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Neuroanatomical pattern classification in a population-based sample of first-episode schizophrenia

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ABSTRACT

Recent neuroanatomical pattern classification studies have attempted to individually classify cases with psychotic disorders using morphometric MRI data in an automated fashion. However, this approach has not been tested in population-based samples, in which variable patterns of comorbidity and disease course are typically found. We aimed to evaluate the diagnostic accuracy (DA) of the above technique to discriminate between incident cases of first-episode schizophrenia identified in a circumscribed geographical region over a limited period of time, in comparison with next-door healthy controls. Sixty-two cases of first-episode schizophrenia or schizophreniform disorder and 62 age, gender and educationally-matched controls underwent 1.5 T MRI scanning at baseline, and were naturalistically followed-up over 1 year. T1-weighted images were used to train a high-dimensional multivariate classifier, and to generate both spatial maps of the discriminative morphological patterns between groups and ROC curves. The spatial map discriminating first-episode schizophrenia patients from healthy controls revealed a complex pattern of regional volumetric abnormalities in the former group, affecting fronto-temporal-occipital gray and white matter regions bilaterally, including the inferior fronto-occipital fasciculus, as well as the third and lateral ventricles. However, an overall modest DA (73.4%) was observed for the individual discrimination between first-episode schizophrenia patients and controls, and the classifier failed to predict 1-year prognosis (remitting versus non-remitting course) of first-episode schizophrenia (DA = 58.3%). In conclusion, using a "real world" sample recruited with epidemiological methods, the application of a neuroanatomical pattern classifier afforded only modest DA to classify first-episode schizophrenia subjects and next-door healthy controls, and poor discriminative power to predict the 1-year prognosis of first-episode schizophrenia.

1. Introduction

Neuroanatomical pattern classification is a new method for brain image analysis which allows high-dimensional voxelwise between-group comparisons and classification of scans at an individual basis (Fan et al., 2007; Klöppel et al., 2012). Given the multivariate nature of their statistical approach, and the possibility to employ both linear and non-linear analysis models, these techniques afford improved sensitivity to uncover complex morphological brain differences in comparison to other voxelwise methods (Fan et al., 2007). Moreover, once the pattern of abnormalities which better discriminates two groups is defined, this morphological signature can be used to classify images at an individual basis, and measures of diagnostic accuracy (DA) can be obtained (Fan et al., 2007; Klöppel et al., 2012). Thus, the use of pattern classification methods is nowadays thought to hold promise as an auxiliary tool to aid clinical diagnoses and outcome prediction in clinical psychiatric practice (Klöppel et al., 2012).

Up until now, a limited number of structural magnetic resonance imaging (MRI) studies have investigated the usefulness of pattern classification methods in the evaluation of schizophrenia, producing variable results. Based on T1-weighted MRI scans, a few of those

Abbreviations: AUC, area under the curve; AUDIT, alcohol use disorders identification test; ARMS, at-risk mental state; COMPARE, classification of morphological patterns using adaptive regional elements; DRAMMS, deformable registration via attribute matching and mutual-saliency weighting; DA, diagnostic accuracy; FSL, FMRIB software library; FLIRT, FMRIB's linear image registration tool; LOOCV, leave-one-out cross validation; MNI, Montreal Neurological Institute; NPV, negative predictive value; PANSS, positive and Negative Syndrome Scale; PPV, positive predictive value; ROC, receiver operating characteristic (curve); RAVENS, regional analysis of volumes examined in normalized space (map); SVM, support-vector machine; VBM, voxel-based morphometry.

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studies reported good classification performances (overall accuracies of up to 91.8%) in the individual classification of subjects with both chronic (Fan et al., 2007; Kawasaki et al., 2007; Sun et al., 2009; Yoon et al., 2007) and first-episode (Borgwardt et al., in press; Pohl and Sabuncu, 2009; Takayanagi et al., 2010, 2011) schizophrenia against controls, with sample sizes as small as 16 subjects per group (Kawasaki et al., 2007; Pohl and Sabuncu, 2009). Also, Koutsouleris et al. (2009, 2012) — using two different cohorts of individuals at an at-risk mental state (ARMS) for the development of psychosis — found good discrimination (accuracies of up to 92.3%) between ARMS and healthy individuals, as well as to predict later conversion to full-blown psychosis after a 4-year follow-up period. However, more recent studies evaluating larger samples of patients with first-episode schizophrenia (Kasparek et al., 2011) or more generally in first-episode psychosis (Mourao-Miranda et al., 2012) have found very modest between-group discrimination, with classification accuracies varying from 54% to 71%. Moreover, Nieuwenhuis et al. (2012), in the largest study of neuroanatomical pattern classification in schizophrenia published so far, have also achieved a modest classification accuracy of only up to 71.4% when comparing two independent samples of, respectively, 128 (training sample, average duration of illness of 10.3 years) and 155 (validation sample, average duration of illness of 5.0 years) schizophrenia patients against matched healthy controls.

