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Altered Default Network Resting State Functional Connectivity in Patients with a First Episode of Psychosis

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Contributors

Author Anna Alonso Solís managed the literature searches, data collection and wrote the first draft. Author Iluminada Corripio designed the study, wrote the protocol and managed clinical data collection. Author Pilar de Castro-Manglano contributed to the literature searches, data analyses and the writing of the manuscript. Author Santiago Duran-Sindreu was involved in the recruitment and assessment of the patients. Authors Manuel García García and Clare Kelly managed the data analyses and interpretation of the results. Authors Enric Alvarez and Beatriz Gómez Ansón conceived the idea and methodology for the study and provided their expertise in schizophrenia. Authors Erika Proal and César Soutullo served as advisors in this project. Author Xavier Castellanos supervised the data analyses, contributed to the writing of the manuscript and provided his expertise in Resting-State Functional Connectivity studies. All authors contributed to the writing of the final version of the manuscript and gave their approval to it.

Conflict of Interest

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Abstract

Background—Default network (DN) abnormalities have been identified in patients with chronic schizophrenia using “resting state” functional magnetic resonance imaging (R-fMRI). Here, we examined the integrity of the DN in patients experiencing their first episode of psychosis (FEP) compared with sex- and age-matched healthy controls.

Methods—We collected R-fMRI data from 19 FEP patients (mean age 24.9 ± 4.8 yrs, 14 males) and 19 healthy controls (26.1 ± 4.8 yrs, 14 males) at 3 Tesla. Following standard preprocessing, we examined the functional connectivity (FC) of two DN subsystems and the two DN hubs ($P < 0.0045$, corrected).

Results—Patients with FEP exhibited abnormal FC that appeared largely restricted to the dorsomedial prefrontal cortex (dMPFC) DN subsystem. Relative to controls, FEP patients exhibited weaker positive FC between dMPFC and posterior cingulate cortex (PCC) and precuneus, extending laterally through the parietal lobe to the posterior angular gyrus. Patients with FEP exhibited weaker negative FC between the lateral temporal cortex and the intracalcarine cortex, bilaterally. The PCC and temporo-parietal junction also exhibited weaker negative FC with the right fusiform gyrus extending to the lingual gyrus and lateral occipital cortex, in FEP patients, compared to controls. By contrast, patients with FEP showed stronger negative FC between the temporal pole and medial motor cortex, anterior precuneus and posterior mid-cingulate cortex.

Conclusions—Abnormalities in the dMPFC DN subsystem in patients with a FEP suggest that FC patterns are altered even in the early stages of psychosis.

Keywords

Resting state functional connectivity; First episode of psychosis; Default mode network; Schizophrenia; Dorsomedial prefrontal cortex; Default network subsystem

1. Introduction

Schizophrenia, a highly incapacitating complex disorder affecting about 1% of the general population, is associated with substantial morbidity and mortality (Dixon et al., 1999; Newman and Bland, 1991). The first episode of psychosis (FEP) usually occurs in adolescence or early adulthood; in 70% of cases the initial disorder becomes chronic (Elhamaoui et al., 2003). FEP diagnoses are by definition tentative and non-specific and can be the precursors of a wide range of clinical conditions and prognoses. Nevertheless, naturalistic FEP studies are optimal starting points for understanding the specific neurophysiological mechanisms underlying the onset of psychosis.

Recently, functional connectivity analyses of resting state functional magnetic resonance imaging (R-fMRI) data have provided a fruitful means of addressing the neurobiological bases of psychiatric disorders such as schizophrenia. Functional connectivity (FC) is defined as the temporal correlation of a neurophysiological parameter measured in distinct brain areas, either during rest (i.e., in the absence of a structured task) or when processing external

stimuli (Friston, 1994). In the context of R-fMRI, FC indexes temporal correlations among spontaneous low frequency fluctuations in the fMRI Blood Oxygen Level Dependent signal that are attributed to intrinsic brain activity (Fox and Raichle, 2007). These patterns of synchronous intrinsic activity delineate numerous neuroanatomical functional circuits (Damoiseaux et al., 2006; Smith et al., 2009). To date, however, few R-fMRI studies have focused on the early stages of schizophrenia.

