

## ORIGINAL PAPER

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## Deficit of social cognition in subjects with surgically treated frontal lobe lesions and in subjects affected by schizophrenia

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**Abstract** The ability of humans to predict and explain other people's behaviour by attributing independent mental states such as desires and beliefs to them, is considered to be due to our ability to construct a "Theory of Mind". Recently, several neuroimaging studies have implicated the medial frontal lobes as playing a critical role in a dedicated "mentalizing" or "Theory of Mind" network in the human brain. In this study we compare the performance of patients with right and left medial prefrontal lobe lesions in theory of mind and in social cognition tasks, with the performance of people with schizophrenia. We report a similar social cognitive profile between patients with prefrontal lobe lesions and schizophrenic subjects in terms of understanding of false beliefs, in understanding social situations and in

using tactical strategies. These findings are relevant for the functional anatomy of "Theory of Mind".

**Key words** schizophrenia · frontal lobe lesions · Theory of Mind · social cognition

### Introduction

Social cognition refers to the ability to perceive, interpret and provide an adequate response to affective and other interpersonal cues [1]. Pioneering studies have found that schizophrenic subjects show social cognitive impairments, in particular in modifying their behaviour when interacting with other people and in recognizing social information cues [2]. People with schizophrenia also show a great deal of social naivety in interpersonal situations [3].

The ability to engage in competent social relations and to understand social information depends on the adequate functioning of a mental mechanism termed Theory of Mind (ToM), that allows people to understand and interpret their own and other people's mental states and hence to predict and explain their behaviour [4, 5]. Evidence from neuroimaging and neuropsychological studies has led researchers to conclude that ToM is subserved by dedicated brain systems, including the amygdala, the temporo-parietal junction, the orbital frontal cortex and, in particular, the medial frontal lobes [6, 7]. The results of these studies have been used to argue that the medial frontal lobes play a critical role in a dedicated mentalizing system [7, 8].

Neuropsychological literature specifically relevant to the medial frontal cortex is scarce. Actually, only three studies have included patients with relatively focal medial frontal lobe damage and have sought to investigate correlations between specific frontal brain areas and performance in ToM tasks [9–11]. However,

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there are important limitations to these investigations. Stuss et al. [10] reported that patients with right frontal and bilateral frontal lobe damage were impaired in their ability to infer visual experience in others. The authors conclude that acquired brain damage to the medial frontal lobes does impact on ToM ability, but aetiology of brain damage for each patient is not reported, the text implies that most of the bifrontal group had suffered head traumas. It is often very difficult to assess the extent of brain damage reliably after head trauma as widespread damage can often occur through axonal shearing and other effects (e.g. [12]). The second neuropsychological study [9] reports that patients with left and right-sided lesions were equally impaired, while lesion size was unrelated to performance and no effect of lesion location was found when comparing patients with focal dorsolateral, medial or orbital frontal lesions.

Also, a recent group study of empathy in patients [11] included an assessment of performance on the Faux Pas Test, a probe of ToM ability. Patients with frontal lobe lesions were impaired in this task. Specifically, patients with ventromedial frontal lobe damage made significantly more errors than patients with posterior lesions or healthy controls in the Faux Pas Test.

However, a detailed analysis of lesion sites associated with ToM deficits in these previous studies revealed a particularly important role for the right ventromedial prefrontal frontal lobe [11, 13]. Damage in these areas induces behavioural changes affecting personality (indifference), impaired social judgement, reduced affect and goal-directed behaviour, self-monitoring deficits [14–16].

More recent studies have provided evidence that is in disagreement with a single area hypothesis involved in ToM processing. In fact, the neural network involving the right and left temporo-parietal-junction (TPJ R and L); the posterior cingulate (PC), and medial prefrontal cortex (MPFC) seems to be crucial in processing the complex reasoning involved in mentalizing [17, 18]. Bird et al. [19] studied a patient affected by extensive damage of the medial frontal lobes reporting, interestingly, a dysexecutive syndrome with confabulation with preserved performance on some ToM tasks.

Saxe and Wexler [20] in an fMRI study in normal subjects, described an equally selective profile of activation of the above-mentioned areas in a multi-component pattern of activation fMRI methodology. Frontal lobe damage in patients has long been linked to impairments in social behaviour [21]; in fact, they have been described as presenting diminished social awareness and a lack of concern for social rules [15, 22].

An interesting approach to social competence deficits in schizophrenic people may be represented by the Machiavellian Intelligence Hypothesis (MIH, [23, 24]).

According to this hypothesis, in the development of intelligence, social, rather than technical, efficiency represents the main selective pressure of human evolution [25]. Social efficiency is represented by the ability to understand the intentions and beliefs of others with the aim of deceiving and manipulating them to achieve relevant objectives, such as control of food sources or sexual partners [26]. Recent literature fosters that these abilities are localised in the ventromedial prefrontal cortex: selective damage to these areas causes a relevant impairment of interpersonal relationships and in regulating behaviour according to social rules [27–30].

