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Mentalizing in schizophrenia: A multivariate functional MRI study

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ABSTRACT

Schizophrenia is associated with mentalizing deficits that impact on social functioning and quality of life. Recently, schizophrenia has been conceptualized as a disorder of neural dysconnectivity and network level analyses offers a means of understanding the underlying deficits leading to mentalizing difficulty. Using an established mentalizing task (The Triangles Task), functional magnetic resonance images (fMRI) were acquired from 19 patients with schizophrenia and 17 age- and sex-matched healthy controls (HCs). Participants were required to watch short animations of two triangles interacting with each other with the interactions either random (no interaction), physical (patterned movement), or mental (intentional movement). Task-based Partial Least Squares (PLS) was used to analyze activation differences and commonalities between the three conditions and the two groups. Seed-based PLS was used to assess functional connectivity with peaks identified in the task-based PLS. Behavioural PLS was then performed using the accuracy from the mental conditions. Patients with schizophrenia performed worse on the mentalizing condition compared to HCs. Task-based PLS revealed one significant latent variable (LV) that explained 42.9% of the variance in the task, with theLV separating the mental condition from the physical and random conditions in patients with schizophrenia, but only the mental from physical in healthy controls. The mental animations were associated with increased modulation of the inferior frontal gyri bilaterally, left superior temporal gyrus, right postcentral gyrus, and left caudate nucleus. The physical/random animations were associated with increased modulation of the right medial frontal gyrus and left superior frontal gyrus. Seed-based PLS identified increased functional connectivity with the left inferior frontal gyrus (liFG) and caudate nucleus in patients with schizophrenia, during the mental and physical interactions, with functional connectivity with the liFG associated with increased performance on the mental animations. The results suggest that mentalizing deficits in schizophrenia may arise due to inefficient social brain networks.

1. Introduction

Schizophrenia is associated with marked deficits on a wide range of cognitive measures, including those assessing social cognitive ability (Bilder, 2009; Gur et al., 2007; Kalkstein et al., 2010; Nuechterlein et al., 2004). Theory of mind (ToM), an aspect of social cognition, refers to the cognitive ability of inferring agency, intentions, and beliefs that oneself and others hold. Several converging lines of research have identified deficits in ToM in patients with schizophrenia (Brune, 2005; Harrington et al., 2005) and explored the underlying neural architecture of these deficits (Sugranyes et al., 2011). Although the relationship between ToM and other neurocognitive domains awaits full explanation (Carrington and Bailey, 2009), specific regional activation differences when performing ToM tasks (Adolphs, 2009), coupled with behavioural evidence for distinct cognitive processes (Mehta et al., 2013), suggest an independent role for ToM in understanding the cognitive dysfunction observed in schizophrenia.

ToM is a broad concept that has been measured using a multitude of tasks. One aspect of ToM thought to be relatively free of other cognitive demands, is implicit ToM ability (Frith and Frith, 2008). ToM can be considered to consist of both automatic, inflexible, implicit responses and thoughtful, mentally demanding explicit processes. Implicit ToM or mentalizing has been measured primarily using tasks that require viewing animated objects and inferring intention (Uddin et al., 2007). One such task is The Triangles Task (Castelli, Happe et al., 2000) that requires participants to watch an animation consisting of

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two triangles interacting in one of three ways; random, physical, or mental. Patients with schizophrenia performed significantly worse than controls at selecting the appropriate label for the animation, with deficits also observed in labeling the emotional content of the animations (Russell et al., 2006). A functional neuroimaging study identified regional activation differences in patients with schizophrenia while performing The Triangles Task, including the right superior temporal gyrus, temporoparietal junction, and bilateral inferior frontal gyri (Das et al., 2012a). To date, the only multivariate approach has employed independent components analysis (ICA), which determines the intrinsic networks independent of task and then investigates differences between the conditions of interest on these predetermined networks. Using this approach, Das et al. (2012b) identified reduced activity in patients with schizophrenia during the ToM condition, in lateralized fronto-temporal and insula networks, in addition to reduced suppression of the default mode network and a medial frontal network across all conditions.

