



Review article

# Social brain dysfunctions in schizophrenia: A review of neuroimaging studies

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Received 22 January 2006; received in revised form 25 April 2006; accepted 10 May 2006

## Abstract

Several studies have indicated that schizophrenic patients show impaired performance in various aspects of social cognition, including theory of mind, emotion processing, and agency judgments. Neuroimaging studies that have compared patients and healthy subjects during such mental activity indicate an abnormal hemodynamic response in the medial prefrontal cortex, the prefrontal cortex, the amygdala, the inferior parietal lobe, i.e., a set of regions known to be critically involved in social cognition. This paper addresses a number of issues raised by schizophrenia research into theory of mind, emotion perception and self-agency with regards to the neural systems that mediate social cognition. In healthy subjects, typical brain patterns are associated with theory of mind, emotion perception and self-agency; some activated clusters overlap, while others are distinct. For instance, activations in the paracingulate gyrus are almost systematically associated with theory of mind tasks, while the amygdala is mainly involved in emotion perception tasks. Additional foci are frequently found activated during those tasks: superior temporal sulcus, inferior frontal area. Moreover, the inferior parietal lobe is thought to contribute to agency judgments. In the light of the data on brain abnormalities and neurochemical dysfunctions in schizophrenia, we discuss the interaction of social cognitive dysfunction with the supposed information processing abnormalities caused by dopamine dysregulation.

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*Keywords:* Schizophrenia; Social cognition; Theory of mind; Emotion perception; Functional imaging

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## 1. Introduction

Our knowledge concerning the cognitive and neural systems mediating social cognition has progressed considerably over the last 10 years. The concept of ‘social cognition’ refers to a relatively large number of psychological constructs ranging from the more complex—such as theory of mind or self-representation—to more elementary ones such as emotion perception, the processing of social cues and action-monitoring. Although the theoretical debate concerning the relations between these different abilities and the extent to which social cognition is domain-specific is unresolved, the validity of these constructs is supported by recent progress in various research fields including neuropsychology and functional cognitive neuroimaging. Furthermore, we believe that any new model will have to account for the fact that the human brain is strongly biased toward processing social stimuli including the behavior of conspecifics. Indeed, evolutionary psychology, developmental science, neuropsychology, neuroimaging, and psychopathology provide some empirical evidence to suggest that a somewhat restricted group of neural circuits is specialized to process social information.

Evolutionary psychologists have suggested that primates’ unusually large brains are the product of the cognitive demands imposed by living in complexly bonded social groups (the social brain hypothesis). Importantly, (Dunbar 1998) demonstrated that there is a correlation between social complexity (e.g., group size) and relative brain size (i.e., the ratio of neocortex volume to the volume of the rest of the brain). The ability to understand, predict others’ mental states and navigate within the social world has its roots in the long and progressive adaptation of the brain architecture imposed by evolutionary pressures. Many of the advanced cognitive skills enjoyed by humans are associated with improved executive functions associated with the expansion of the frontal cortex (Barrett et al., 2003). Notably, the anterior cingulate cortex, a key structure for cognitive and emotional control (Bush et al., 2000), is distinctive in that it contains neurons specific to pongids and hominids, the spindle cells (Nimchinsky et al., 1999). In an attempt to reconcile evolutionary considerations and neuro-architectonic findings, Allman et al. (2001) speculated that these spindle cells play a part in coordinating widely distributed neural activity involving emotion and cognition. Interestingly, some theorists proposed that psychosis may be considered as a price paid by humans for having developed such complex brain systems underlying complex social skills (Burns, 2004).

Over the last decade, great interest has been shown in the issue of the cerebral implementation of social cognition. Converging empirical evidence from electro-

physiological and lesion studies in monkeys points to a restricted network of regions, namely the superior temporal cortex, the orbitofrontal cortex and the amygdala, that are reliably involved in social cognition (Brothers et al., 1990; Jellema et al., 2000). Similarly, neuropsychological observations in humans have emphasized the role of the orbitofrontal cortex in the regulation of social behavior (Eslinger and Damasio, 1985) and that of the amygdala in emotion perception (Adolphs et al., 1994). In addition, these findings have been extended by a large number of functional neuroimaging studies in healthy participants (see below).

Psychopathological research is another important source of knowledge concerning the mechanisms of social cognition. For instance, it has been suggested that some pathological conditions such as Asperger’s syndrome and autism are the expression of an abnormal development of social cognitive skills in early infancy (Perner et al., 1989). Baron-Cohen and colleagues reported a dissociation between theory of mind skills and the understanding of physical causality in autistic children, whereas children suffering from Down’s syndrome did not exhibit the same type of performance pattern (Baron-Cohen et al., 1986). It has been suggested that autism shares common features with schizophrenia such as impaired social performances or social withdrawal (Frith, 1992). In an early theoretical account, Frith also suggested that a specific impairment in metarepresentation is involved in the genesis of schizophrenic symptoms. More recently, Frith proposed that only explicit theory of mind (as opposed to the implicit processing of other people’s mental states) is impaired (Frith, 2004b). Other scholars have attributed the disorganization syndrome to this deficit in attributing intentions to others and have discussed the relationship between this clinical dimension and the inability to process contextual information (Hardy-Baylé, 1994). It is worth noting that most of these accounts have focused on specific aspects of social cognition, i.e., theory of mind or emotion perception, while often excluding other aspects. The various theories therefore often fail to account for the widespread abnormalities found in the social cognition of schizophrenic patients at many different levels.

We believe that there are two ways in which psychopathology may benefit from neuroimaging investigations: Firstly, by demonstrating that schizophrenic patients present abnormal brain activity during various processing tasks involving social cognition. This consideration is crucial to studies that claim to have a basis in cognitive neuropsychology because the dysfunctions which occur at the neural level are used to validate the psychopathological

construct. Secondly, the use of the knowledge acquired about normal brain functioning may help to formulate new questions about pathology and make it possible to generate testable hypotheses. This approach is similar to the one advocated by [Willingham and Dunn \(2003\)](#) which holds that one heuristic strategy in psychology requires researchers to “use existing knowledge of the brain to shape psychological theory.”