Patients with lesions to the orbitofrontal cortex also have disinhibited/socially inappropriate behaviour. Grafman interpreted the patient's impairment in terms of an inability to access "social schema knowledge" stored in the frontal lobes [31]. Social schema knowledge is thought to inhibit aberrant behaviour. Patients with orbitofrontal cortex lesions who cannot access social schema knowledge fail to inhibit aberrant behaviour, such as physical threats and aggression.

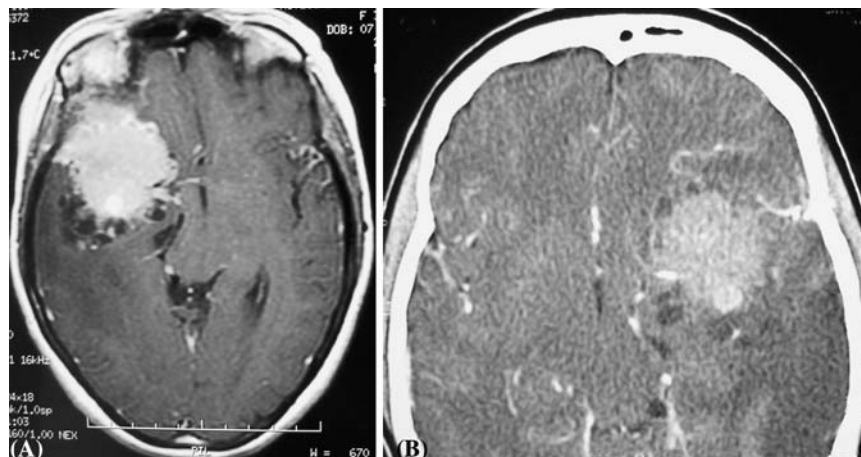
The prediction of a similar cognitive profile in terms of ToM abilities and social competence between frontal lesion subjects and schizophrenic people has been investigated and confirmed [6, 7]. An extensive and careful review recently published [32], reported a general agreement about the nature and extension of ToM dysfunctions in people affected by schizophrenia. These dysfunctions are symptoms related [33], disease specific and state independent.

The neural architecture of the social cognitive dysfunction of schizophrenia is of paradigmatic importance for the understanding of social cognitive dysfunction and, more importantly, for the understanding of the consequences at the behavioural level [34]. A previous seminal study provided evidence that structural orbitofrontal cortex abnormalities are related to social dysfunction in schizophrenic people [35]. Moreover this prefrontal area has been unequivocally involved in the social cognitive deficits associated with this disorder [36].

However, empirically controlled investigations in which the cognitive profile of brain damaged patients was compared with schizophrenic subjects with an appropriate set of ToM and social intelligence tasks are lacking, thus leaving several crucial questions largely unresolved.

In the current study, we examined the performance of stabilized schizophrenic outpatients, inpatients with focal damage of left and right ventromedial prefrontal lobes and healthy controls, in ToM abilities, in social competence and tactical strategy (Machiavellian Intelligence), to clarify whether schizophrenic patients demonstrate impairment similar to ventromedial prefrontal lesion patients and whether their performance in these tasks can be differentiated from their performance in tasks sensitive to neuropsychological dysfunction, including "exec-

**Fig. 1** (A) MRI T1 weight (axial view) with gadolinium showing low density abnormalities (meningioma excised, patients L.F.) orbitofrontal cortex on the left side. (B) CT scan image showing low density abnormalities (meningioma excised, patients L.G.) orbitofrontal cortex on right sides



utive” functions. Our prediction is that an overlapping dysfunctional cognitive profile should emerge between brain damaged and schizophrenic subjects, when compared to healthy subjects. We also addressed several methodological issues raised by earlier studies using social cognition tasks created for adults and not for children.

## Methods

### ■ Participants

The subjects for this study included 18 adult neurosurgical patients with unilateral frontal lobe lesions who had undergone surgery at the Department of Neurosurgery of “S. Salvatore” Hospital, L’Aquila, Italy. The patients were consecutively enrolled in the study from January 2003 to September 2005.

Only patients with exclusive frontal lesions were identified and brain damage was confirmed through neuroimaging, with pre- and postoperative CT scanning and MRIs.

Nine subjects with left side medial prefrontal cortex (LMPFC) lesions and nine subjects with right side medial prefrontal cortex (RMPFC) lesions were studied and underwent neuropsychological examinations (Fig. 1A, B).

Thirteen subjects had intra- or extra-axial tumours (72%); 3 had spontaneous haemorrhage (17%) and 2 (11%) had intracerebral haemorrhage from ruptured aneurysms.

In the RMPFC group seven patients had a tumour removed (four had a meningioma excised, 2 had a high grade glioma excised and 1 had an oligodendroglioma excised), one had a right anterior communicating artery (ACoA) aneurysm clipped, following rupture and one had spontaneous intracerebral haemorrhage with no evidence of arterial malformations. Of the LMPFC patients, six had a tumour removed (five had a meningioma excised and one had a high grade astrocytoma excised), two had spontaneous intracerebral haemorrhage with no evidence of arterial malformations and one had a left ACoA aneurysm clipped following rupture.

The location of the experimental group’s lesions were defined anatomically as medial (Brodmann area 9 and 46) and orbital (Brodmann areas 10, 11, 12 and 25) and further classified according to the prefrontal sectors of functional significance into which the lesions encroached (Tables 1, 2).