Of the many functional circuits detectable using R-fMRI methods, the Default Network (DN) (Fox and Raichle, 2007) is of particular interest from a neuropsychiatric perspective (Buckner et al., 2008). The DN is a large scale brain network activated by tasks that evoke “internal mentation,” such as episodic memory processes and self-referential cognition (Andrews-Hanna et al., 2010) while a range of tasks involving externally directed attention are associated with decreases in DN activity relative to a resting baseline (Shulman et al., 1997). The DN comprises medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and medial temporal lobe (MTL) regions including the hippocampus, and the lateral temporoparietal area (Buckner et al., 2008).

Several groups have examined the DN in chronic schizophrenia, although methods have varied widely across studies (Greicius, 2008). Stronger FC between the PCC and frontal and temporal gyri was reported in patients with schizophrenia or schizoaffective disorder (Woodward et al., 2011). Further, FC between PCC and left middle frontal gyrus was positively significantly correlated with symptom severity (Woodward et al., 2011). In contrast, most studies have found reduced FC involving DN regions such as PCC and MPFC in patients with chronic schizophrenia relative to controls (Bluhm et al., 2007; Camchong et al., 2011; Zhou et al., 2008).

Recently, R-fMRI analyses were conducted in 19 patients with early-onset schizophrenia and an equal number of controls. A broad range of abnormalities was reported, although they were uncorrected for multiple comparisons (Zhou et al., 2010). Moreover, during an N-back working memory task, FEP patients showed a profound failure to deactivate MPFC DN regions (Guerrero-Pedraza et al., 2011).

Here, in examining the DN using R-fMRI in patients with FEP, we took advantage of the fractionation of the DN into two distinct subsystems and a validated set of 11 seed regions-of-interest (Andrews-Hanna et al., 2010). Specifically, Andrews-Hanna et al. described a dorsal MPFC (dMPFC) DN subsystem that is activated when attention is directed to the self and a MTL DN subsystem that is activated when awareness is directed to the future (Andrews-Hanna et al., 2010; Johnson et al., 2002). We hypothesized that we would detect FC DN abnormalities in FEP patients compared to controls, and reasoned that the presence of such differences would suggest that they index the pathophysiology of the disorder, rather than its chronicity or lengthy treatment.

2. Materials and methods

2.1 Participants

FEP patients and healthy control subjects were recruited from inpatient and outpatient services at the Santa Creu i Sant Pau Hospital (SCSPH) in Barcelona, Spain. The SCSPH IRB (IRB # 08/057/863, principal investigator Iluminada Corripio) approved this study and all subjects provided written informed consent prior to participation.

Inclusion criteria were age 18 to 35 years, and presence of positive and negative symptoms for less than one year. Exclusion criteria included neurological disease that could explain the present psychopathology. Subjects were administered the Structured Clinical Interview for

Diagnosing DSM-IV Disorders (SCID) (First et al., 1995.) to confirm diagnoses in patients and rule out current or past psychiatric illness in healthy controls. Clinical symptoms in patients were quantified with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Nineteen patients with FEP (mean age 24.9 ± 4.7 years, 14 males, all right-handed) and 19 healthy controls (25.9 ± 4.7 years, 14 males, all right-handed), were scanned within the first 6 months of illness (mean interval from diagnosis to scan: 3.4 ± 1.9 months).

At the time of scanning, most patients were being treated with an atypical antipsychotic; risperidone ($n=4$); olanzapine ($n=9$); or aripiprazole ($n=3$). One patient was being treated only with citalopram, one patient on olanzapine also received escitalopram, one patient was unmedicated when scanned and one was medication-naïve. The mean duration of treatment was 3.4 ± 1.9 months. Mean duration of untreated psychosis was 66.3 days. Mean PANSS Positive Scale score at the time of scanning was 12.1 ± 5.6 ; mean PANSS Negative Scale score was 17.05 ± 6.0 ; PANSS General score was 28.6 ± 7.8 . (Table 1).