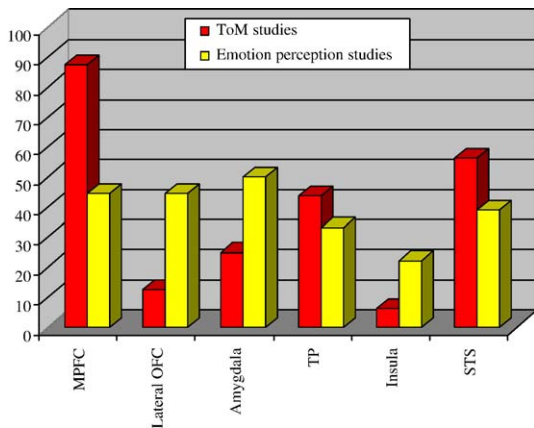


Fig. 1. Percentage of the studies reporting activation in different brain regions during theory of mind tasks (in red, [Baron-Cohen et al., 1999](#); [Brunet et al., 2000](#); [Castelli et al., 2000, 2002](#); [Fletcher et al., 1995](#); [Goel et al., 1995](#); [Ruby and Decety, 2003](#); [Vogeley et al., 2001](#); [Russell et al., 2000](#); [Martin and McDonald, 2003](#); [Ramnani and Miall, 2004](#); [Gallagher et al., 2000](#); [Sprengelmeyer et al., 1997](#); [Vollm et al., 2006](#); [Walter et al., 2004](#)) and emotion perception tasks (in yellow, [Dolan et al., 1996](#); [Abel et al., 2003](#); [Blair et al., 1999](#); [Phillips et al., 1998](#); [Kesler-West et al., 2001](#); [Wright et al., 2002](#); [Lange et al., 2003](#); [Phillips et al., 1997](#); [Sprengelmeyer et al., 1998](#); [Gur et al., 2002a](#); [Gorno-Tempini et al., 2001](#); [Hariri et al., 2002b](#); [Hempel et al., 2003](#); [Nakamura et al., 1999](#); [Wicker et al., 2003b](#); [Mitchell et al., 2003](#); [Buchanan et al., 2000](#); [Kotz et al., 2003](#)). References and short description of the conditions are reported in [Table 1](#). To ensure an accurate comparison between the studies, we retained only those papers meeting the criteria described below from those defining themselves as theory of mind or emotion recognition studies. In the case of the neuroimaging studies of theory of mind, the index condition had to involve the prediction of the behavior or the determination of the mental state of an agent. The comparison condition was not permitted to involve such a decision. When multiple comparison conditions were included in the original paper, the closest to the index condition was adopted. In the case of the studies of emotion recognition, the index condition either had to include the display of an emotional expression or require the subject to make a decision about a facial expression or a prosodic verbal stimulus. The comparison condition either did not require such a judgment or did not contain emotional displays. Another criterion was that the studies had to report activation coordinates without any restriction other than the threshold level. This level had to be at least equivalent to  $P < 0.05$ . The coordinates were converted into Talairach and Tournoux stereotactical space, while taking account of the differences between this reference space and the MNI space. We defined the medial prefrontal region as the volume  $20 < X < 20, Y > 20$  in Talairach space.

This article addresses the question of the social cognition impairments observed in schizophrenia by presenting a review of the experimental data obtained in the field of social cognitive neuroscience. Its primary motivation lies in the observation that social cognitive performances are related to the ability to solve concrete interpersonal problems ([Corrigan and Toomey, 1995](#); [Toomey et al., 1997](#)), to the occurrence of socially deviant behavior ([Brüne, 2005](#)), and to the global social functioning of patients ([Mueser et al., 1996](#); [Penn et al., 1995](#)). A better understanding of these issues should contribute to this research field by providing a more precise description of the psychopathological mechanisms involved in social cognition. We will focus on the involvement of three key regions—the medial prefrontal cortex, the amygdala, and the inferior parietal lobule—in the social cognitive deficits exhibited by schizophrenic patients. Although many experiments proved that several other regions were highly involved in social cognition (superior temporal sulcus, temporal poles, inferior parietal lobe, and cerebellum) the choice of those three cortical parts is grounded on their highly documented contributions to three main aspects of social deficits arising in schizophrenia: impairments of theory of mind, emotion perception and agency. We will indicate a possible link with the fields of neuropathology and neurochemical disorders within a simple, yet speculative, model.

## 2. Functional abnormalities in the medial prefrontal cortex and mentalization impairments in schizophrenia

The most frequently replicated finding from the neuroimaging studies of theory of mind is the involvement of the medial prefrontal cortex. Indeed, as [Fig. 1](#) indicates, nearly all mentalizing tasks are associated with single or multiple clusters of activation in this region. In addition, half of the neuroimaging studies of emotion processing reviewed here also found activation in this region. Thus, mentalizing and the perception of emotion commonly seem to recruit similar portions of the medial prefrontal cortex ([Fig. 2](#)), although less consistently so in the case of emotion perception. This finding is consistent with several neuropsychological studies which have demonstrated reduced performance in theory of mind tasks among patients suffering prefrontal damage ([Happé et al., 2001](#); [Rowe et al., 2001](#); [Stone et al., 1998](#)), especially when the right medial prefrontal region is injured ([Stuss et al., 2001](#)). For instance, [Happé](#) and colleagues demonstrated that patients with right prefrontal lesions have difficulties in comprehending humor, emotions, irony and indirect requests ([Happé et al., 1999](#)).

Table 1  
Labels of studies on figures

Label	Study	Index condition	Control condition
<i>Emotion recognition studies</i>			
a	Dolan et al. (1996)	Recall of emotional faces (happiness)	Recall of non-emotional faces
b	Gur et al. (2002a,b)	Decide emotional valence of a face	Decide the age of a face
c	Abel et al. (2003)	Decide sex of fearful faces	Decide sex of neutral faces
d	Blair et al. (1999)	Decide sex of emotional faces (sad, angry)	Decide sex of neutral faces
e	Phillips et al. (1998)	Decide sex of fearful faces	Decide sex of neutral faces
f	Phillips et al. (1998)	Decide sex of disgusted faces	Decide sex of neutral faces
g	Kesler-West et al. (2001)	View angry faces (concentrate on expression)	View neutral faces (concentrate on expression)
h	Kesler-West et al. (2001)	View fearful faces (concentrate on expression)	View neutral faces (concentrate on expression)
i	Kesler-West et al. (2001)	View happy faces (concentrate on expression)	View neutral faces (concentrate on expression)
j	Kesler-West et al. (2001)	View sad faces (concentrate on expression)	View neutral faces (concentrate on expression)
k	Wright et al. (2002)	View hand-drawn emotional faces (happy and sad)	View hand-drawn neutral faces
l	Lange et al. (2003)	View fearful faces	View neutral faces
m	Gomo-Tempini et al. (2001)	Decide emotion or sex on emotional faces (happiness, disgust)	Detect a shape
n	Hariri et al. (2002a,b)	Match fearful faces	Match shapes
o	Phillips et al. (1997)	Decide sex of fearful faces	Decide sex of neutral faces
p	Hempel et al. (2003)	Affect discrimination task	Looking at neutral faces
q	Hempel et al. (2003)	Affect labeling task	Looking at neutral faces
r	Nakamura et al. (1999)	Decide emotional valence of face	Decide the background color
s	Sprengelmeyer et al. (1998)	Decide sex of disgusted faces	Decide sex of neutral faces
t	Sprengelmeyer et al. (1998)	Decide sex of fearful faces	Decide sex of neutral faces
u	Sprengelmeyer et al. (1998)	Decide sex of angry faces	Decide sex of neutral faces
v	Blair et al. (1999)	Decide sex of angry faces	Decide sex of neutral faces
w	Lange et al. (2003)	Decide sex of fearful faces	Decide sex of neutral faces
x	Lange et al. (2003)	Decide emotion on fearful faces	Decide emotion on neutral faces
y	Wicker et al. (2003a,b)	Judge others' emotions	Judge eye direction
<i>Prosody recognition studies</i>			
z	Mitchell et al. (2003)	Listen to congruent prosody	Listen to neutral prosody
A	Buchanan et al. (2000)	Detect a specific verbal emotion while listening to words	Detect a specific word (prosody is present)
B	Kotz et al. (2003)	Evaluate emotion during prosodic speech (happiness)	Evaluate emotion during neutral speech
C	Kotz et al. (2003)	Evaluate emotion during prosodic speech (anger)	Evaluate emotion during neutral speech
<i>Theory of mind studies</i>			
D	Fletcher et al. (1995)	ToM stories	Physical stories
E	Russell et al. (2000)	Eyes task ToM	Gender decision
F	Baron-Cohen et al. (1999)	Eyes task ToM	Gender decision
G	Vogeley et al. (2001)	ToM stories	Physical stories
H	Castelli et al. (2000)	ToM animations of shapes	Random animations of shapes
I	Gallagher et al. (2000)	ToM stories	Physical stories
J	Gallagher et al. (2000)	ToM comic strips	Non-ToM comic strips
K	Goel et al. (1995)	ToM other's knowledge	Memory retrieval
L	Castelli et al. (2002)	ToM animations of shapes	Random animations of shapes
M	Brunet et al. (2000)	ToM comic strips	Physical comic strips
N	Gallagher et al. (2000)	Game against human	Game against computer
O	Ruby and Decety (2003)	Third person perspective knowledge	First person perspective knowledge
P	Martin et al. (2003)	Animation of shapes with social trajectories	Animation of shapes with mechanical trajectories
Q	Saxe and Kanwisher (2003)	Read implicit ToM stories	Read physical stories
R	Ramnani and Miall (2004)	Predict third person	Computer
S	Ruby and Decety (2004)	Third person perspective emotions	First person perspective emotions
T	Walter et al. (2004)	Private intention by one agent comic strips	Physical causality comic strips
U	Vollm et al. (2006)	ToM comic strips	Physical causality comic strips
<i>Schizophrenia studies</i>			
V	Russell et al. (2000)	Eyes task ToM	Gender decision
W	Gur et al. (2002a,b)	Emotional valence discrimination task	Rest
X	Brunet et al. (2003a,b)	ToM comic strips	Physical comic strips

