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Network modeling of resting state connectivity points towards the bottom up theories of schizophrenia

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ABSTRACT

The dysconnectivity theory of schizophrenia proposes that schizophrenia symptoms arise from abnormalities in neuronal synchrony. Resting-state Functional Connectivity (FC) techniques allow us to highlight synchronization of large-scale networks, the Resting-state Networks (RNs). A large body of work suggests that disruption of RN synchronization could give rise to specific schizophrenia symptoms. The present study aimed to explore within- and between-network FC strength of 34 RNs in 29 patients suffering from schizophrenia, and their relationships with schizophrenia symptoms. Resting-state data were analyzed using independent component analysis and dual-regression techniques. Our results showed that both within-RN and between-RN FC were disrupted in patients with schizophrenia, with a global trend toward weaker FC. This decrease affected more particularly visual, auditory and crossmodal binding networks. These alterations were correlated with negative symptoms, positive symptoms and hallucinations, indicating abnormalities in visual processing and crossmodal binding in schizophrenia. Moreover, we stressed an anomalous synchronization between a visual network and a network thought to be engaged in mental imaging processes, correlated with delusions and hallucinations. Altogether, our results supported the assumption that some schizophrenia symptoms may be related to low-order sensory alterations impacting higher-order cognitive processes, i.e. the “bottom-up” hypothesis of schizophrenia symptoms.

1. Introduction

The dysconnectivity theory of schizophrenia proposes that many symptoms may be related to a failure to integrate the activity of local and distributed neural circuits (van den Heuvel and Fornito, 2014). One way of assessing brain connectivity is to study how multiple brain regions functionally interact while an individual is not engaged in a specific task, i.e. using resting-state blood oxygen level-dependent Functional Connectivity (FC) (Rogers et al., 2007).

Numerous FC studies conducted on healthy volunteers reported that the brain exhibited a structured neural activity during the resting state (Bressler and Menon, 2010; Doucet et al., 2011). This can be observed at different scales: the system scale, the module scale (Fig. S1 Supplementary data) and the Resting-state Network (RN) scale (Fig. S2 Supplementary data). Among these scales, the partition into RNs appears to be the most relevant in the context of schizophrenia research. RNs have been suggested to overlap with the networks subtending the brain in action (Smith et al., 2009). In other words,

Abbreviations: AH, Auditory Hallucinations in medical history; ANCOVA, Analysis Of COVAriance; ANOVA, ANalysis Of Variance; AVH, Auditory and Visual Hallucinations in medical history; BNFC, Between-Network Functional Connectivity; C-FD, Cumulated Framewise Displacement; Cpz-eq, average Chlorpromazine equivalent; DMN, Default-Mode Network; FC, Functional Connectivity; FD, Framewise Displacement; HC, Healthy Controls; ICA, Independent Component Analysis; MANOVA, Multivariate ANalysis Of Variance; MICCA, Multi-scale Individual Component Clustering Analysis; MINI, Mini International Neuropsychiatric Interview; MRI, Magnetic Resonance Imaging; NBS, Network-Based Statistics; NH, No Hallucinations in medical history; PANSS, Positive And Negative Syndrome Scale; PANSS-N, Negative symptoms subscale of the PANSS; PANSS-P, Positive symptoms subscale of the PANSS; RN, Resting-state Network; PS, Patients with Schizophrenia; WNFC, Within-Network Functional Connectivity

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functional networks seem to be continuously and dynamically "active" even when the brain is "at rest". RNs have already been shown to be of potential clinical value as rich and sensitive markers of disease (Menon, 2011). They offer several advantages: the full repertoire of RNs can be tested in a single scanning session without having to decide a priori what functional paradigm is most likely to be useful, and minimal individual participation is required during scanning. This latter point can be critical in clinical settings (e.g. Autism Spectrum Disorders, severe schizophrenia or Alzheimer Disease). As a consequence, the study of RNs allows exploring cognitive processes that are either understudied or examined under simplifying assumptions due to scanning constraints (Papo, 2013; Smith et al., 2009). Moreover, disruptions of RNs may contribute to specific patterns of cognitive and behavioral impairments, providing new insights into aberrant brain organization in several psychiatric and neurological disorders (Menon, 2011; Papo, 2013).

Several authors reported within-RN connectivity disruptions in schizophrenia during the resting state. Almost all of these studies were hypothesis-driven, hence the authors selected a few RNs on the basis of their relevance regarding the physiopathology of schizophrenia. As schizophrenia is usually seen to be related to higher-order cognitive dysfunctions, higher order RNs were chosen: DMN, central executive, attentional, language or salience networks (Orliac et al., 2013; Rotarska-Jagiela et al., 2010; Wolf et al., 2011; Woodward et al., 2011).

A few studies examined between-RN connectivity in schizophrenia during the resting state (Arbabshirani et al., 2013; Jafri et al., 2008; Khadka et al., 2013; Mamah et al., 2013; Meda et al., 2012; Yu et al., 2012). It should be noted that, apart from Yu et al. (2012) who studied 57 RNs, these studies have focused on less than 20 RNs. All of these reported reduced between-RN connectivity in patients with schizophrenia, except Jafri et al. (2008) and Khadka et al. (2013) who reported both connectivity increases and decreases.

