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First episode psychosis moderates the effect of gray matter volume on cognition

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ABSTRACT

Patients with first episode psychosis (FEP) present with cognitive deficits and volume differences in certain brain areas. Brain volumetric information further correlates with cognitive testing, and multiple brain areas shows different strengths of correlation with the cognitive functions being tested. Traditionally, these cognitive functions are independently related to volumetric differences, but these functions share variance. Failing to account for this aspect of cognition hinders the proper representation of cognition in neuroimaging studies. We used modeling methods which account for this shared variance to investigate the differences of correlations between cognitive abilities and brain areas. A multiple-groups structured equation model (SEM) approach was used to design and test a model representing the relation between gray matter volumetric data and neuropsychological test scores in a sample of 100 Brazilian FEP patients and 94 controls. Models with a latent variable formed by neurological measures and reflecting cognitive measures performed better on fit tests. FEP moderated the relation between gray matter volumes and cognition by altering the profile of correlations between groups. This moderation had a large effect size. SEM provides a fine grained picture of the interdependence of structural brain changes and cognition.

1. Introduction

Patients in their first episode of psychosis (FEP) usually have deficits on cognitive testing (Ayres et al., 2007; Bilder et al., 2000; Eastvold et al., 2007). By the time of their first assessment, they present with reduced scores on the domains of verbal memory (Barch et al., 2001; Barnett et al., 2005) and attention (Nuechterlein et al., 2006) performance, as well as in psychomotor speed (Chan et al., 2006). Together with these cognitive deficits, brain structural alterations are also found. Reduced gray matter has been reported in prefrontal and temporal regions, hippocampus, parahippocampal gyrus and insula of FEP patients (Chua et al., 2007; Schaufelberger et al., 2007).

Brain volumes can be assessed through several methods, most typically voxel-based and ROI-based approaches. The process of inferring correlation involves the analysis of descriptive measures of association, like coefficients, between voxels or areas of interest and cognitive performance in tests. Although useful, these methods cannot account for the shared variance in the data, because cognitive abilities are represented by variables and correlated to clusters of voxels as if the different abilities were independent. This would make sense in a neuropsychology in which the mind is composed of distinct and categorical faculties, a model of cognition that has been largely abandoned (Barrett, 2011). Cognitive abilities are deeply intertwined, they usually share variance and their scores are positively correlated (Van Der Maas et al., 2006); performing numerous independent comparisons in a large set of these variables (even if corrected for multiple comparisons) will lead to more correlations than there actually are, because of the variance they share. Adding model designs to these traditional methods permit elaborated ways of representing data (Kievit et al., 2011), while maintaining parsimony in the number of comparisons. Furthermore, modeling data underlies an important feature of the latest classification systems, for instance it permits representing domains and units of analysis in the RDoC framework (Castro-de-Araujo et al., 2016).

Not much is known about the relation of FEP patients' regional volumes to cognition. One paper reports temporo-parietal and prefrontal correlation to cognitive performance in FEP patients (Minatogawa-Chang et al., 2009), another reports correlation between cognition and brain volume directly as well as mediated through an intermediary liability phenotype (Toulopoulou et al., 2015). This paper aims to further explore alterations in brain volume and cognition with

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structural equation modeling (SEM), which can be used to design models and latent variables, while solving for correlations between several brain volumetric data and cognitive performance tests.

This paper also focuses on clarifying whether the relationship between gray matter structure and cognitive performance differs in FEP patients as compared to healthy subjects. The presence of such a difference might suggest gray matter in ill subjects support cognition differently than it does in healthy ones. A multiple groups structured equation model approach was used, as it is an optimal method to evaluate the relationship between several variables, and to design and test a model representing these relations. The model was specified with a latent variable representing cognitive ability (*ng*), which was correlated to gray matter volumetric data and to neuropsychological test scores. Based on the aforementioned cognitive impairment in patients with FEP, we hypothesized that its presence would moderate the effect of gray matter structure on cognitive performance and that this moderation would be reflected in the latent variable mean, i.e., we expected a large effect size when comparing the mean of the latent variable between the groups.

2. Methods

2.1. Subjects

Our sample of FEP patients and healthy controls were recruited for an epidemiologically-based neuroimaging study that investigated the presence of brain volume changes in patients experiencing their first episode of psychosis in the city of São Paulo, Brazil (Menezes et al., 2007; Minatogawa-Chang et al., 2009; Schaufelberger et al., 2007). This study was led jointly by the University of Sao Paulo (Brazil) and Kings College London (UK), and they granted us access to the clinical, neuropsychological and MRI data.