Table 1 (continued)

Label	Study	Index condition	Control condition
<i>Schizophrenia studies</i>			
Y	Hempel et al. (2003)	Affect discrimination task	Looking at neutral faces
Z	Hempel et al. (2003)	Affect labelling task	Looking at neutral faces

Index and control conditions are reported.

The prefrontal cortex occupies a large section of the frontal lobe and encompasses many different cortical areas (anterior cingulate cortex, paracingulate gyrus, frontopolar region, dorsal medial prefrontal cortex, ventromedial cortex). These areas can be distinguished by their different cytoarchitecture (Rajkowska and Goldman-Rakic, 1995; Ongur and Price, 2000; Ongur et al., 2003), cell distribution (Allman et al., 2002; Nimchinsky et al., 1999), and anatomical connectivity (Ongur and Price, 2000). As illustrated in Fig. 2, the anterior cingulate cortex reveals the presence of certain activated foci, a fact which is consistent with the idea that this region is important for “emotional self control as well as focused problem-solving, error recognition, and adaptive response to changing conditions” (Allman et al., 2001). Activation in the cingulate cortex is not systematic and many clusters are located in the paracingulate gyrus. Bush et al. (2000) suggested a functional distinction between the anterior part and the posterior part of the anterior cingulate cortex in terms of emotional task content. After conducting a large-scale meta-analysis of emotion induction and purely cognitive neuroimaging studies, Steele and Lawrie (2004) extended this distinction to the entire medial prefrontal region. The “emotional” portion of the medial prefrontal region is found to be activated in almost 90% of the theory of mind studies and in half of the emotion perception studies that we have reviewed.

The scattered distribution of clusters of activation in the medial prefrontal cortex makes it difficult to ascribe a unique and specific function to this region, as does the fact that this region is activated during a wide range of cognitive tasks including episodic memory retrieval (see meta-analysis in Cabeza and Nyberg, 1997; Duncan and Owen, 2000), high-level language processing (Bottini et al., 1994; Nichelli et al., 1995; Maguire et al., 1999; Ferstl and von Cramon, 2002), various syllogistic reasoning tasks (Goel et al., 1997; Zysset et al., 2002), and the learning of new response rules (Matsumoto and Tanaka, 2004). Nevertheless, Gallagher and Frith (2003) proposed that this region acts in the service of a ‘decoupling mechanism’ which refers to the process that makes it possible to dissociate the representation of an agent’s mental state from the objective representation of reality.

Our review of neuroimaging studies also shows that theory of mind tasks often involve co-activations in the

medial prefrontal cortex and temporal structures including the temporal pole or the superior temporal gyrus (Castelli et al., 2000; Castelli et al., 2002; Brunet et al., 2000, 2003b; Baron-Cohen et al., 1999; Russell et al., 2000; Goel et al., 1995; Martin and Weisberg, 2003; Ruby and Decety, 2003; Gallagher et al., 2000; Frith, 2004a). Similarly, several studies have reported that the prefrontal and temporal lobes exhibit simultaneous hemodynamic responses during emotion perception (Dolan et al., 1996; Gur et al., 2002a; Blair et al., 1999; Phillips et al., 1998, 1997; Wright et al., 2002; Gorno-Tempini et al., 2001; Sprengelmeyer et al., 1998; Wicker et al., 2003b).

Overall, these findings suggest that the medial prefrontal cortex may not only mediate reasoning about mental states. Its function should be understood in terms of the interaction between high-level cognition and social and emotional processing. We suggest that, given the established involvement of the prefrontal cortex in planning, response selection, and short term memory, then the greater the extent to which social cognition requires decoupling, switches between one’s own and others’ perspectives, and the inhibition of responses, the greater the neural response exhibited by the medial region will be. Moreover, each sub-region of the prefrontal cortex recruited by theory of mind processing may also be involved in maintaining and updating a global contextual representation of one’s own or others’ mental representations. This view is compatible with Stone and Gerrans’ proposal that theory of mind is the result of an interaction between domain-general abilities and lower-level mechanisms representing social information (Stone and Gerrans, 2006).

