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Mentalizing in male schizophrenia patients is compromised by virtue of dysfunctional connectivity between task-positive and task-negative networks

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Abstract

Schizophrenia can be conceptualized as a disorder of functional connectivity within the fronto-temporal (FT) and/or default-mode (DM) networks. Recent evidence suggests that dysfunctional integration between these large neural networks may also contribute to the illness, and that the ability to *mentalize* or have a '*theory of mind*' (ToM) is discernibly impaired in patients with schizophrenia. Hence in this study, we examined whether impaired functional network connectivity (FNC) contributes to a compromise in the ability to mentalize in patients with schizophrenia. Functional magnetic resonance imaging data were acquired from 20 male schizophrenia patients and 19 matched healthy controls whilst performing a well-known ToM task. The study revealed that relative to non-ToM the engagement of ToM produced reduced neural activity in the lateral FT and insula networks in patients, as compared to healthy subjects. The findings also indicated that in comparison to healthy subjects the DM and medial FT networks are *less* suppressed in patients irrespective of the task (ToM/non-ToM). Further, FNC analyses showed that the degree of functional connectivity between task-positive (lateral FT and insula) and task-negative (medial FT, posterior DM) networks was significantly *reduced* in patients as compared to controls. Of note, a significant correlation between the functional connectivity strength of the lateral FT network with the medial FT and the degree to which this is modulated by the ToM task, suggest that mentalizing deficits in male schizophrenia patients may stem from

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Contributors: Authors Malhi and Das conceptualized the analysis;
Author Das performed the data analyses with assistance from author Calhoun and wrote the initial draft of the manuscript;
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impaired communication between neural networks that comprehend the mental states of self (medial FT) and others (lateral FT).

Keywords

functional network connectivity; FNC; independent component analysis; ICA; fMRI; schizophrenia; theory of mind

Introduction

Phenotypically, schizophrenia is a heterogeneous psychiatric disorder of neurodevelopmental origin (Murray and Lewis, 1987) that stems from disturbances in brain circuits and neurotransmitter systems (Weinberger, 1987). Likewise genetically, schizophrenia appears to be a complex trait that manifests via equally complicated endophenotypes (Flint and Munafo, 2007). However, clinically, one of its characteristic features is a diminished ability to empathise with others (Bleuler, 1950). This capacity to appraise the internal state of others is broadly referred to as '*mentalizing*', and is often used interchangeably with the term "*Theory of Mind*" (ToM) (Premack and Woodruff, 1978) even though technically mentalizing has both emotional and cognitive components whereas ToM places greater focus on the cognition. Consequently, ToM is applied more specifically to the appraisal of others as opposed to one's self however, with the conceptualization of the mirror neuron system (MNS) ToM is now also thought to involve self-attribution. Therefore, mentalizing is actually the process by which ToM is acquired.

Applying these concepts somewhat broadly a growing number of neuropsychological studies indicate that ToM is perhaps impaired in schizophrenia (Bora et al., 2009; Brüne, 2005; Harrington et al., 2005), but few studies to date have used neuroimaging to identify the neurobiological substrate of any such impairment (Andreasen et al., 2008; Brüne et al., 2008; Brunet et al., 2003; Das et al., 2012; Russell et al., 2000; Walter et al., 2009). Those studies that have used functional MRI (fMRI) have relied primarily on the general linear model (GLM) to identify the brain regions that show task-related neural activity differences between healthy controls and schizophrenia patients. This approach is appropriate for localization but does *not* allow the identification of 'interconnectedness' *per se*, between functionally related brain regions, or networks and this is critical because current cognitive and affective models of impairment in schizophrenia suggest that the illness stems from abnormal functional connectivity (FC) between distant brain regions (Andreasen et al., 2008; Calhoun et al., 2009; Das et al., 2007; Friston and Frith, 1995; Garrity et al., 2007). Encompassing some of these regions is the fronto-temporal (FT) network, which includes both ventral and dorsal areas of the medial (MPFC) and lateral (LPFC) prefrontal cortices and superior temporal lobe (Friston and Frith, 1995; Wolf et al., 2007). This network is thought to have a pivotal role in schizophrenia but in recent years, the focus of research has shifted towards the 'default-mode' (DM) (Raichle et al., 2001) network (Bluhm et al., 2007; Calhoun et al., 2009; Garrity et al., 2007; Zhou et al., 2007), which by virtue of being more active during rest than during active cognitive processes is thought to provide the neural substrates of task-independent self-relevant information processing. Like the FT network the

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DM network also involves the MPFC that in turn includes the ventral anterior cingulate cortex (ACC). Other brain regions attributed to the DM network include the posterior cingulate cortex (PCC) extending as far as the precuneus (PC), and the lateral parietal cortex (Raichle et al., 2001). Abnormal activity and connectivity within the DM network in patients with schizophrenia has been identified (Bluhm et al., 2007; Calhoun et al., 2009; Garrity et al., 2007; Zhou et al., 2007). Interestingly, fMRI studies in healthy subjects have found that regions of the DM and FT networks such as MPFC, PC, PCC, the superior temporal sulcus (STS), temporo-parietal junction (TPJ) also contribute to mentalizing (Frith and Frith, 2003; Gallagher and Frith, 2003; Saxe and Wexler, 2005; Vogeley et al., 2001).

