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Investigating brain structural patterns in first episode psychosis and schizophrenia using MRI and a machine learning approach

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A B S T R A C T

In this study, we employed the Maximum Uncertainty Linear Discriminant Analysis (MLDA) to investigate whether the structural brain patterns in first episode psychosis (FEP) patients would be more similar to patients with chronic schizophrenia (SCZ) or healthy controls (HC), from a schizophrenia model perspective. Brain regions volumetric data were estimated by using MRI images of SCZ and FEP patients and HC. First, we evaluated the MLDA performance in discriminating SCZ from controls, which provided a score based on a model for changes in brain structure in SCZ. In the following, we compared the volumetric patterns of FEP patients with patterns of SCZ and healthy controls using these scores. The FEP group had a score distribution more similar to patients with schizophrenia (p-value = .461; Cohen's d = −.15) in comparison with healthy subjects (p-value = .003; Cohen's d = .62). Structures related to the limbic system and the circuitry involved in goal-directed behaviours were the most discriminant regions. There is a distinct pattern of volumetric changes in patients with schizophrenia in contrast to healthy controls, and this pattern seem to be detectable already in FEP.

1. Introduction

Decrease in brain gray matter volume and ventricle enlargement are the most replicated findings in neuroimaging studies of patients with schizophrenia (SCZ)(Haijma et al., 2013; Shepherd et al., 2012). Even in early stages, such as the first episode psychosis (FEP), morphometric differences were found in comparison to healthy control subjects (HC) (Chan et al., 2011; Shepherd et al., 2012). Although several studies have reported progressive gray matter volume (GMV) changes along the course of SCZ (Andreasen et al., 2011; Chan et al., 2011; Haijma et al., 2013; Shepherd et al., 2012; van Haren et al., 2008), the specificity and diagnostic value of structural MRI are still not established (Linden, 2012).

Three issues challenge the advance in this field. First, brain changes observed in SCZ are subtle and widespread, which requires analysis methods suitable to deal with multivariate patterns (Shepherd et al., 2012). Second, most studies in the literature concentrate in chronic patients populations, which are subject to many confounders, such as long term medication effects (Fusar-Poli et al., 2013). Third, schizophrenia patients can manifest a wide range of symptoms varying from paranoid delusions to catatonic behaviour (Kennedy et al., 2014).

Machine learning and pattern recognition techniques have been shown to be promising tools in neuroimaging data analysis (Kloppel et al., 2012; Schnack et al., 2014). Given the multivariate nature of these methods, it is possible to examine the information in a manner to capture subtle distributed neuroanatomical differences. Indeed, the current literature comprises studies based on machine learning classifiers to discriminate patients with SCZ from HC (Davatzikos et al., 2005; Kambeitz et al., 2015; Zarogianni et al., 2013). Some studies have reported high predictive accuracies (about 80–90%) (Fan et al., 2007; Orru et al., 2012; Schnack et al., 2014; Veronese et al., 2013). For example, using structural MRI (T1 weighted images), Fan et al. (2007) were able to classify 46 patients with SCZ and 41 HC with an accuracy of 90.8% using a combination of deformation-based morphometry, feature selection procedures, and Support Vector Machine based classification. However, when analysing large sample groups, the classifiers

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accuracies can drop substantially. For example, Nieuwenhuis et al. (2012), also using structural MRI, achieved about 70% in two independent samples with over 200 subjects each. One possible confounder to interpret brain imaging data on schizophrenia are the effects of antipsychotics and/or disease progression, both leading to structural changes (Emsley et al., 2013; Ho et al., 2011). Nonetheless, machine learning techniques have not been extensively used to investigate the neuroanatomical patterns in FEP, although few studies have reported promising findings (Borgwardt et al., 2013; Pettersson-Yeo et al., 2013; Squarcina et al., 2017). Moreover, neuroimaging data analysis requires handling several features (voxels or brain regions), which difficult the utilization of conventional methods (such as LDA) due to singularity problems, the so called "curse of dimensionality". However, the Maximum Uncertainty Linear Discriminant Analysis (Thomaz et al., 2004) (MLDA) classification model was reported to be very promising in previous studies (Kasparek et al., 2011; Sato et al., 2008; Thomaz et al., 2004). This method was developed with main concern of dealing with high data dimensionality (Thomaz et al., 2006), avoiding matrix singularity and instability problems.

In the current exploratory study, we applied MLDA to analyse chronic and FEP patients' brain patterns based on MRI. Our aim was to evaluate whether the volumetric patterns of FEP patients were more similar to chronic SCZ patients or the pattern of HC. We hypothesized that FEP patients would at least present a brain structural pattern in between HC and SCZ.