Interestingly, abnormalities in hemodynamic activation within the medial prefrontal cortex in schizophrenic patients have been reported during tasks involving theory of mind processing (attribution of intention) by Brunet et al. (2003b) as well as by Hempel et al. (2003) using a facial affect recognition paradigm. Given the functional significance of medial prefrontal activation during theory of mind tasks, these results suggest that schizophrenic patients fail to process social information when contextual processing, decoupling, or response inhibition are required. Such impairments have been conceptualized as a key feature of the disorganization syndrome (Hardy-Baylé et al., 2003) in line with experimental results obtained both

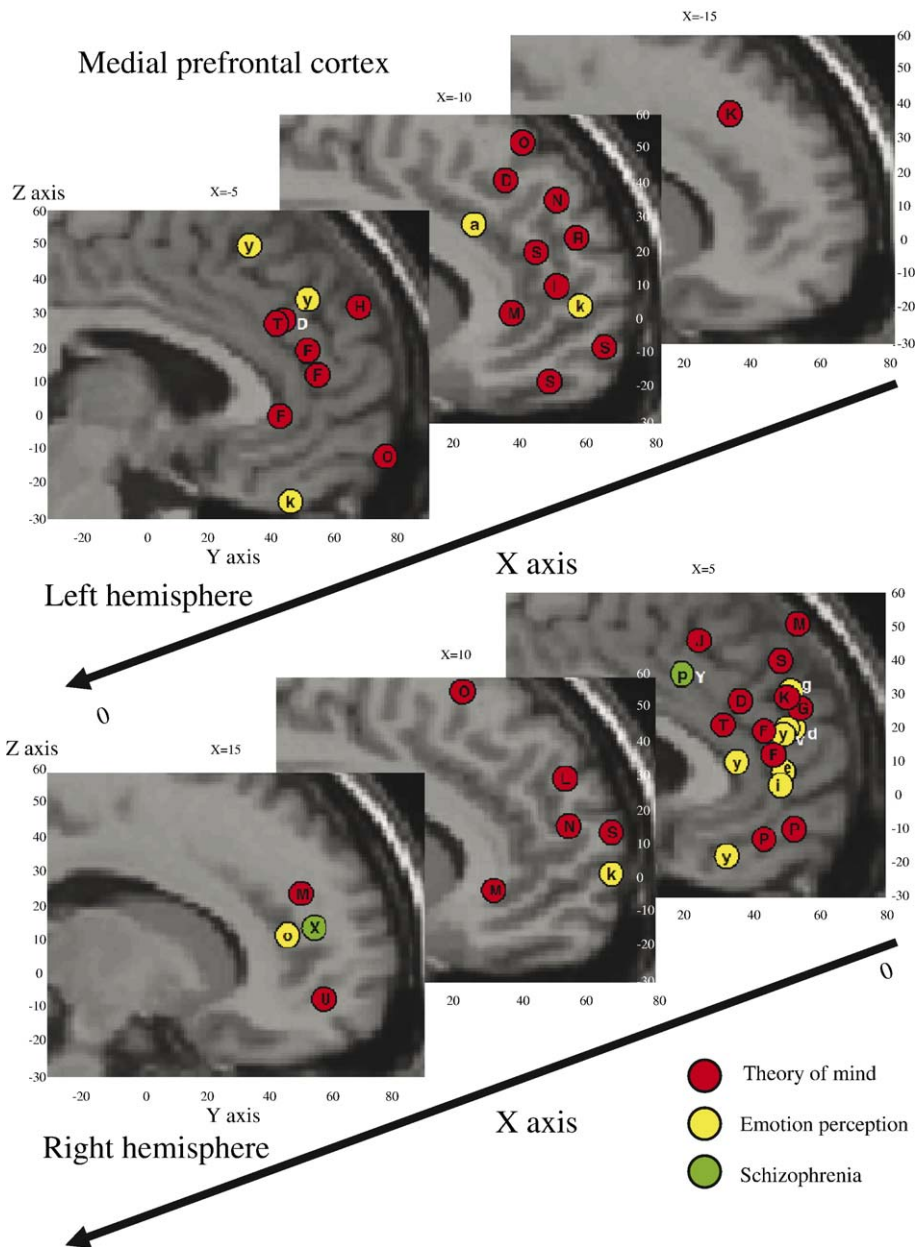


Fig. 2. Foci of activation in the right and left medial prefrontal cortex including the anterior cingulum (defined as the volume  $20 < X < 20, Y > 20$ ) in theory of mind (red) and emotion perception tasks (yellow) in normal subjects superimposed on several sagittal sections of the MNI brain. Green discs represent the regions where schizophrenic patients exhibit abnormal hemodynamic changes compared to healthy subjects in one theory of mind task (Brunet et al., 2003b) and an emotion perception study (Hempel et al., 2003). Labels are reported in Table 1.

in psycholinguistics (Besche et al., 1997; Kostova et al., 2003; Bazin et al., 2000) and social cognition (Schenkel et al., 2005). Such a view is consistent with a body of experimental evidence which shows that theory of mind deficits in schizophrenia are associated with the disorganization syndrome. Patients with a behavioral syndrome corresponding approximately to disorganization (Cor-

coran et al., 1995; Corcoran and Frith, 1996; Frith and Corcoran, 1996; Doody et al., 1998; Drury et al., 1998; Pickup and Frith, 2001), formal thought disorder (Sarfati, 1995; Sarfati et al., 1997a,b, 1999; Sarfati and Hardy-Baylé, 1999; Langdon et al., 2002) or psychotic disorganization signs (Schenkel et al., 2005) always exhibit the poorest performance whatever group they are

compared to. Some researchers have found a similar deficit in paranoid patients (Corcoran et al., 1995; Corcoran and Frith, 1996; Frith and Corcoran, 1996) but this result remains unclear given the existence of certain contradictory findings (Stephenson et al., 1996; Drury et al., 1998; Sarfati et al., 1997a,b). The negative syndrome is the object of a similar controversy (Sarfati et al., 1997a; Corcoran et al., 1995; Mazza et al., 2001).

Another unresolved question concerns the relation between the deficit in social cognition and other cognitive deficits frequently found in schizophrenic patients. Interestingly, a similar issue is currently being discussed in the field of developmental research and points towards a close interrelation between the development of executive functioning (especially inhibitory control) and theory of mind abilities in children (Carlson et al., 2004). A finding common to several patient-based studies is that IQ is correlated with performances in the attribution of intention. However, when IQ is taken into account as a covariable, the deficit in the schizophrenic patients persists (Drury et al., 1998; Brunet et al., 2003a; Brüne, 2005). In contrast, Stephenson and colleagues (1996) found a relation between performance in mentalizing tasks and IQ (measured by the NART). Brüne (2003) found that the difference measured between disorganized patients and

normal subjects disappears when verbal IQ is taken into account (2003). Similar contradictions can be found in the literature on emotion perception in schizophrenia (see review in Edwards et al., 2002). Bryson et al. (1997) have suggested that a substantial proportion of the variance in performance in emotion recognition can be explained by other cognitive measures that are either related to face recognition (Kerr and Neale, 1993; Addington and Addington, 1998; Mueser et al., 1996), visual processing (Silver and Shlomo, 2001; Silver et al., 2002), executive function (Bell et al., 1997), attention (Addington and Addington, 1998; Penn et al., 1996), motor sequencing (Silver and Shlomo, 2001; Silver et al., 2002), or memory (Bryson et al., 1997; Kee et al., 1998; Penn et al., 1996; Schneider et al., 1995).