Consequently, the traditional view of schizophrenia as a disorder of functional connectivity *within a network*, is being revised and the disorder is being conceptualised as emerging from dysfunctional integration *among neural networks* that are spatially independent but functionally correlated (Demirci et al., 2009; Jafri et al., 2008). In support of this perspective, changes in the functional network connectivity (FNC) 'between' the major networks of the brain have been identified in patients with schizophrenia both at rest (Jafri et al., 2008), and when engaged in cognitive tasks (Demirci et al., 2009). One possible explanation for this is that in order to remain alert and attuned to changes in the external and internal environments the brain repeatedly toggles between "task-positive" and "task-negative" (or task-independent) oriented modes (Fransson, 2005; Raichle et al., 2001). Naturally any functional impairment within either mode, or between the two can impair essential information processing (Eichele et al., 2008; Fox et al., 2005).

In the current study, we set out to investigate whether ToM deficits in male patients with schizophrenia are due to impaired functional connectivity among task-positive and task-negative networks. In order to do this we used fMRI and a well-established ToM task. The details of this study are described in full in an earlier publication in this journal (Das et al., 2012) however, for convenience we have provided a detailed outline.

Subjects and methods

Participants & Clinical Assessment

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 on the basis of age and handedness participated in the study. Data from three subjects in each group could not be analysed (failure to complete task/movement artefact) and therefore the sample sizes for analysis were 20 and 19 respectively. Inclusion criteria for the study were that participants must be male, between 18-50 years of age, right handed, and able to give informed consent. Patients were also required to have a primary diagnosis of DSM-IV schizophrenia with no additional Axis-I/Axis-II psychiatric diagnosis. Exclusion criteria included: history of neurological disease, closed head injury, medical disorder necessitating treatment or a history of substance misuse. All participants provided written informed consent according to the Hospital and University ethics committee's protocols. A diagnosis of schizophrenia was assigned using the structured clinical interview for DSM-IV (SCID-P) (First, 1995) and clinical symptoms were rated using the positive and negative syndrome scale (PANSS) (Kay, 1986). Insufficient information in relation to duration of illness and clinical

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symptomatology was recorded on three patients. The remaining 17 patients had a mean illness duration of 9.4 years (SD = ±6.5) and scored 18.21 (SD = ±5.2) on the PANSS negative symptom subscale and 10.05 (SD = ±3.0) on the PANSS positive symptom subscale. Of those that underwent scanning all except one were taking antipsychotic medications and in addition, four patients were taking lithium and nine were taking sertraline. The latter two medications were prescribed for the treatment of mood symptoms in the context of schizophrenia.

fMRI task

The task used in this study has previously been used to investigate ToM deficits in schizophrenia (Das et al., 2012), bipolar disorder (Malhi et al., 2008), and autism (Castelli et al., 2002). This task is designed to capture the implicit components of mentalizing. It comprises a series of silent animations of two triangles, a large red triangle and a small blue triangle (Castelli et al., 2000) and involves the attribution of mental states to these moving shapes. Participants viewed two types of animations: those involving ToM and those not involving Tom, referred to as non-ToM. In ToM animations the two triangles mimicked human behaviour such as bluffing, persuading, surprising and mocking one another, whereas in non-ToM animations the triangles drifted and bounced off the walls randomly with no meaningful interaction between them. In total, participants viewed 16 blocks of animation, in which four distinct ToM and four random-motion (non-ToM) sequences were each presented twice. Each animated block lasted 36s and between juxtaposed animation blocks there was a six-second fade-in / fade-out segment. The ToM conditions alternated with non-ToM but were still counterbalanced. 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 further details for scoring have been published previously (Castelli et al., 2000).

Functional MRI Acquisition Parameters

Images were acquired using a 3T Siemens Trio scanner. Twenty-eight consecutive axial slices (5mm thickness with no gap) parallel to the anterior and posterior commissure covering the whole brain were imaged using a T2*-weighted gradient echo EPI sequence:

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TE = 35 ms; TR = 3000 ms; matrix = 64 × 64; flip angle = 90°; FOV=240mm, in-plane resolution = 3.75mm. For each functional run a total of 224 whole brain scans were collected. For anatomical reference, a high-resolution T1 weighted image was also acquired: TR = 1570ms; TE = 3.22 ms; flip angle = 15°; matrix 512 × 512 × 192.

fMRI Data Analysis

Analysis overview

First, 20 spatially independent but temporally correlated networks were determined from the pre-processed data of all participants using independent component analysis (ICA) (Calhoun et al., 2001b). This analysis captures the complex nature of fMRI data and produces consistent spatial components or networks (Turner and Twieg, 2005). Second, components for FNC analysis were selected by virtue of fulfilling one of two criteria: either component represented the DM or FT network or it displayed significantly differential modulation by the ToM task in the two groups. Third, FNC among these chosen networks was calculated for each subject and significant differences between groups in FNC were then identified. Finally, in order to understand whether any impairment in FNC contributes to ToM deficits, the relationship between FNC strength and the degree of modulation by the ToM task (compared to non-ToM task) was investigated.