2. Methods

2.1. Subjects

Psychiatrists assessed 82 HC, 143 patients with chronic SCZ from an outpatient unit of the Federal University of São Paulo (UNIFESP), and 32 FEP patients from the psychiatric emergency unit at Santa Casa de Misericórdia de São Paulo (Table 1). Exclusion criteria for all participants were history of neurological diseases, substance abuse or traumatic brain injury with loss of conscience. The SCZ patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for SCZ, based on the Structured Clinical Interview of the DSM-IV (SCID-I). The severity of their symptoms was assessed using the PANSS (Positive and Negative Syndrome Scale).

FEP was defined by a distinct period characterized by the emergence of psychotic symptoms. To determine the beginning of the psychotic episode, we determined the last time point at which the individual clearly did not show psychotic symptoms. The diagnosis of a psychotic disorder was established by trained psychiatrists, according to the criteria of DSM-IV using SCID-I. Exclusion criteria were: age (only participants between 16 and 40 years of age were selected) and prior history of antipsychotic medication exposure. Only patients that were initially diagnosed with schizophrenia were included.

All SCZ and FEP were using antipsychotics. The SCZ outpatient could be in use of any antipsychotic. The FEP patients were all initially treated with risperidone, the dose between 2 and 6 mg. The MRI scans for FEP patients were acquired approximately within 2 months of the beginning of antipsychotic treatment. The duration of untreated psychosis differed greatly for FEP subjects, ranging from 1 week to 2 years.

The HC group were composed of antipsychotic-naïve, healthy volunteers assessed for personal and familiar history of psychiatric disorders according to the criteria of the SCID-I. Table 1 presents the demographical and clinical data of the sample used in this study. The HC and SCZ groups were matched by age and gender. All subjects provided informed written consent for participation in accordance with the approval of local research ethics committees.

2.2. MRI data acquisition

The subjects were scanned by using a 1.5T Siemens scanner (Magnetom Sonata A.G.; Siemens Medical Solutions, Erlangen, Germany), equipped with an 8-channel head coil using 3D spoiled gradient-recalled-echo (SPGR) sequences. T1-weighted sagittal images acquisition parameters were: TR = 2000 ms; TE = 3.42 ms; FOV = 245 mm; flip angle = 15°; matrix size = 256 × 256; NEX = 1; up to 192 slices, 1.0-mm slice thickness with no gaps. In some cases, the voxels size was increased up to .1 mm for whole-brain coverage.

2.3. Imaging processing

The T1-weighted structural images of all participants were processed with FreeSurfer image analysis suite (version 5.0, http://surfer.nmr.harvard.edu). The "recon-all" standard procedure estimated the volume of brain regions according to the Desikan-Killiany atlas, using an automated cortical, subcortical and white matter segmentation process (Fischl et al., 2004). Ninety-nine regions were considered in the following analyses (see Supporting Table 1). Before recon-all pipeline the images were visually inspected for excessive motion artifacts. No manual corrections were applied, since this could potentially introduce arbitrary artifacts that could bias the analyses. All subjects used in this study were successfully processed in recon-all.

Table 1
Demographic and clinical information. The statistical tests were performed between HC and SCZ groups.

	Healthy Control (n = 82)	First Episode Psychosis (n = 32)	Patients with chronic SCZ (n = 143)	Statistics
Age, years (mean ± SD)	35.66 ± 11.05	27.09 ± 7.98	37.12 ± 10.99	t = 1.10, df = 227, P = .27
Sex, n (%)				X^2 = .41, df = 1, P = .52
Men	51(62%)	15(47%)	95(66%)	
Women	31(38%)	17(53%)	48(34%)	
PANSS (mean ± SD)				
Positive	–	–	12.74 ± 4.46	
Negative	–	–	16.92 ± 5.50	
General	–	–	29.06 ± 7.35	
Total	–	–	58.59 ± 14.47	
Medication load[a]				
Olanzapine			34%(14.80 ± 6.43)	
Clozapine			31%(22.56 ± 7.96)	
Quetiapine			12%(18.00 ± 6.13)	
Risperidone			8%(11.50 ± 5.02)	
Aripriprazole			4%(20.10 ± 11.01)	
others			11%(29.08 ± 28.64)	

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SCZ, Schizophrenia; SD, standard deviation.

[a] The medication load is present as "percentage of patients users % (average of mg/day in Olanzapine equivalent ± standard deviation).