Subjects were assessed with neuropsychological test batteries 20–40 days after surgery.

A control group of schizophrenic subjects and a control group of psychiatrically and neurologically healthy subjects were studied as well.

Twenty male patients, all native Italian speakers, whose symptoms satisfied the DSM-IV criteria for schizophrenia [37], participated in the study. They were all patients of the Department of Psychiatry of the University of L’Aquila and diagnosis was re-confirmed on admission to (and 6 months after discharge from) the Day-Hospital (DH) using a non-structured interview conducted by two psychiatrists (M.C., R.R) referring to DSM-IV criteria.

All the subjects, whose assessment took place when clinically stable within a month of admission to the DH and establishment/confirmation of diagnosis, were treated with maintenance antipsychotic drugs. The mean daily dose was 310.3 (SD 143.67) mg/equivalents of Chlorpromazine [38]; this dose-equivalence with a typical antipsychotic is necessary in order to compare the different antipsychotic drugs as their strength may be different when administered to patients.

Twenty neurologically and psychiatrically healthy control subjects (matched for age and education) were included. Exclusion criteria were: history of neurological disease including epilepsy, head trauma or mental retardation. All subjects provided informed consent to participate in the study.

## Materials and procedure

### ■ Clinical assessment

Clinical assessment in the sample with MPFC lesions was performed by using a non-structured clinical interview and Brief Psychiatric Rating Scale (BPRS) version 4.0 translated into Italian by [39] and through the neuropsychiatric Inventory (NPI), a semistructured clinicians interview using the protocol described by [40].

For the schizophrenic sample, frequency and severity of current symptomatology was registered by using a non-structured clinical interview and Brief Psychiatric Rating Scale (BPRS) version 4.0 (Modified 24-item version, translated into Italian by [39] and Clinical Global Impression scale (CGI) [40].

The prevalent symptomatology was also investigated using the Scale for the assessment of Positive Symptoms (SAPS; [41]) and Scale for the assessment of Negative Symptoms (SANS; [42]).

The SAPS consists of 34 items and is divided into four subscales: hallucinations, delusions, bizarre behaviour and formal thought disorder. The SANS consists of 25 items and is designed to measure five domains: affective flattening or blunting, alolia, apathy, asociality and impaired attention.

We also evaluated social function with AD-Disability Assessment [40]. Socio-demographic and clinical data are reported in Table 3.

**Table 1** Socio-demographic details of subjects with ventromedial frontal lobe lesions

Subjects	Site	Age	Education	Aetiology
M.D	Right frontal lesion	56	13	Meningioma
F.S.	Right frontal lesion	50	8	Meningioma
L.G.	Right frontal lesion	44	8	Meningioma
P.G.	Right frontal lesion	63	5	Oligodendroglioma
T.R.	Right frontal lesion	62	5	Glioma grade III
E.G.	Right frontal lesion	69	8	Spontaneous intracerebral haemorrhage
S.M.	Right frontal lesion	64	13	Glioma grade IV
A.U.	Right frontal lesion	35	18	Intra-cerebral haemorrhage from aneurismal sac rupture
M.U.	Right frontal lesion	44	18	Meningioma
L.F.	Left frontal lesion	41	8	Meningioma
L.P.	Left frontal lesion	30	5	Meningioma
M.N.	Left frontal lesion	68	13	Spontaneous intra-cerebral haemorrhage
M.M.	Left frontal lesion	55	13	Spontaneous intra-cerebral haemorrhage
R.M.	Left frontal lesion	54	8	Meningioma
D.S.	Left frontal lesion	62	8	Meningioma
R.T.	Left frontal lesion	73	13	Astrocytoma grade III
A.C.	Left frontal lesion	59	8	Meningioma
R.G.	Left frontal lesion	38	8	Intra-cerebral haemorrhage from aneurismal sac rupture

**Table 2** Classification of the RMPFC and LMPFC experimental group according to the prefrontal sectors of functional significance into which the lesions encroached

Patient	Sex	Age (years)	Aetiology	Lesion location	
				Fronto-orbital	Medial
RF1	F	56	Meningioma	+	
RF2	F	50	Meningioma		+
RF3	M	44	Meningioma		+
RF4	F	63	Oligodendroglioma	+	
RF5	M	62	Glioma grade III	+	
RF6	M	69	SIH		+
RF7	F	64	Glioma grade IV	+	
RF8	F	35	lhAsc		+
RF9	M	44	Meningioma	+	
LF1	M	41	Meningioma		+
LF2	M	30	Meningioma	+	
LF3	F	68	SIH		+
LF4	M	55	SIH	+	
LF5	M	54	Meningioma		+
LF6	M	62	Meningioma		+
LF7	M	73	Astrocytoma grade III		+
LF8	F	59	Meningioma		+
LF9	M	38	lhAsc	+	

SIH = spontaneous intracerebral haemorrhage; lhAsc = intracerebral haemorrhage from aneurismal sac rupture

### ■ Neuropsychological assessment

All the schizophrenic subjects, with the exception of two positive schizophrenics, were also administered three neuropsychological tests for assessment of executive functions: the WCST, the Tower of London Test and a Phonemic Verbal Fluency Test (Table 4).

