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Mentalizing impairment in schizophrenia: A functional MRI study

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ABSTRACT

Background: A deficit in Theory of mind (ToM) or 'mentalizing' has been purported to underlie the poor social functioning seen in patients with schizophrenia. To understand the neural basis of this deficit studies have primarily used tasks requiring 'off-line' or explicit mentalizing but, in daily life, successful social interactions depend upon implicit or 'on-line' mentalizing. Therefore in the present study we used functional neuroimaging and a task that elicits 'on-line' mentalizing to investigate the neural basis of ToM deficits in schizophrenia.
Methods: Functional MRI images were acquired from 20 male patients with established schizophrenia and 19 age and gender matched healthy controls while they watched animated sequences involving two triangles. In the control condition the two triangles moved at random whereas in the experimental condition they moved interactively with implied intentions. The identification of ToM networks and differential responses between groups, within this network, was investigated using a random effects model. To account for differences in educational status between the groups this was included as a covariate in the between group analysis. Correlation analysis was performed to examine the relationship between neural activity change during mentalizing and the clinical and functional outcomes of patients.
Results: Patients with schizophrenia had significantly diminished activity in the right superior temporal gyrus (STG) at the temporoparietal junction (TPJ) and bilaterally within the inferior frontal gyri (IFG). Interestingly, frontal neural activity showed significant correlation with functional outcomes in patients with schizophrenia.
Conclusions: Findings from this novel study suggest that the ToM deficit in male schizophrenia patients may reflect impairment in the automatic or implicit processing of mentalizing. If replicated, this is an important finding that provides additional insight into the neural basis of impairments in social functioning that are experienced by patients with schizophrenia.

1. Introduction

Clinically, schizophrenia is characterized by a range of positive and negative symptoms that are thought to reflect deficits in cognition (Keshavan et al., 2008). Research has therefore understandably focused on executive, attention and mnemonic functions with more recent extrapolation to new domains such as emotional regulation and the processing of reward and salience. Another novel aspect that has attracted increasing research interest in recent years is that of social cognition. This is clearly important with respect to the development of relationships, psychological adjustment and quality of life and consequently, some have conceptualized schizophrenia as a costly by-product of social brain evolution and termed this 'the social brain hypothesis' (Burns, 2006). Within this domain of social cognition a promising area of study is Theory of Mind (ToM), otherwise known as mentalizing.

ToM refers to the cognitive ability of an individual to 'infer the mental states of others' (Premack and Woodruff, 1978) and as such is fundamental to interpersonal communication and essential for achieving social competence. In schizophrenia, ToM neurocognitive deficits have been identified (Brüne, 2005; Harrington et al., 2005) across all subtypes of the illness, in both medication-free (Andreasen et al., 2008), and remitted patients (Marjoram et al., 2006) indicating that social cognition and in particular mentalizing is discernibly compromised and that it is possibly an illness-trait (Harrington et al., 2005; Sprong et al., 2007). A correlation has also been reported between ToM behavioral deficits and functional outcome in patients with schizophrenia (Roncone et al., 2002; Bora et al., 2006). Therefore, understanding of the neural basis of ToM deficits in schizophrenia is of considerable importance.

Functional neuroimaging studies in healthy subjects have found that during mentalizing a sophisticated neural network that encompasses the medial prefrontal cortex (mPFC), precuneus (PC), posterior cingulate cortex (PCC), the superior temporal sulcus (STS), temporo-parietal junction (TPJ) and the anterior temporal poles is activated (Vogeley et

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al., 2001; Gallagher and Frith, 2003; Saxe and Wexler, 2005). In addition by virtue of involvement of the mirror neuron system (MNS) the inferior frontal gyrus (IFG), and inferior parietal lobule (IPL) are also included in this extensive network (Carr et al., 2003; Rizzolatti and Craighero, 2004).

The process of mentalizing is complex and current findings suggest that comprehending the minds of others involves a number of inter-related operations: the more basic, automated, 'implicit' operations of decoding facial expressions, biological motion, and the understanding of actions, and the more controlled cognitively demanding, high-level representations that enable us to reason 'explicitly' the mental states of others (Wolf et al., 2010). In support of this view a growing number of studies have identified differential neural underpinnings for implicit versus explicit reasoning of mental states. Specifically, *implicit* automated components engage the fusiform face area (FFA), STS, IFG, and premotor areas (Allison et al., 2000; Dapretto et al., 2006; Malhi et al., 2008), whereas *explicit* mental state reasoning recruits the mPFC and the TPJ (Saxe and Wexler, 2005; Amodio and Frith, 2006).

To date, neuroimaging studies investigating ToM deficits in schizophrenia have favored the use of explicit or 'off-line' mentalizing tasks in which participants have to retrospectively attribute mental states to others upon explicit instruction to do so. (Russell et al., 2000; Brunet et al., 2003; Andreasen et al., 2008; Brüne et al., 2008; Walter et al., 2009). In reality, ToM inferences in everyday life are automatic and arise implicitly. Therefore tasks requiring deliberate inferences are unlikely to tap into the core processes that underpin real-world social interactions. Hence, in the current study, we use a novel 'on-line' implicit mentalizing task that has been successfully employed previously to examine the neural basis of ToM in autism and bipolar disorder.

