyrus.

Before going into the interpretation of these main results, we will briefly interpret the motor

activations we obtained when contrasting '0°', '25°', '50°' and 'other' conditions with the C2 control condition (passive observation of the movements of the joystick). This contrast revealed activation in brain areas typically associated with motor tasks involving the right hand (bilateral sensorimotor cortex, left cerebellum, right dorsolateral prefrontal cortex and bilateral ventral premotor cortex). However, these activations were not very high since most of them do not survive correction for multiple comparisons at the voxel level. Two explanations can account for this result. First, previous studies have shown that during simple and complex finger movements, patients with schizophrenia present reduced activation in motor areas such as sensorimotor cortex and SMA (Guenther et al., 1994; Schröder et al., 1995; Spence et al., 1997; Schröder et al., 1999). However, these results are not consistent since some studies did not find any differences in sensorimotor cortex and SMA activations between patients with schizophrenia and controls (Buckley et al., 1997; Müller et al., 2002). It should be noted that all our patients were under antipsychotic treatment, and thus medication could also account for this difference. Indeed it has been proposed that deactivation may not be related to schizophrenia, but rather to drug or treatment effects (Braus et al., 1999, 2000). Even so, the studies by Buckley et al. (1997) and Müller et al. (2002) did not find any differences in motor activation between unmedicated, patients with schizophrenia, medicated patients with schizophrenia and controls. On the contrary, Schröder et al. (1999) found activation changes to be more pronounced in an unmedicated patient than in medicated patients and control subjects. Another potential explanation of the weakness of these activations could be the choice of the control condition ('C2') where patients had to observe passively the movements of the virtual hand. Several studies have shown a functional equivalence between action generation and observation of action (Jeannerod, 1994). Activations in motor areas such as SMA and the dorsal premotor cortex have been observed both when subjects execute an action and when they observe an action (see Grèzes and Decety, 2001 for a review). These common motor representations may explain the absence or weakness of activations usually associated with action execution when contrasting the conditions where the patients execute and visualize the movements of the virtual hands with a condition where they passively observe these movements.

Behavioral results showed that patients did not fully distinguish between the '0°' and the '25°' conditions, since they did not always recognize a deviation of their movements of 25°. This impaired recognition, which was not found in normal subjects (Farrer et al., 2003), echoes a previous finding by Franck et al. (2001) that patients with schizophrenia with delusions of control are impaired in the recognition of their own actions. These patients tended to recognize a distortion of their own movements with a 30° bias, whereas normal subjects and patients with schizophrenia who do not report delusions of control recognized a distortion of 15°. Such a result is consistent with the body of studies showing that patients with Schneiderian symptoms are impaired in source monitoring (Bentall et al., 1991; Brébion et al., 2000; Baker and Morrison, 1998; Morrison and Haddock, 1997; Daprati et al., 1997; Johns and McGuire 1999; Johns et al., 2001). It has been postulated that distinguishing between one's own actions and another's actions depends upon an internal forward model of the action. Forward modeling allows the central nervous system to represent the predicted sensory consequences of a movement (Kawato et al., 1987; Wolpert et al., 1995). Such a prediction is derived from a copy of the motor command, the so-called 'efference copy' (von Holst and Mittelstaedt, 1950), and can be compared to the reafferent signals (i.e. signals arising as a consequence of the movement itself). If the sensory changes are correlated with the predicted sensory feedback, they are registered as consequences of one's own action. If not, by contrast, they are registered as originating from an external source (von Holst and Mittelstaedt, 1950; Frith, 1992; Wolpert et al., 1995; Blakemore et al., 1999). Frith et al. (2000) have proposed that patients with delusions of control suffer from a deficit in the awareness of the predicted sensory consequences of their own actions. This hypothesis is supported by experiments that involve distor-

tions of the sensory feedback of the patient's actions. Studies show that patients with hallucinations tend to attribute their own distorted speech to another agent more than non-hallucinated patients and normal subjects (Cahill et al., 1996; Johns and McGuire, 1999). Recently, Blakemore et al. (2000) have shown that patients with Schneiderian symptoms failed to show a difference between the perception of self-produced and externally produced tactile sensations. This result demonstrates that these patients might be abnormally aware of the sensory consequences of their own movements. Anomalous integration of the different action-related signals might explain inaccurate recognition of their own actions and misattributions of their actions to others. At the physiological level it has been shown that patients with delusions of control show over-activity in right inferior parietal cortex when making voluntary movements (Spence et al., 1997). Similar over-activity is also seen in normal volunteers who, through hypnosis, believe that they are not the authors of their arm movements (Blakemore et al., 2003). Both psychiatric and neurological patients with abnormal experience of agency show abnormal hyperactivity in right inferior parietal cortex (Franck et al., 2002; Simeon et al., 2000). On the other hand, patients with hallucinations show over-activity in temporal cortex when speaking (Ford et al., 2001).

