# 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

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)

(Kay et al., 1987). Both patients and controls were screened for substance use with the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) and the South Westminster Questionnaire (Menezes et al., 1996); when appropriate, diagnoses of substance use disorders in the psychoses groups were made using the SCID. A general medical history, including medication use, was obtained directly with each participant or with his/her relatives, and also through reviewing of medical records.

All clinical assessment tools, including the SCID, were administered to the participants both at baseline (T0) and at the 1-year follow-up evaluation (T1). At T1, the outcome of first-episode schizophrenia was also determined using the DSM-IV course (remitting/ non-remitting) specifier (remitting course meaning a single episode in full remission and absence of clinically important symptoms and a non-remitting course meaning continuous, episodic or residual symptoms) (American Psychiatric Association, 1994).

### 2.3. Neuroimaging data acquisition and analysis

Imaging data were acquired using two identical MRI scanners (1.5 T GE Signa scanner, General Electric, Milwaukee WI, USA). Exactly the same acquisition protocols were used (a T1-SPGR sequence providing 124 contiguous slices, voxel size $= 0.86 \times 0.86 \times 1.5$ mm, TE $=$ 5.2 ms, TR $= 21.7$ ms, flip angle $= 20$, FOV $= 22$ cm, matrix $= 256 \times 192$ pixels). The images of 41 first-episode schizophrenia patients (66.1%) and 38 healthy controls (61.3%) were acquired using Scanner #1.

All images were visually inspected by an experienced radiologist with the purpose of identifying artifacts during image acquisition and the presence of silent gross brain lesions.

Fig. 1 summarizes the pipeline of image processing and analysis employed in the present study.

Initially, the T1-weighted images were pre-processed as follows: skull-stripping; manual removal of the cerebellum in order to improve the tissue segmentation of the temporal lobe; and correction for signal inhomogeneities. The images were subsequently segmented into their 3 principal brain tissue compartments (gray matter, white matter, and cerebrospinal fluid space) through an automated routine. Images were then spatially registered to a Montreal Neurological Institute (MNI) single-subject brain template through two steps (Fig. 1). Firstly, an affine transformation was performed using the FLIRT (*FMRIB's Linear Image Registration Tool*) tool of the FSL

(*FMRIB Software Library*, http://www.fmrib.ox.ac.uk/fsl/flirt) in order to align the major brain structures to the MNI template, and also to correct for differences in head positioning. Secondly, a robust method for elastic registration called *Deformable Registration via Attribute Matching and Mutual-Saliency weighting* (DRAMMS) (Ou et al., 2011) was employed. The deformation field resulting from the spatial registration of each T1-weighted image to the MNI template was applied to the segmented images in order to generate mass-preserved volumetric maps, named *Regional Analysis of Volumes Examined in Normalized Space* (RAVENS) maps of the gray matter, white matter, and cerebrospinal fluid compartments (Shen and Davatzikos, 2003). An automated algorithm was used to isolate the cerebral ventricles (lateral ventricles and third ventricle) from the remaining cerebrospinal fluid space, resulting in a ventricular RAVENS map. In the RAVENS maps, the tissue density reflects the amount of tissue present in each subject's image at a given location, after mapping to the standardized template space (Shen and Davatzikos, 2003). Thus, a region of decreased density indicates a reduced volume in this structure, for example. Lastly, the RAVENS maps (gray matter, white matter and ventricles) were corrected for the total brain volume (given by the sum of all voxels of brain tissue and cerebrospinal fluid space) and smoothed with 8 mm Gaussian kernels.

