Schizophrenia Research 148 (2013) 74–80

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia

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ARTICLE INFO

Article history:
Received 22 November 2012
Received in revised form 14 April 2013
Accepted 8 May 2013
Available online 31 May 2013

Keywords:
Psychosis
Rest
Dysconnectivity
Cingulate
Striatum

ABSTRACT

Neuroimaging data support the idea that schizophrenia is a brain disorder with altered brain structure and function. New resting-state functional connectivity techniques allow us to highlight synchronization of large-scale networks, such as the default-mode network (DMN) and salience network (SN). A large body of work suggests that disruption of these networks could give rise to specific schizophrenia symptoms. We examined the intra-network connectivity strength and gray matter content (GMC) of DMN and SN in 26 schizophrenia patients using resting-state functional magnetic resonance imaging and voxel-based morphometry. Resting-state data were analyzed with independent component analysis and dual-regression techniques. We reported reduced functional connectivity within both DMN and SN in patients with schizophrenia. Concerning the DMN, patients showed weaker connectivity in a cluster located in the right paracingulate cortex. Moreover, patients showed decreased GMC in this cluster. With regard to the SN, patients showed reduced connectivity in the left and right striatum. Decreased connectivity in the paracingulate cortex was correlated with difficulties in abstract thinking. The connectivity decrease in the left striatum was correlated with delusion and depression scores. Correlation between the connectivity of DMN frontal regions and difficulties in abstract thinking emphasizes the link between negative symptoms and the likely alteration of the frontal medial cortex in schizophrenia. Correlation between the connectivity of SN striatal regions and delusions supports the aberrant salience hypothesis. This work provides new insights into dysfunctional brain organization in schizophrenia and its contribution to specific schizophrenia symptoms.

1. Introduction

Neuroimaging data support the idea that schizophrenia is a brain disorder with altered brain structure and function (Shenton et al., 2001; Brown and Thompson, 2010). The dysconnectivity theory of schizophrenia proposes that schizophrenic symptoms arise from abnormalities in neuronal connectivity (Bullmore et al., 1997), and the existence of a widespread anatomical disconnection is now well established for the condition (Stephan et al., 2006). Several meta-analyses have documented widespread gray matter (GM) changes in the brain in patients with schizophrenia (Honea et al., 2005; Ellison-Wright et al., 2008), and the most affected loci were anterior cingulate cortex, medial temporal structures, superior temporal and inferior frontal gyri. One way of assessing brain connectivity is to study how multiple brain regions functionally interact while a subject is not engaged in a specific task, i.e., using resting-state blood oxygen level-dependent (BOLD) functional connectivity (Rogers et al., 2007). Resting-state functional connectivity is an interesting approach because it allows partitioning of the brain into functional networks (Damoiseaux et al., 2006; Naveau et al., 2012). Furthermore, resting-state networks have been proposed to overlap the networks subtending the brain in action (Smith et al., 2009). In other words, functional networks seem to be continuously and dynamically "active" even when the brain is "at rest." Disruptions of these networks 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). Regarding schizophrenia, dysfunction of two networks seems to play a prominent role: the default mode network (DMN) and the salience network (SN) (Menon, 2011; Palaniyappan et al., 2011; Woodward et al., 2011; Palaniyappan and Liddle, 2012).

DMN is a well-known entity, initially described in late 1990s positron emission tomography studies as a set of brain regions where activity is more important during resting-state than during a cognitive task (Shulman et al., 1997; Mazoyer et al., 2001). Subsequent work

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http://dx.doi.org/10.1016/j.schres.2013.05.007

stressed the link between DMN activity and stimulus-independent thoughts, i.e., mind-wandering (McKiernan et al., 2006). Some authors argue that this network underlies the construction of complex self-referential simulations, such as mental time travel, perspective-taking, and theory of mind (Buckner and Carroll, 2007; Molnar-Szakacs and Arzy, 2009). The interaction among these processes would, according to this idea, lead to the construction of a unique, integrated representation: the Self (Molnar-Szakacs and Arzy, 2009). Several functional connectivity studies have reported DMN abnormality in schizophrenia, but the results are mixed: connectivity increase (Zhou et al., 2007; Whitfield-Gabrieli et al., 2009; Mannell et al., 2010; Skudlarski et al., 2010), connectivity decrease (Bluhm et al., 2007, 2009; Rotarska-Jagiela et al., 2010; Camchong et al., 2011; Jang et al., 2011), or both (Ongur et al., 2010; Mingoia et al., 2012). Moreover, one study has found no significant difference between patients and controls (Wolf et al., 2011). A DMN alteration has been associated with negative symptoms (Camchong et al., 2011; Mingoia et al., 2012), positive symptoms (Whitfield-Gabrieli et al., 2009; Camchong et al., 2011), attention/concentration deficits (Camchong et al., 2011), and disorganization symptoms (Rotarska-Jagiela et al., 2010). According to Salgado-Pineda et al. (2011), GM alterations could constitute a neuroanatomical underpinning of disturbed DMN function in schizophrenia.

