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Default mode network activity in schizophrenia studied at resting state using probabilistic ICA

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ABSTRACT

Alterations in brain function in schizophrenia and other neuropsychiatric disorders are evident not only during specific cognitive challenges, but also from functional MRI data obtained during a resting state. Here we apply probabilistic independent component analysis (pICA) to resting state fMRI series in 25 schizophrenia patients and 25 matched healthy controls. We use an automated algorithm to extract the ICA component representing the default mode network (DMN) as defined by a DMN-specific set of 14 brain regions, resulting in z-scores for each voxel of the (whole-brain) statistical map. While goodness of fit was found to be similar between the groups, the region of interest (ROI) as well as voxel-wise analysis of the DMN showed significant differences between groups. Healthy controls revealed stronger effects of pICA-derived connectivity measures in right and left dorsolateral prefrontal cortices, bilateral medial frontal cortex, left precuneus and left posterior lateral parietal cortex, while stronger effects in schizophrenia patients were found in the right amygdala, left orbitofrontal cortex, right anterior cingulate and bilateral inferior temporal cortices. In patients, we also found an inverse correlation of negative symptoms with right anterior prefrontal cortex activity at rest and negative symptoms. These findings suggest that aberrant default mode network connectivity contributes to regional functional pathology in schizophrenia and bears significance for core symptoms.

1. Introduction

Functional magnetic resonance imaging (fMRI) has mostly been used to assess deficits of task-induced activation, e.g. during working memory tasks (Minzenberg et al., 2009). More recent studies have provided evidence for alterations detectable already under "resting state" conditions, i.e. without performing a specific cognitive task. While such resting-state abnormalities have been observed in several neuropsychiatric disorders (Greicius, 2008; Broyd et al., 2009), these findings bear particular significance for schizophrenia, as they might be related to cognitive impairment and clinical symptoms.

The approaches to analyse resting-state fMRI data in schizophrenia all exploit the fact that the BOLD signal shows low-frequency fluctuations (Auer, 2008), which are assumed to be linked to resting-state networks (Damoiseaux et al., 2006). While some studies have demonstrated changes on regional amplitude of low-frequency fluctuations during rest (Huang et al., 2009; Hoptman et al., 2010), others have used either correlation of seed-regions such as the posterior cingulate cortex (PCC) with other brain areas (Bluhm et al., 2007), or have used independent component analysis (ICA) to extract sets of regions following a similar time course (Garrity et al., 2007). Despite different methodologies, these studies appear to overlap in alteration of nodes of the default mode network (DMN), esp. the medial prefrontal cortex.

The default mode network (DMN) is a concept based on an interconnected set of areas showing higher activity during rest than task-related activity (Raichle et al., 2001; Raichle and Snyder, 2007). This network has been defined by initial studies of Shulman et al. based on changes of cerebral blood flow during visual tasks (Shulman et al., 1997). Since then it has been studied extensively with both seed-ROI based correlations and ICA methods (Raichle and Snyder, 2007; van den Heuvel and Hulshoff Pol, 2010), and linked to electrophysiological activity in the beta and gamma band (Mantini et al., 2007).

Recent studies on DMN activity in schizophrenia have suggested medial prefrontal cortical areas of the DMN network to show aberrant connectivity or activity, although the evidence is not completely converging on this area and direction of effects differ across studies (Zhou et al., 2007; Kim et al., 2009; Whitfield-Gabrieli et al., 2009; Ongur et al.,

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2010; Woodward et al., 2011). However, these studies show links to both cognitive deficits and to symptoms (Rotarska-Jagiela et al., 2010), which links them to the relevant pathophysiology of schizophrenia. Moreover, other findings suggest a relative specificity of certain abnormalities for schizophrenia (Calhoun et al., 2008).

In the present study, we aimed to analyse resting state data, devoid of any directed cognitive task, using probabilistic independent component analysis (pICA) in a cohort of chronic schizophrenia patients in order to test the hypothesis of activity differences across the nodes of the DMN. More specifically, we aimed to test that prefrontal differences in resting state DMN activity are evident in resting-state conditions in the absence of cognitive stimulation, and in patients with remission of psychotic episode. We applied an algorithm using an overall approach similar to Greicius (Greicius et al., 2004, 2007), focussing on an automated detection/extraction of the DMN component and group comparison, in order to eliminate the necessity for observer-dependent interventions such as placement of seed regions. We tested the hypothesis of impaired frontal cortical connectivity by studying remitted patients, i.e. not during a psychotic episode, and correlated data with negative symptoms.