a) Pre-processing—Pre-processing was performed using statistical parametric mapping (SPM5, version 958) (http://www.fil.ion.ucl.ac.uk/spm). Each subject's functional and structural images were first visually inspected for scanner artifacts and gross anatomical abnormalities, and then re-oriented so that the image origin lies within 3cm of the anterior commissure (AC). For each subject, images were first corrected for susceptibility-by-movement artefacts 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 functional images and then spatially normalized to the Montreal Neurological Institute (MNI) template. Parameter estimates determined from the spatial normalization of the structural image to the MNI template were then applied to spatially normalize functional images to the MNI template. The normalized functional data were then smoothed using a Gaussian smoothing kernel of 8mm full-width at half-maximum (FWHM) to improve the signal to noise ratio. Following spatial normalization, the data (originally acquired at 3.75 × 3.75 × 5 mm^3) were slightly subsampled to 3 × 3 × 3 mm^3, resulting in 53 × 63 × 46 voxels.

b) Identification of components that showed ToM related activity differences between groups—Group spatial ICA analysis was performed using the GIFT Toolbox, version 2.0d (http://icatb.sourceforge.net) on the data of all participants to identify 20 spatially independent networks. A complete description of the methods implemented in ICA has been published (Calhoun et al., 2001a; Calhoun et al., 2001b) but briefly, the time series data for each participant was first reduced by using principal components analysis (PCA), and then the data from all participants was temporally concatenated and further reduced by PCA. A group ICA was then performed on all the subjects at once using the infomax algorithm (Bell and Sejnowski, 1995). To ensure reliability of the components, the ICA algorithm was run 20 times using ICASSO software (http://www.cis.hut.fi/projects/ica/icasso). The resulting output is an independent component (IC) spatial map and a single

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associated ICA timecourse for every component and subject. Components were then spatially reconstructed and visually inspected for artifacts. To visualize the spatial maps of a component, all subjects' maps for that particular component were entered into a random-effect analysis model (1 sample t-test in SPM5). Brain regions were considered to be within each network if they met a height threshold of $p < 0.00001$ corrected for multiple comparisons using the family-wise error (FWE) and an extent threshold of 50 voxels.

To identify components that have shown experimental task relevance, a regression was performed on the ICA component time-course with the general linear model (GLM) design matrix taken from SPM5. This design matrix represents a combination of the experimental onsets convolved with a canonical hemodynamic response function. This resulted in a set of beta weights for every experimental regressor (ToM, non-ToM) associated with a particular subject and component. Beta weight associated with a particular regressor shows how much that component has been modulated by that regressor or task. To identify components that have been significantly differentially modulated by the contrast condition (ToM - non-ToM) in a group, first beta weights associated with the contrast were computed for each subject and then entered into a one sample t-test and thresholded at $p<0.05$. To identify among these components those that were significantly different between groups, differences in beta weights were entered into a series of two sample t-tests.

c) Components chosen for FNC analysis—Components that showed significant differences between groups in ToM activity along with FT and DM networks were chosen for the analysis.

d) Group differences in FNC—The procedure described by Jafri et al. (Jafri et al., 2008) was followed to determine FNC. For each subject, the time-series associated with the selected n components were extracted, temporally filtered via a band pass filter of 0.017-0.067 Hz, and paired to form n!((n-2)!*2) combinations. Correlations between pair-wise combinations were then calculated using a lagged-correlation approach where the lag was specified as ±6s. The maximal positive correlation value and corresponding lag were saved for each time course pair and later correlation values were transformed to a z-score. Correlation and lag values were averaged separately for control and patient groups, and a functional network connectivity map for each group was created. Significant correlations (corrected for multiple comparisons using a false discovery rate, $p<0.05$) were determined by using non-parametric tests.

To identify group differences in correlations, two sample t-tests were computed, and p-values were determined using a non-parametric permutation approach. For each component combination, a null distribution of group mean differences was created by randomly re-sampling 39 participants into two groups for 5000 times and calculating the group difference each time. An adjusted p-value was then created by calculating the percentage of times the null representation was higher than the observed mean difference, and a significant difference was determined by thresholding at $p<0.05$.

e) Relation between FNC strength and ToM activity—In order to understand whether impaired FNC contributes to ToM impairment in patients with schizophrenia FNC

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strengths shown to be significantly different between the groups (from step d) were correlated with the beta weights associated with the experimental contrast (ToM – non-ToM) for the components that have showed ToM related activity differences between groups (from step b).

Results

Identification of components that showed ToM related activity differences within and between groups

In both control and schizophrenia groups the within group analysis (ToM compared to non-ToM task) produced significant increased activity in the lateral visual (IC8), lateral FT (IC11), and occipito-temporal (IC12) networks and decreased activity in the medial visual (IC2) network (Table 1, Figure 1). Additional increased activity in the insula (IC5) network and decreased activity in the medial FT (IC20) (Table 1, Figure 1) was found only in controls. The between group (controls versus schizophrenia) analysis of differences, comparing ToM and non-ToM task activity, found less positive modulation of the lateral FT (IC11) ($t = 2.5$, $p < 0.02$) and insula (IC 5) ($t = 2.3$, $p < 0.03$) (Figure 2) networks in patients with schizophrenia compared to controls.