The SN is a network responsible for the integration of sensations, internally generated thoughts and information about goals and plans to update expectations about the internal and external environment. If a salient stimulus is presented, SN would allow allocation of attention, stimulus processing, and initiation of an action (Palaniyappan and Liddle, 2012). Indeed, this network would have a key role in switching among the DMN, the executive control network, and external attention networks (Sridharan et al., 2008; Doucet et al., 2011). Yet only a few studies have examined SN functional connectivity in schizophrenia: Two reported no differences between schizophrenia patients and healthy controls (Woodward et al., 2011; Repovs and Barch, 2012), and two others reported a functional connectivity decrease in schizophrenia patients (White et al., 2010; Tu et al., 2012). SN alteration has been linked to delusions, disorganization symptoms, and psychomotor poverty syndrome (Palaniyappan and Liddle, 2012; Yuan et al., 2012). No study, to our knowledge, has explored the relation between SN function and GM alteration in schizophrenia, but Schultz et al. (2012) reported that a disturbed neuronal activation of the dorsal anterior cingulate cortex (a key region of the SN) during a working memory task was linked to decreased prefrontal GM thickness.

The inconsistency of findings in schizophrenia patients, especially concerning DMN connectivity, can be striking. Part of the problem may be different analysis techniques: seed-based analysis and independent component analysis (ICA). Moreover, results of seed-based analysis rely on the a priori selection of the seed voxel or region, which differs from one study to another. Concerning ICA, results rely largely on the reference maps obtained for DMN and SN, which are based on data from a small number of subjects. As a consequence, reference maps are also quite variable from one study to another.

To avoid such a bias, here we used reference maps from an ICA analysis on a large dataset (resting-state functional magnetic resonance imaging [fMRI] from 282 healthy volunteers). In this way, we were able to reliably explore the functional connectivity of DMN and SN in schizophrenia patients and its relationships to schizophrenia symptoms. When a functional connectivity alteration was found, a structural analysis was carried out to determine whether this functional alteration was linked to a structural (GM) alteration.

2. Materials and methods

2.1. Participants

Twenty-six patients with schizophrenia (SP group) attending at the Department of Psychiatry of Caen University Hospital and twenty-six matched healthy controls (HC group) were included in the study. All participants spoke French as their mother tongue. The patient and control groups were matched for age, sex, handedness, and educational level on a one-to-one basis. All participants had 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.

SP 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), negative (PANSS-N), and general psychopathology (PANSS-G) symptoms. Daily antipsychotic medication dosage was converted to chlorpromazine equivalents (mg/d).

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

2.2. Imaging procedure

2.2.1. Data acquisition

Data acquisition was performed on a 3 T 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."

2.2.2. Functional data

2.2.2.1. Pre-processing. Pre-processing of the functional data was based on the methods described in Naveau et al. (2012). Briefly, it included motion correction, slice-timing correction, band-pass filtering (0.01 Hz < f < 0.1 Hz), co-registration to structural scan, spatial normalization to the Montreal Neurological Institute template, and spatial smoothing (6 mm Gaussian kernel). Each subject's structural scan was segmented into gray matter, white matter, and cerebrospinal fluid using the unified segmentation approach implemented in Statistical Parametric Mapping 5 (SPM5; Wellcome Department of Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm5).

2.2.2.2. Reference maps for DMN and SN. Reference maps for DMN and SN were estimated on a large dataset (resting-state fMRI from 282 healthy volunteers) using a novel group ICA approach based on multi-scale individual component clustering (MICCA), see Naveau et al. (2012) for more demographic and methodological considerations. Within the 34 resting-state networks identified by the MICCA analysis, we retained without ambiguity the two ICA components (i.e., networks) corresponding to the DMN and SN descriptions (Beckmann et al., 2005; Sridharan et al., 2008). Reference maps for DMN and SN are presented in Fig. 1. The DMN consists of eight clusters: a large medial frontal cluster extending up to the superior frontal gyrus; a posteromedial cluster including the precuneus and part of the posterior cingulate; the angular gyrus bilaterally; a large part of the middle temporal gyrus bilaterally; and a medial temporal cluster bilaterally. The SN map is composed of five main clusters: a large medial cluster