A subset of 100 first episode psychosis (FEP) was used in this analysis. The inclusion criteria were: age between 18 and 50 years; patients presented DSM-IV criteria for the diagnosis of psychosis (APA, 1994) assessed with the Structured Clinical Interview for DSM-IV-SCID (First et al., 1997). The exclusion criteria for patients and healthy subjects: psychosis due to general medical condition, substance-induced psychoses, history of head injury, neurological and organic disorders affecting the central nervous system, and the usual contraindications for MRI scanning.

Only executive function measurements were recorded in this dataset. The two cognitive measures used were the forward digit span test from the Wechsler Memory Scale – Third Edition (Wechsler, 1995) and the Controlled Oral Word Association Test (COWAT) (Benton and Hamser, 1983). The analysis was performed using the raw scores. In conjunction, these measures can gauge attention, working memory and executive function.

Ninety-four healthy subjects were drawn from the same study (Menezes et al., 2007; Schaufelberger et al., 2007). They had similar demographic characteristics as the patients, except for more years of education (Table 1).

From the 100 FEP patients, 56 subjects had schizophrenia, 37 had affective psychosis (bipolar disorder or psychotic major depression), and 7 were classified under other psychosis categories (schizoaffective disorder, brief psychosis and psychotic disorder not otherwise specified) according to DSM-IV (APA, 1994). At the time of the neuropsychological evaluation, 34 subjects were not taking medication and 66 were. The sample comprised 58 males and 42 females, with a mean age of 28.37 years; 89 subjects were right-handed, 8 left-handed and 3 mixed-handed.

2.2. Neuroimaging

Images were obtained using two 1.5 T GE Sigma scanners (General Electric, Milwaukee WI, USA) at the University of São Paulo Clinics Hospital. One-hundred and twenty four contiguous axial coronal images were acquired using a T1-SPGR sequence, TE/TR = 5.2 ms/21.7 ms, flip angle = 20o, field of view = 22 cm, matrix = 256 × 192, and voxel dimensions 0.86 × 0.86 × 1.5 mm.

Table 1
Summary of group's characteristics.

Variables	Healthy subjects (n = 94) mean (sd)	Patients with FEP (n = 100) mean (sd)	*p*-value
Age	30.21(8.4)	28.37 (8.30)	0.09[a]
Gender			
Male (%)	56.4%	58%	0.88[b]
Female (%)	43.6%	42%	
Time from onset in days	NA	297.6 (376.6)	
Education (mean, in years)	10.03 (4.15)	8.87(3.85)	0.048[a]
PANSS total score	NA	45.29 (11.64)	
Gray Matter Total Volume	570252.2 mm^3 (88302.54 mm^3)	586776.4 mm^3 (85992.90 mm^3)	0.21[a]
Forward digit and COWAT raw scores sum	32.96 (12.24)	30.19 (14.68)	0.04[a]
Handedness			
Right	96.8%	89%	0.12[b]
Left	2.1%	8%	
Mixed	1%	3%	

[a] Wilcoxon-Mann-Whitney test was used for the continuous variables.
[b] The correlation of the categorical variables was carried out using Fisher exact test. n, number of patients; sd, standard deviation.

2.3. Image processing, assumption testing and statistical packages

Images from the subjects were in Analyze format; parcellations, segmentations, and cortical reconstruction were calculated with FreeSurfer's recon-all command (version 5.3.0, freely available at http://surfer.nmr.mgh.harvard.edu/). Cortical parcellation was performed in FreeSurfer via automated assignment of neuroanatomical labels to the locations on a cortical surface model. This pairs the Desikan-Killiany Atlas neuroanatomical convention on a training set with geometrical information from the cortical model. The technical details of these procedures are described in previous papers (Dale et al., 1999; Ségonne et al., 2004). The recon-all command generates tables in plain text containing the multiple areas and their volumes in mm^3, which were then imported into R.

Latent variable modeling was carried out using R (version 3.0.2). The R lavaan package was used to specify the models and later run the structural equation (Rosseel, 2012). Standard notation in SEM was used: boxes to represent measures (referred to as indicators), circles to represent latent variables, arrows to represent regressions. Note, however, that the residuals and correlations between the areas are not represented in the diagrams.

We had access to volumes of several brain areas, but in order to follow Kline's (2004a, 2004b) recommendation of 10–20 observations per indicator we focused on a subset of these (Kline, 2004a). A modification indices test was performed in a reflective model including all available neuroanatomical and cognitive variables regressing to the latent variable. The most influential areas in this model were used. The modification indices test is part of the lavaan package. It iteratively removes one indicator at a time from the model and then calculates the difference that this removal causes to the chi-square value. Each indicator is then ranked from the most to the least influential to the model. The resulting set of areas used comprised left fusiform area, right pars triangularis, left rostral middle frontal area, right rostral anterior cingulate area, left insula, left and right superior supramarginal area, right pericalcarine area, left parahippocampal area, left pars opercularis, right middle temporal area, left paracentral area.