The WCST (128 cards) was administered with standard instructions, as described by Spreen and Strauss [43], whereas scoring followed Heaton's [44] rules. Scoring and administration instructions for the Tower of London Test were those described by Krikorian et al. [45]. Scoring and administration instructions of the Phonemic Verbal Fluency Test were those described by Novelli et al. [46].

Visuo-spatial intellectual level was assessed by means of Raven's Progressive Matrices [47].

### ■ Theory of mind tasks

Four stories were read to the participants individually to assess ToM competence. The stories were structured to assess the ability to understand first and second order false beliefs in adult subjects [9]. First order false beliefs require a subject to make an inference about the state of the world. To assess first order ToM two stories were used: The washing machine task [9] and The Cigarette Task [48].

Second order stories measure the capacity to understand other people's false beliefs. To assess second order ToM two stories were used; The Burglar [49] and The Wallpaper Story [9]. These stories were presented to the subjects in a series of cartoons in which the various actions of the characters are depicted in sequences.

All the subjects were asked a ToM question and three control questions:

*False belief test question.* This was designed to elicit a response that demonstrated the ability to make inferences about another individual's mental state, namely, that a character in the story holds a false belief.

*Fact question.* This was posed to determine whether subjects understood the actual sequence of relevant events that had occurred in the story which is in contrast with the sequence as understood by one of the characters in the story and that leads to his coming to a false conclusion.

*Memory question.* This was used to assess whether memory for story details was approximately intact. The stories were the same for all the subjects examined. Each subject obtained a score ranging from 0 to 1 in the case of a correct answer to a False-belief question, to the fact question and to the memory question, where 0 = incorrect answer; 1 = correct answer. If the subject gave a correct answer to both the first order stories, s/he had a global score for first order ToM equal to 1 (non-casual performance). For second order false belief stories we followed the same methods.

### ■ Social cognition tasks

The following tasks addressed two aspects of social cognition.

The ability to process the appropriateness of behaviour in different social contexts [21]; and the ability to use tactical strategy (Machiavellian Intelligence).

#### Social situations task

This task investigates the capacity to judge the appropriateness of behaviour that may induce anger in observers.

**Table 3** Socio demographic, clinical details in the total sample

	Schizophrenia (no. 20)	Right medial prefrontal cortex lesion (no. 9)	Left medial prefrontal cortex lesion (no. 9)	Healthy controls (no. 20)
Sex (M:F)	7:13	5:4	2:7	15:6
Age (years)	42.7 (1.8)	49.6 (10.3)	46.4 (18.6)	38.9 (2.8)
Education (years)	8.8 (0.8)	9.2 (2.6)	12.2 (3.97)	13.4 (1.2)
Day since surgery	–	91.4 (11.6)	88.8 (13.7)	–
IQ level	88.8 (5.7)	93.1 (2.4)	98.7 (3.6)	–
NPI total score	6 (0)	10 (0)	9.8 (5.3)	–
Duration of illness (years)	12.30 (4.13)	–	–	–
BPRS total score	44 (11.1)	52.5 (4.9)	55.5 (17.5)	–
C.G.I.	4.5 (0.6)	–	–	–
SANS	50.42 (20.9)	–	–	–
SAPS	42.57 (19.1)	–	–	–
Social function (AD)	2.5 (1.1)	–	–	–

The values are means; standard deviation are in parenthesis

**Table 4** Neuropsychological detailed of total sample

	Schizophrenia (no. 20)	Right medial prefrontal cortex lesion (no. 9)	Left medial prefrontal cortex lesion (no. 9)	Healthy controls (no. 20)
Verbal fluency	33.1 (10.4)	21.2 (8.39)	11.3 (4.19)	38.7 (7.5)
Tower of London	29.8 (4.4)	26.3 (6.5)	19.2 (4.3)	34.6 (1.9)
WCST no. of category	3.46 (2.41)	2.66 (1.7)	1.87 (2.1)	5.7 (0.3)
WCST % of perseverative errors	27.66 (15.12)	42.9 (22.6)	50.7 (21.3)	2.9 (2.6)
Verbal memory	19.1 (8.7)	28.6 (8.01)	8.3 (2.25)	29.6 (3.01)

The values are means; standard deviation are in parenthesis

**Procedure.** Nine short stories describing social situations incorporating behaviour were read by the patient. At various points in each story, the patient was asked to comment on how appropriate the behaviour was, giving a score from A to D. “A” scores meant that he judged the situation as normative. “B” to “D” scores meant that he judged the situation as a norm violation and indexed the extent of the violation (“B” scores being mild and “D” being serious). Blair and Cipollotti [21] report that previous piloting on a large, independent sample of healthy controls had resulted in the identification of a set of consistently identified normative situations and violations.

Two scores were obtained for this task: one referring to the number of normative situations and the other to the number of violations correctly identified. The third refers to the extent to which the patient judged the violations to be socially inappropriate.

For each situation, the participant obtained a score between 0 and 3, matching their response of “A” to “D” (i.e. “A” = 0, “D” = 3).

