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Structural covariance in schizophrenia and first-episode psychosis: An approach based on graph analysis

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ABSTRACT

Schizophrenia is a neurodevelopmental disorder that produces abnormalities across different brain regions. Measuring structural covariance with MRI is a well-established approach to investigate common changes in distinct systems. We investigated structural covariance in schizophrenia in a large Brazilian sample of individuals with chronic schizophrenia (n = 143), First Episode Psychosis (n = 32), and matched healthy controls (n = 82) using a combination of graph analysis and computational neuroanatomy.

Firstly, we proposed the connectivity-closeness and integrity-closeness centrality measures and them compared healthy controls with chronic schizophrenia regarding these metrics. We then conducted a second analysis on the mapped regions comparing the pairwise difference between the three groups.

Our results show that compared with controls, both patient groups (in pairwise comparisons) had a reduced integrity-closeness in pars orbitalis and insula, suggesting that the relationship between these areas and other brain regions is increased in schizophrenia. No differences were found between the First Episode Psychosis and Schizophrenia groups. Since in schizophrenia the brain is affected as a whole, this may mirror that these regions may be related to the generalized structural alteration seen in schizophrenia.

1. Introduction

Structural neuroimaging studies of schizophrenia have classically framed brain alterations in terms of either regional volume or thickness disruptions, whereas cerebral abnormalities in schizophrenia appear to be widely distributed (Haijma et al., 2013).

Network perspectives improve descriptions of brain function as both segregated and distributed processing are crucial to cognitive and sensorimotor functions (Bassett and Bullmore, 2006). This framework is particularly relevant to schizophrenia, as it has been suggested that the disorder could be better understood as being caused by a disruption of connections between brain regions (Crossley et al., 2009; Friston and Frith, 1995) or in the interaction of

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more complex circuitry such as the cortical-thalamic-cerebellar-cortical circuit (Andreasen et al., 1999). There is a growing body of evidence supporting anatomical (Canu et al., 2015; Dazzan, 2014) and functional dysconnectivity (Fitzsimmons et al., 2013) in schizophrenia. Connectivity-based disease model may link structural and functional brain abnormalities seen in the disorder (Williams, 2008). In fact, it has been recently found that connectivity patterns may be used to differentiate between schizophrenia patients and healthy controls (Kaufmann et al., 2015), and more interestingly differentiate schizophrenia group from major depressive disorder patients (Guo et al., 2013). Therefore, connectivity measures could potentially be used as disease biomarkers in future studies (Dazzan, 2014).

Structural covariance (or interregional covariance) is an approach that examines whether anatomical change in one region correlates with changes in other brain regions (Lerch et al., 2006; Sato et al., 2013). Structural covariance has been shown to be similar to structural connectivity (Lerch et al., 2006), but also to coordinated developmental changes in the brain, suggesting that it is a signature of developmental processes (Alexander-Bloch et al., 2013). As such, this approach seems suitable to explore neurodevelopmental abnormalities, which have been hypothesized to play a significant role in the pathophysiology of schizophrenia (Murray and Lewis, 1987; Weinberger, 1987). Exploring structural covariance is also suitable to study diffuse pathological brain processes in an interconnected brain (Fornito et al., 2015), such as those observed in schizophrenia (Fornito et al., 2009; Haijma et al., 2013; Wright et al., 2000). Schizophrenia does not seem to fully target specific regions, which could lead to an increase in covariance lead by common pathological factors.

A promising extension of structural covariance analysis is the utilization of graph theory descriptors. Graph analysis yields many different measures when applied to brain imaging (for review, see (Bullmore and Sporns, 2009)). It can be used to study network community structure and topology, characterize system properties (clustering coefficient, path length and network efficiency) or even provide a measure of the importance of a determined node in the system through the use of centrality measures (degree, betweenness, closeness and eigenvector centrality) (Telesford et al., 2011).

