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Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia

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Abstract

Theory of mind (ToM), the specific ability to attribute thoughts and feelings to oneself and others is generally impaired in schizophrenia. Previous studies demonstrated a deficit of the attribution of intentions to others among patients having formal thought disorder. During nonverbal tasks, such a function requires both the visual perception of human figures and the understanding of their intentions. These processes are considered to involve the superior temporal sulcus and the medial prefrontal cortex, respectively. Are the functional patterns of activation associated with those processes abnormal in schizophrenia? Seven schizophrenic patients on medication performed a nonverbal attribution of intentions task as well as two matched physical logic tasks, with and without human figures, while H_2O^{15} PET-scanning was performed. Data from the patients were compared to those of eight healthy controls matched for verbal IQ and sex. The experimental design allowed dissociating the effect of the perception of human figures from that of the attribution of intentions. During attribution of intentions, significant activations in the right prefrontal cortex were detected in the control subjects. Those activations were not found in the schizophrenic group. However, in both groups, the perception of human figure elicited bilateral activation of the occipitotemporal regions and of the posterior part of the superior temporal sulcus. Schizophrenic patients performing a nonverbal attribution of intentions task have an abnormal cerebral activity.

Keywords: Theory of mind; Neuroimaging; Schizophrenia; Medial prefrontal cortex; Superior temporal sulcus

1. Introduction

Theory of mind (ToM) is a psychological construct which describes our ability to understand the mental states of others, and appreciate how these differ from our own. Several authors have argued that schizophrenia is associated with impaired ToM skills, suggesting that some of the symptoms such as delusions of control or communication disorders are partially explained by the inability to attribute mental states to others (Frith, 1992; Hardy-Baylé, 1994). A large number of experiments have demonstrated such an impairment in schizophrenic patients with tasks that require the attribution of mental states as intentions or false beliefs (Corcoran, Cahill, & Frith, 1997; Corcoran, Mercer, & Frith, 1995; Doody, Götz, Johnstone, Frith, & Cunningham Owens, 1998; Drury, Robinson, & Birchwood, 1998; Frith & Corcoran, 1996; Pickup & Frith, 2001; Pilowsky, Yirmiya, Arbelle, & Mozes, 2000). For instance, Sarfati et al. used a nonverbal task involving attribution of intentions to others and showed a deficit of performances in disorganized schizophrenic patients (Sarfati, Hardy-Baylé, Besche, & Widlöcher, 1997; Sarfati, Hardy-Baylé, & Brunet, 1999; Sarfati, Hardy-Baylé, Nadel, Chevalier, & Widlöcher, 1997). The subjects were presented with three-picture comic strips involving a character and then had to choose the logical end of the story from the set of three pictures. Nonverbal tasks are interesting because they minimize (or even exclude) the contribution of language processes in ToM reasoning. The functional relation between ToM and language, their evolutionary origins, and their development in children are still a matter of debate and empirical research (Malle, 2002). Furthermore, in nonverbal attribution of intentions tasks, memory demand is kept as low as possible by presenting the subject with the whole comic strip until he/she answered (Brunet, Sarfati, & Hardy-Bayle, 2003).

The interest in ToM has been strengthened by the fact that mentalizing tasks are mediated by a highly circumscribed region in the medial prefrontal cortex. Although the many neuroimaging explorations of mentalization have shown multiple and complex brain activities, most of them have found activations in the medial region of the prefrontal cortex during the attribution of various complex mental states such as intentions, desires or beliefs (Brunet, Sarfati,

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Hardy-Baylé, & Decety, 2000; Castelli, Happé, Frith, & Frith, 2000; Fletcher et al., 1995; Gallagher et al., 2000; Goel, Grafman, Sadato, & Hallet, 1995; Vogeley et al., 2001). Further evidence in favor of a specific role of the medial prefrontal cortex is provided by studies of neurological patients. ToM abilities can be selectively impaired following stroke in the medial prefrontal cortex, especially in the right hemisphere (Happé, Brownell, & Winner, 1999; Stuss, Gallup, & Alexander, 2001).