2.2 Imaging Data Acquisition

Participants were scanned on a 3T Philips Achieva Scanner. T1-weighted images were acquired in an axial orientation (TR/TE=13/7.4 ms, flip angle=8°, field of view (FOV) 23cm with in-plane resolution of 256×256 and 1-mm slice thickness. Functional images were collected using a gradient echo planar imaging sequence (TR/TE=2000/30 ms, flip angle=90°, FOV=23 cm, 80 volumes). Whole-brain volumes were acquired with 40 contiguous 3.5-mm thick transverse slices.

2.3 fMRI Procedure

2.3.1 Data Preprocessing—In line with previously described methods (Di Martino et al., 2008), image processing was performed using Analysis of Functional NeuroImages (AFNI, <http://afni.nimh.nih.gov/>) (Cox, 1996) and FSL (FMRIB Software Library, www.fmrib.ox.ac.uk) (Smith et al., 2004). Preprocessing comprised slice timing correction, motion correction, despiking (detection and reduction of extreme time series outliers using an hyperbolic tangent function), spatial smoothing (using a Gaussian kernel of full width at half maximum 6mm), mean-based intensity normalization of all volumes by the same factor, temporal bandpass filtering (0.009–0.1Hz) and linear and quadratic detrending. Each participant's preprocessed 4-D volume was regressed on 9 nuisance covariates (global signal, cerebrospinal fluid, white matter, and motion covariates), and the resultant volume was spatially normalized by registration to the MNI152 (Montreal Neurological Institute) template with 2-mm³ resolution, using a 12 degrees-of-freedom linear affine transformation, refined using non-linear registration (Andersson et al., 2007a; Andersson et al., 2007b). Since Power et al. have recently demonstrated that subject motion can substantially impact resting state functional connectivity measures (Power et al., 2011), we examined group differences in motion, as quantified by Framewise Displacement (FD) (Power et al., 2011). Overall motion was low, and no group differences ($p=0.72$) in FD were observed (FEP group mean FD = 0.13 ± 0.011 ; healthy controls mean FD = 0.11 ± 0.012).

2.3.2 Functional Connectivity Analysis—Following Andrews-Hanna et al. (Andrews-Hanna et al., 2010), we examined DN FC, including the two hub regions: the posterior cingulate cortex (PCC; MNI coordinates -8, -56, 26) and the anteromedial prefrontal cortex (aMPFC; -6, -52, -2), and the two DN subsystems: the Dorsomedial prefrontal cortex subsystem [(dMPFC; 0, 52, 26); Temporal parietal junction (TPJ; -54, -54, 28); Lateral temporal cortex (LTC; -60, -24, -18); Temporal pole (TempP; -50, 14, -40)] and the Medial temporal lobe (MTL) subsystem [Ventral medial prefrontal cortex (vMPFC; 0, 26, -18);

Posterior inferior parietal lobule (pIPL; -44, -74, 32); Retrosplenial cortex (Rsp; -14, -52, 8); Parahippocampal cortex (PHC; -28, -40, -12); and Hippocampal formation (HF; 22, -20, -26)].

We created spherical seed regions of interest (ROIs) with radius 4mm in 2mm³ MNI space, centered on each of the coordinates listed above. For each participant, and each seed ROI, we generated an image quantifying the voxel-wise temporal correlation between the mean time series of the seed ROI and that of every other voxel in the brain.

2.3.3 Group-Level Analyses—Group-level analyses and group comparisons were carried out using a mixed-effects ordinary least squares model as implemented in the FSL program *flameo*. This group-level analysis produced thresholded Z-score maps (“networks”) of positive and negative FC for each seed ROI, for each group separately. To test for significant group-related differences, direct voxel-wise group comparisons (patients with FEP>Controls, Controls>patients with FEP) were performed using group-level contrasts. Corrections for multiple comparisons were carried out at the cluster level using Gaussian random field theory using an omnibus cluster-level Bonferroni correction to account for the 11 seeds examined (min $Z > 2.3$; cluster significance: $P < 0.0045$, corrected).

2.3.4 Correlation Analyses—For each significant seed, we computed the partial correlation, adjusting for nuisance covariates, between each individual’s FC strength and their PANSS scores using SPSS 17.