Differences in the pipelines for image processing, feature extraction/dimensionality reduction and pattern recognition methods, might at least partly account for the above discrepancies across structural MRI studies (Caprihan et al., 2008; Fan et al., 2007; Nieuwenhuis et al., 2012; Pohl and Sabuncu, 2009). Nevertheless, conflicting findings have been observed even across pattern classification studies that employed similar methods (Ardekani et al., 2011; Caprihan et al., 2008; Castellani et al., 2012; Kasparek et al., 2011; Kawasaki et al., 2007; Pohl and Sabuncu, 2009). Another potential factor that might contribute for this heterogeneity of findings is the occurrence of biases in the selection of cases and controls for each MRI study. In this regard, it is relevant to note that none of the investigations of schizophrenia employing neuroanatomical pattern classification to date have employed population-based approaches. In population-based studies, epidemiological methods are used to identify and recruit large and representative samples of incident cases of first-episode schizophrenia and demographically-matched controls from the same, circumscribed geographical area. The use of such designs to recruit participants is desirable to reduce selection biases by ensuring that control individuals truly represent the population from which the cases came from (Grimes and Schulz, 2005; Lee et al., 2007).

In the present morphometric MRI study, a sample of patients with first-episode schizophrenia disorder and a group of demographically-matched healthy controls were recruited using an epidemiologic approach. All subjects were followed-up naturalistically over a 1-year period, with re-interviews carried out for diagnostic confirmation and assessment of prognosis (remitting versus non-remitting course). A support-vector machine (SVM) classifier was employed with the following purposes: 1) to ascertain how distinguishable are schizophrenia individuals from healthy controls at the time of FE using T1-weighted MRI data acquired by 1.5 T scanning; 2) to evaluate the performance of the classifier in correctly predicting 1-year outcome of first-episode schizophrenia patients; and 3) to describe patterns of complex morphological features significantly associated with schizophrenia at an early course of the illness.

2. Methods

2.1. Participants

Patients fulfilling Diagnostic and Statistical Manual for Mental Disorders, 4th edition, (DSM-IV) (American Psychiatric Association, 1994) criteria for first-episode schizophrenia/ schizophreniform disorder were selected from a large sample of first-episode psychosis individuals who took part in a population-based case-control study investigating the incidence of psychotic disorders in a circumscribed region of São Paulo city, as previously described (Menezes et al., 2007; Schaufelberger et al., 2007).

In the original epidemiological investigation, cases were identified by active surveillance of all people that made contact for the first time with the mental healthcare services for that region between 2002 and 2005 due to a DSM-IV defined psychotic disorder, regardless of its severity (both outpatients and inpatients were recruited), duration of illness or compliance to treatment. Patients with psychotic disorders due to a general medical condition or substance-induced psychosis were excluded. The research team provided general guidance to patients but they were referenced to treatment at the health services located in the geographical region where they lived in.

For the present study, only the cases diagnosed as having schizophrenia or schizophreniform disorder according to the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) were considered. From the total pool of 122 FE psychosis individuals identified in the original neuroimaging investigation (Schaufelberger et al., 2007), 62 fulfilled DSM-IV diagnostic criteria for schizophrenia or schizophreniform disorder and thus constituted our study group. All the individuals who remained under the schizophreniform disorder diagnosis have achieved symptomatic remission before completing 6 months of illness duration during the follow-up (the only DSM-IV criterion differentiating schizophrenia from schizohreniform disorder). In order to make it simpler for the reader, we decided to refer to this group simply as "first-episode schizophrenia" throughout the manuscript. Details about the other psychosis cases not included in the present investigation can be found elsewhere (Colombo et al., 2012; Schaufelberger et al., 2007).

In order to obtain a population-based psychosis-free sample of controls, next-door neighbors matched for age (within 5 years) and gender with psychosis cases were initially screened to exclude the presence of psychotic symptoms using the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995), and interviewed with the SCID (non-patient version) for the assessment of other psychiatric disorders. This approach resulted in an initial pool of 94 psychosis-free epidemiological controls eligible for the neuroimaging investigation (Colombo et al., 2012; Schaufelberger et al., 2007), from which 5 individuals fulfilled criteria for substance misuse and 12 individuals fulfilled criteria for anxiety disorders (Colombo et al., 2012). For the present investigation, aiming at selecting a homogeneous control sample to be used by the classifier, 62 age, gender and educationally-matched healthy individuals free of any Axis I disorder (including lifetime substance abuse and/ or dependence) other than specific phobia were selected and formed our control group.

Other inclusion criteria for both schizophrenia cases and controls were: (a) current age between 18 and 50 years; (b) residence for 6 months or more in defined geographic areas of Sao Paulo. The exclusion criteria consisted of: (a) history of head injury with loss of consciousness; (b) presence of neurological disorders or any organic disorders that could affect the central nervous system; (c) moderate or severe mental retardation; and (d) contraindications for MRI scanning.

Both first-episode schizophrenia patients and healthy controls were followed-up naturalistically over a 1-year period, with re-interviews carried out for diagnostic confirmation and assessment of prognosis (remitting versus non-remitting course in the patients).

The study was approved by local ethics committees, and all subjects provided informed written consent.

2.2. Clinical assessment scales

The severity of psychotic symptoms in the schizophrenia patients was assessed using the Positive and Negative Syndrome Scale (PANSS)