Components that represented FT and DM networks

Components 9, 10 represented the anterior and posterior DM respectively (Table 2, Figure 3). Components 11 and 20 represented the lateral and medial FT networks respectively (Table 1, and Figure 1). Default mode networks did not show significantly different modulation by ToM compared to non-ToM tasks but fronto-temporal networks did. Both groups showed significantly greater positive modulation of the lateral FT (IC11) network by the ToM task relative to non-ToM task and this modulation was greater in controls (Figure 2). Significantly greater negative modulation (or suppression) of medial FT (IC20) network by ToM (relative to non-ToM) was seen only in controls (Figure 1). Irrespective of task (ToM or non-ToM) two DM networks, anterior (IC9) and posterior (IC10), and also medial FT (IC20) network were significantly less suppressed in patients compared to controls (Figure 3).

Between group differences in FNC

In both groups a total of ten calculated component combinations (each combination represents coupling between two networks) displayed significant coupling. Among them three sets of coupling were significantly different between groups with controls displaying greater coupling than patients. Coupling 1: between the Insula (IC5) and posterior DM (IC10) networks; coupling 2: between the lateral FT (IC11) and medial FT (IC20) networks; and coupling 3: between the posterior DM (IC10) and medial FT (IC20) networks (Figure 4). These three sets of coupling were all significantly positively correlated among themselves. Correlation between coupling 1 and 2 were ($r = .319$, $p=0.048$), coupling 1 and 3 were ($r = .566$, $p = 0.0005$), and coupling 2 and 3 were ($r = .503$, $p = 0.001$).

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Relation between FNC connectivity strength and the degree of modulation by the ToM task (compared to non-ToM task)

A significant correlation (r = 0.351, p=0.028) between the functional connectivity strength of the lateral FT network (IC11) with the medial FT network (IC20) (Coupling 2) and the degree to which this network (lateral FT displayed strongest modulation by ToM task in both groups) was modulated by the ToM task was observed.

Discussion

A key feature of schizophrenia is the compromise experienced by patients in their ability to mentalize and thereby understand social interactions. This study investigated whether this putative impairment is a result of *miscommunication* between spatially independent but temporally correlated large networks of the brain. Findings from this study suggest that in male schizophrenia patients this deficit is perhaps related to functional impairment between task-positive and task-negative networks.

The most significant difference between groups was seen in the lateral FT (IC11) network. Among all computed networks this network showed strongest modulation by the experimental contrast (ToM – non-ToM) in both patients and controls. Within this network robust activation was seen in the inferior frontal gyrus (IFG), superior temporal gyrus (STG) including temporo-parietal junction (TPJ), and precuneus (PC). This result is consistent with our earlier findings (Das et al., 2012) (using GLM in these same subjects) of reduced activity in the IFG and STG in patients with schizophrenia compared to healthy controls during ToM engagement. Among the activated regions of this network the STG showed the most significant activity. Interestingly, activity within the STG is implicated in reasoning concerning the contents of another person's mind (Saxe and Kanwisher, 2003). Maximum activity in this network in response to an implicit ToM task is consistent with the suggestion that the implicit automated component of ToM recruits the IFG while explicit mental state reasoning recruits the MPFC (Wolf et al., 2010). Of note, the IFG is also a component of MNS, an observation execution matching system that is thought to provide a neural mechanism for automatically understanding the actions and intentions of others (Rizzolatti and Craighero, 2004).

Diminished responsiveness in these key brain regions in patients as compared to controls when attempting to mentalize, coupled with reduced activity in the insula network (only found in the ICA analysis), is interesting because MNS activity in conjunction with limbic system processing is thought to subserve the comprehension of emotions in others (Leslie et al., 2004). In this context, the insula provides a conduit between these two systems that enables observed emotional behaviour to be internalized and assigned affective salience (Carr et al., 2003). Consequently, insula activation correlates with empathy (Singer et al., 2004), a form of social cognition governed by emotion. Reduced activity in these networks in patients with schizophrenia may therefore provide a neural explanation for their inability to mentalize and may also underpin their inability to empathize with others (Bleuler, 1950).

Networks that showed significantly less suppression by experimental tasks in schizophrenia patients were the two (anterior and posterior) DM networks (IC9 and IC10) and the medial

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FT network (IC20). These networks contain brain regions (midline MPFC, PCC, and PC) that are consistently associated with task-induced deactivations and all three networks overlap within the frontal anterior cingulate region. ACC dysfunction has been implicated in schizophrenia by numerous strands of scientific investigation. Our finding of less suppression of these networks in patients with schizophrenia is consistent with the findings of Whitfield-Gabrieli and colleagues (Whitfield-Gabrieli et al., 2009) who similarly found less suppression of midline regions of the DM network, such as the PCC/PC and the MPFC by a working memory task in schizophrenia patients as compared to healthy controls. This is important because suppression of the DM network has been found to be associated with better performance on an attention-demanding task in healthy subjects (Weissman et al., 2006). A lack of suppression that results in hyperactivity of the DM network in patients possibly reflects abnormal connectivity between the regions within the network (Bluhm et al., 2007; Whitfield-Gabrieli et al., 2009) or may be a consequence of abnormal connectivity of this network with other networks (Garrity et al., 2007; Zhou et al., 2007).

