



Theory of mind in patients with schizophrenia: Is mentalizing delayed?

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ABSTRACT

Objective: Functional imaging studies have used numerous neurocognitive designs to investigate brain activation during theory of mind (ToM) tasks in patients with schizophrenia. The majority of studies asks participants to retrospectively attribute mental states to others. We used a novel animated task to investigate implicit mentalizing online. Because behavioral studies have revealed slower ToM performance reaction times in patients with schizophrenia, we hypothesized that time would influence functional MRI (fMRI) activation patterns also.

Methods: We applied the “Moving Shapes” paradigm, which involves two interacting triangles, to a functional MRI block design and investigated the neural activation patterns of 15 patients with schizophrenia and 14 healthy controls. We additionally analyzed the first and second halves of each video separately to assess time-related differences.

Results: Overall, patients with schizophrenia showed increased activation in the inferior and middle frontal gyri, the superior temporal gyrus, the precuneus and the cerebellum compared with controls during ToM versus non-ToM videos. Most importantly, patients with schizophrenia had predominantly increased activation in ToM-related brain areas during the second half of the ToM paradigm, whereas the activation in areas of the ToM-network in healthy controls occurred during the first half of the presentation.

Conclusions: Our results confirm recent findings of significantly stronger neural activations that encompass the fronto-temporo-parietal cerebral areas in patients with schizophrenia compared with controls during ToM tasks. The observation of slower cognitive processing in patients with schizophrenia during mentalizing might explain some of the contradictory imaging findings in these patients and have implications for cognitive remediation.

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1. Introduction

Theory of mind (ToM), the ability to think about mental states such as thoughts and beliefs in oneself and others, is a complex cognitive function that requires the integration of information from multiple sources. Substantial evidence has accumulated that patients with schizophrenia have impaired ToM functions (Sprong et al., 2007; Bora et al., 2009) that result in social-interactive deficits. Whereas phenomenology focuses on the intersubjective experience of patients proposing a disturbance of prereflexive attunement in schizophrenia causing specific psychopathological symptoms, empirical studies have attempted to evaluate impaired social functions on a behavioral level and to correlate specific impairments with

psychopathology, cognitive functions and clinical outcome (Dimaggio et al., 2011; Lincoln et al., 2011; Lysaker et al., 2011a,b; Salvatore et al., 2011; Stanghellini and Ballerini, 2011). Studies on the relationship between psychopathology and ToM functions have shown inconsistent results. Whereas positive, especially persecutory ideas, have been associated with excessive attribution of mental states, impairment in mentalizing (undermentalizing) has repeatedly been related to negative symptoms (Frith, 2004; Lincoln et al., 2011; Lysaker et al., 2011a,b; Montag et al., 2011; Salvatore et al., 2011).

Imaging studies investigating the functional correlates of ToM abilities in healthy controls suggest that a “social” brain network encompasses the superior temporal gyrus (STS), the temporoparietal junction (TPJ), the medial prefrontal cortex (MPFC), the precuneus and, occasionally, the amygdala (Carrington and Bailey, 2009; Van Overwalle, 2009). During ToM task performance, brain activation patterns in the MPFC or the inferior parietal lobe of patients with schizophrenia differ from those of healthy controls. In some studies these brain areas are activated to a weaker extent (Brunet et al., 2003; Lee et al., 2006; Walter et al., 2009).

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On the other hand, patients with schizophrenia featuring hallucinations or delusions revealed stronger activations in the MPFC, right temporal brain areas and the left TPJ but less activation in the cingulate cortex and insula compared with controls during a ToM cartoon task (Bruene et al., 2008). Additionally, Bruene et al. (2011) reported that high-risk individuals with prodromal states of psychosis activated ToM-relevant brain areas, especially the prefrontal cortex (PFC), the posterior cingulate cortex, and the temporoparietal cortex more than healthy controls and patients with schizophrenia. Marjoram et al. (2006) found stronger PFC activations in extreme high-risk relatives of patients with schizophrenia.

Because several subcomponents of ToM (e.g., motion perception, social perception and inferential processes see Brunet-Gouet and Decety, 2006) are differentially involved depending on the task, this inconsistency might lead to divergent functional MRI study results. In addition, most studies of patients with schizophrenia use designs in which participants attribute mental states to others after viewing cartoons or pictures, whereas the Moving Shapes paradigm is an implicit mentalizing task that allows for online investigations of ToM processing. Interestingly, electrophysiological data on early cortical processing in ToM (Wang et al., 2010) imply that participants first collect biological motion information before mentalizing. Cohen and German (2010) reported an advantage in reaction time in healthy subjects for a false-belief task compared with a general location-targeting task, which supports the idea of time-dependent ToM task performance. Moreover, patients with schizophrenia have repeatedly shown slower reaction times compared with healthy controls in ToM tasks (Irani et al., 2006; Walter et al., 2009).