The superior temporal sulcus (STS) is another region found activated in neuroimaging experiments of mentalizing abilities. This region is involved in processing explicit behavioral information such as the perception of intentional behavior from visual cues (Allison, Puce, & McCarthy, 2000; Blakemore & Decety, 2001). In monkeys, neurons of the upper bank of the STS respond to the sight of moving hands and faces as well as to the direction of the gaze but not to movements of inanimate objects (Jellema, Baker, Wicker, & Perrett, 2000; Malle, 2002). In humans, neuroimaging studies have obtained similar results. The perception of biological motion (i.e. the motion produced by an intentional organism) activates the posterior part of the STS (Grèzes et al., 2001; Grossman & Blake, 2001). This region is also activated by the observation of actions performed by other individuals (Grèzes, Costes, & Decety, 1998), and by eye gaze processing (Calder et al., 2002; Wicker, Perret, Baron-Cohen, & Decety, 2002). Altogether, these studies converge to suggest that the initial analysis of social cues (the actions of others) occurs in the STS region (Allison et al., 2000; Blakemore & Decety, 2001). This region is anatomically situated to integrate information derived from both the ventral (what) and dorsal (where) visual pathways. The correct functioning of this STS region may be an essential requisite for the development of theory of mind abilities.

Thus, it seems relevant to investigate the attribution of intentions to others from both components: the point of view of the perception of others and the representation of the others' intentions. In one neuroimaging experiment performed by our group (Brunet et al., 2000), the comparison conditions that involved attribution of intentions to others with conditions that involved physical causality resulted in a strong activation in the right medial prefrontal cortex. In contrast, conditions involving physical causality with or without human figures was primarily associated with increased activity in the occipitotemporal region.

Since performances in attribution of intentions are reduced in schizophrenic patients, this impairment is likely to be associated to an abnormal pattern of regional cerebral blood flow (rCBF). In this experiment, neurohemodynamic changes were measured in a group of schizophrenic patients while performing a series of nonverbal tasks as previously described in the study by Brunet et al. (Brunet et al., 2000). In order to compare the functional brain images of schizophrenic patients and healthy individuals, the PET data from both groups were analyzed together. The design of the study allowed an assessment in both groups of brain regions associated with processing the perception of human figures and processing the representation of intention to these figures.

This neuroimaging experiment uses an extension of Sarfati's material. Like Baron-Cohen et al. (Baron-Cohen, Leslie, & Frith, 1986), we compared theory of mind skills to the comprehension of physical causality. The understanding of causal relations with respect to physical objects is known to be acquired in early infancy (Spelke, Vishton, & Von Hofsten, 1996). Two comparison tasks were included: one involved human figures and the other involved objects only. In all conditions, the apparatus, instructions and presentations remained the same. In a previous study, we validated such an experimental design by showing that the performance in the attribution of intentions of schizophrenic patients having normal performances in the understanding of causal relations differed from that of normal controls (Brunet et al., 2003).

2. Material and methods

2.1. Subjects

Seven male patients, all native French speakers, whose symptoms satisfied the DSM-IV criteria for schizophrenia (APA, 1994), participated in the study. Table 1 reports clinical assessment of the patients using DSM-IV categories and the Positive and Negative Syndrome Scale (PANSS, Kay, Fisz-Bein, & Opler, 1987). Six individuals were out-patients and one was about to leave the hospital when he participated in the study. The patients were right-handed according to the Edinburgh Inventory. A medical examination was carried out by an experienced clinician to search for exclusion criteria such as neurological illness or drug abuse and dependence. The mean age of the patients was 31 (standard deviation, S.D. = 6.5) years. The estimated mean verbal IQ was 111 (S.D. = 15) based on the Binois and Pichot vocabulary scale (Binois & Pichot, 1947). It is worth noting that the positive symptoms were moderate in this sample and that the patients did not report hallucinations during the PET session. While we did not formally assess the motor side effects, none of the patients suffered tardive dyskinesia or tremor interfering with the tasks.

As a control group, we collected the data from our previous PET study in which eight healthy right-handed males were included. The mean age of those control subjects was 23.3 (S.D. = 1.68, range = 20–25 years), which is significantly different from the patients (Mann–Whitney rank sum test, $U = 2$, $P < 0.05$). Their estimated mean verbal IQ was 119 (S.D. = 6.3), which is not significantly different from that of the patients (Mann–Whitney rank sum test, $U = 16.5$, $P = 0.35$).