3. Results

As Figures 1 and 2 show, relative to controls, patients with FEP exhibited several alterations in the dMPFC subsystem. Specifically, FEP patients exhibited weaker positive FC between the dMPFC ROI and PCC/precuneus, extending laterally through the parietal lobe towards the posterior angular gyrus. In addition, in patients with FEP, the LTC ROI exhibited weaker negative FC with the intracalcarine cortex (medial occipital lobe), bilaterally. Both the PCC and TPJ ROIs exhibited weaker negative FC with the right fusiform gyrus, extending to the lingual gyrus and lateral occipital cortex (for TPJ only), relative to controls.

By contrast, in patients with FEP, the temporal pole showed stronger negative FC with medial motor cortex, anterior precuneus and posterior mid-cingulate cortex. PANSS scores were not significantly correlated with any DN FC correlation coefficients.

4. Discussion

In this, one of the first studies examining intrinsic connectivity networks in patients with FEP, we found altered FC both within the DN, and between the DN and other large-scale networks, relative to healthy controls. Specifically, we found weaker positive FC between dMPFC and the precuneus and posterior cingulate. We also found weaker negative FC for patients compared to controls for the LTC, PCC and TPJ. By contrast, for the temporal pole ROI, we found significantly stronger FC in patients with medial motor regions and the anterior precuneus. It is noteworthy that all the group differences were within the dMPFC subsystem of the DN; no significant group differences were observed for any of the ROIs comprising the DN Medial Temporal Lobe subsystem.

As noted by Andrews-Hanna et al., the dMPFC subsystem is activated when individuals infer the mental states of others (Gallagher et al., 2000; Saxe et al., 2006), when affective information is referenced to the self, and during social cognition more broadly (Andrews-Hanna et al., 2010). We note that the schizophrenia prodrome and early-onset schizophrenia are characterized by marked difficulties in maintaining social relationships (Ballon et al.,

2007; Corcoran et al., 2011). In fact, social behavior is one of the major domains of dysfunction observed before the onset of psychosis (Brunner et al., 1993; Ramirez et al., 2010; Tarbox and Pogue-Geile, 2008) and uniquely contributes to the prediction of psychosis (Cannon et al., 2008). A retrospective study assessing a FEP in adolescents found that social problems do not represent a sequelae of the disease but predate the emergence of a FEP (Muratori et al., 2005). Accordingly, we speculate that the specific implication of the dMPFC subsystem, as opposed to the MTL subsystem, may reflect such social difficulties. Future studies should aim to characterize social deficits in FEP and relate them to dMPFC subsystem integrity.

We observed weaker positive or negative FC in FEP patients compared to controls for four of the five dMPFC subsystem seeds. Our results are thus in broad agreement with several prior studies assessing the DN in patients with chronic schizophrenia (Bluhm et al., 2007; Camchong et al., 2011; Zhou et al., 2008). Converging lines of evidence strongly implicate the dMPFC in schizophrenia and related disorders. For example, an independent component analysis (ICA) analysis of R-fMRI data revealed abnormal dMPFC functional connectivity that was common to patients with both schizophrenia and bipolar disorder (Ongur et al., 2010). Another recent study demonstrated abnormalities in the patterns of positive and negative functional connectivity associated with MPFC that were specific to schizophrenia patients, relative to both bipolar patients and controls. Schizophrenia patients did not show the expected pattern of negative FC between MPFC and bilateral dorsolateral prefrontal cortex, nor between MPFC and ventrolateral prefrontal cortex and insula (Chai et al., 2011).

Beyond R-fMRI studies, there is ample evidence of medial prefrontal abnormalities in schizophrenia. Hypoactive dMPFC metabolism on positron emission tomography was correlated with physical anhedonia in patients with schizophrenia (Park et al., 2009). Similarly, Pomarol-Clotet et al. found convergent abnormalities in schizophrenia in the dMPFC in task-based fMRI, voxel-based morphometry, and diffusion tensor imaging data (Pomarol-Clotet et al., 2010). Further, in a review of 37 voxel-based morphometry studies, dMPFC gray matter volume was significantly reduced in patients with schizophrenia compared with healthy controls (Fornito et al., 2009). The dMPFC was also reported by Zhou et al. as one of the main regions differentiating patients with early-onset schizophrenia from controls (Zhou et al., 2007).