The distributed nature of the areas involved in social cognition and their complex relation with executive functions may explain why various correlations are observed between the deficits in mentalization or emotion perception and other cognitive measures which all involve complex mental activities. At the same time, the neural networks involved in social cognition are all characterized by the fact that they involve certain regions that are highly reactive to social stimuli (amygdala, STS, medial prefrontal cortex),

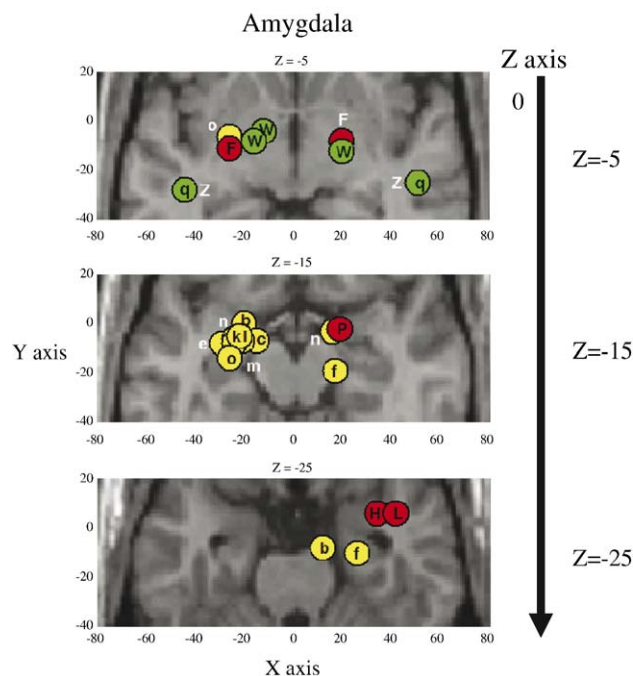


Fig. 3. Activated foci in the amygdala during theory of mind (red) and emotion perception tasks (yellow), superimposed on a horizontal sections of the MNI brain. We included all the foci explicitly labeled as amygdala in the studies or localized at less than 15 mm from those coordinates:  $(27, 9, -15)_{\text{mmi}}$  or  $(-27, 9, -15)_{\text{mmi}}$ . Green discs represent the regions where schizophrenic patients exhibit abnormal hemodynamic changes compared to healthy subjects in two emotion perception studies (Hempel et al., 2003; Gur et al., 2002b). Labels are reported in Table 1.

something which is not the case for executive functions, language processing, or perceptual skills.

### 3. Functional abnormalities in the amygdala and social cognition deficits

No one doubts that the amygdala is involved in emotional experience and social perception. However, its exact role is still unclear, especially when epistemic mental states (without affective content) are considered. Indeed, the amygdala is a key component in emotional processing and it has been claimed that it processes the online perception of other people's basic emotions (Blair and Cipolotti, 2000; Adolphs, 2002), especially when these emotions are negative as in the case of fear, sadness, disgust or anger (Adolphs, 2003; Calder et al., 2001). This view is supported by a number of neuroimaging studies reported in Fig. 1 which have found activation in the amygdala. However, as illustrated in Fig. 3, the activated foci are scattered and some of them extend to the hippocampal formation and the temporal pole (Gur et al., 2002a; Hariri et al., 2002b; Hempel et al., 2003; Lange et al., 2003; Phillips et al., 1997, 1998; Wright et al., 2002). Thus, the perception of explicit information about other people's emotional states also involves the amygdala.

It is an acknowledged fact that the perception of emotions is impaired in schizophrenic patients, especially with regard to the recognition of sadness and fear (Bryson et al., 1997; Edwards et al., 2001; Kohler et al., 2003; Sachs et al., 2004; Schneider et al., 1995). It is, therefore, not surprising that such patients exhibit hypo-activation in the amygdala during tasks that involve these emotions (Hempel et al., 2003; Gur et al., 2002b; Phillips et al., 1999). However, two studies have reported elevated activation in the right amygdala during emotion recognition (Kosaka et al., 2002) or fearful and neutral faces observations (Holt et al., 2006). This discrepancy may, logically, be the consequence of group, medication, and subtle task differences. It should also be borne in mind that hyperactivation in the amygdala contradicts the theory that a lesion of the amygdala is associated with a reduction of neural response and an inability to process other people's emotions. It might be better to describe these results as pointing to a dysregulation of the amygdalar response to social stimuli. One hypothesis holds that the influence of the prefrontal cortex may be lacking, with the result that social information is processed in the absence of the information provided by this lobe. Indeed, the orbitofrontal cortex sends inhibitory projections to the amygdala, the temporal pole, and to the non-isocortical insula (Elliott et al., 2000). A neuroimaging study has demonstrated the importance of the prefrontal modulation on amygdalar activity, thus indicating a strong

top-down influence (Ochsner et al., 2002). Moreover, using an emotion reappraisal task, Ochsner and colleagues showed that decreases in self-ratings of experienced negative affects are correlated with reduced amygdalar activity and increased orbitofrontal activity (Ochsner et al., 2004). The abnormal prefrontal activity found in schizophrenic patients during social cognition should result in a dysfunction in the modulatory role of the anterior prefrontal cortex on the amygdala.

Recent advances in our understanding of the neuropsychological and functional role of the amygdala will help us gain a deeper insight into the relation between abnormal emotion perception and mentalization. Studies of patients suffering from amygdalar lesions have demonstrated that these can result in the impairment of more complex social judgments such as the judgment of trustworthiness (Adolphs et al., 1998) and also in a theory of mind deficit (Stone et al., 2003, 2002). In our review of theory of mind research, we found that 25% of neuroimaging studies report activation in this region (see Fig. 1). The studies which reveal such an activation are based on the inference of mental states from eye expressions (Baron-Cohen et al., 1999) or from the trajectories of geometrical shapes (Castelli et al., 2000, 2002; Martin and Weisberg, 2003). In addition, the region adjacent to the amygdala in the temporal pole seems to be involved both in emotion processing and theory of mind. Such results suggest that the amygdala's role in social cognition is not restricted to basic and explicit emotional states but also concerns higher-order non-affective mental states. However, Shaw et al. (2004) have demonstrated that only early damage to the amygdala (during the fetal period) provokes theory of mind impairments, in contrast to the consequences of adulthood lesions of the amygdala. These authors emphasized the role of the amygdala as a pivotal structure involved in the precursors of theory of mind such as shared attention and explicit emotion perception.

At this point, it seems reasonable to suggest that schizophrenic patients suffer from deficits in attributing both epistemic mental states and affective mental states and that this is reflected by abnormal prefrontal and amygdalar activity. Persecutory delusions may arise from an impaired evaluation of social threats (Green and Phillips, 2004) associated with a lack of modulation through the representation of other people's mental states. It would be interesting to investigate social emotions (e.g., shame, pride, and guilt), which represent a more elaborate level of emotion processing because they do not only rely on facial emotion recognition but also on mentalizing. These emotional states cannot be inferred on the sole basis of facial expression, gesture or mimicry. Instead, they make it

necessary to take account of desires, beliefs, and personality traits. We hypothesize that this type of processing involves the medial prefrontal cortex to a greater extent than basic emotion perception does. Furthermore, such a view receives support from the work of Takahashi and colleagues who found bilateral medial prefrontal activations when subjects read sentences conveying guilt and embarrassment compared to neutral stimuli (Takahashi et al., 2004). One prediction might be that patients should also be impaired in social emotion recognition and exhibit an abnormal metabolism in the medial prefrontal region during such tasks.