All subjects gave written informed consent after the procedure had been fully explained. The experiment was performed in accordance with the guidelines from the

Table 1
Description of the schizophrenic volunteers

Subject	Age	Verbal IQ	Clinical form	PANSS Positive	PANSS Negative	PANSS General	Medication	Dosage (mg/day)
1	40	18	Residual	11	21	33	Loxapine Oxazepam Tropatenine	150 10 5
2	25	18	Undifferentiated	12	21	20	Olanzapine Haloperidol decanoate Dipotassic clorazepate Tropatepine	15 200[a] 25 20
3	30	26	Undifferentiated	33	22	39	Haloperidol decanoate	250[a]
4	25	29	Paranoid	–	–	–	Risperidone Paroxetine	6 20
5	27	31	Paranoid	19	18	40	Risperidone Citalopram	6 20
6	40	26	Disorganized	18	22	33	Olanzapine	10
7	33	35	Paranoid	14	13	22	Olanzapine	10

Demographic and clinical description of the schizophrenic patients.

[a] In mg/month.

Declaration of Helsinki and with the approval of the local Ethics Committee (Centre Léon Bérard, Lyon).

2.2. PET scanning

H_2O^{15} PET scanning was performed with a Siemens CTI HR + tomograph (63 slices, 15.2 cm axial field of view). A video projector displayed black-and-white comic strips on the screen at which the subject could look in the reflection of a mirror. The subjects answered by pressing on a three-button pad with their right hand. Eight injections containing 9 mCi of the radioactive tracer were administered. The functional data were acquired during a 60 s period starting approximately 30 s after the injection. The minimum time interval between each scan was 10 min.

2.3. Activation conditions

PET scanning was performed during three conditions (plus an additional rest condition not described here):

1. Attribution of intentions (AI);
2. Physical causality with human figures, PC-Ch (standing for physical causality with characters);
3. Physical causality condition involving objects only, PC-Ob.

Each condition was repeated twice in a pseudo-counter-balanced order. In each condition, nine comic strips succeeded one another at the frequency of one every 11 s.[1] The task started at the moment of the injection so that the cognitive stimulation covered the scanning period. During the first 5 s, three pictures depicting a brief story were displayed in the upper half of the screen. Then, three answer-pictures were added in the lower half of the screen in a random order. The subjects were required to choose spontaneously the logical ending of the story from these answers without looking for traps or humor and to press the corresponding button as quickly as possible. Only one of the answers ended the story logically. In each condition a global score was defined as the number of correct answers (thus, the maximum score in a given condition was 18).

In the AI condition, the stories involved human agents whose situations or behaviors in the correct-answer picture required inferring their intentions (Fig. 1). The stories were designed to depict simple first-order intentional behavior. A special effort was made to avoid emotional situations or expressions, social interaction between figures, behavior underpinned by beliefs, and higher order mental states. The PC-Ch and PC-Ob conditions relied on the comprehension of physical causality: in order to find the right answer, the subject had to use their knowledge of the physical properties (position, speed, weight, size, material properties, etc.) of objects or human bodies. In PC-Ch, human figures were represented (Fig. 2) whereas PC-Ob involved objects only (Fig. 3). In the PC-Ch condition, the behavior of the human figure and his/her putative mental state were not relevant to find the correct answer. Furthermore, among the 18 comic strips of this condition, the behaviors were much more stereotyped and passive than in the AI condition. The task was implicit because the response strategies, using attribution of intentions or physical causality, were not suggested by the experimenter.

Subjects received a short training session, before the PET examination, consisting of three comic strips of each type. During this training, the experimenter made sure that the