#### ■ Mach IV Scale

We used the Mach IV Scale to assess the “Machiavellian Intelligence” of participants [50]. This is a self-report Likert scale, with scores ranging from 1 to 7 (where 1 = I totally disagree; 4 = no opinion; 7 = I totally agree), composed of 20 items, each consisting of a statement.

The Mach IV scale is a method for assessing awareness and social functioning in a social context characterised by interpersonal deception (“Machiavellianism”).

From the 20 statements of the Mach IV Scale we extracted two groups of items: (1) 5 items describing duplicity tactics, e.g.: “It is wise to flatter important people” (“tactics+”) and (2) 4 items describing a disagreements with tactics duplicity, e.g.: “When you ask someone to do something for you, it is best to give the real reason” (“tactics–”).

The items were labelled for coding as follows:

Positive tactics (tactics+): subjects must agree with statements reporting the ability to manipulate other people’s intentions and actions, according to Niccolò Machiavelli’s beliefs.

Negative tactics (tactics–): subjects must agree with statements reporting judgements of correct and honest behaviour; for this reason they cannot use “intentional deception” mechanisms involved in the Machiavellian Intelligence Hypothesis. These features depend on an accurate interpretation of even the most particular intention of respondents [32, 51].

Human nature components referring to “people’s knowledge”, in particular the degree of cynicism concerning other people’s intentions and decisions are strictly related to the ability to interpret other people’s mental states.

#### ■ Statistical analysis

One-way ANOVA was used to compare demographic, clinical information and neuropsychological Assessment and social cognition tasks. The Kruskal ± Wallis test was used to analyse the level of significance of patients’ scores on ToM tasks.

## Results

No differences among groups emerged for age [ $F(3,40) = 0.271$ ,  $P = 0.751$ ], years of education [ $F(3,38) = 0.387$ ,  $P = 0.51$ ] and estimated IQ [ $F(3,38) = 0.44$ ,  $P = 0.64$ ] (Table 2).

#### ■ Clinical assessment

Neither were differences found between the four subgroups in age [ $F(3,38) = 0.271$ ,  $P = 0.751$ , sex ratio, standard of education [ $F(3,38) = 0.387$ ,  $P = 0.51$ ], IQ [ $F(3,38) = 0.387$ ,  $P = 0.51$ ], in BPRS total scores

[ $F(3,38) = 0.345, P = 0.72$ ] and in NPI total score [ $F(3,38) = 0.748, P = 0.508$ ].

### Executive function

The three groups differed significantly in the planning Tower of London task [ $F(3,40) = 22.568, P = 0.000$ ]; Verbal Fluency [ $F(3,40) = 40.023, P = 0.000$ ], and No. of categories achieved in the WCST [ $F(3,40) = 9.578, P = 0.000$ ] and perseverative errors [ $F(3,40) = 10.694, P = 0.000$ ]. The performance data for the four groups on the tests of executive functioning are shown in Table 3.

The LSD method was used for post hoc comparisons. This revealed that in Verbal Fluency both frontal groups (LMPFC and RMPFC) performed significantly worse than the schizophrenic group and control subjects. Bonferroni tests on the Tower of London task showed impaired performance for the LMPFC group only when compared to both the schizophrenic and healthy subjects control groups. The LMPFC group performed significantly worse than the RMPFC subjects.

### First-order false belief tasks

**False-belief test question:** Groups differed significantly on the non-parametric Kruskal–Wallis test:  $\chi^2(3) = 14.664, df = 3, P < 0.002$ . Post hoc (*Bonferroni methods*) comparisons showed that the RMPFC group's performance, differed significantly from that of the LMPFC (RMPFC vs. LMPFC mean differences =  $-0.665; P < 0.005$ ) but not from schizophrenic subgroups, and that the overall percentage of correct scores for patient groups was significantly lower than those of the normal control group.

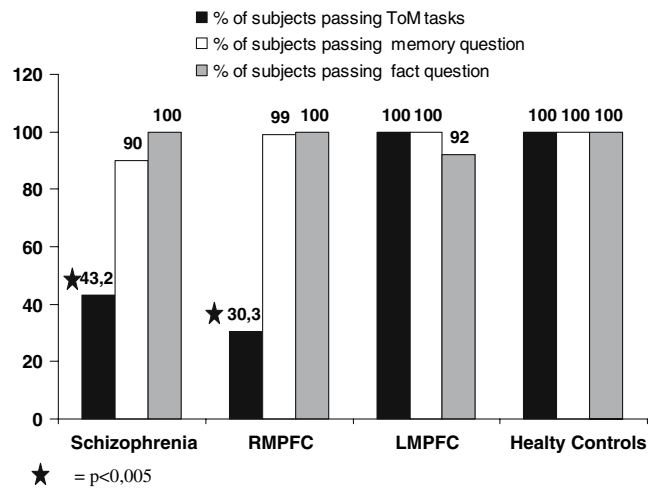
**Fact questions:** The percentage of correct scores revealed no significant overall differences between groups.