Compared to controls, patients with schizophrenia displayed reduced coupling between task positive and task negative networks and also between task-negative networks, but it is the reduced coupling between the task-positive and task-negative networks that showed significant correlation with the ToM activity in patients (Figure 4).

Impaired interaction between this task-positive and task-negative network in schizophrenia patients perhaps reflects an impairment of information processing (Eichele et al., 2008; Fox et al., 2005). The medial MPFC is thought to be involved in processing information about self and others in more abstract, evaluative terms that helps in understanding complex psychological aspects of others, whereas the more lateral FT network that includes the temporo-parietal junction (TPJ) may provide essential physical self-to-other mapping that is needed for comprehending the physical actions of intentional agents (Uddin et al., 2007). Interaction between these networks is therefore essential to the integration of information needed for maintaining self-other representations across multiple domains (Uddin et al., 2007). Therefore, one possibility is that the deficits in mentalizing in schizophrenia are a consequence of impairments in higher cognition, namely, the capacity to adopt a perspective different from the self, an ability that is fundamental to the comprehension of the mental states of one's self and others. This inference is in keeping with the problems observed in self-other differentiation clinically in patients with schizophrenia.

Study limitations

Before drawing firm conclusions from this study, it is important to acknowledge that there are many networks that are important to the pathophysiology of schizophrenia and subserve aspects of ToM, and that in this study we have not considered all of these. Further, though our findings cannot be generalized to female schizophrenia patients, the investigation of males in this study does have the advantage of minimising the potential confound of gender differences in ToM (Schulte-Ruther et al., 2008). Finally, as this was a real-world study there were significant differences in years of education, medication regimens, and clinical variables between patients and controls. These may also act as potential confounds in

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interpreting these preliminary findings, but it is of note that no significant correlations were found between these variables and functional connectivity strength.

Conclusion

In summary, our findings indicate that in patients with schizophrenia there is reduced coupling between task-positive and task-negative networks, especially between those networks that sub-serve the mapping of one's self to others. This reduction in coupling perhaps disrupts social construct information processing to the extent that it produces a clinically discernible deficit in mentalizing ability. As a consequence, patients with schizophrenia may experience discernible social compromise that makes it difficult for them to comprehend interpersonal interactions.

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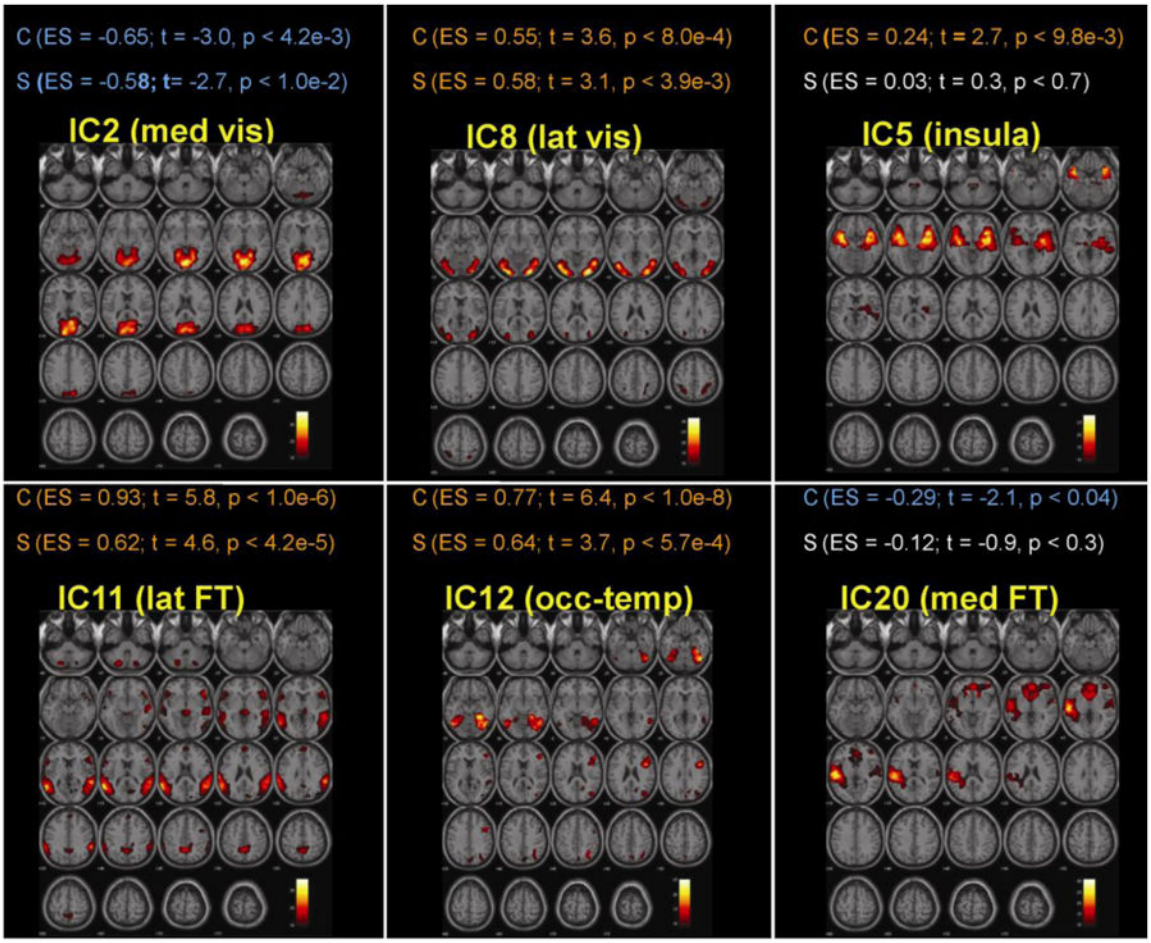