Few studies have addressed structural covariance in schizophrenia; however, there appear to be differences in structural covariance when comparing schizophrenia subjects with unaffected controls, including reduced inter-regional correlations between prefrontal, anterior cingulate and temporal regions, and between posterior cingulate and hippocampus (Woodruff et al., 1997). More recently, structural covariance graphs have been investigated in relation to mental disorders. Bassett et al. (2008) used *a priori* hub definitions and found that schizophrenia patients exhibit loss of frontal hubs, increased connection distance and reduced hierarchy. Another study showed that schizophrenia patients had decreased betweenness centrality in associative regions of the cortex and increased centrality in limbic and paralimbic regions (Zhang et al., 2012). Despite previous work, many questions regarding the relationship between structural covariance and complex behavioral disorders such as schizophrenia remain unresolved (Telesford et al., 2011).

Previous work shows that cortical thinning (Ziermans et al., 2012) and cognitive deficits (Bora et al., 2014) are present very early in the course of the disease. Despite differences in distribution and less consistent findings, first-episode group of patients have gray matter deficits very similar to those found in chronic schizophrenia (Williams, 2008). Additionally there is compelling evidence for a decline in gray matter volume during the course of the disease (Haijma et al., 2013; Woods et al., 2005), and this appears to be more prominent in the first years after disease onset (Takahashi et al., 2010; van Haren et al., 2007; Yoshida et al., 2009). It is now recognized that gray matter changes are related to a number of confounding factors, such as antipsychotic treatment (Ho et al., 2011), cannabis use, and disease outcome (Van Haren et al., 2013). However, there is no consensus as to when in the course of the disease volume reduction of specific regions occurs. If network measures reflect underlying biological characteristics that are central to disease onset, any illness-related abnormalities are likely to be similarly present in chronic schizophrenia and FEP patients.

When considering these previous findings, we are challenged by a paradox. On one hand, the connectivity disruptions frequently described in schizophrenia naturally lead to a hypothesis of a reduced structural covariance in patients, when compared to controls. Alternatively, common neurodegenerative/volumetric reductions driven by the disease may result in an increase in structural covariance.

The aim of the current study was to tackle this paradox by the investigation of differences in structural covariance among healthy controls, schizophrenia and FEP groups from a graph theory perspective, based on closeness measures. We propose two different metrics: connectivity-closeness and integrity-closeness. Graph-related alterations of key hub regions in the whole-brain networks are likely to reflect the impairment of integration and contextualization of different stimuli into complex representations, as well as higher cognitive functions such as working memory or executive functioning (Rubinov and Bullmore, 2013). We hypothesize that the regions exhibiting abnormal structural covariance patterns would be related to functional brain networks that are impaired in schizophrenia, specifically alterations of the nodes related to the fronto-parietal-temporal and limbic network.

2. Material and methods

2.1. Subjects

One hundred and forty-three patients (68% males; mean age = 37.18 years, s.d. = 11.05) with a diagnosis of chronic schizophrenia, 82 healthy matched controls (63% males; mean age = 35.48 years, s.d. = 11.16) and 32 subjects with FEP (53.12% males; mean age = 27.09 years, s.d. = 7.98) were included in the study.

Individuals were recruited from the Schizophrenia Program (PROESQ) at the Federal University of São Paulo (UNIFESP) and from an emergency unit at the Santa Casa de Misericordia de São Paulo. The Structured Diagnostic Interview for DSM-IV (SCID), applied by trained psychiatrists, was used to confirm the DSM-IV criteria for schizophrenia and FEP. FEP was defined by a distinct period characterized by the emergence of psychotic symptoms. The beginning of the psychotic episode was determined as the most recent time point at which the individual clearly did not show psychotic symptoms. Additionally FEP group individuals were recruited at the time they were seeking help for psychotic symptoms for the first time.

Patients with psychotic episodes due to a general medical condition, substance-induced psychotic disorder or mental retardation were excluded, as well as patients with diagnoses of psychotic episodes related to bipolar disorder or depression. All FEP individuals were using risperidone and patients in chronic schizophrenia group were receiving treatment as usual at the time of the scan. In the FEP group all patients were scanned during the first three months of treatment, assessing the potential confounding effect of long-term use of antipsychotics and illness chronicity. Patients with chronic schizophrenia had at least two years of disease. All chronic schizophrenia patients were being treated in an