



## Neurobiological correlates of theory of mind in psychosis proneness

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### ABSTRACT

Theory of mind (ToM) refers to the capacity to infer one's own and other persons' mental states. ToM abilities are compromised in schizophrenia, in association with dysfunctional activity in predominantly prefrontal brain regions. Prior behavioral studies have also suggested ToM deficits in healthy individuals with psychosis proneness (PP), although no study to date had investigated the associated neural mechanisms in such a sample. Here we used functional magnetic resonance imaging (fMRI) to compare brain activation of subjects with high versus low scores on positive-dimension PP and a ToM task. The ToM task involved first and second order attribution of cognitive and affective mental states to a cartoon character based on verbal and eye-gaze cues. No between-group differences were found on behavioral performance. fMRI analyses revealed a group interaction in anterior prefrontal cortex (BA 10), with the high PP group showing significantly more activity thereof, relative to the low PP, during second order mentalizing than during first order mentalizing. Further between-group differences were observed in dorsomedial and lateral prefrontal regions (BA 46/9), with the high PP group also showing greater activation during second order mentalizing. These results suggest that subjects with positive-dimension PP require more activation of prefrontal areas to adequately mentalize. Differences in the neural mechanisms underlying ToM might be associated with vulnerability to psychosis.

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### 1. Introduction

Theory of mind (ToM) refers to the ability to attribute mental states to others, such as beliefs and desires, enabling us to explain and predict their behavior in order to adaptively function in a social environment. ToM disruptions have been consistently reported in schizophrenia (Bora, Yucel, & Pantelis, 2009). Such deficits have relevant implications for the patients, as they are thought to contribute to impaired social functioning (Brüne, 2005), and to play a role in the genesis of psychotic symptoms of the positive (Frith, 1992; Frith & Corcoran, 1996) as well as of the negative and disorganized dimensions (Sarfati, Hardy-Baylé, Brunet, & Widlöcher, 1999; Sprong, Schothorst, Vos, Hox, & van Engeland, 2007). From a neurophysiological point of view, key regions for ToM in the healthy brain have been identified in the temporal poles, the posterior superior temporal sulcus, and most robustly in the prefrontal cortex (PFC) (Carrington & Bailey, 2009; Singer, 2006). In patients with schizophrenia, a number of imaging studies have documented

abnormal hemodynamic response in several regions involved in ToM, such as medial and lateral portions of the PFC, relative to healthy controls (Brunet-Gouet & Decety, 2006).

The substantial body of evidence for ToM abnormalities in schizophrenia has led to the hypothesis that, albeit more severe in acute phases, mentalizing impairments might be a trait characteristic of the disorder (Bora et al., 2009). However, this hypothesis is still a matter of debate (Pousa, Ruiz, & David, 2008). Impaired ToM performance on the behavioral level has been observed in remitted patients (Bora et al., 2009; Sprong et al., 2007), first-episode schizophrenia (Bertrand, Sutton, Achim, Malla, & Lepage, 2007; Kettle, O'Brien-Simpson, & Allen, 2008), subjects in prodromal phases (Chung, Kang, Shin, Yoo, & Kwon, 2008; although see Couture, Penn, Addington, Woods, & Perkins, 2008 for lack of significant differences), subjects at genetic risk (Irani et al., 2006; Marjoram, Miller, et al., 2006), and healthy subjects who have been psychometrically defined as being prone to psychosis (Langdon & Coltheart, 1999, 2001, 2004; Meyer & Shean, 2006; Pickup, 2006; Platek, Critton, Myers, & Gallup, 2003; Platek & Gallup, 2002; although see Fernyhough, Jones, Whittle, Waterhouse, & Bentall, 2008; Fyfe, Williams, Mason, & Pickup, 2008; Jahshan & Sergi, 2007 for lack of differences). In addition, support for the trait hypothesis has been recently suggested by a meta-analysis of ToM studies in schizophrenia (Bora et al., 2009). The authors concluded that,

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although the accumulated findings of ToM deficits in remitted and non-remitted patients suggest that there is indeed a trait-related ToM impairment in schizophrenia, more careful research is needed to investigate this ability in symptom-free patients and people at risk for developing psychosis.

Schizotypy describes a continuum of personality characteristics and experiences related to psychosis in the general population (Claridge et al., 1996). Schizotypal traits can be psychometrically identified in healthy people (Claridge, 1997; Lenzenweger, 1994; Stefanis et al., 2002). There is evidence to suggest that schizotypal traits fall into a factor organization similar to that in schizophrenia, consisting of positive (e.g., magical ideation, perceptual aberration), negative (e.g., physical anhedonia, social anhedonia), and disorganized (e.g., disorganized speech and behavior) symptom dimensions (Claridge et al., 1996; Kerns, 2006; Liddle, 1987). In fact, several studies that have investigated unaffected relatives of patients and samples from the general population provide compelling evidence for continuity between subclinical (e.g., schizotypal traits) and clinical (e.g., schizophrenia) forms of psychosis. For instance, Vollema, Sitskoorn, Appels, and Kahn (2002) studied relatives of patients with schizophrenia and reported that the risk percentage for the development of schizophrenia was reflected in the score on the positive-dimension scale of a schizotypal personality questionnaire, which suggests that positive schizotypy reflects the biological-genetic vulnerability to schizophrenia. A large general population twin study investigating 3685 individuals, including 1438 complete twin pairs, found evidence for familial resemblance and a genetic effect for both positive and negative schizotypy dimensions as measured psychometrically (Hay et al., 2001), which represented a replication of the results found with clinical samples. Furthermore, Fanous, Gardner, Walsh, and Kendler (2001) reported that positive symptoms in probands with non-affective psychosis were predictive of positive schizotypy in the relatives, while negative symptoms in the probands were predictive of negative schizotypy, which further suggests continuity of psychotic symptoms. Thus, there is evidence for familial, and possibly genetic, homotypy of these psychosis dimensions (Myin-Germeys, Krabbendam, & van Os, 2003).