Figure 1.

Within group analyses displayed significant positive modulation of the lateral visual (lat vis, IC8), lateral fronto-temporal (lat FT, IC11), and occipito-temporal (occ-temp, IC12) networks and negatively modulation of the medial visual (med vis, IC2) network by the experimental contrast (ToM – non-ToM) in both schizophrenia and control groups. In controls, the contrast also displayed positive modulation of the insula (IC5) and negative modulation of the medial fronto-temporal (med FT) networks. The nature of any modulation (positive, negative or lack of significant) is represented in different colours: Orange represents significant positive modulation, blue represents significant negative modulation and white represents non-significant modulation. Abbreviation used: C = Controls, S = Schizophrenia; ES = Effect Size.

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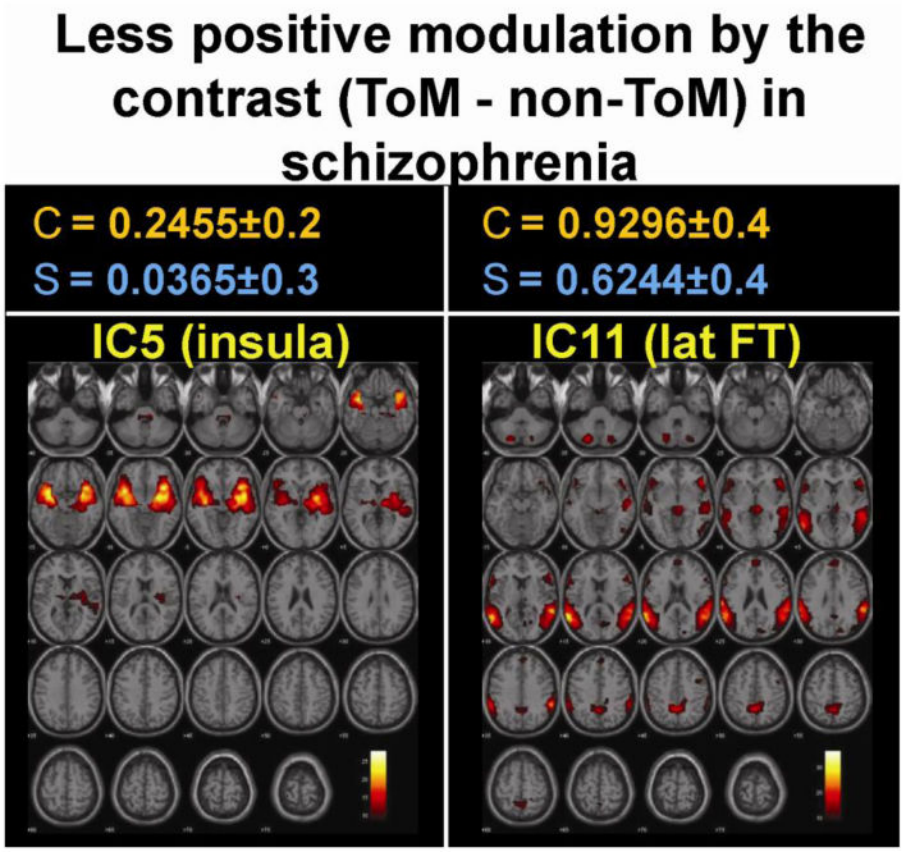

Figure 2.

Between group analysis revealed that in comparison to controls, positive modulation of the lateral fronto temporal (lat FT) and insula networks by ToM (compared to non-ToM) task were significantly less in patients with schizophrenia. Top panel shows the mean effect size (± SD) of the contrast in controls (C) and schizophrenia (S).