In the light of this literature, and by contrast with our previous hypothesis-driven work (Orliac et al., 2013), it seemed relevant to explore RN functional connectivity in schizophrenia as exhaustively as possible. To achieve this, we studied both within-RN and between-RN functional connectivity strength of 34 networks encompassing 98% of the cerebral gray matter, including low-order and high-order networks, and their relationships with schizophrenia symptoms.

2. Methods

2.1. Participants

Twenty-nine Patients with Schizophrenia (PS group) attending the Department of Psychiatry of Caen University Hospital and twenty-nine matched healthy controls (HC group) were included in the study. We used a sample expanded from a previous study (Orliac et al., 2013). PS and HC groups were matched for age, sex, handedness, and educational level on a one-to-one basis. All participants were required to be between 18 and 60 years of age. All were screened for magnetic resonance imaging (MRI) contraindications, and participants with a history of a major medical condition, neurological disease, or substance abuse were excluded from the study.

PS group participants were diagnosed by an experienced clinician using the Mini International Neuropsychiatric Interview (MINIplus v.4.5). They were required to have been stable on antipsychotic medication for at least four months prior to the study. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess positive (PANSS-P) and negative (PANSS-N) symptoms. Daily antipsychotic medication dosage at the time of inclusion was recorded and converted into chlorpromazine equivalents (mg/d).

Our findings pointed towards a need for post-hoc analyses. For this purpose, PS patients were classified into three subgroups according to their hallucinatory status (items A6b and A7b of the MINIplus): No Hallucinations in medical history (NH group), Auditory Hallucinations in medical history (AH group), or Auditory and Visual Hallucinations in medical history (AVH group).

The local ethics committee (CPP de Basse-Normandie, France) approved the study. All participants gave written informed consent.

2.2. Image acquisition

Data acquisition was performed on a 3T Philips Achieva MRI scanner. Structural data were acquired using a high-resolution, three-dimensional T1-weighted volume (repetition time (TR) = 20 ms; echo time (TE) = 4.6 ms; flip angle = 10°; inversion time = 800 ms; turbo field echo factor = 65; sense factor = 2; field of view = 256 × 256 × 180 mm; 1 × 1 × 1 mm^3 isotropic voxel size), and a T2*-weighted, multi-slice acquisition (T2*-weighted fast-field echo; TR = 3500 ms; TE = 35 ms; flip angle = 90°; sense factor = 2; 70 axial slices; 2 × 2 × 2 mm^3 isotropic voxel size). Spontaneous brain activity was monitored using BOLD fMRI while the participants performed a resting-state condition for 8 min (T2*-echo planar imaging; 240 volumes; TR = 2 s; TE = 35 ms; flip angle = 80°; 31 axial slices; 3.75 × 3.75 × 3.75 mm^3 isotropic voxel size). Immediately before fMRI scanning, participants were instructed to "keep their eyes closed, to relax, to refrain from moving, to stay awake, and to let their thoughts come and go."

2.3. Image processing

Pre-processing of the functional data was based on the methods described in Naveau et al. (2012). Briefly, it included slice-timing correction, motion correction, co-registration to structural scan, spatial normalization to the MNI template and spatial smoothing (6 mm Gaussian kernel). Each individual's structural scan was segmented into gray matter, white matter, and cerebrospinal fluid using the unified segmentation approach (Statistical Parametric Mapping 5; www.fil.ion.ucl.ac.uk/spm5). Time series for white matter, cerebrospinal fluid, and the six motion parameters were regressed out of the data. Finally, fMRI data were temporally filtered using band-pass filtering (0.01 Hz < f < 0.1 Hz).

2.4. Motion control

Head motion correction has become a prominent concern in the field of resting state FC, especially during clinical studies. As a matter of facts, several authors have reported that small amounts of movement can produce substantial changes in the timecourses of resting state data, and cause spurious but spatially structured patterns in FC (Power et al., 2012; Satterthwaite et al., 2012).

As a consequence, an index of quality control was computed for each participant: the Framewise Displacement (FD) of head position, calculated as the sum of the absolute values of the 6 translational and rotational realignment parameters (Power et al., 2012). Every participant exhibiting FD higher than 0.5 mm in more than 10% of the 240 volumes was excluded from the study. Then, a single motion index was calculated for each participant: the Cumulated Framewise Displacement (C-FD), defined as the sum of FDs over all 240 images. C-FD values were tested for group differences and added as covariate of no interest in our connectivity analyses (see 2.9.) to control for this potentially confounding factor.

2.5. Reference maps of the RNs

Reference maps for RNs were estimated from BIL & GIN cohort (Mazoyer et al., 2016) resting-state datasets ($n = 282$), using a group ICA approach based on multi-scale individual component clustering (MICCA, see Naveau et al. (2012)). The MICCA analysis retained 34 non-artifactual RNs. The positive map of each RN was thresholded using a mixture model ($p > 0.95$) (Beckmann and Smith, 2004).

Additionally, voxels exhibiting a probability of being included in the