The gray matter, white matter and ventricular RAVENS maps were used as inputs for a previously described and validated SVM-based pattern classifier named *Classification of Morphological Patterns Using Adaptive Regional Elements* (COMPARE) (Fan et al., 2007) (https://www.rad.upenn.edu/sbia/software/index.html#compare). In this method, voxelwise correlations between RAVENS maps and group membership are used to identify voxels that are candidates to be useful for intergroup discrimination. To achieve the necessary dimensionality reduction, a watershed segmentation algorithm is then used to group voxels into regional clusters and to identify the most relevant features to classification (group discrimination) (Fan et al., 2007). This approach also works as an initial feature selection step, reducing the initial dimensionality of the data from millions of variables to a relatively small set of regional volumetric measurements, which the subsequent classifier can handle successfully. In order to improve the spatial consistency of the watershed-derived regional volumetric elements and also to minimize the inclusion of voxels not relevant for the classification (which might reduce the discriminative power), the degree of agreement among all features in its spatial neighborhood is computed by an intraclass
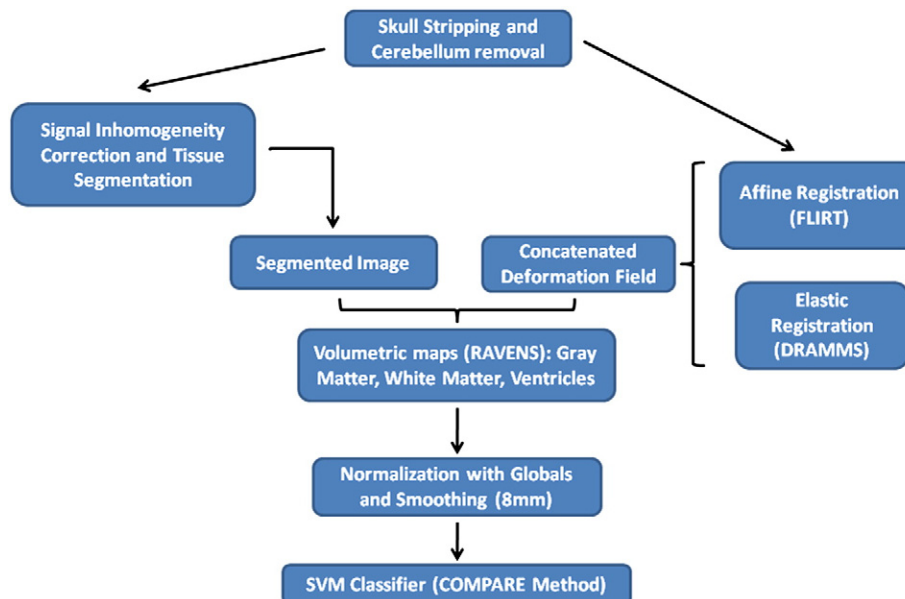


**Fig. 1.** Routine employed for the processing and analysis of T1-weighted MRI images.

correlation coefficient, and a region-growing method based on the Pearson correlation coefficient is employed (Fan et al., 2007). Here, the voxel with the highest discriminative power in each watershed-derived region is first selected, and the neighboring voxels are included as long as their inclusion will not decrease the discriminative power of the regional feature. Finally, a feature-selection technique based on SVM criteria is used to select a sub-set of the top-ranked features that optimizes the performance of the classifier, constituting the "morphological signature" of each group under study which is used by the classifier (Fan et al., 2007). The COMPARE classifier, then, employs a non-linear SVM method to assign a class label to each image under study (individual classification of the MRI scans) through a Gaussian radial basis function kernel.

Although other theoretical frameworks for pattern recognition analyses are available (Caprihan et al., 2008; Kasparek et al., 2011; Sun et al., 2009), SVM with sufficient dimensionality reduction is currently one of the most widely employed pattern classification models in the study of neuropsychiatric disorders (Fan et al., 2007; Klöppel et al., 2012; Koutsouleris et al., 2009; Mourao-Miranda et al., 2012; Nieuwenhuis et al., 2012). SVM is a powerful patter classification method that works finding a line or "decision boundary" that better separates two groups (Lao et al., 2004). This boundary may be depicted either by a hyperplane — in the case of linear classifiers – or by a more general hypersurface — when a non-linear SVM is used — in the high-dimensional feature space where the vectors representing each brain under study are projected (Lao et al., 2004). Differently from other hyperplane-based classifiers, however, the SVM focus its analysis on those brains (or vectors) that are more closely located to or on the hypersurface separating the two groups, which are called the "support vectors", maximizing the distance between the nearest vectors of the two groups. Thus, a SVM classifier inherently focuses on subtle between-group morphological differences and not on gross differences that are easily identifiable (Lao et al., 2004).

The diagnostic performance of the COMPARE classifier in the individual discrimination of first-episode schizophrenia versus healthy control subjects was estimated using the leave-one-out cross validation (LOOCV) method. In each LOOCV experiment, one subject was first selected as a testing subject, and the remaining subjects were used for the entire adaptive regional feature extraction, feature selection, and training procedure. Then, the classification result on the testing subject using the trained SVM classifier was compared with the ground-truth class label, to evaluate the classification performance. By repeatedly leaving each subject out as a testing subject, we obtained the average classification rate from all of these LOOCV experiments (Fan et al., 2007).