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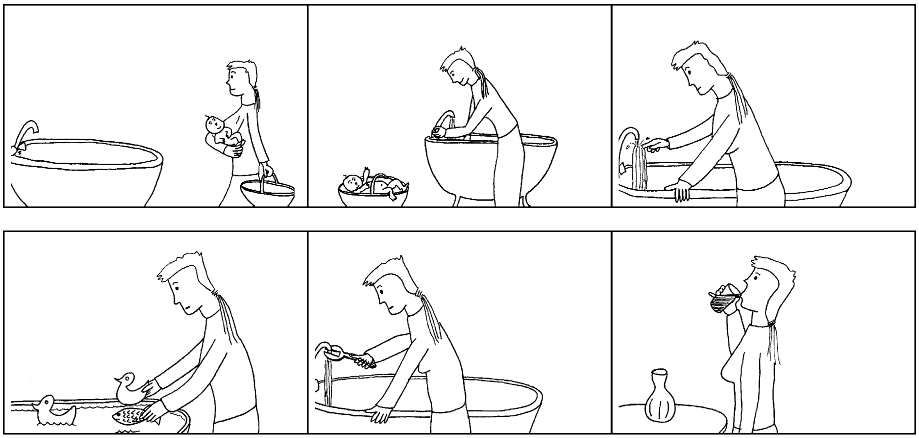
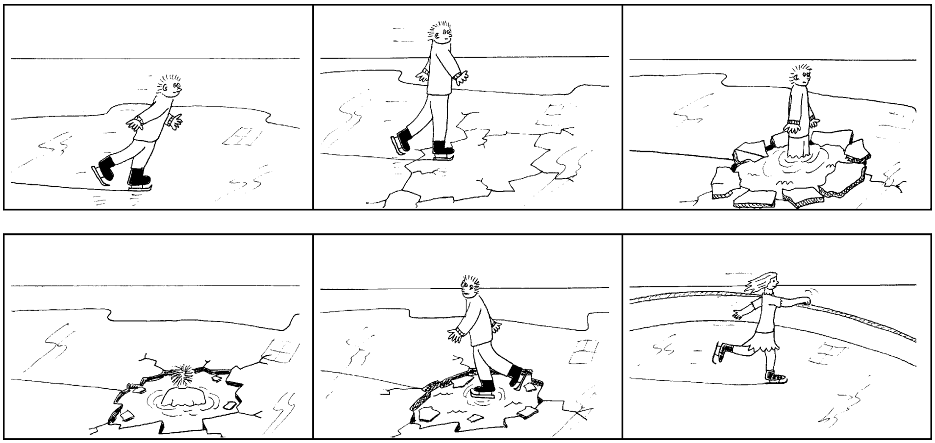
[1] It should be noticed that in Brunet et al. (2000) there was a mistake about the frequency of presentation of the comic strips.



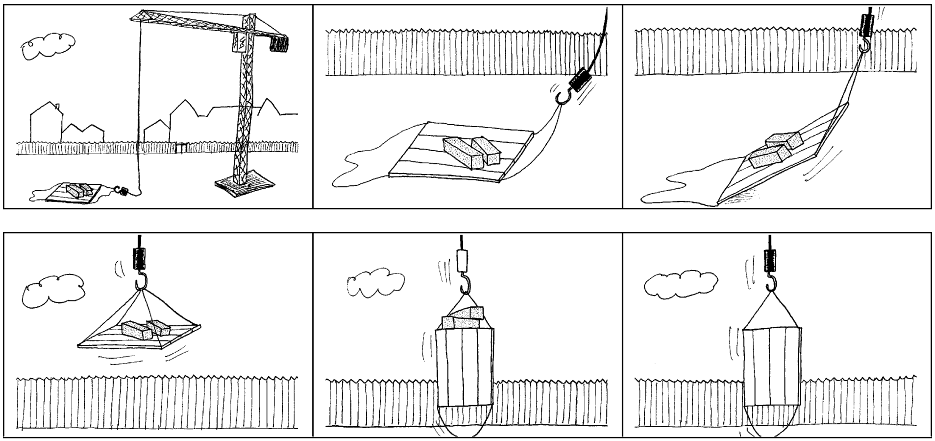
Correct answer Distracter Distracter

Fig. 1. Example of an attribution of intentions comic strip. The top three pictures depict a story. The bottom three pictures are the proposed answers. Here the correct answer is the first picture on the left.



Correct answer Distracter Distracter

Fig. 2. Example of a PC-Ch comic strip.



Distracter Distracter Correct answer

Fig. 3. Example of a PC-Ob comic strip.

patients had clearly understood the instructions. Between each scan, the experimenter verified that the subjects had no problems following the instructions and gave them encouragement.

2.4. Data analysis

Data analysis was performed with the group of patients and the group of controls as a whole ($N = 15$) using the Statistical Parametric Map software (SPM99; Welcome Department of Cognitive Neurology, London) implemented in MATLAB (Mathworks Inc., Sherborn). For each subject, images were realigned to the first scan, then normalized into the Montreal Neurological Institute space using the MNI-305 picture template. Data were convoled using a gaussian filter with full-width half maximum (FWMH) parameters set to (10, 10, 20) millimeters. For each scan, the voxels' values were divided by the value of the condition's global activity.