#### **4. From shared representation to the question of self–other distinction: implication of the inferior parietal lobe**

Recent work on the neural networks underpinning social cognition has emphasized the role of brain circuits which are recruited both for the representation of the self and others. This mechanism accounts for the automatic mapping between self and other (Decety and Jackson, 2004). It is primarily based on perception–action coupling and has been described within the framework of the common coding theory (Prinz, 1997). This theory states that perception of an action should activate one's own action representations to the degree that the perceived and the represented action are similar (Knoblich and Flach, 2003). Furthermore, when two individuals socially interact with one another, this overlap creates shared representations, i.e., neural networks that are temporarily and simultaneously activated in the brains of the two agents (Decety and Sommerville, 2003). The concept of shared representations has been extensively investigated on the basis of motor paradigms (see Decety and Grezes, 2006 for a review). The perception–action coupling mechanism accounts (at least partly) for emotion processing and empathy, as suggested by Preston and de Waal (2002) and Decety and Jackson (2004). In this context, the perception of emotion activates the neural mechanisms that are responsible for the generation of emotions (Adolphs, 2002). Such a system prompts the observer to resonate with the emotional state of another individual, with the observer activating the motor representations and associated autonomic and somatic responses that stem from the observed target, i.e., it is a sort of inverse mapping.

At the behavioral level, evidence has been found for such a mechanism in the recognition of emotion from facial expressions in studies involving healthy volunteers. For instance, viewing facial expressions triggers subtle expressions on one's own face, even in the absence of conscious recognition of the stimulus (Dimberg et al.,

2000; Wallbott, 1991). Likewise, making a facial expression is associated with feeling the corresponding emotion and generates changes in the autonomic nervous system (Levenson et al., 1990).

The finding of paired deficits shared between emotion production and emotion recognition also provides neurophysiological arguments in support of the sharing mechanism. A lesion study involving a large number of neurological patients conducted by Adolphs et al. (2000) found that damage within the right somatosensory-related cortices (including the primary and secondary somatosensory cortices, insula and anterior supramarginal gyrus) impairs the judgment of other people's emotional states when viewing their faces. The same authors also reported that there is an association between impairments to the somatic sensation of one's own body and to ability to judge other people's emotions. A subsequent study of brain-damaged individuals found that recognizing emotions on the basis of prosody is dependent on the integrity of the right fronto-parietal cortex (Adolphs et al., 2002). This result is consistent with the hypothesis that the recognition of emotion in others requires the perceiver to reconstruct images of somatic and motor components that would normally be associated with producing and experiencing the emotion depicted in the stimulus.

A number of dramatic case reports support the idea that similar neural systems are involved both in the recognition and in the expression of specific emotions. For instance, patient S.M., whose amygdala was bilaterally damaged due to a metabolic disorder, was found to be impaired in the recognition of fear from facial expressions as well as in the phenomenological experience of fear (Adolphs et al., 1995). Another case, N.M, who suffered from bilateral amygdala damage and left thalamic lesion was found to be impaired in recognizing fear from facial expressions and exhibited an equivalent deficit affecting fear recognition on the basis of body postures and emotional sounds (Sprengelmeyer et al., 1999). The patient also reported reduced anger and fear in his everyday experience of emotion. There is also evidence for paired deficits in the emotion of disgust. Another interesting case, patient N.K., who suffered left insula and putamen damage, was selectively impaired in recognizing social signals of disgust from multiple modalities (facial expressions, non-verbal sounds, and emotional prosody), and was less disgusted than controls by disgust-provoking scenarios (Calder et al., 2000).

Neuroimaging studies have provided evidence in support of a mechanism of shared emotion processing. Ekman and Davidson (1993) were able to demonstrate similar patterns of electroencephalographic activity for

spontaneous and voluntary forms of smiling. Recently, an fMRI experiment confirmed and extended these findings by showing that when participants are required to observe or to imitate facial expressions corresponding to various emotions, increased hemodynamic activity is detected in the superior temporal sulcus, the anterior insula and the amygdala, as well as in areas of the premotor cortex that correspond to the facial representation (Carr et al., 2003). Disgust is a strong negative emotion that, like fear, carries important survival cues. Phillips et al. have shown that normal volunteers presented with both strong and mild expressions of disgust exhibited activation of the anterior insular cortex but not the amygdala, and that strong disgust was also associated with the activation of structures linked to a limbic cortico-striatal-thalamic circuit (1997). Another fMRI study has extended these findings by showing that similar brain networks are involved in both the recognition (watching video clips of facial expression) and the experience (inhaling odorants) of disgust (Wicker et al., 2003a). The authors found that observing facial expressions and feeling disgust activated the same sites in the anterior insula and anterior cingulate cortex.

Furthermore, the activity of the medial prefrontal cortex, which is modified during theory of mind tasks, is also modulated by self-referential tasks (Gusnard et al., 2001). Thus, it is likely that, at least when we consider brain function at the macroscopic level (i.e., neuroimaging and brain lesion studies), most of the systems involved in attributing mental states to others also underlie the processing of self-related representations. There are two reasons why this intrinsic relation between self and other processing is especially relevant to the understanding of schizophrenia. Firstly, it can provide a parsimonious explanation of why this illness is associated with deficits in social cognition as well as self-representation deficits and impairments of emotional experience. However, the relation between the well-documented reduction of emotional expression in schizophrenia and a putative impairment of emotional experience is currently being debated. For instance, Kring and Neale (1996) observed that schizophrenic patients reported as much positive or negative emotional experience as normal subjects while viewing emotionally charged videos although their emotional expression was diminished. In this study, the patients' skin conductance reactivity was greater than that of controls during positive or negative emotion induction as well as in the neutral condition. This finding has been replicated in similar conditions (Earnst and Kring, 1999) and in role playing situations (Aghevli et al., 2003). Using randomly-paced self-evaluations, other authors have shown that schizo-

phrenic patients experience a greater range of negative emotions and a nearly equivalent range of positive emotions as normal subjects in their everyday lives (Myin-Germeys et al., 2000). Despite the fact that self-reports from patients seem normal, some functional abnormalities in emotional experience appear to exist in schizophrenia. In response to a sadness induction protocol, schizophrenic patients did not demonstrate amygdala activation although their ratings matched those of normal controls (Schneider et al., 1998). Furthermore, Paradiso and colleagues showed that unmedicated schizophrenic patients had reduced blood flows in the amygdala during the evaluation of the emotional valence of pictures (Paradiso et al., 2003). Additional experimental results will be necessary in order to clarify the relation between disturbances in the perception of one's own and other people's emotional experience in schizophrenia.

