NeuroImage: Clinical 9 (2015) 253–263

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Assessing brain structural associations with working memory related brain patterns in schizophrenia and healthy controls using linked independent component analysis

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ARTICLE INFO

Article history:
Received 6 May 2015
Received in revised form 17 July 2015
Accepted 17 August 2015
Available online 21 August 2015

Keywords:
Schizophrenia
Structure–function
Fronto-parietal
Default-mode
Functional magnetic resonance imaging
Linked independent component analysis

ABSTRACT

Schizophrenia (SZ) is a psychotic disorder with significant cognitive dysfunction. Abnormal brain activation during cognitive processing has been reported, both in task-positive and task-negative networks. Further, structural cortical and subcortical brain abnormalities have been documented, but little is known about how task-related brain activation is associated with brain anatomy in SZ compared to healthy controls (HC). Utilizing linked independent component analysis (LICA), a data-driven multimodal analysis approach, we investigated structure–function associations in a large sample of SZ (n = 96) and HC (n = 142). We tested for associations between task-positive (fronto-parietal) and task-negative (default-mode) brain networks derived from fMRI activation during an n-back working memory task, and brain structural measures of surface area, cortical thickness, and gray matter volume, and to what extent these associations differed in SZ compared to HC. A significant association ($p < .05$, corrected for multiple comparisons) was found between a component reflecting the task-positive fronto-parietal network and another component reflecting cortical thickness in fronto-temporal brain regions in SZ, indicating increased activation with increased thickness. Other structure–function associations across, between and within groups were generally moderate and significant at a nominal p-level only, with more numerous and stronger associations in SZ compared to HC. These results indicate a complex pattern of moderate associations between brain activation during cognitive processing and brain morphometry, and extend previous findings of fronto-temporal brain abnormalities in SZ by suggesting a coupling between cortical thickness of these brain regions and working memory-related brain activation.

1. Introduction

Schizophrenia (SZ) is a debilitating illness characterized by delusions, hallucinations and disorganized thought. Impairments of cognitive functions, such as working memory, are also considered core features of the disorder (Green, 2006; Kahn and Keefe, 2013; Park and Gooding, 2014) and have been linked to genetic liability (Agnew-Blais and Seidman, 2013; Reichenberg and Harvey, 2007). However, little is known about how cognitive dysfunction is related to underlying brain anatomy and brain function, and improving our understanding of these associations may help uncover the neuronal substrates of the disease (Kahn and Keefe, 2013; Schultz et al., 2012a).

Neuroimaging studies have identified brain regions and networks involved in cognitive processing (Alnaes et al., 2015; Cabeza and Nyberg, 2000; Cole et al., 2014), and both hypo- and hyperactivation (Brandt et al., 2014; Glahn et al., 2005; Kraguljac et al., 2013; Ragland et al., 2007), as well as brain network dysconnectivity (Brandt et al., 2015; Fornito et al., 2012b; Kaufmann et al., 2015; Pettersson-Yeo et al., 2011) have been reported in SZ. In particular, fMRI studies have demonstrated abnormal neuronal recruitment during working memory

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http://dx.doi.org/10.1016/j.nicl.2015.08.010

processing (Anticevic et al., 2013; Callicott et al., 2003; Glahn et al., 2005; Henseler et al., 2009; Karlsgodt et al., 2007; Kim et al., 2010; Potkin et al., 2009; Schneider et al., 2007; Thormodsen et al., 2011) reflecting dysfunction of a fronto-parietal network including the lateral prefrontal cortex and posterior parietal cortex, as well as anterior cingulate and other regions related to execution of challenging cognitive tasks (Owen et al., 2005). This network shows increased activation during cognitive processing and is thought to reflect focus on task-relevant information, like updating information in working memory. Similar networks have been referred to as central executive (Bressler and Menon, 2010; Sridharan et al., 2008), executive control (Seeley et al., 2007), and task-positive (Fox et al., 2005) networks. The function of such a task-positive fronto-parietal network and its interactions with a task-negative default-mode network (DMN) are considered to play important roles in cognition (Cocchi et al., 2013; Fornito et al., 2012a). The DMN shows task-related deactivation and has been hypothesized to reflect the suppression of task-irrelevant internal activity to optimize goal-directed cognition (Anticevic et al., 2012). Cognitive impairments in SZ may not only be associated with the failure to recruit the fronto-parietal network, but also a relative lack of DMN deactivation (Whitfield-Gabrieli and Ford, 2012). In line with this, a failure of DMN deactivation may reflect a key feature of SZ (Broyd et al., 2009; Landin-Romero et al., 2015; Pomarol-Clotet et al., 2008), and the reciprocity between these two networks may be affected in patients (Anticevic et al., 2013; Nygard et al., 2012; Whitfield-Gabrieli et al., 2009).