The statistical analysis consisted of a voxel-by-voxel analysis of variance using fixed and random effects models. T statistics were computed on the following contrasts in both groups: AI minus PC-Ch, AI minus PC-Ob and PC-Ch minus PC-Ob. The regions unambiguously concerned by attribution of intentions were determined as the intersection (SPM's inclusive mask) of AI minus PC-Ch and AI minus PC-Ob. The activated clusters associated to human figure perception were computed by intersecting AI minus PC-Ob and PC-Ch minus PC-Ob. In those intersection, simple subtractions were computed with a threshold corresponding to a 0.01 P value (uncorrected) and then masked. Only clusters having a Z value above 3.20 were reported in the results. The differences concerning the attribution intentions effect between groups were calculated using a random effect model as the intersection of (1) the subtraction of (AI minus PC-Ch) in the patients group to (AI minus PC-Ch) in the control group and (2) the subtraction of (AI minus PC-Ob) in the patients group to (AI minus PC-Ob) in the control group.

3. Results

3.1. Subjects' behavioral performances

The performance of each group in the three conditions is given in Table 2. The patients and control groups differed significantly in the three conditions (Mann–Whitney rank sum test, $P < 0.05$); the schizophrenic patients had lower performances. Nevertheless, those reduced performances were unambiguously above the chance-level and may not be interpreted as the effect of a non-observance of the instructions. The reaction times (defined as the latency of the responses when the answer pictures are displayed) are also reported in Table 2. The patients were significantly slower than the controls in the three conditions (Mann–Whitney rank sum test, $P < 0.05$). The increase in reaction time in the schizophrenic group represented 8.1% of the duration of the scan in the AI condition and 9.5 and 7.2%, respectively, in the PC-Ch and PC-Ob conditions. The time differences are stable across the conditions.

Table 2
Mean numbers of correct answers and mean reaction times for each condition and groups (maximum = 18)

Condition	Schizophrenic patients ($N = 7$)		Normal controls ($N = 8$)	
	Mean	S.D.	Mean	S.D.
Reaction times				
AI	15.1	1.9	17	1.3[a]
PC-Ch	15.4	2.7	17.75	0.5[a]
PC-Ob	16	0.8	17.9	0.3[a]
Performances				
AI	3675	787	2781	493[a]
PC-Ch	3623	766	2585	509[a]
PC-Ob	3177	811	2383	483[a]

[a] Indicate significant differences between groups with $P < 0.05$ using a Mann–Whitney rank sum test. *Performances:* for AI, $U = 10.5$; for PC-Ch, $U = 7$; and for PC-Ob, $U = 1$. *Reaction times:* for AI, $U = 8$; for PC-Ch, $U = 6$; and for PC-Ob, $U = 8$.

3.2. Functional data associated with the attribution of intentions

In the healthy controls, the effect of attribution of intentions revealed two foci in the right prefrontal cortex (Table 3 reports the results of the intersection of AI minus PC-Ch and AI minus PC-Ob). Increased rCBF were detected in the posterior orbital gyrus and the medial prefrontal gyrus in both subtractions AI minus PC-Ch and AI minus PC-Ob. In the schizophrenic group, no such activations were found in the simple subtraction AI minus PC-Ch. Table 4 reports the clusters in which an elevation of rCBF occurred in schizophrenic patients. Regions such as the right middle frontal gyrus, the left middle occipital gyrus, the left hippocampus and the cerebellum were concerned. Those regions were qualitatively different from those found among healthy subjects. Furthermore, many of those clusters did not survive in the intersection analysis: the intersection of AI minus PC-Ch and AI minus PC-Ob only revealed activations in the left middle occipital, in the hippocampus and in the cerebellum on both sides.