The second reason for the importance of shared representations in schizophrenic social cognition is that there should be specific computational systems that distinguish between the self and others. This type of source monitoring system prevents us from being contaminated by other people's thoughts or feelings (Decety and Jackson, 2004). Several neuroimaging studies have compared self and other processing using imitation (Chaminade and Decety, 2002), episodic memory retrieval (Lou et al., 2004), and perspective-taking paradigms (Ruby and Decety, 2003; Ruby and Decety, 2001; Seger et al., 2004). These studies have demonstrated the involvement, among other regions, of the right inferior parietal lobule, posterior cingulate, and the right frontopolar cortex. Other investigations have shown that the experience of agency during the production of an action involves the right inferior parietal lobule (Farrer et al., 2003, 2004). For instance, a PET study conducted by Spence et al. (1997) found that normal subjects exhibit a replicable pattern of cerebral activation associated with freely chosen and pre-specified voluntary motor acts. However, schizophrenic patients fail to activate certain components of this motor system (prefrontal and motor areas) normally when engaging in such acts. Patients experiencing passivity exhibit reversible hyperactivation of the right inferior parietal lobule and cingulate gyrus. Both of these regions have previously been found to be involved in the etiology of 'alienation' in organic brain disorders. Interestingly, a recent study involving schizophrenic patients showed that this region is abnormally activated during source monitoring (Farrer et al., 2004), a finding that is consistent with the fact that schizophrenic patients exhibit abnormal source monitoring performances (Haggard et al., 2003; Daprati et al., 1997; Brébion et al., 2000). These results suggest that schizophrenic patients are impaired in

the monitoring of their own actions and/or when they make self/other distinctions.

The exact link between impairments in mentalization and in the distinction between self and others is a matter for debate. While a causal relation (in either direction) between the two is possible, the inability to keep track of the agent associated with mental state representations may clearly lead to a profound impairment in the attribution of mental states. Furthermore, it would be clinically irrelevant to reduce schizophrenia to a parietal-lesion syndrome. While it has been proved that schizophrenia is associated with an impaired sense of agency, experiments have also shown that this impairment occurs when confounding action-feedback is presented to subjects (Daparti et al., 1997). We hypothesize that schizophrenic delusions of control arise when the deficit in agency is combined with abnormal representations of one's own and other people's mental states.

### 5. Links between social cognition and neurobiological abnormalities in schizophrenia

There is evidence that schizophrenic patients exhibit variable social performances at different period of the illness (Edwards et al., 2002; Frith and Corcoran, 1996; Pickup and Frith, 2001) despite the fact that, globally, impairments in emotion perception and theory of mind are not correlated with medication (Kerr and Neale, 1993; Poole et al., 2000; Sarfati et al., 1997a,b). To our knowledge, experimental attempts to test the hypothesis that theory of mind performance is a state variable or a mixed state-trait variable are rare (Drury et al., 1998) and the existence of discrete abnormalities in remitted patients is still poorly documented (Herold et al., 2002).

Discrete cognitive impairments are compatible with the existence of neural abnormalities in several neural regions: the amygdala (Bogerts et al., 1993), as well as in the dorsolateral prefrontal cortex (Selemon et al., 2003). Using computational morphometry, Marcelis et al. (2003) identified several clusters of gray matter reduction in schizophrenic patients compared to control subjects in a number of regions including the cingulate gyrus, the inferior frontal gyrus, the insula, and the amygdala. Other authors have reported abnormalities in the gyrification of the paracingulate cortex in males with early-onset schizophrenia (Le Provost et al., 2003), as well as impairments of the integrity of the cingulum bundle (Kubicki et al., 2003). However, the neuropathology underlying such structural abnormalities remains unclear (Harrison, 1999). In a recent review, Harrison and Weinberger emphasized the existence of a continuous gradient between structural cellular neuropathology associated with

cognitive traits and neurochemical dysregulations leading to psychotic symptoms. This continuum is associated with a wide set of genetic factors (Harrison and Weinberger, 2005). For instance, the catechol-*O*-methyl transferase val158met polymorphism may be considered as a weak but tangible susceptibility factor for the development of schizophrenia (see discussion in Weinberger, 2002).

In line with this view, one hypothesis that may account for changes in symptoms and social cognitive performance is that theory of mind and emotion perception are influenced by the neurochemical status of the patient. This type of observation has also been made in connection with other pathological conditions. For instance, in Parkinson's disease the patient's dopaminergic state, which is partially controlled by the treatment, modulates activity in the amygdala during emotion perception tasks (Tessitore et al., 2002). The same kind of modulation has been replicated in normal subjects asked to perform the same task following the administration of dextroamphetamine which increases dopaminergic levels (Hariri et al., 2002a). In schizophrenic patients, the neurotransmission of dopamine fluctuates during the course of the illness with exaggerated transmission during psychotic states (Abi-Dargham et al., 1998). However, as pointed out by Kapur "schizophrenia is not as simple as abnormal dopamine in a normal brain" (Kapur, 2003, p. 18). While there is widespread agreement that dopaminergic transmission varies considerably during the course of this illness, the clinical expression of these disturbances is modified by cognitive abnormalities specific to schizophrenia which have their roots in genetic factors, early cerebral damage, neurodevelopmental disorders, and, maybe, in the personal history of the individuals.

The cellular effects in the prefrontal cortex resulting from dopaminergic transmission are of extraordinary complexity since the direction of the modulatory effect changes with time, concentration, and with receptor, synaptic and neuronal categories (Seamans and Yang, 2004). Several authors have proposed theories about the relation between abnormal cognition and abnormal dopamine signaling. One view proposes that, at least in rats, the prefrontal cortex receives information from the dopaminergic system that may be related to the error prediction of reward, a signal which is critical to learning mechanisms (Schultz, 1998, 2002). At the cognitive level, it has been hypothesized that increased levels of dopaminergic transmission play a pivotal role in the genesis of psychotic symptoms by interfering with the ability to assign the correct "salience to external objects and internal representations" (Kapur, 2003).

Other authors have suggested that the dopamine signal conveys no information but instead modifies the signal-to-

noise ratio of cortical microcircuits and consequently contributes to the stability of neural representations (Winterer and Weinberger, 2004). Dopamine is released and produces postsynaptic effects that outlast the initial event. Seamans and Yang (2004) have proposed that the balance between D1 and D2 receptor activation may lead to a variation in the capability of the prefrontal cortical maps to modify their stored representations or to stabilize them. We speculate that from a cognitive point of view, dopaminergic transmission may regulate the way that short-term contextual representations are updated in response to the inflow of information (externally or internally generated). As research concerning the dopaminergic

afferences to the prefrontal cortex shows that the anterior cingulate cortex receives a large quantity of such fibers (Allman et al., 2001; Paus, 2001), it is possible that social cognition may be affected by dopaminergic levels, especially when mentalization is performed. The inability to maintain a stable and relevant social context for the processing of one’s own or other people’s mental representations and the impairment of the ability to modify this type of context may arise from acute neurotransmitter disturbances. In Fig. 4, we present an attempt to link the neurochemical dimension with social cognitive knowledge through an oversimplified model, which does not take into account quantitative aspects of dopamine dysregulation.