**Memory questions:** The percentage of correct scores showed no significant group differences (Fig. 2).

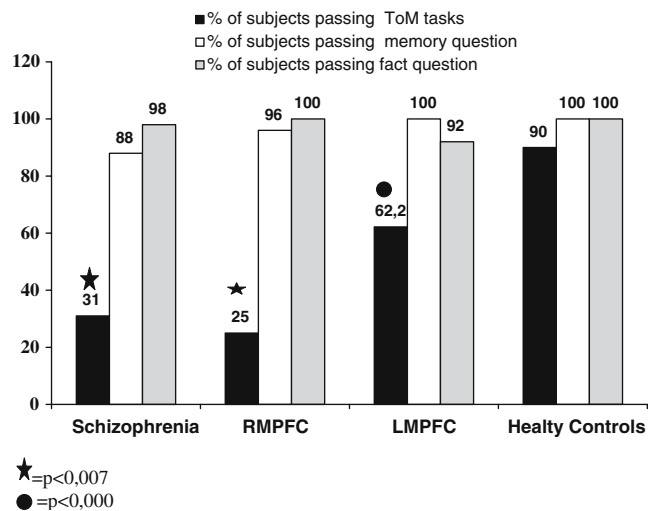
### Second order theory of mind

**False-belief test question:** Groups differed significantly: Kruskal–Wallis  $\chi^2(3) = 11.72, df = 3, P = 0.008$ . Post hoc (*Bonferroni methods*) analyses revealed the most impaired performance for the RF and schizophrenia groups when compared to LMPFC (LMPFC vs. RMPFC mean differences =  $-0.598; P < 0.007$ ; LMPFC vs. schizophrenics mean differences =  $-0.623; P < 0.000$ ). However the overall percentage of correct scores for patient groups was significantly lower than those of the normal control group.

**Fact questions:** The percentage of correct scores revealed no significant overall difference between the groups.



**Fig. 2** Performance of study groups (schizophrenics, Right Medial Prefrontal Cortex—RMPFC Lesion Subjects, Left Medial Prefrontal Cortex—LMPFC Lesion Subjects and healthy controls) on First-order False Belief tasks



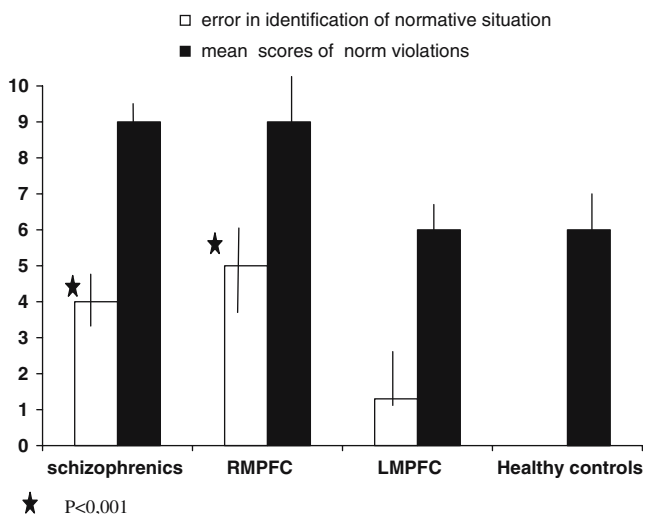
**Fig. 3** Performance of study groups (schizophrenics, Right Medial Prefrontal Cortex—RMPFC Lesion Subjects, Left Medial Prefrontal Cortex—LMPFC Lesion Subjects and healthy controls) on second-order False Belief tasks

**Memory questions:** The percentage of correct scores showed no significant group differences (Fig. 3).

### Social situation task

The ANOVA comparison between RMPFC, LMPFC, schizophrenics and healthy controls showed statistically significant differences in the ability to identify normative situations [ $F(3,58) = 3.179, P = 6.073$ ].

Post hoc (*Bonferroni methods*) comparisons showed that the RMPFC group's performance, differed significantly from that of the LMPFC (RMPFC vs. LMPFC mean differences =  $-1.904; P < 0.001$ ;



**Fig. 4** Performances on social situation task in all groups (schizophrenics, Right Medial Prefrontal Cortex—RMPFC Lesion Subjects and Left Medial Prefrontal Cortex—LMPFC Lesion Subjects). The figure reports the scores in correct identification of normative situation and the mean scores of norm violations

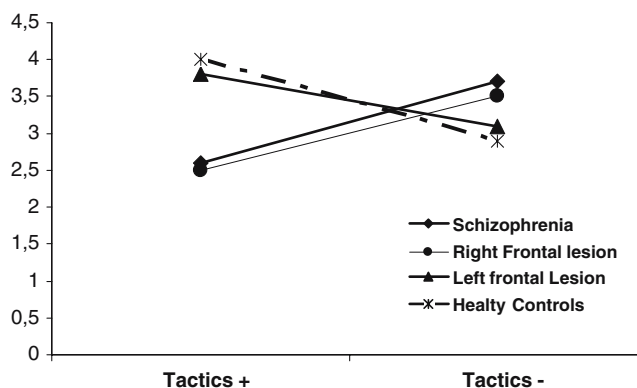
LMPFC vs. schizophrenics mean differences = 1.623;  $P < 0.002$ ) and healthy controls but not from schizophrenics. There were no significant differences between the four groups in the total score of the norm violations (Fig. 4).