A high-dimensional spatial map of the brain regions that constitute a pattern of brain tissue distribution characteristic of the first-episode schizophrenia group relative to healthy controls was generated by COMPARE as previously described and validated (Davatzikos et al., 2005; Fan et al., 2007, 2008). For this purpose, this spatial feature map shows how frequently a particular region/feature was selected during all the LOOCV tests, displaying regional brain volume changes as one follows the path of the abnormality score from positive (patient-like) to negative (control-like). A scale ranging from 0 to 1 is set for each region, reflecting the relative importance for between-group discriminations based on the LOOCV experiments (Fan et al., 2007). For example, a region in the spatial map with a value of 0.76 means that it was used in 76% of the LOOCV tests as a distinguishing feature between the two groups. The classifier integrates volumetric measurements from a number of brain regions in a multivariate nonlinear statistical model that optimally separates first-episode schizophrenia patients from healthy controls. Thus, it is possible to determine which brain regions contributed the most to the separation of the two groups, that is, which dimensions in the high-dimensional space of regional volumetric measurements have the highest discriminatory power,

which collectively form a structural pattern. The anatomic location of each resulting cluster was determined using a stereotaxic MNI atlas (Oishi et al., 2011).

It is important to notice, however, that this discriminative morphological pattern generated by the classifier displays a set of brain regions needed for between-group classification, but not necessarily all areas of regional brain volume differences between the groups under study.

Two additional comparisons were conducted, respectively, aiming to determine the performance of the SVM classifier in the prediction of 1-year prognosis of the first-episode schizophrenia patients (i.e., remitting versus non-remitting course), and also to assess the potential influence of good prognosis cases in the discrimination power of the classifier for the schizophrenia versus healthy controls comparison:

- First-episode schizophrenia individuals who were remitted at T1 versus a subsample of matched non-remitted schizophrenia patients at T1;
- First-episode schizophrenia individuals excluding the patients with remitting course at follow-up versus matched healthy controls.

### 2.4. ROC curve analysis

The classification scores obtained by the COMPARE analyses were evaluated using a *receiver operating characteristic* (ROC) curve aiming to visualize the diagnostic performance of the classifier in each of the pairwise comparisons and to calculate area under the curve (AUC) measure.

Indices of diagnostic performance such as DA (overall classification rate), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using a $2 \times 2$ contingency table. In the ROC curves, the individual $Z$ scores obtained by the SVM classifier were plotted in a graph according to the true positive rate (Y axis, corresponding to the sensitivity measure) versus false positive rate (X axis, corresponding to 1 — specificity) generated in the group classification (Metz, 2006). This procedure allowed us to adjust the threshold used by the SVM classifier according to the desired sensitivity/ specificity relationship. We will report herein the sensitivity and specificity values observed when the highest classification accuracy was achieved.

The AUC measure of a classifier is equivalent to the probability that the classifier will rank a randomly chosen (truly) positive diagnosis higher than a randomly chosen negative diagnosis (Metz, 2006). Thus, the AUC provides an estimate of the discriminative power of the classifier for a given condition, regardless of both the chosen threshold (classifier's score which separates the 2 groups under study) and the sample size of each group.

## 3. Results

### 3.1. Demographic and clinical details

Demographic and clinical data for both first-episode schizophrenia individuals and healthy controls are summarized in Table 1.

No significant difference was observed between the proportion of schizophrenia patients and healthy controls examined using Scanners #1 and #2 (chi-square $= 0.31$, $df = 1$, $p = 0.575$).

Regarding comorbid psychiatric diagnoses other than substance misuse, 1 schizophrenia patient fulfilled criteria for specific phobia and two patients had comorbid obsessive-compulsive disorder. From the 62 healthy controls, 3 individuals fulfilled criteria for specific phobia.

At the end of the 1-year follow-up period, from the 62 first-episode schizophrenia individuals with confirmed diagnoses of schizophrenia or schizophreniform disorder, 15 (24.2%) had a remitting course of their psychotic symptoms (remitted subgroup), whereas 44 (71%) showed recurrence or a continuous course (non-remitted subgroup),

**Table 1**
Demographic and clinical information for first-episode schizophrenia patients and matched healthy controls.

| | SCH (n = 62) | HC (n = 62) |
|---|---|---|
| Age (mean ± sd) | 27.74 ± 8.00 | 28.32 ± 7.85 |
| Gender (no. males;%) | 45 (72.6%) | 45 (72.6%) |
| Years of Education (mean ± sd) | 8.58 ± 3.88 | 10.19 ± 4.12 |
| Handedness (no. right-handed;%) | 55 (88.7%) | 60 (96.8%) |
| Substance misuse[a] | 22 (35.5%) | - |
| Duration of Illness (days; mean ± sd) | 363.6 ± 458.6 | - |
| Duration of Untreated Psychosis (days; mean ± sd) | 267.6 ± 450.0 | - |
| Medication use at the MRI (n; %) | | |
| Antipsychotics | 40 (64.5%) | - |
| Mood stabilizers[b] | 4 (6.5%) | - |
| Antidepressants | 8 (12.9%) | - |