Structural brain abnormalities have been consistently reported in patients with SZ, including reductions in cortical thickness, surface area, gray matter volumes, and gyrification (Ellison-Wright and Bullmore, 2010; Gupta et al., 2015; Nesvag et al., 2014; Rimol et al., 2010; Rimol et al., 2012), global and subcortical volumes (van Erp et al., 2015), as well as white matter microstructure as measured by diffusion tensor imaging (DTI) (Ellison-Wright and Bullmore, 2009). Gray matter reductions have been identified in widespread brain regions, but are particularly pronounced in fronto-temporal regions (Glahn et al., 2008; Gupta et al., 2015; Nesvag et al., 2008; Rimol et al., 2010; Schultz et al., 2010), including the insula (Glahn et al., 2008; Shepherd et al., 2012). It has been suggested that these structural brain alterations are associated with abnormal integration of information between frontal and temporal cortical areas (Friston and Frith, 1995; Schultz et al., 2012b). Similarly, functional neuroimaging studies have reported disrupted fronto-temporal connectivity in SZ related to cognitive processing including working memory (Cocchi et al., 2014; Crossley et al., 2009; Meyer-Lindenberg et al., 2001; Wolf et al., 2007), indicating that cognitive impairment is a result of underlying brain dysconnectivity.

In order to understand more of the relationship between structural and functional brain abnormalities in SZ, several studies have examined associations between structural MRI and neuropsychological performance (Ehrlich et al., 2012; Gutierrez-Galve et al., 2010; Hartberg et al., 2010), or between brain structure and brain activation during cognitive tasks using different methods and modalities (see Schultz et al., 2012a for review). A common finding has been significant structure–function associations in patients, but not in healthy controls (Fusar-Poli et al., 2011b; Pujol et al., 2013; Schultz et al., 2012b), indicating differential patterns of associations. Previous studies have however often performed separate analyses of brain structure and function without correlating them directly (Pomarol-Clotet et al., 2010; Skudlarski et al., 2010), while only a few have combined structural and functional measures in the same analysis allowing for interpretation of joint features across modalities (Calhoun et al., 2006; Correa et al., 2008; Michael et al., 2011).

Further, a common approach has been to use structural and functional regions of interest (Harms et al., 2013; Pujol et al., 2013; Schultz et al., 2012b), thus restricting the anatomical interpretations to these regions. The sample size has often been small, comprising around 15 patients and 15 controls (Calhoun et al., 2006; Fusar-Poli et al., 2011a; Pujol et al., 2013; Rasser et al., 2005), which have limited the generalizability. Thus, there is a need for studies combining structural and functional modalities in the same analysis in large samples of patients and controls. Lastly, despite the relevance of task-positive and task-negative networks in cognition and SZ, only one regions-of-interest based study comprising a small number of patients has investigated the relationship between these functional brain systems and brain anatomy in SZ (Pujol et al., 2013).

Summarized, functional and structural imaging has documented a plethora of brain abnormalities in SZ. However, more knowledge is needed to map task-related brain activation onto underlying brain structure in SZ and HC, and to assess if patients show differential structure–function relationships compared to HC. These are important questions pertaining to the fundamental aim of delineating associations between structural and functional properties of the brain, and for increasing the understanding of the mechanisms of severe mental illness, such as SZ.

Thus, the main aim of the current study was to determine structure–function relationships in a large sample of SZ ($n = 96$) and HC ($n = 142$) by combining patterns of fMRI activation during a working-memory paradigm (n-back) and key brain morphometric properties including vertex- and voxel-based measures of surface area, cortical thickness, and gray matter volume. We used linked independent component analysis (LICA), a data-driven approach in which several imaging modalities may be combined (Groves et al., 2011; Groves et al., 2012), and tested for associations between LICA components reflecting brain structural features and functional brain networks related to task-positive and task-negative activation, respectively, and to what degree these associations were different in SZ compared to HC. Based on the few previous studies examining associations between task-related fMRI activation and gray matter structure in SZ (Calhoun et al., 2006; Fusar-Poli et al., 2011a; Harms et al., 2013; Michael et al., 2011; Pujol et al., 2013; Rasser et al., 2005; Schultz et al., 2012b), we hypothesized that strong task-related activation and deactivation would be associated with brain patterns reflecting increased structural integrity, including cortical thickness and gray matter volume in overlapping brain regions. Further, we expected that any group differences in the structure–function relationships would reflect disruptions of fronto-parietal, default-mode, and fronto-temporal brain regions in SZ. Lastly, likely related to larger between-subject variance, we expected stronger structure–function associations in SZ compared to HC.

2. Material and methods

2.1. Sample

Table 1 summarizes participant demographics and clinical variables. 238 participants, overlapping with Brandt et al. (2014, 2015), were recruited as part of the Thematically Organized Psychosis (TOP) study, comprising 96 DSM-IV-diagnosed patients with schizophrenia spectrum disorders (70 schizophrenia, 15 schizoaffective disorder, 11 schizophreniform disorder), referred to as SZ, and 142 healthy controls (HC).

Patients were recruited consecutively from psychiatric units at four major hospitals in Oslo. Healthy controls were randomly selected from the same catchment area as the patient group using statistical records. 28% replied to the invitation and consented to participate, and of these 37.4% participated in the MR scanning. The study is approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Written informed consent was obtained from all participants according to the Declaration of Helsinki.

All participants had to be aged 18–65 years and speak a Scandinavian language. Exclusion criteria were presence of a developmental disorder or serious brain damage, and having metal implants, cardiac pacemaker or other MRI contraindications. Healthy controls were