### Mach IV scale

The ANOVA comparison between RMPFC, LMPFC, schizophrenics and healthy controls showed statistically significant differences on the following Mach IV items (tactics+) item “Trusting someone means getting into trouble” [ $F(3,58) = 3.179$ ,  $P = 0.035$ ]; (tactics+) “It’s hard to be successful without taking short-cuts” [ $F(3,58) = 3.959$ ,  $P = 0.000$ ]; (tactics-) “There is no need to deceive anyone” [ $F(3,58) = 7.759$ ,  $P = 0.021$ ]; (tactics-) “It is possible to be good in all situations” [ $F(3,58) = 3.406$ ,  $P = 0.027$ ]. Post hoc multiple comparison (*Bonferroni methods*) showed that RMPFC score lower for items indicating agreement in strategic thinking (tactics+); than LMPFC, schizophrenics and controls showed higher scores for items indicating disagreement with strategic thinking (Tactics). Results are displayed in Fig. 5.

### Correlation analyses

No significant correlations were found between ToM first order and ToM second order questions and executive functions (verbal fluency, WCST number of categories and perseverative errors, Tower of London) in normal controls, and in subjects with left and right frontal lesions.



**Fig. 5** Performance on items of Mach IV Scale in the four groups for strategic thinking

No significant correlations were found between the Mach IV scales (good tactical strategy and negative tactical strategy) and executive functions (verbal fluency, WCST no. of categories and perseverative errors, Tower of London) in normal controls, and in subjects with left and right MPFC.

There was a significant correlation between first order ToM scores and duration of illness ( $r = -0.375$ ;  $P < 0.029$ ); between first order ToM scores and SANS total scores ( $r = -0.562$ ;  $P < 0.03$ ); between first order and second order ToM scores and social functioning total scores (AD) (first order =  $-0.489$ ;  $P < 0.036$ ; second order  $r = -0.543$ ;  $P < 0.029$ ).

The significant correlation was also found in the schizophrenic sample between ToM performances and verbal fluency ( $r = -0.527$ ;  $P < 0.000$ ).

No significant correlations were found between the Mach IV scale and social cognition task and psychopathological and clinical variable (SANS, SAPS and CGI).

## Discussion

One of the distinctive attributes of human social cognition is our propensity to build models of other people’s minds: to make inferences about the mental states of others. Several neuroimaging studies have attempted to elucidate the neural substrates that support this distinctively human ability that is impaired in people with schizophrenia.

The main aim of the present paper is to establish whether patients affected by schizophrenia show an impairment in several social cognitive tasks as demonstrated in other researches [5, 52–54] and if this cognitive profile is comparable to patients with a unilateral brain lesion involving orbito-ventromedial areas of the frontal lobes.

Our results are in line with other studies: in people with schizophrenia there was an impairment of social cognitive abilities and this deficit appears to be related to negative symptomatology [55] and to be a key

determinant of functional outcome, including social outcome [56]. It has been suggested that theory of mind deficit make unable schizophrenic subjects to interact effectively with their social environment, but that a lack of certain aspects of social cognition will lead to social misperceptions.

In addition to these clinical and outcome goals, there is increasing interest in identifying the neural substrates that underlie social cognitive deficits in schizophrenia. For all of these reasons we compared the performances on social cognition tasks of schizophrenic subjects with the performances of MPFC subjects.

Among the several studies which investigated the effects of frontal lobe lesions (dorsolateral and ventromedial/orbital) on performance in ToM tasks [9–11, 57–59], some of these including patients with bilateral frontal lobe damage, are limited because of a lack of detailed anatomical specification of lesion location [10, 11, 57]. Moreover, most of patients with bilateral lesions had suffered head trauma, an aetiology associated with rather diffuse brain damage that is particularly likely to impinge on orbitofrontal brain areas.

Thus, the present study strictly tests the hypothesis that the unilateral (right or left) medial frontal cortex is implicated in the neural network sub serving ToM [8] which is based on well established evidences suggesting the implication of the ventromedial frontal lobe areas in playing a critical role in a dedicated “mentalizing” or ToM network in human brains ([7, 28, 60] for a review).

We found out that subjects with RMPFC lesion are impaired in ToM tasks of “false beliefs”, showing thus a very similar cognitive dysfunctional profile to people affected by schizophrenia in all Theory of Mind tasks and in all social cognition tasks. A normal performance on control questions indicates an unimpaired comprehension of stories and suggest that the task was sensitive in detecting TOM impairments.

In addition, schizophrenics and subjects with RMPFC lesion also showed impairment in the social cognition tasks, in fact they both failed to discriminate in judging inappropriate behaviour likely to induce anger in observers. This was unlike patients with LMPFC who showed no impairment on any of these tasks.

This is clear evidence that the medial frontal cortex plays a critical role in a dedicated “mentalizing” brain network that underpins ToM ability [7, 8].

Our findings are in agreement with previous “lesional” studies, showing the association between right medial area damage and more severe ToM deficits [11, 13]. Siegal et al. [13] reported that ToM impairments seem to be associated with right hemisphere damage.

In the present study we report a dissociation in RMPFC damage patients who displayed a defective

ToM performance in contrast to LMPFC patients. LMPFC subjects show lower performances than RMPFC subjects in other cognitive competences but have normal performance in ToM competences and our results confirm the results obtained by Siegal and Surian [61].