SCH, schizophrenia/schizophreniform disorder; HC, healthy controls; MRI, magnetic resonance imaging.
[a] Number of patients with a positive diagnosis of DSM-IV substance use disorder (prevalence).
[b] Lithium, carbamazepine and/or sodium valproate/ divalproex.

and 3 (4.8%) lost contact with the research team. Table 2 displays the clinical and demographical details for both the remitted and non-remitted subgroups of the schizophrenia sample. These subgroups did not differ with regard to compliance to treatment at T1 (Table 2). As expected, the non-remitted schizophrenia patients presented significantly higher mean total PANSS scores at T1 relative to the non-remitted individuals (Table 2).

Thus, the two additional analyses with the COMPARE classifier were conducted as follows:

- First-episode schizophrenia individuals who were remitted at T1 (n = 15) versus matched non-remitted schizophrenia patients at T1 (n = 21);
- First-episode schizophrenia individuals excluding the patients with remitting course at follow-up (n = 44) versus matched healthy controls (n = 57).

### 3.2. Diagnostic performance of the classifier in first-episode schizophrenia against healthy controls

Table 3 and Fig. 2 show, respectively, the diagnostic measures and ROC curves from the comparisons between the first-episode schizophrenia group versus healthy controls.

Initially, the SVM classifier attained modest discrimination between the first-episode schizophrenia and control individuals, with an overall DA of 73.4% (Table 3 and Fig. 2). When this comparison was repeated after excluding those schizophrenia patients who later showed a remitting course (good prognosis) over the 1-year follow-up period, the classification performance substantially worsened (Table 3 and Fig. 2), with an overall DA of 64.3%.

### 3.3. Performance of the classifier in predicting 1-year outcome of the schizophrenia patients

The SVM classifier showed a poor diagnostic performance in the differentiation between first-episode schizophrenia who were remitted at T1 (n = 15) versus matched non-remitted schizophrenia patients at T1 (n = 21) using the baseline (T0) MRI scans only: AUC = 0.51, accuracy = 58.3%, sensitivity = 38.1%, specificity = 86.7%, PPV = 80.0% and NPV = 50.0% (Fig. 3).

### 3.4. High-dimensional discriminative morphological pattern between first-episode schizophrenia and control individuals

Fig. 4 shows the neuroanatomical pattern of morphological (i.e., volumetric reduction or enlargement) abnormalities affecting the gray matter, white matter and ventricular compartments of the first-episode schizophrenia used by the SVM classifier to discriminate them from the healthy controls.

This high-dimensional morphometric analysis revealed that the diagnosis of first-episode schizophrenia is associated with a complex pattern of regional gray matter morphometric abnormalities, mostly volumetric reductions, affecting bilaterally the dorsolateral and orbital frontal cortices, temporal cortex and insula, and also the left posterior cingulate cortex. In addition, an area of increased gray matter volume was observed in the right anterior cingulate cortex of schizophrenia

**Table 2**
Demographic and clinical information of schizophrenia patients subgrouped according to remission or non-remission after 1 year.

| | Remitted (n = 15) | Non-Remitted (n = 44) | Statistical tests |
|---|---|---|---|
| Age at T0 (mean ± sd) | 25.00 ± 7.30 | 28.80 ± 8.30 | t = −1.57, df = 58, p = 0.121 |
| Gender (no. males;%) | 8 (53.3%) | 35 (79.5%) | $\chi^2 = 3.89$, df = 1, p = 0.049 |
| Years of Education at T0 (mean ± sd) | 8.73 ± 2.34 | 8.66 ± 4.32 | t = 0.63, df = 58, p = 0.934 |
| Handedness (no. right-handed;%) | 14 (93.3%) | 38 (86.4%) | $\chi^2 = 0.52$, df = 1, p = 0.471 |
| Substance misuse [a] | 3 (20.0%) | 18 (40.9%) | $\chi^2 = 2.13$, df = 1, p = 0.144 |
| Duration of Illness at T0 (days; média ± DP) | 238.1 ± 205.2 | 420.7 ± 521.8 | Mann–Whitney, p = 0.508 |
| Duration of Untreated Psychosis at T0 (days; média ± DP) | 129.8 ± 187.3 | 331.7 ± 510.4 | Mann–Whitney, p = 0.216 |
| Compliance to treatment at T1[b] | 4 (26.7%) | 16 (36.4%) | $\chi^2 = 0.47$, df = 1, p = 0.493 |
| Total PANSS scores at T0 (mean ± sd) | 43.53 ± 8.94 | 49.36 ± 12.29 | t = −1.69, df = 58, p = 0.097 |
| Total PANSS scores at T1 (mean ± sd) | 37.07 ± 6.56 | 49.59 ± 12.40 | t = −4.79, df = 53, p < 0.001 |
| Medication use at the MRI (n; %) | | | |
| Antipsychotics | 9 (60.0%) | 29 (65.9%) | $\chi^2 = 0.17$, df = 1, p = 0.680 |
| Mood stabilizers [c] | 1 (6.7%) | 2 (4.5%) | $\chi^2 = 0.10$, df = 1, p = 0.747 |
| Antidepressants | 1 (6.7%) | 7 (15.9%) | $\chi^2 = 0.81$, df = 1, p = 0.367 |