Considering the number of subjects in each group, a random effect model consisting of another intersection analysis was adopted to evaluate the difference of activation during attribution conditions between the controls and the schizophrenics groups (i.e. intersection of (AI minus PC-Ch) in normal group minus (AI minus PC-Ch) in patient group and (AI minus PC-Ob) in normal group minus (AI minus PC-Ob) in patient group). Healthy subjects had higher brain responses in three regions (Table 3), but only one cluster ($x = 20$ mm, $y = 48$ mm, $z = 14$ mm) reached

Table 3
Foci of significant rCBF increase in the intersection of simple subtractions

Z value	*x*	*y*	*z*	Region
Intersection of (AI minus PC-Ch) and (AI minus PC-Ob) in the control group				
4.15	34	22	−20	Posterior orbital gyrus
3.77	20	48	20	Medial prefrontal cortex
Intersection of (AI minus PC-Ch) and (AI minus PC-Ob) in the schizophrenic group				
3.64	−40	−88	4	Middle occipital gyrus
3.48	−8	−40	−12	Cerebellum, lobule III/IV
3.33	20	−68	−28	Cerebellum, crus I
Intersection of (AI minus PC-Ob) and (PC-Ch minus PC-Ob) in the control group				
4.74	56	−74	0	Middle temporal gyrus/Superior temporal sulcus
4.60	46	−78	−10	Middle occipital gyrus
4.29	42	−50	−18	Fusiform cortex
4.07	16	−102	6	Cuneus
3.96	58	−52	18	Superior temporal gyrus
3.41	54	8	−28	Middle temporal gyrus, anterior part
3.26	−12	24	−12	Posterior and internal part of orbital gyrus close to the subcallosal region
3.24	−14	−42	22	Posterior cingulate
Intersection of (AI minus PC-Ob) and (PC-Ch minus PC-Ob) in the schizophrenic group				
5.49	54	−70	10	Middle occipital gyrus
3.56	56	−48	14	Posterior part of the superior temporal sulcus
3.47	62	−60	14	Superior temporal sulcus
4.33	−46	−70	10	Middle occipital gyrus
3.51	8	70	8	Frontopolar gyrus
3.26	−4	−62	34	Precuneus
Intersection of (AI minus PC-Ch) in control group minus (AI minus PC-Ch) in schizophrenic group and (AI minus PC-Ob) in control group minus (AI minus PC-Ob) in schizophrenic group				
3.28	20	48	14	Medial prefrontal cortex
2.97	−18	−36	6	Pulvinar
2.97	58	−22	8	Superior temporal gyrus

SPM inclusive masking was used with an uncorrected *P* value of 0.01 for both conditions. Then, activations were reported in this table if *Z* was superior to 3.20 (except for the last two lines). Extend threshold ($k = 10$ voxels). Anatomical names were found using Duvernoy's atlas of brain anatomy (Duvernoy, 1999) and Schmahmann et al.'s atlas of cerebellum (Schmahmann, Doyon, Toga, Petrides, & Evans, 2000). Coordinates (*x*, *y*, *z*) are given in millimeters using the MNI-305 reference space.

Table 4
Foci of significant rCBF increase in the simple subtractions in the schizophrenic group

Z value	*x*	*y*	*z*	Region
AI minus PC-Ch				
3.86	44	14	58	Middle frontal gyrus
3.64	−40	−88	4	Middle occipital gyrus
3.52	−8	−40	−10	Cerebellum, lobule III/IV
3.47	−32	−8	−20	Hippocampal region
3.33	20	−68	−28	Cerebellum, crus I
3.27	−10	−106	−12	Gyrus lingualis
PC-Ch minus PC-Ob				
5.49	54	−70	10	Middle temporal gyrus/middle occipital/Superior temporal sulcus
4.39	64	−64	8	Superior temporal sulcus
3.71	58	−48	12	Middle temporal gyrus
4.33	−46	−70	10	Middle occipital/Middle temporal gyrus
4.16	4	−50	42	Posterior cingulate
4.03	10	68	10	Gyrus frontalis medialis
3.64	38	58	22	Superior frontal gyrus

SPM's contrasts in the schizophrenic group. Activations were reported in this table if *Z* was superior to 3.20. Extend threshold ($k = 10$ voxels).

the significance level ($Z = 3.28$, $P < 0.001$). The values of the (AI minus PC-Ch) contrast for each individual in this cluster (44 voxels) are plotted and presented in Figs. 4 and 5. One observes that the differences between the AI condition and the two other conditions are greater or equal for each control subject comparatively to schizophrenic subjects.