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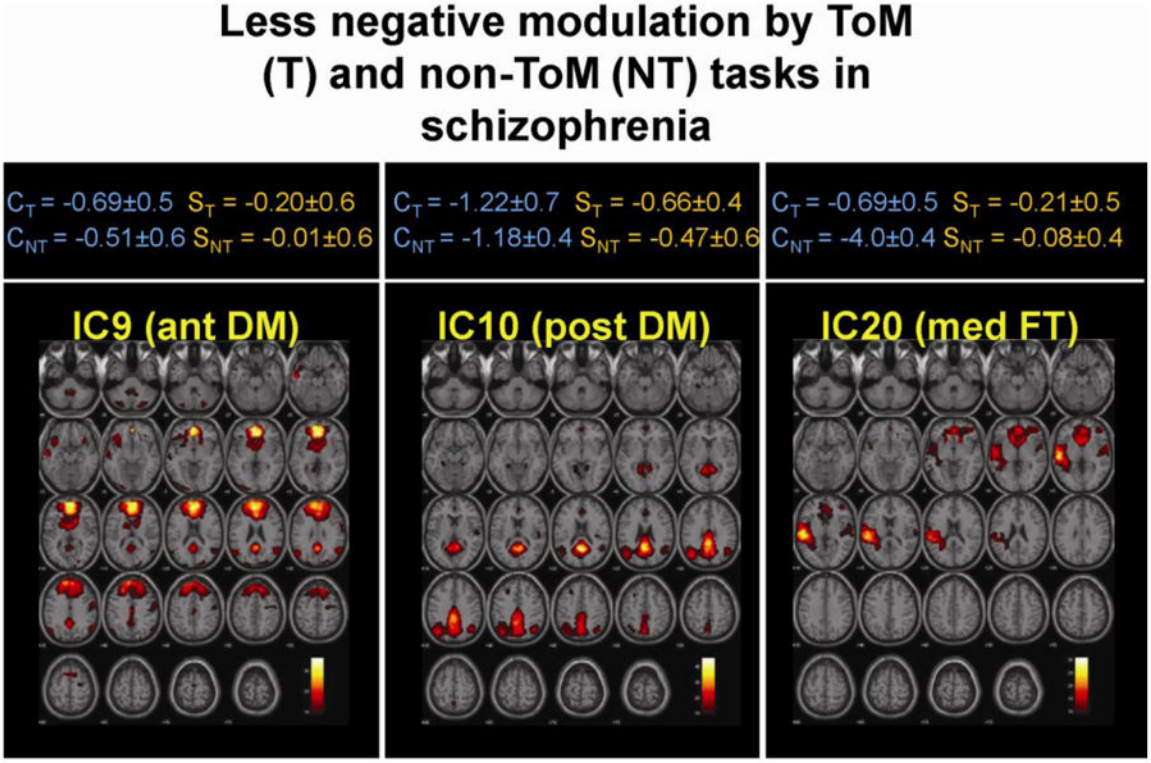

Figure 3.

Between group analyses showed that in patients the anterior (ant DM) and posterior (post DM) and medial fronto temporal (Med FT) networks were less negatively modulated (or suppressed) by both ToM and non-Tom tasks. The top panel shows mean effect size (± SD) of modulation by ToM (T) and non-ToM (NT) tasks in controls (C) and schizophrenia (S).

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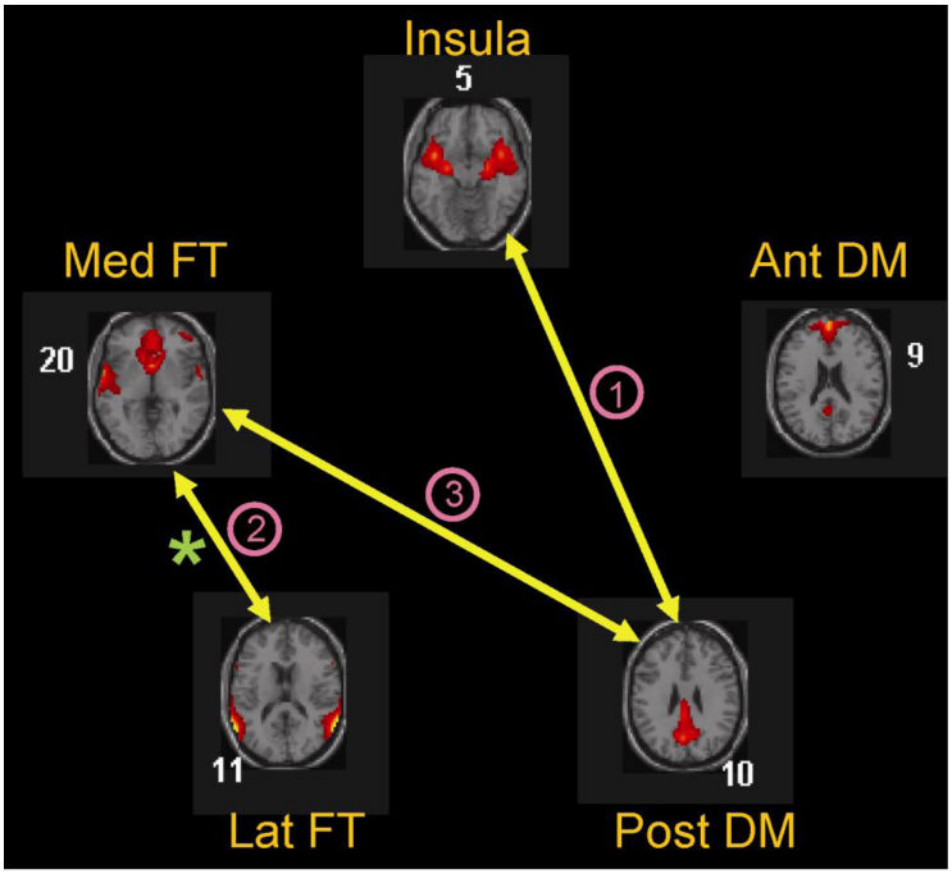

Figure 4.