T0, baseline (moment of the first-episode); T1, 1-year follow-up; PANSS, Positive and Negative Syndrome Scale.
[a] Number of patients with a positive diagnosis of DSM-IV substance use disorder (prevalence).
[b] Number of patients in continuum treatment (%).
[c] Lithium, carbamazepine and/or sodium valproate/ divalproex.

**Table 3**
Diagnostic performance of the SVM classifier in the individual discrimination of first-episode schizophrenia cases (SCH) versus healthy controls.

| Pairwise Comparison | AUC[a] | Accuracy | Morfological features [b] | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|
| SCH ($N=62$) X Matched Controls ($n=62$) | 0.75 | 73.4% | 69 | 79.0% | 67.7% | 71.0% | 76.3% |
| SCH-NR ($N=44$) X Matched Controls ($n=57$) | 0.61 | 64.3% | 147 | 52.3% | 73.7% | 60.5% | 66.6% |

SCH, schizophrenia/schizophreniform disorder; NR, non-remitted at T1; PPV, positive predictive value; NPV, negative predictive value.
[a] Area under the curve;
[b] Number of morphological features used for the best classification rate (accuracy).

patients. Moreover, regional white matter morphometric abnormalities affecting bilateral fronto-limbic-occipital circuits were observed in the schizophrenia patients relative to healthy controls. Enlargements of the 3rd ventricle and the posterior (occipital) horn of the left lateral ventricle were also observed as significantly contributing to the diagnosis of first-episode schizophrenia.

When the resulting spatial map is limited to the top 10% ranked morphometric features used for classification, the anatomical regions most significantly associated with the diagnosis of first-episode schizophrenia are: bilateral dorsolateral and orbital frontal cortices, temporal cortex and temporal-occipital junction bilaterally, right anterior cingulate and left posterior cingulate cortices; fronto-temporal-occipital white matter circuits; and enlargement of the third ventricle. Fig. 5 shows a 3D rendering of the top 10% ranked morphometric features used for classification. Tables 4 and 5 present the top 10% ranked regions of, respectively, gray and white matter volume abnormalities which contributed the most for the discrimination between first-episode schizophrenia and healthy controls.

## 4. Discussion

To our knowledge, the present study is the first to evaluate the diagnostic performance of a neuroanatomical pattern classifier in a sample of schizophrenia using an epidemiologic approach to recruit both patients and controls. This is also the largest study conducted so far with neuroanatomical pattern classification in first-episode schizophrenia.

In regard to the individual classification of single subjects, we observed only a modest discrimination between first-episode schizophrenia versus healthy controls, with diagnostic performance measures (Table 3) similar or slightly better than those reported by the most recent studies evaluating subjects with first-episode schizophrenia (Kasparek et al., 2011) or a group of more general first-episode psychosis (Mourao-Miranda et al., 2012). Our DA measures were also similar to those reported in the largest study of neuroanatomical pattern

classification in schizophrenia published to date (Nieuwenhuis et al., 2012), which evaluated two independent samples of more than 100 patients with mainly chronic schizophrenia versus matched controls. However, a great heterogeneity of findings has been reported across different studies which have employed neuroanatomical pattern classification in schizophrenia to date (Ardekani et al., 2011; Borgwardt et al., in press; Caprihan et al., 2008; Castellani et al., 2012; Fan et al., 2007; Kasparek et al., 2011; Kawasaki et al., 2007; Nieuwenhuis et al., 2012; Pohl and Sabuncu, 2009; Sun et al., 2009; Takayanagi et al., 2010, 2011; Yoon et al., 2007). The adequate selection of relevant features for between-group discrimination is one important methodological step of neuroanatomical pattern classification studies (Caprihan et al., 2008; Fan et al., 2007). However, the stability of the model generated by the classifier and how generalizable this model is to the full range of schizophrenia patients in the general population relies heavily on an adequate sample size (Nieuwenhuis et al., 2012) and also on the method employed for recruitment of cases and controls for the study (Grimes and Schulz, 2005; Lee et al., 2007; Walsh et al., 2011).