2. Methods

2.1. Study participants

We studied 25 patients with DSM-IV schizophrenia (8 female; mean age 30 years, SD 7.3; age range 21–49 years) and 25 healthy controls (10 female; mean age 29.1 years, SD 8.6; age range 22–55 years), of which three patients were left-handed as determined by the Edinburgh Handedness Scale (Oldfield, 1971). Proportion of left-handers did not differ between groups (Fisher Exact Probability Test $p > 0.23$). All participants gave written informed consent to participation in this study, which was conducted as part of the EUTwinsS project (European Twin Study Network on Schizophrenia) and approved by the Ethics Committee of the Friedrich-Schiller-University Medical School, Jena. None of the participants had a neurological condition of history of traumatic brain injury or learning disability. We carefully interviewed all participants to exclude candidates with a present or previous neurological CNS condition, history of traumatic brain injury, or learning disability. In addition, patient records were reviewed, where available, to ensure patients did not meet any of these exclusion criteria. According to chart review, none of the patients had a concurrent axis II disorder. In addition, all participants were screened using the MWT-B, a standardised and widely-used German test assessing (pre-morbid) IQ, to ensure that none of the participants had an IQ below 80.

Patients were recruited from the in-patient and out-patient services of the Department of Psychiatry and Psychotherapy in Jena. All patients had a diagnosis of schizophrenia established using DSM-IV criteria (American Psychiatric Association). A board-certified psychiatrist (I.N.) assessed each patient, conducting an additional chart review where necessary, and also rated current psychopathology using the Scale for Assessment of Negative Symptoms (SANS), the Scale for Assessment of Positive Symptoms (SAPS), and the Brief Psychiatric Rating Scale (BPRS). All patients were remitted, i.e. none of them was experiencing an acute psychotic episode at the time of the study, and hence they showed mostly residual negative psychopathology and only little positive symptoms.

Healthy control subjects were recruited from the local community and matched to the patients with regard to age, gender, and handedness (details of demographics and comparison are given in Table 1; T-Test for age difference: $p > 0.66$, two-tailed; Chi-square test for gender: $p > 0.53$; Fisher Exact Test for handedness: $P > 0.11$, one-tailed). They underwent a semi-structured interview to exclude personal history or any current psychiatric disorder.

Table 1
Demographical data of subject samples.

	Patients	Controls
Number	25	25
Gender	8 females, 17males	10 females, 15 males
Age (mean ± SD)	30 ± 7.3 years	29.1 ± 8.6 years
SANS total score (mean ± SD)	40.3 (14.5)	N/A
SAPS total score (mean ± SD)	21.8 (11.7)	N/A
BPRS total score (mean ± SD)	38.9 (7.3)	N/A

2.2. Data acquisition and pre-processing

We obtained resting-state fMRI series on a 3 T Siemens Tim Trio system (Siemens, Erlangen, Germany) using the 12-channel head matrix coil. Subjects were instructed to relax and keep their eyes closed (without falling asleep, which was confirmed immediately after the scanning session). Foam pads were used for positioning and immobilisation of subjects' heads during scanning. We obtained a series of 210 T2*-weighted whole-brain volumes over approx. 9 min, using a standard BOLD-sensitive EPI sequence (TR 2550 ms; TE 30 ms; flip angle 90°; 45 contiguous axial slices with 3 mm thickness, no gap, matrix 64 × 64; in-plane resolution of 3 × 3 mm; field-of-view 192 mm × 192 mm). In addition, we acquired a high-resolution structural scan for co-registration using a 3D MPRAGE sequence with 192 contiguous sagittal slices of 1 mm thickness (TR 2300 ms; TE 3 ms; TI 900 ms; echo time 8.9 ms; flip angle 9°; matrix size 256 × 256; isotropic voxel dimensions of 1 × 1 × 1 mm).

Both functional and structural images series underwent a quality assurance protocol, including visual inspection, and none of the participants showed such artefacts.

Data analysis was performed using SPM5 (Institute of Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm) for pre-processing as well as later voxel-wise statistics, and FSL MELODIC for independent component analysis (FMRIB, University of Oxford, UK; www.fmrib.ox.ac.uk/fsl/melodic2/index.html).

We first discarded the first three images of each functional series to avoid T1 saturation effects. In order to remove movement artefact, images were realigned using a least-squares approach and a 6-parameter rigid body spatial transformation. A two-pass procedure was used to register the images to the mean of the images after the first realignment. We applied smoothing with a 4 mm FWHM Gaussian kernel before estimating the realignment parameters. None of the participants exceeded the pre-defined movement limits (3 mm translation on x, y, or z axis or 3° rotation), which were also part of the quality assurance protocol.

Within-subject registration was performed between functional images (used as reference image) and the anatomical image. Then, the co-registered anatomical images was segmented using tissue probability maps of the ICBM template (International Consortium for Brain Mapping; based on T1 scans of 452 subjects; http://www.loni.ucla.edu/ICBM/ ICBM_TissueProb.html), which were aligned with an atlas space, corrected for scan inhomogeneities, and classified into grey matter, white matter, and CSF. These data were then registered with affine transformation to MNI space and down-sampled to 2 mm resolution.

Functional images were then spatially normalised to Talairach and Tournoux space using spatial normalisation parameters estimated in the segmentation process. Images were re-sampled to 2 mm using sinc interpolation, and then smoothed with an 8 mm FWHM Gaussian kernel to account for residual inter-subject anatomical differences.

2.3. Probabilistic ICA and automated extraction of DMN component

We applied independent component analysis (ICA) using FSL software. For each subject, pre-processed functional images were