FNC analysis showed that compared to controls, schizophrenia patients display reduced coupling between: (1) the posterior DM (Post DM) and insula networks, (2) the two fronto-temporal networks, namely the medial (Med FT) and the lateral (Lat FT), and (3) the Post DM and Med FT networks. In addition a correlation analysis revealed that the degree of modulation of the Lat FT network by ToM correlated significantly with the degree to which this network was coupled with the Med FT network (denoted by asterisk).

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Table 1

Showing brain regions within each component that showed significantly different modulation by the experimental contrast (ToM - non-ToM) in groups.

Independent Component (Network)	BA	cluster size	t_{max}	Coordinate
IC 2 (Medial visual)				
Bi Lingual Gyrus	17,18	4824	37.87	-3, -82, -2
L Precentral Gyrus		33	7.75	-45, -10, 55
IC5 (Insula)				
L Insula	13	4681	27.87	-39, 8, -11
R Insula			27.28	39, 14 -11
IC8 (Lateral visual)				
R Middle Occipital Gyrus	18	1455	31.72	33, -85, -5
R Inferior/Middle Temporal Gyrus	37	1397	29.5	45, -70, -2
R Superior Parietal Lobule	40	204	13.9	27, -58, 55
L Superior Parietal Lobule	40	136	13.12	-27, -55, 55
Postcentral Gyrus	3	22	11.24	66, -19, 40
Midbrain		36	11.15	-9, -25, -8
Medial Frontal Gyrus	10	41	9.76	-3, 50, -5
Posterior Cingulate Gyrus	23	13	9.67	-3, -49, 22
IC11(Lateral fronto-temporal)				
L Superior Temporal Gyrus	22	2255	36.49	-60, -55, 13
L Inferior Frontal Gyrus	44		15.34	-60, 11, 7
R Superior Temporal Gyrus	22	2629	27.47	60, -43, 10
R Inferior Frontal Gyrus	44		17.54	57, 26, 7
Bi Superior Frontal Gyrus	9	212	15	3, 53, 28
Bi Precuneus	7	688	20.57	0, -52, 43
L Cuneus	18	42	13.37	-9, -79, 16
R Cuneus	19	164	12.26	12, -82, 28
Midbrain		242	19.25	6, -25, -5
L Cerebellum		195	19.17	-21, -76, -35
R Cerebellum		114	13.91	21, -73, -35
IC12 (Occipito-temporal)				
R Fusiform Gyrus	37	1570	25.13	36, -40, -17
L Occipitotemporal Gyrus	37	601	19.68	-48,-61,-14
R Inferior Frontal Gyrus		509	19.21	45, 8, 28
R Middle Temporal Gyrus		390	15.14	45,-76,22
Caudate		19	11.78	-9,17,4
L Middle Frontal Gyrus		28	10.64	-45,26,22
R Postcentral Gyrus		22	10.37	57,-25,49
R Precentral Gyrus		28	10.33	27, -31,70
IC20 (Medial fronto-temporal)				
L Superior Temporal Gyrus	41	2310	30.95	-57, -22, 7

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Independent Component (Network)	BA	cluster size	t_{max}	Coordinate
R Superior Temporal Gyrus		402	14.48	60, -1, 4
Bi Anterior Cingulate	32	1539	20.69	3,44, -2
Cerebellum		16	10.01	-9, -58, -17
Paracentral Lobule	7	36	9.66	6, -40, 70

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Table 2

Brain regions of the anterior and posterior default mode networks that showed significant less suppression by both ToM and non-ToM tasks in schizophrenia patients (compared to healthy subjects).

Independent Component (Network)	BA	Cluster size	t_{tmax}	Coordinate
IC9 (Anterior default mode)				
Bi Anreior Cingulate Cortex	24	6688	36.28	-3,38,1
Bi Posterior Cingulate Gyrus	31	760	25.85	-3,-55,28
L Angular Gyrus	39	201	19.54	-48,-67,28
R Angular Gyrus		270	17.57	57, -58, 34
Cerebellum		193	15.62	9, -52, -38
L Inferior Occipital Cortex	18	288	14.99	-24,-97,-11
R Precentral Gyrus	9	347	14.7	60,5,31
IC10 (Posterior default mode)				
L Posterior Cingulate Cortex	23	4802	45.63	-3, -55, 22
R Inferior Parietal Lobule	39,40	463	23.68	39, -64, 40
Bi Anterior Cingualte				
Cortex/Medial Frontal Gyrus	10, 32	228	15.33	3, 53, -5
R Middle Temporal Gyrus	21	41	13.39	54, -7, -14
L Middle Frontal Gyrus	8	64	11.24	-24, 26, 46
R Middle Frontal Gyrus	8	41	10.86	24, 29, 43
R Supramarginal Gyrus	40	95	10.34	51, -16, 16
L Thalamus		19	10.05	-6, -19, -7
R Cerebellum		17	11.13	24, -82, -20