Up until now, there has been a lack of studies applying pattern classification methods to the investigation of population-based samples of individuals with schizophrenia compared to healthy controls recruited in the same catchment areas. Population-based designs are likely to reduce selection biases by ensuring that control individuals represent the population from which the cases came from, therefore providing a valid estimate of the exposure of interest in that population (Grimes and Schulz, 2005; Lee et al., 2007). Psychiatric case-controls investigations employing such approach for the recruitment of study participants are known to yield results that differ from those obtained when convenience samples are used (i.e. students and employees of the research institution and/or subjects recruited through advertisement) (Lee et al., 2007; Walsh et al., 2011). Moreover, population-based studies allow the inclusion of schizophrenia individuals presenting with a widely variable range of symptom severity and medium/long-term prognosis, as expected in the general population of psychosis sufferers over time. This is particularly
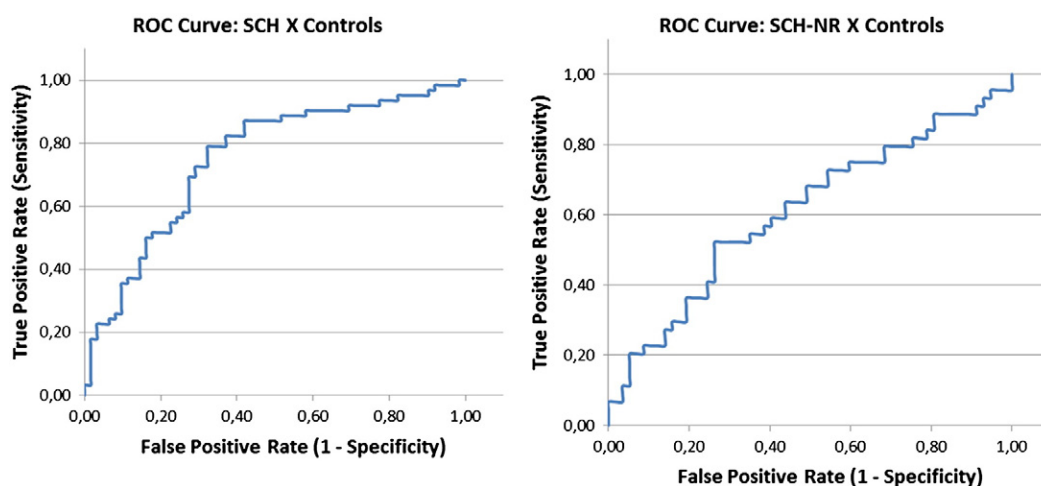


**Fig. 2.** ROC curves for the comparisons between first-episode schizophrenia individuals (SCH), schizophrenia patients with a non-remitting course at T1 (SCH-NR) and healthy controls.
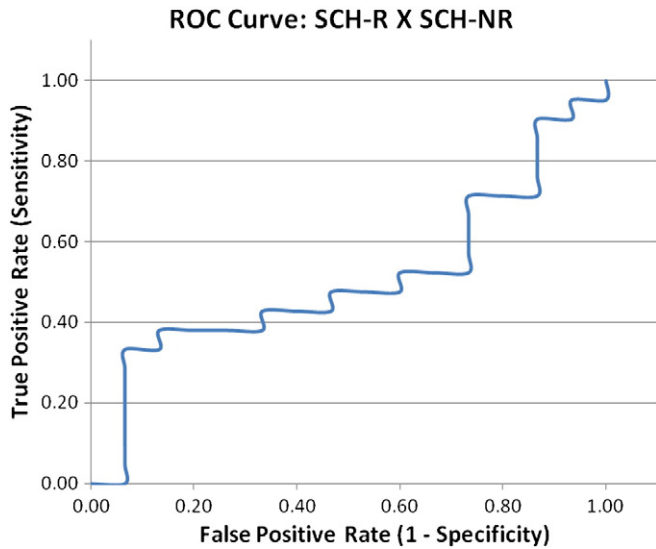
## ROC Curve: SCH-R X SCH-NR



**Fig. 3.** ROC curve for the comparison between remitted (SCH-R) and non-remitted schizophrenia (SCH-NR) at T1 using the baseline (T0) images.

important for the ultimate goal of developing neuroimaging tools to aid in single-case diagnostic and prognosis evaluations in clinical psychiatric practice, as "real world" patient samples are likely to display different kinds of clinical comorbidities (such as substance use disorders), as well as widely variable disease courses. Considering that schizophrenia patients with a chronic course of their illness are expected to display more widespread morphological brain abnormalities than first-episode patients (Bora et al., 2011), the fact that we found a degree of DA similar to that reported in the large, representative schizophrenia sample recruited by Nieuwenhuis et al. (2012) reinforces the notion that population-based designs provide a valid estimate of the exposure of interest in the general population.