Schizotypal traits are therefore thought to constitute a range of enduring, biologically determined, personality and cognitive traits that predispose to schizophrenia (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Lenzenweger, 2006). The detection of schizotypal traits in healthy subjects is used as an indicator of *psychosis proneness* (PP) (Meyer & Hautzinger, 2002), which is conceptualized as a subclinical manifestation of the same underlying biological factors of schizophrenia-spectrum disorders (Johns & van Os, 2001; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Indeed, several prospective studies have shown that about 10% of subjects psychometrically identified as psychosis-prone will go on to develop a schizophrenia-spectrum disorder (Chapman et al., 1994; Hanssen, Bak, Bijl, Vollebergh, & Van Os, 2005; Meehl, 1990; see Van Os et al., 2009 for review). A high score on a questionnaire measuring schizotypal personality traits can therefore be conceptualized as a phenotypic marker of risk for schizophrenia (Chapman et al., 1994; Squires-Wheeler, Skodol, & Erlenmeyer-Kimling, 1991). In particular, scales measuring *positive* schizotypy demonstrate characteristics of vulnerability indicators to schizophrenia and schizophrenia-spectrum disorders (Horan, Blanchard, Clark, & Green, 2008).

Research in PP has revealed impairments on measures of emotional, social and cognitive functioning parallel to those of schizophrenia patients (Henry et al., 2009; Horan, Reise, Subotnik, Ventura, & Nuechterlein, 2008; Mohanty et al., 2008; Mohanty et al., 2005; Van't Wout, Aleman, Kessels, Larøi, & Kahn, 2004), as well as in brain function and structure (Modinos, Mechelli, et al., 2010). Thus far there is evidence to suggest a mentalizing

disturbance in people with PP (see Sprong et al., 2007), in line with the notion that it may be an underlying marker of vulnerability. Such evidence has been commonly provided by studies which have not differentiated between symptom dimensions in PP, with the exception of Pickup (2006), who reported significant ToM deficits in association with the positive rather than with the negative dimension. Moreover, subjects with positive-dimension PP (experiencing e.g., unusual beliefs and aberrant perceptions) show elevated social anxiety and poorer social functioning (Brown, Silvia, Myin-Germeys, Lewandowski, & Kwapil, 2008; Kwapil, Barrantes-Vidal, & Silvia, 2008), which is thought to be related to ToM deficits.

Patients with schizophrenia show functional (see Brunet-Gouet & Decety, 2006 for review) and structural brain abnormalities in ToM-relevant regions (Benedetti et al., 2009; Herold et al., 2009; Yamada et al., 2007). Interestingly, a previous fMRI study in individuals at genetic risk for schizophrenia reported abnormal brain activation in prefrontal regions relevant to ToM processing (Marjoram, Job, et al., 2006). In fact, it has been recently suggested that functional and structural abnormalities within brain regions dedicated to self and other-referential processing may be implicated early in the pathophysiology of the disorder (Nelson et al., 2009). To date, however, no study has examined brain activation during ToM in psychosis-prone individuals. Research on such a sample has several strengths, as it allows for the study of mechanisms relevant to psychotic experiences without the confounding factors of medication, illness duration, institutionalization or other consequences of the clinical disorder.

Here we used functional magnetic resonance imaging (fMRI) to examine brain function associated with ToM in a group of individuals with high positive-dimension PP, comparing them with a group of subjects with low positive-dimension PP. In light of recent evidence that tasks involving inference regarding *cognitive* mental states and tasks involving inference regarding *affective* mental states are differentially impaired in individuals with schizophrenia (Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007), we adapted a task that had previously allowed for the study of these components in schizophrenia (Shamay-Tsoory, Shur, et al., 2007). We tested the hypothesis that high positive-dimension PP individuals would show differences in activation, relative to low positive-dimension PP individuals, in prefrontal regions involved in ToM during the correct attribution of mental states, consistent with the one available fMRI study in high-risk relatives of patients with schizophrenia (Marjoram, Job, et al., 2006).

## 2. Materials and methods

### 2.1. Participants

Six hundred undergraduate students were screened with the positive subscale of the Community Assessment of Psychic Experiences questionnaire (CAPE; Stefanis et al., 2002). They all gave written informed consent to complete the CAPE. According to their CAPE scores, 36 subjects were ultimately recruited for the actual fMRI experiment. Eighteen right-handed individuals with a high score on the CAPE positive dimension (above the 75th percentile, as recommended in Konings, Bak, Hanssen, van Os, & Krabbendam, 2006) were assigned to the "high PP" group (10 men, mean age  $19.8 \pm 1.9$  years, range 18–24, mean CAPE positive-dimension score  $1.74 \pm 0.13$ ), and 18 right-handed individuals scoring below the 25th percentile of the distribution were included in the low psychosis-prone group ("low PP"; 10 men, mean age  $21 \pm 2.8$  years, range 18–27, mean CAPE positive-dimension score  $1.12 \pm 0.04$ ). Thus, groups were matched for age, sex, handedness, and level of education. These subjects were screened for exclusion criteria using a self-report checklist for healthy subjects, comprising the following points: (1) no personal history of neurological or psychiatric illness; (2) no family history of psychotic or neurological illness in first-degree relatives; (3) no use of illicit substances; and (4) no changes in overall level of functioning, including academic performance over the past 6 months. All 36 participants gave written informed consent for participating in the fMRI experiment after a detailed explanation of the experimental protocol, approved by the Medical Ethical Committee of the University Medical Center Groningen. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

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