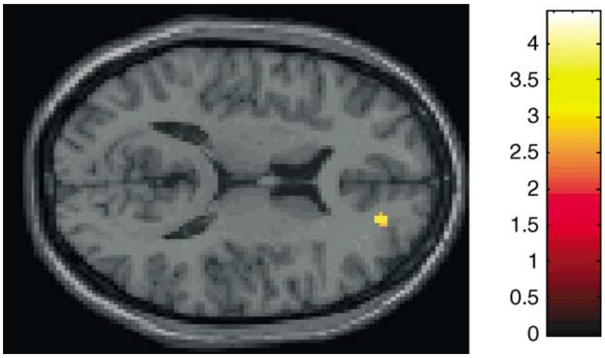


Fig. 4. Reconstructed slices at $z = 14$ mm in the right hemisphere of the subtraction of (AI minus PC-Ch) in schizophrenic patients to (AI minus PC-Ch) in healthy subjects. Activations with a significance level *P* lower than 0.01 are kept. The color scale for *Z* is given.

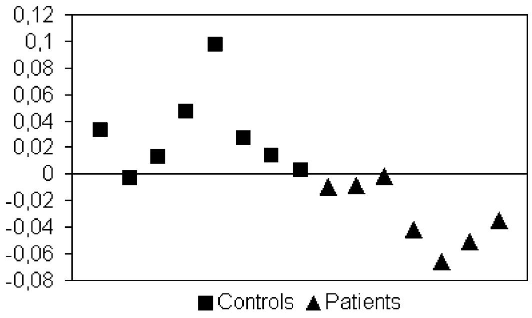
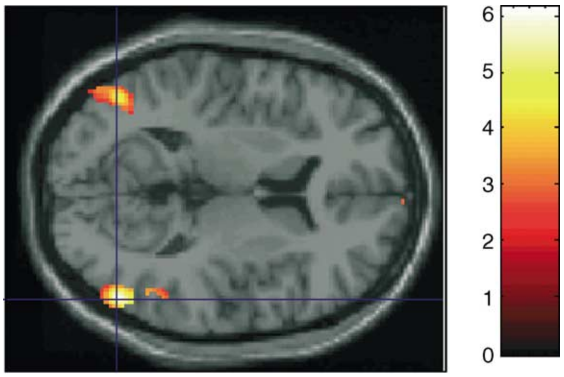


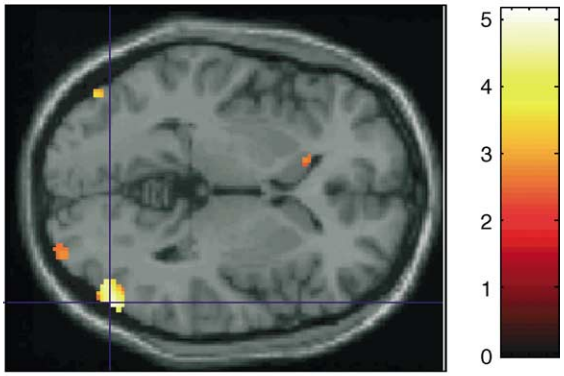
Fig. 5. Values of the AI minus PC-Ch contrast in the cluster $x = 20$ mm, $y = 48$ mm, $z = 14$ mm, 44 voxels, for each subject (in arbitrary units).

3.3. *Functional data associated with the perception of human figures*

Among healthy controls, the intersection associated with the presence of human figures (AI minus PC-Ob and PC-Ch minus PC-Ob) revealed an rCBF increase in several occipital and temporal regions with a relative predominance in the right hemisphere (see Table 3 and Fig. 6). The middle temporal gyrus, the posterior region of the superior temporal sulcus (1679 voxels in the right hemisphere cluster), the middle occipital gyrus, the fusiform gyrus, and the superior temporal gyrus were involved. There was also activation in the posterior cingulate cortex and in the anterior part of the middle temporal gyrus.



Schizophrenic patients



Healthy subjects

Fig. 6. Reconstructed slices of the intersection of AI minus PC-Ob and PC-Ch minus PC-Ob in schizophrenic patients at $z = 14$ mm (*top*) and normal subjects at $z = 0$ (*bottom*). Activations with a threshold value for P lower than 0.01. The color scale for Z is given.

In the patient group, the pattern of activation was similar in several regions in the simple subtraction (Table 4) as well as in the intersection of AI minus PC-Ob and PC-Ch minus PC-Ob. Activation in the posterior part of the right superior temporal sulcus was found. An activated cluster was detected in the middle occipital gyrus, as well as in the right frontopolar cortex.