Task-related studies have consistently demonstrated failure to deactivate (Kim et al., 2009; Salgado-Pineda et al., 2011) medial PFC areas in schizophrenia, such as dorsolateral, ventromedial PFC and anterior cingulate during working memory tasks (Pomarol-Clotet et al., 2008). For example, FEP patients failed to deactivate the MPFC during an *n*-back working memory task, relative to controls. Further, in line with our findings, FEP patients also exhibited weaker FC between the MPFC and PCC/precuneus during the working memory task (Guerrero-Pedraza et al., 2011). As with other neural correlates of schizophrenia, MPFC deficits may extend beyond patients with schizophrenia to include unaffected relatives. Jang et al. showed that, relative to controls, patients with schizophrenia and their relatives exhibited weaker task-related suppression of MPFC during WM performance (Jang et al., 2011). The investigation of potential deficits in MPFC function and FC in unaffected relatives of schizophrenia patients merits future study.

Study limitations include a moderate sample size, short acquisition time and mixed medication histories. Although our patients had received treatment for less than six months, we cannot rule out medication effects on FC (Achard and Bullmore, 2007). Thus caution should be exercised in interpreting our positive findings pending independent replication. Additionally, it is still unknown if FC alterations in the DN are peculiar to schizophrenia or are common to psychotic symptoms. On the other hand, treatment with olanzapine has been

reported to be associated with increases in DN FC with ventromedial prefrontal cortex (Sambataro et al., 2010). Additionally, DN abnormalities have been found in individuals at genetically high risk of schizophrenia (Jang et al., 2011), which, together with our results and those of other investigators (Guerrero-Pedraza et al., 2011; Zhou et al., 2010) lend further support to the possibility that abnormal DN alterations are present from the beginning of illness onset.

To conclude, in this first R-fMRI study in FEP of the DN, we found a specific alteration in the dMPFC subsystem, suggesting that FC patterns are altered even in the early stages of psychosis. Future R-fMRI prospective studies comparing patients who develop schizophrenia to patients who do not will be expected to advance our understanding of the pathophysiology of schizophrenia in the service of developing personalized therapeutic approaches targeting the early stages of the psychotic process.

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Figure 1. Group-level FC and regions exhibiting significant group differences in FC for the dMPFC and TempP seed ROIs

Positive FC is shown in red-orange, negative FC is shown in light blue. Regions exhibiting significantly weaker FC (corresponding to stronger negative FC in the case of the TempP seed) in FEP patients, relative to controls, are shown in dark blue. Mean FC values within the regions exhibiting significant group differences are shown on the scatter plots; FEP patients appear in red, controls are shown in dark blue. FC: Functional connectivity; FEP: First Episode of psychosis; HC: Healthy controls; dMPC: dorsomedial prefrontal cortex; TempP: Temporal Pole.

Figure 2. Group-level FC and regions exhibiting significant group differences in FC for the PCC, TPJ, LTC seeds

Positive FC is shown in red-orange, negative FC is shown in light blue. Regions exhibiting significantly weaker negative FC in FEP patients, relative to controls, are shown in red. Mean FC values within the regions exhibiting significant group differences are shown on the scatter plots; FEP patients appear in dark blue, controls are shown in red. FC: Functional Connectivity; FEP: First episode of psychosis; HC: Healthy controls; PCC: Posterior Cingulate Cortex; TPJ: Temporoparietal junction; LTC: Lateral temporal cortex.

Table 1

Demographic Data

Table 1	Patients	Controls	p	t	df
N	19	19			
Age (mean±SD)	24.9 ± 4.7	25.9 ± 4.7	0.54	0.09	37
Gender	14 males	14 males			
DUP (days)	66.3 ± 66.9				
Illness Duration (months)	3.4 ± 1.9				
PANSS Positive	12.1 ± 5.6				
PANSS Negative	17.05 ± 6.0				
PANSS General	28.6 ± 7.8				

DUP: Duration untreated psychosis; PANSS: Positive and Negative Syndrome Scales. Significance threshold defined at $P < 0.05$