In the Moving Shapes paradigm (Abell et al., 2000), animated geometric shapes that have previously been shown to evoke social interaction descriptions (Abell et al., 2000; Bowler and Thommen, 2000; White et al., 2011) are shown with the following types of interaction: random or no interaction (e.g. drifting), goal-directed or physical interaction (e.g. chasing) and ToM or mental interaction (e.g. coaxing). The paradigm has successfully activated ToM-related brain areas in other imaging studies (e.g., Castelli et al., 2000; Moriguchi et al., 2007). Taking advantage of the online mentalizing characteristics of the paradigm, we also analyzed the first and second halves of the videos separately. We hypothesized that patients would need longer than healthy participants to interpret ToM animations. To our knowledge, this study is the first to investigate the aspect of time in ToM processing among patients with schizophrenia using functional imaging.

2. Methods

2.1. Participants

We recruited 15 inpatients from the Department of Psychiatry at the University of Muenster and the Psychiatric Hospital of the Regional Association of Westphalia-Lippe (LWL) who met the DSM-IV criteria for schizophrenia (SCID-I). The treating clinician confirmed diagnoses with a chart review and consultation. Patients with histories of other psychiatric disorders were excluded from this study. We also recruited 14 healthy control participants. We excluded controls with personal (SCID-I) or family histories of psychiatric disorders from the study. The exclusion criteria for both groups included neurological disorders, brain damage, serious head injury, substance abuse, and any MRI-scan contraindications. All participants had normal vision, were right-handed (Edinburgh Handedness Inventory; Oldfield, 1971) and natively spoke German. These groups did not differ in age, sex, years of education or WAIS-R vocabulary according to the German version of the Wechsler Adult Intelligence Scale (Tewes, 1991). At testing, all patients were stabilized after an acute psychotic episode and psychopathology was rated by the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Table 1 depicts

Table 1

The demographic and clinical characteristics of patients with schizophrenia and controls (raw scores; values are given as the mean \pm SD).

	Patients with schizophrenia (n = 15)	Controls (n = 14)	F/ χ^2	p
Age (years)	29.0 \pm 8.2	29.9 \pm 8.8	0.271	.788
Gender (male:female)	9:6	9:5	0.117	.943
Years of education	11.5 \pm 1.5	11.9 \pm 1.3	0.619	.541
WAIS vocabulary	20.5 \pm 5.6	21.3 \pm 6.0	0.362	.721
Duration of illness (months)	66.6 \pm 75.6	–		
Chlorpromazine equivalent dosage (mg/day)	629.6 \pm 395.0	–		
PANSS total	55.9 \pm 12.2	–		
PANSS positive scale	10.9 \pm 2.8	–		
PANSS negative scale	14.9 \pm 5.4	–		
PANSS general	30.1 \pm 6.5	–		

WAIS = Wechsler Adult Intelligence Scale; PANSS = Positive and Negative Symptom Scale.

demographic and clinical characteristics. All patients received anti-psychotic medications (chlorpromazine equivalent dosages; mean = 629.6 mg/day [SD = 395.0]) at stable doses for at least two weeks before the MRI scan. The following drugs were distributed across patients: amisulpride (n = 2), aripiprazole (n = 4), clozapine (n = 4), flupentixole (n = 2), paliperidone (n = 1), perazine (n = 1), quetiapine (n = 7), risperidone (n = 2), sertindole (n = 1), and some combination of neuroleptics (n = 9). Participants provided written informed consent prior to the study. The local ethics committee approved this study according to the Declaration of Helsinki (1974).

2.2. The Moving Shapes paradigm

The animations in this paradigm depict a small blue triangle and a large red triangle moving across a framed white background. Abell et al. (2000) created the original silent animations, which we edited to 24 s each. We displayed the animations on a projector-mirror system during the scan (Sharp XG-PC10XE with high frequency shielding) to investigate the neural correlates of ToM abilities. The stimuli consisted of three types of animations. The first included ToM animations with interaction that referenced mental states (e.g., coaxing), and the non-ToM animations included random movements (RMs; e.g., drifting) and goal-directed (GD) interaction (e.g., chasing). We applied three different videos for each type of animation. All animations were matched according to length and the absence of an enclosure. Before the MRI scan, participants were informed of the different types of animations and instructed to classify each animation as RM, GD, or ToM immediately after its presentation. Classifications were recorded using bilateral keypads. A 3-s fixation cross separated each trial.

2.3. Verbal ratings of the animations

The animations were presented again after the scans in a random order. Participants' verbal descriptions were recorded and coded with regard to three independent dimensions: (1) intentionality, which conveyed the extent to which mental state terms were used; (2) appropriateness, which reflected description adequacy; and (3) the length of the clauses within each description. The intentionality scores ranged from 0 to 5: a score of 0 indicated that the descriptions reflected no purpose or goal in the agent's actions; 1 signified that the agent acted with a purpose but no interaction; 2 represented an interaction between the agents; 3 indicated that the agents responded to one another's actions; 4 meant that the agents responded to one another's mental states; and 5 indicated that the agent's actions were meant to influence or manipulate the other agent's mental state. Appropriateness was measured on a scale of 0–2 in which

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