4. Discussion

In this study, we measured functional hemodynamic response in a group of schizophrenic patients during a nonverbal theory of mind task. The design of the conditions and the analysis distinguished two processes that participate in the attribution of intentions to others: first, the visual perception of other people; second, the construction of a representation of their intentions. In healthy subjects, both processes are systematically associated with involvement of the posterior superior temporal sulcus and the right medial and posterior orbital prefrontal cortex (Blakemore & Decety, 2001). In the schizophrenic group, the cerebral activation is different from those of controls.

In most neuroimaging studies of normal subjects performing ToM tasks, the medial part of the prefrontal cortex is consistently activated on the right or on the left side. In this study, another focus of activation is found in the right posterior orbital cortex. Based on a study of patients with brain injury, Stone and Baron-Cohen claimed that this region plays a major role in ToM (Stone, Baron-Cohen, & Knight, 1998). It is noteworthy that those important regions remained ‘quiet’ when schizophrenic patients performed the task. It is also relevant to mention Russell’s finding that schizophrenic patients performing a task requiring to describe mental states reflected in photographed eyes show abnormally low activation in the left prefrontal cortex (Russell et al., 2000). These results seem broadly consistent with ours despite their lateralization and some anatomical differences. Both mentalizing tasks seem to evoke normally prefrontal activations which are missing in schizophrenia.

Happé et al. have shown that individuals suffering from Asperger’s syndrome have an anatomically different prefrontal activation pattern when they perform a verbal theory of mind task (Happé et al., 1996). These authors hypothesized that “the patients were using a more general purpose mechanism in order to infer mental states” (p. 200). In our study, the patients did not exhibit non-ambiguous brain activation related to attribution of intentions (no common prefrontal activation was found in the intersection of AI minus PC-Ch and AI minus PC-Ob) while they expressed performances clearly above chance-level. Since the task requires an implicit use of ToM skills (no information was given about the answer-strategy or the design of the conditions), one could hypothesize that the patients may not use the brain systems which would efficiently solve the task as the healthy controls naturally do. However, our conditions were not designed to determine the brain systems activated by the general reasoning mechanisms common to the three conditions. Although it is an attractive hypothesis, one cannot say whether the patients reached their performance level by using general reasoning skills. The precise role of some areas activated in the AI minus PC-Ch subtraction among schizophrenic patients remains to be explained.

Among healthy subjects, the role of the superior temporal sulcus in social perception from visual cues such as the movement of the eyes, the mouth or the hands is well documented (Allison et al., 2000; Baron-Cohen et al., 1999; Frith & Frith, 1999; Grèzes & Decety, 2001). Furthermore, biological motion activates this region (Blakemore & Decety, 2001). It is noteworthy that wide activations in the middle temporal gyrus and the superior temporal sulcus were found in both groups as it indicates that the perception of social cues is processed. The presence of human figures mobilizes some specific cognitive functions among patients as well as among healthy controls. There are functional differences between groups that should be further explored in another study to decide whether this perceptual level is impaired or not. A functional cooperation of the occipitotemporal system and the medial prefrontal cortex may play a critical role in the whole process of attribution of intentions to others. One can expect that such results feed the debate about the relations between high level processes and perceptual processes in schizophrenia.

This study suffers some limitations, which stem from differences between groups. First, age was significantly different between groups, schizophrenic patients being, on average, eight years older. Effect of age on brain perfusion, on theory of mind and on psychosis may account for some variance in the rCBF between groups in a rather unpredictable way. Second, reaction times differed from the one group to the other: it is possible that the rCBF differences reflect differences in the dynamics of cerebral activation rather than differences in the tasks that were processed. Third, as in many neuroimaging studies of psychiatric groups, the patients were on medication while the controls were medication-free. Beyond ethical considerations, this criticism applies to this protocol. As it is difficult to conduct such a study with medication-free schizophrenic patients, one possible solution would be, in a future work, to measure brain activation related to theory of mind in other psychiatric populations treated with antipsychotics such as mood disorders.

Parallel to structural brain abnormalities found in schizophrenia, the first theory trying to link schizophrenia to an impaired brain function stated that the main functional abnormality was an hypoactivation of the prefrontal cortex explaining the deficit symptoms (Andreasen et al., 1992; Ingvar & Franzen, 1974). We propose that ToM provides a new insight on the hypofrontality issue as it is the appropriate means to activate regions devoted to social cognition and to discriminate the synergetic participation of prefrontal and occipitotemporal regions.

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