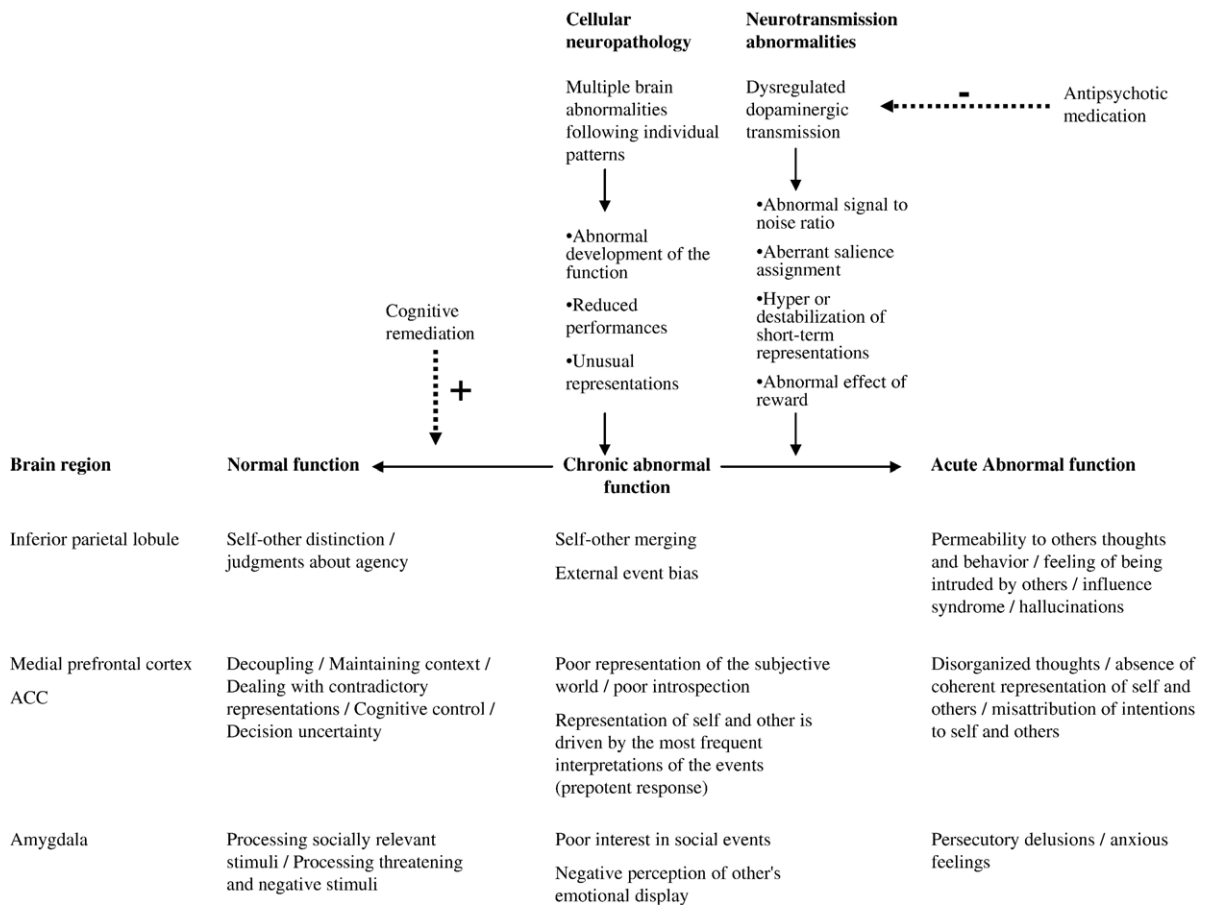


Fig. 4. A model of social cognitive impairments occurring at different stages of schizophrenia. This type of schema emphasizes the complexity of the interaction between impairments of social cognitive subprocesses and neurochemical factors. The arrows represent the mutual influence of the elements in the schema rather than strict causal relations: as we mention in this paper, it is extremely difficult to determine the direction of causal links between psychopathological phenomena occurring in the brain. This scheme confounds dopamine overactivity and underactivity into the term ‘dysregulated transmission’ because the relations between cognitive processes and neurochemical status remain highly speculative. However, it is established that those two extreme neurochemical status lead to different clinical patterns, such as, respectively, positive signs with hallucinations and negative signs with reduced social functioning. Various impairments in the social domain may arise from different levels of dopamine transmission. Two therapeutic strategies are mentioned in this scheme in accordance with their respective psychopathological targets: antipsychotic medication and cognitive remediation. The former should reduce dopaminergic transmission or ideally stabilize it. Remediation aimed at social cognitive processes should reinforce or overcome deficits.

Whatever their causal relations, the convergence of two phenomena, i.e., abnormal social cognition and abnormal neurotransmission, provokes aberrant thoughts about one's own and other people's intentions or emotions. We can also hypothesize that the same impairment occurs in the case of agency judgments. Clearly, these phenomena may result in persecutory delusions and a passivity syndrome. Given that there is a diversity of symptom patterns among schizophrenic patients, different individuals may exhibit different levels of impairment in each of the processes we have described.

## 6. Conclusion

Schizophrenia is a clinical qualification of the mental conditions associated with chronic impairments of volition, thought organization, emotional drive and representation of reality. Within a cognitive neuropsychological framework, which is supported by recent findings in the field of cognitive neuroscience, schizophrenia encompasses disruptions of the ability to represent one's own and other people's mental states including intentions and emotions, and to dissociate accurately between oneself and others. At the neurobiological level, it seems plausible that the variability of these different disorders during the course of the illness is reflected, or maybe caused, by extreme variations of dopaminergic transmission: the abnormal transmission of monoamines should be associated with disturbed stabilization of contextual representations and the persistence of false cognitions. Moreover, it is possible that these chronic or repeated dysfunctions induce long-term changes that can be conceptualized as cortical map distortions (Spitzer, 1995), and that these may result in a vicious circle. Anxiety and discomfort provoked by abnormal thoughts and perceptions lead patients to avoid social interaction, thus reducing their social training and diminishing their opportunity to confront their abnormal cognitions with reality and other people's points of view. As a result, social situations and interpersonal relations may not be pleasant or rewarding, with possible conflicts arising from pathological family or social situations. This lack of a positive motivation for social life (also called social withdrawal) can, in turn, diminish the cognitive resources that are allocated to interpersonal problem-solving during relations with others, and, consequently, further impair the abnormal cognitive processing of social cues.

## Acknowledgments

We would like to thank Philip Jackson for helpful discussions. Eric Brunet-Gouet was supported by the Association Francaise de Psychiatrie Biologique associée

aux Laboratoires Sanofi-Synthélabo, by the Fondation Lilly, and by the Université Versailles-Saint Quentin.

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