In the present study, we also observed over-activity in parietal cortex in the condition with zero distortion in patients who had reported recent experiences of FRS. In addition these patients failed to show the normal increased parietal activity with increasing distortion between made and observed movements (Farrer et al., 2003). This lack of change at a physiological level could explain the patients' relative difficulty in distinguishing between '0°' trials and '25°' trials.

Only in the case of extreme discrepancies where the movements seen on the screen were actually controlled by another agent (the 'other' condition) did the patients show an increase in parietal activity significantly above that seen in the '0°' condition. This increase was significantly greater in those patients who were most prone to experience FRS. In the normal case high activity in this region of parietal cortex indicates that another agent is acting (Ruby and Decety, 2001; Decety et al., 2002; Farrer and Frith, 2002; Farrer et al., 2003). In patients with schizophrenia, activity in this region is high when the action is clearly self-generated, but this is accompanied by a lack of modulation by discrepancies between expected and observed consequences of self-action. In those patients for whom such modulation still occurs, activity is more likely to go above the threshold which signals that someone else is acting. Hence it is these patients who are most likely to attribute their own actions to another.

It has been hypothesized that hallucinations and delusions are best understood in terms of abnormal interactions or integration between different cortical areas. This dysfunctional integration is expressed at a physiological level as abnormal connectivity and at a cognitive level as a failure to integrate perception and action (Friston and Frith, 1995). The failed integration of perception and action proposed by Friston and Frith (1995) at the cognitive level is very similar to the mechanism we have discussed above, that is, the comparison process between sensory feedback of an action and its predicted sensory consequences derived from the motor command. At the physiological level, several studies have revealed a disconnection between frontal regions and more posterior regions in patients with schizophrenia (Dolan et al., 1999; Fletcher et al., 1999, for review). Specifically, this disconnection will disrupt the modulation by frontal regions of those more posterior brain areas involved in the processing of the sensory consequences of an action (Frith and Dolan, 1996; Frith et al., 2000). This will make it difficult to identify the source of the perceptions as internal (self) or external (other) (Frith and Dolan, 1996).

The absence of modulation obtained in the present study can be explained in this framework. Attributing an action to its correct origin requires a comparison process between the different action-related signals. In a previous study we showed that brain areas involved in such attribution judgments show a modulation of their activation as a function of the mismatch between these different signals. If this process is impaired, it will lead at the cognitive level to misattribution judgments and

at the physiological level to abnormal activations, e.g. an aberrant modulation of brain activity as we found in the present study.

It is worth noting that this abnormal neural integration can also account for the hypothesis by Georgieff and Jeannerod (1998) explaining misattributions judgments. This hypothesis relies on the observation that the generation of an action and the observation of an action performed by another agent, respectively, are subserved by distinct neural networks, which partially overlap. Monitoring the activation of these respective neural networks would be the basis for correctly attributing the corresponding action to its proper agent. However, changes in the pattern of cortical connectivity could alter the form of the network corresponding to different representations, or the relative intensity of activation in the areas composing these networks. The degree of overlap between these representations may increase in such a way that the representations would become undistinguishable from each other, leading to misattribution judgments (Jeannerod et al., 2003).

Activation in the right inferior parietal lobule in the 'other' condition compared with the '0°' condition showed that when these patients did not manifest symptomatology, there was not an absence of modulation but rather an abnormal neurofunctional process that underlies the feeling of being in control of an action. In addition, behavioral results showed that patients perfectly distinguished the '0°' and the 'other' conditions since they gave 100% correct responses ('Self' responses for '0°' condition and 'Other' responses for the 'Other' condition).

The aberrant modulation can hardly be attributable to antipsychotic or other medication, since we found an activation of the angular gyrus in the 'Other' condition compared with the '0°' condition that correlated with the Schneiderian score. This result shows that patients with Schneiderian symptoms, even when their symptoms are not currently manifest, differ from controls for subtle modulations of brain activity, but not for greater differences. What needs to be discovered is how these abnormalities become exaggerated so that they lead to the manifestation of symptoms.

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