In addition, when a more sophisticated social ability is required in order to perform second order false belief tasks correctly, also LMPFC damaged subjects fail to perform at a normal level and show a statistically significant impairment, even though to a lesser degree, when compared to subjects with RMPFC and schizophrenic people. A possible explanation is that LMPFC is involved in more sophisticated mentalizing tasks and that an intact right hemisphere structure is nevertheless required [58]. Normal subjects and neurosurgical subjects with unilateral LMPFC lesions perform fairly well on tasks unrelated to tactical strategy, showing correspondingly low scores on the ingenuity aspect of thinking.

The present study also provides further data on the neural prefrontal areas involved in social cognition tasks and in strategic thinking [21]. Social efficiency is represented by the ability to understand the intentions and beliefs of others with the aim of deceiving and manipulating them to achieve relevant objectives, such as control of food sources or sexual partners [26]. Recent literature fosters that these abilities are localised in the frontal cortex [27, 28]; the ability to recognise and manipulate hierarchical states to achieve some advantage would be localised in the amygdala and right hemisphere [62].

Schizophrenic people and subjects with RMPFC lesion showed impaired performance on tactical strategy associated with relatively “high levels” of social ingenuity and have an impaired ability to access “social schema knowledge” which is stored in the frontal lobes [31]. Such patients cannot access social schema knowledge and fail to inhibit aberrant behaviour, such as physical threats and aggression [21, 63]. Interestingly a completely reversed pattern characterizes the performance of LMPFC lesion subjects and healthy controls, in fact we found out a complete disassociation of the neural prefrontal areas located in the medial part of the hemisphere in sub serving human ability to think strategically, indicating that the cortical organization related to tactical aspects of Machiavellian Intelligence is lateralized to the right hemisphere [64]. Our results are at slight variance with the pioneering study of Rowe et al. [9] who found a significantly impaired performance of both the RMPFC and LMPFC subjects in first and second order ToM tasks. In this study cortical lesions were non-exclusive medial hemisphere but includes subjects with dorsolateral prefrontal cortex (DLPC) damage.

Studies of normal subjects have used a variety of imaging techniques, designs, and test materials, but especially PET and fMRI to define brain regions specifically activated during a ToM task [8, 65]. Such



studies have consistently shown activation of the medial prefrontal gyrus (MPFG) and the Temporo Parietal Junction.

Frith and Frith [7], reporting data on studies carried out in adults, have revealed an MPFC system of three components that are consistently activated during both implicit and explicit mentalizing tasks. This brain region is probably the basis of the decoupling mechanism that distinguishes mental state representations from physical state representations. We can speculate, according to the Edelman model [66, 67], that a hierarchical organization of mental operation, when disrupted at a specified level, impairs the integrity of final output via an interruption of the chain of events required to perform a task. This study is limited by the small number of patients with unilateral frontal lobe lesions due to the rarity of such lesion.

Despite this limitation, this study provides further evidence that social competence is compromised in RMPCF subjects very closely to schizophrenics and these data seem to elucidate the possible neuroanatomic structure alteration present in schizophrenia. However, we are confident that there is a wide range of behavioural manifestations of frontal lobe dysfunction, and ToM impairments clearly cannot account for all of these, nor is it likely to be responsible for all reported difficulties in social cognition. In contrast, ToM tests are designed with the aim of isolating those aspects of social cognition associated with two-way reciprocal interactions that rely crucially on ToM ability and false belief tasks have facilitated the demonstration of a mentalizing impairment in subjects with lesions of the prefrontal cortex, which is independent of non-mental state inference.

In conclusion, our findings provide evidence that lesions to the right MPCF determine an incapacity to understand ToM “false belief” stories and to use tactical strategy and understanding of social schema. Other authors have reported the same results: subjects with right hemisphere damage, but not subjects with left hemisphere damage, had difficulties in performing simple theory of mind tasks [13, 68].

The difficulties shared by subjects with right hemisphere damage and young children on ToM tasks may have a similar origin [61]. These may both derive from a pragmatic deficit that prevents subjects from interpreting the implicit questions correctly, rather than from a conceptual deficit concerning the ability to represent mental states.

The response pattern of subjects with ventromedial prefrontal damage on ToM tasks adds new evidence to the growing literature on the effects of the right hemisphere on various pragmatic aspects of language production and comprehension [13].

The good performance of subjects with RMPCF lesions in executive function and verbal memory tasks suggests that their difficulties are due to a reduced

sensitivity to the constraints that guide the interpretation and production of contextually appropriate utterances [61].

It may be concluded that the ToM disorder in RMPCF subjects does not stem from executive function or memory deficits and that deficits in ToM and executive functioning in subjects with frontal lobe lesions are not causally related, even though our findings are in disagreement with Channon and Crawford [69] who found a relationship between executive functioning and ToM ability in adults with damage to the frontal lobes [70].

We support two positions: first, that a specialized, discrete ToM module, or set of modules, is located in the frontal lobes, but is functionally independent and second that these deficits can co-occur, on the basis of the proximity of the respective underlying neural areas.

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