It is particularly intriguing that the present study, together with the large investigation conducted by Nieuwenhuis et al. (2012) using chronic schizophrenia subjects, have both yielded DA measures inferior to those found by Koutsouleris et al. (2009, 2012), who also employed a SVM-based neuroanatomical pattern classifier to compare more modest groups of mainly unmedicated ARMS individuals against healthy controls. Interestingly, Koutsouleris et al. (2012) reported high classification accuracy in the comparison of ARMS subjects who subsequently converted to full-blown psychosis versus healthy controls (92.3%), but not between non-converters and controls (66.9%). It is conceivable
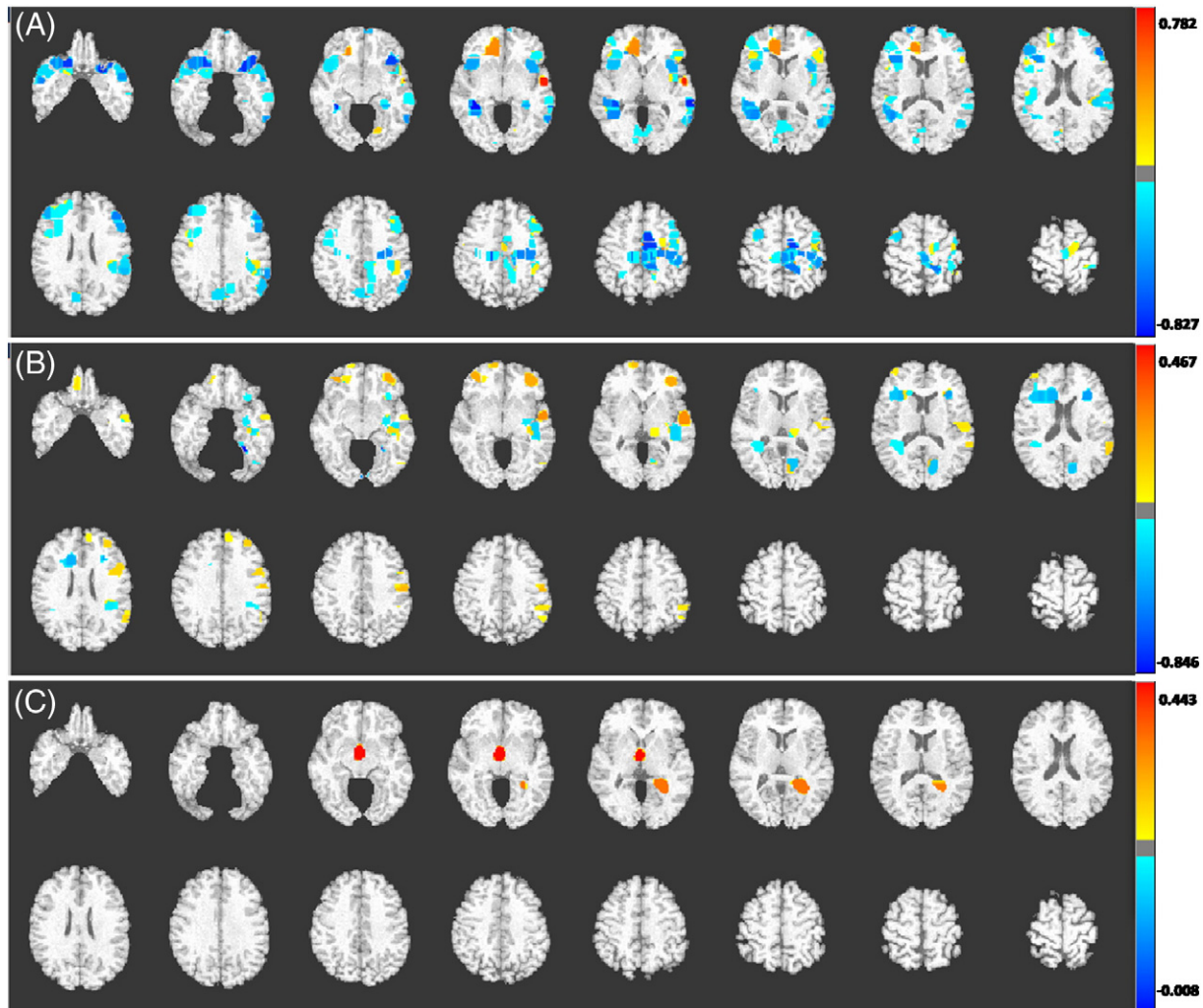