We hypothesized that patients with schizophrenia would show a difference in neural activity within ToM network components, and that blood oxygen level dependent (BOLD) activity change in these key regions would correlate with measures of social functioning.

2. Methods

2.1. Subjects

Twenty-three right-handed male patients with schizophrenia (Mean age = 34.5 years, SD = ±8.4) and 22 healthy males (Mean age = 33.5 years, SD = ±8.4), matched with respect to age and handedness participated in the study but data from 3 subjects in each group could not be analyzed (See 3.2 fMRI data), and therefore the sample sizes were 20 and 19 respectively. Exclusion criteria for both groups were a lifetime history of neurological disease, closed head injury or a medical disorder necessitating treatment, and a twelve-month history of substance misuse or dependence. Patients had no additional Axis-I or Axis-II psychiatric diagnoses. A joint hospital and university ethics committee approved the study, and after complete description of the study to the subjects, all participants provided written informed consent.

Diagnosis was assigned by a research psychiatrist using the Structured Clinical Interview for DSM-IV (SCID-P) (First et al., 1995) and all subjects fulfilled criteria for schizophrenia. Clinical symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1986). Social functioning was assessed by using the Life Skills Profile (LSP) (Rosen et al., 1989). Patients with schizophrenia had a mean duration of illness of 9.4 years (SD = ±6.5). On the PANSS, the mean score for negative symptoms was 18.2 (SD = ±5.2) and for positive symptoms 10.1 (SD = ±3.0). Further, at the time of scanning, four patients were on lithium (mood stabilizer), nine were on sertraline (antidepressant), and all except one were on antipsychotic medications.

2.2. Stimuli and task design

The study employed an animated task designed to capture '*on-line*' implicit aspects of mentalizing. The task involved the attribution of mental states to moving geometric shapes that have previously been used in both behavioral and imaging studies to investigate ToM deficits in autism and bipolar disorder (Castelli et al., 2002; Malhi et al., 2008). Participants viewed 16 blocks of silent animation using two triangles, a big red triangle and a small blue triangle, moving about the computer screen against a framed white background (Castelli et al., 2000). Two types of animations were used: four ToM animations in which the two triangles mimicked human behavior such as *bluffing*, *persuading*, *surprising* and *mocking* one another, and four control animations in which the two triangles moved randomly such as drifting and bouncing off the walls with no meaningful interaction between them. Each animated sequence lasted 36 s and between adjacent animation sequence blocks there was a six-second fade-in/fade-out segment. The four distinct ToM and four random-motion sequences were each presented twice. The ToM conditions were counterbalanced while still alternating these with the random-motion presentations. The ToM and random-motion animated sequences were matched as closely as possible for basic visual characteristics such as overall speed, shape and orientation (Castelli et al., 2000).

Prior to scanning each participant was instructed as follows: "You will see two triangles on the screen. One triangle will be larger than the other and both will move around with respect to each other. You will need to observe carefully how both triangles move around the screen and interact with each other and we will be asking you some questions about what you have been shown following the scan." Immediately following the MRI scanning session, patients were again shown the animated stimuli and asked: "What was happening in the animation?" The verbal descriptions were noted and rated using specific criteria (Castelli et al., 2002) on two dimensions. The first, 'intentionality', captures the degree of appreciation of mental states and is rated from 0 (appreciation of a non-deliberate action) to 5 (appreciation of a deliberate action aimed at affecting another's mental state). The second dimension, 'appropriateness', assesses how well the underlying script in an animation is understood and is rated from 0 (in the event of no answer or a response of 'don't know') to 3 (an appropriate, clear answer). The complete procedures and full details for scoring have been published previously (Castelli et al., 2000).

2.3. fMRI acquisition

Imaging was performed on a 3T Siemens Trio scanner. Twenty-eight axial slices (5 mm thickness, no gap) parallel to the anterior and posterior commissure covering the whole brain were imaged using a T2*-weighted gradient echo EPI sequence: TE = 35 ms; TR = 3000 ms; matrix = 64 × 64; flip angle = 90°; and FOV = 240 mm, inplane resolution = 3.75 mm. For each functional run a total of 224 whole brain scans were collected. For anatomical reference, high-resolution whole brain images were also acquired: TR = 1570 ms; TE = 3.22 ms; flip angle = 15°; and matrix 512 × 512 × 192. Movement was minimized using a foam pad and an fMRI compatible eye movement system was used to ensure that participants attended to the stimuli, and in particular, did not close their eyes during the experiment.

2.4. Data analyses

2.4.1. Behavioral data analysis

Independent t-tests were performed, using SPSS (version 16.0), to compare the two groups with respect to demographics, and ratings of ToM stimuli for *intentionality* and *appropriateness*.

2.4.2. fMRI data analysis

Images were pre-processed using Statistical Parametric Mapping Version 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm). For each subject, images were first corrected for susceptibility-by-movement artifacts and then realigned to the first volume of the time series. The high-resolution structural MR image was then aligned to the mean of the T2*-weighted