Although ICA represents an excellent approach to understanding intrinsic brain networks, Partial Least Squares (PLS) allows for the analysis of a network of regions constrained based on task requirements (McIntosh et al., 1996). This method allows for the assessment of neural commonalities and differences within experimental conditions and between groups. Several lines of research have proposed that the integration and segregation of neural circuits are key components of efficient cognition (Fornito et al., 2015; Sporns et al., 2005), with evidence that disruption of this segregation and integration may lie behind the cognitive dysfunction associated with schizophrenia (Pettersson-Yeo et al., 2011). As ToM is a complex higher order cognitive ability subserved by a dynamic network of inter-related regions (Adolphs, 2009; Das et al., 2012b; Mohnke et al., 2015), this approach may further the identification of structure-function correlates in healthy and clinical groups such as schizophrenia. Previous studies have not incorporated all conditions of the Triangles Task into the fMRI analyses (Das et al., 2012a, 2012b). Although contrasting the mental condition with the random condition may provide hints at the social brain network important for mentalizing, a more nuanced analysis should include the physical (or goal-directed) condition, as this controls for patterned or complex interaction without a mental component. Previous studies may have omitted this condition to simplify their analysis, but an approach like PLS allows for task complexity to be simplified within the analysis by reducing the data to latent variables able to explain the variance inherent in the data. Furthermore, PLS allows us to explore brain-behaviour relations; behavioural data has not previously been analyzed in parallel with imaging, this type of analysis has the potential to identify the underlying aberrant neural connectivity directly associated with mentalizing deficits in patients with schizophrenia.

In line with previous studies, we predicted that behavioural and neural differences would be identified between patients with schizophrenia and healthy controls. Specifically, we hypothesized that patients would perform worse on matching the intention-type with the animation, especially for the animations displaying mental interaction. Moreover, PLS analysis would identify neural commonalities between the three conditions, but crucially, would identify unique neural representations associated with mentalizing compared with the goal-directed or random interactions. Peaks associated with the mental condition will be further investigated using seed-based and behavioural PLS to investigate whole-brain functional connectivity differences with these regions in patients with schizophrenia and in association with accuracy on the mental condition. These differences were expected to be in key 'social brain' regions, such as the medial prefrontal cortex, inferior frontal gyri, temporoparietal junctions, and superior temporal gyri.

2. Methods

2.1. Participants

Nineteen patients with schizophrenia were recruited from the Queensland Centre for Mental Health Research (QCMHR). Individuals were comprehensively ascertained by trained clinicians using: (i) the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) (ii) Family Interview for Genetic Studies (FIGS) (Gershon et al., 1988; Maxwell, 1992); (iii) information extracted from all available medical records; (iv) Narrative summary prepared by the interviewer and based on all information obtained from the DIGS, FIGS and medical records. The narrative summary was invaluable in recording the first-hand impressions of the interviewer. This facilitated diagnostic assessment by augmenting the DIGS interview information, especially when the participant's responses lacked clarity; (v) Best Estimate Final Diagnosis (BEFD) (Leckman et al., 1982) was assigned by two experienced research psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis; one of us (BM) reviewed every case. Diagnostic inter-rater reliability was assessed using standard procedures (Suarez et al., 2006). Age and sex matched Healthy Controls (HCs) (N=17) were also recruited through QCMHR. The HCs had no history of psychiatric or neurologic illness.

2.2. Intelligence testing

Full-scale IQs were ascertained using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), which comprised four subtests (Vocabulary, Similarities, Block Design, Matrix Reasoning). IQ assessments were carried out by a trained researcher (AM) and a trained psychiatric nurse, under the supervision of a clinical neuropsychologist (GR).

2.3. Behavioural statistical analysis

All analyses were carried out in SPSS version 20.0.0. Accuracy scores were calculated for each participant in each of the 3 conditions (out of 4) plus total correct (out of 12). Number of each interaction type selected was also compared between groups. A repeated measures Analysis of Variance (RM-ANOVA) was used to assess specific differences across conditions (random, physical, and mental) across the two groups (HCs and SZ). Independent samples *t*-tests were also used to assess differences between groups on the individual measures. Pearson's correlations were employed to investigate association between IQ and brain activation.

2.4. fMRI behavioural task and procedure

The Triangles Task (Castelli et al., 2000) is a measure of mentalizing used in previous fMRI studies with patients with schizophrenia (Das et al., 2012a, 2012b; Pedersen et al., 2012). It involves viewing animations consisting of a large and small triangle interacting on a screen for a period of 36 seconds. Following each animation was a rest period of 15 seconds in which time the participant was prompted to make a judgment as to whether the interaction was a) random – no meaningful interaction b) physical – the actions or movements of one triangle are dependent on the other triangle or c) mental – the triangles interact in such a way that it appears that one triangle is trying to influence or manipulate the thoughts or emotions of the other triangle. Prior to the fMRI, all participants viewed one example of each condition to familiarize them with the task. Four videos per condition were presented, resulting in a total of 12 videos.

Participants completed the task while undergoing an MRI scan; the videos in the task were presented using E-Prime software (https://www.pstnet.com/eprime.cfm) on a computer screen that was seen by