**Fig. 4.** Discriminative pattern of volumetric abnormalities in patients with first-episode schizophrenia versus healthy controls as seen in the gray matter (A), white matter (B) and ventricles (C). Brain regions which contributed the most for between-group discrimination were overlaid on to the single-brain MNI template. The relative importance of each region for between-group discrimination is translated here in a scale ranging from −1 to 1, reflected in the color brightness of each cluster. The red clusters (positive) indicate regions of volumetric increase in patients relative to controls, whereas the blue clusters (negative) show regions of volumetric decrease in the patients compared to controls. Images are displayed in radiological convention (the left side of the brain corresponds to the right side of the figure).
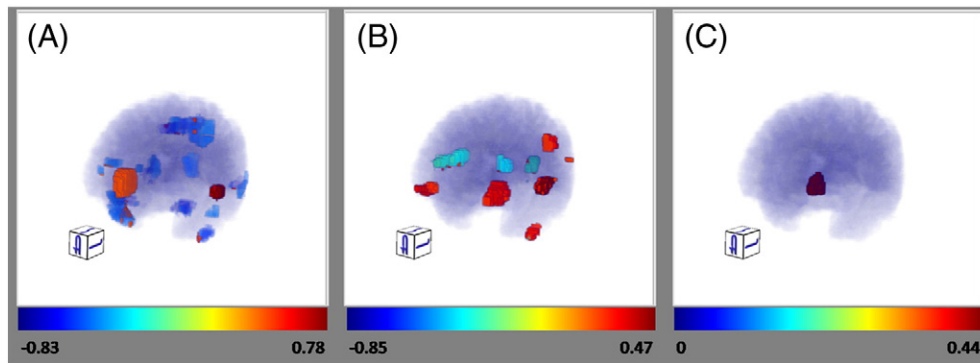
**Fig. 5.** 3D rendering showing the top 10% ranked gray matter (A), white matter (B) and ventricular (C) morphometric features which contributed the most for the discrimination between first-episode schizophrenia and healthy controls. The relative importance of each region for between-group discrimination is translated here in a scale ranging from −1 to 1, reflected in the color brightness of each cluster. The red clusters (positive) indicate regions of volumetric increase in patients relative to controls, whereas the blue clusters (negative) show regions of volumetric decrease in the patients compared to controls.

that, in ARMS groups who will later develop schizophrenia, there is an excess of subjects who already present clear brain structural abnormalities than in samples of subjects who have full-blow psychosis but which include not only individuals who had prodromal symptoms but also others with a more abrupt onset of psychosis (DeLisi et al., 1998). This would be consistent with the findings of retrospective clinical studies which have indicated that schizophrenia patients with antecedents of clearly defined and long-lasting prodromal symptoms display more severe symptoms and social function impairments at follow-up when compared to schizophrenia patients with a more abrupt onset of psychotic features (van Mastrigt and Addington, 2002).

The high-dimensional discriminative morphological map comparing first-episode schizophrenia patients and healthy controls revealed a complex pattern of regional volumetric abnormalities affecting both gray and white matter fronto-temporo-occipital regions bilaterally, including the inferior fronto-occipital fasciculus, as well as the third and lateral ventricles. This pattern is consistent with previous studies employing high-dimensional morphometry to study patients with chronic schizophrenia and their unaffected relatives (Davatzikos et

al., 2005; Fan et al., 2007, 2008), as well as with meta-analyses of voxel-based morphometry (VBM) and diffusion tensor imaging studies of first-episode schizophrenia (Bora et al., 2011). As expected, the high-dimensional and multivariate nature of the present analysis uncovered a greater number of clusters of gray and white matter volume abnormalities than previously observed with VBM in this same sample (Colombo et al., 2012; Schaufelberger et al., 2007), although there are some overlapping findings, particularly regarding to the involvement of the bilateral prefrontal cortex, left superior temporal gyrus and bilateral insula.

Based on previous studies, we predicted that the SVM classifier would be capable of distinguishing between schizophrenia patients with better versus worse prognoses. In the only study published to date attempting to use neuroanatomical pattern classification to predict prognosis of psychotic disorders, Mourao-Miranda et al. (2012) used a linear SVM classifier to assess 6-year outcome in a sample of subjects with first-episode psychosis, and reported modest discrimination between first-episode psychosis patients who later showed continuous ($n=28$) versus episodic ($n=28$) course (overall accuracy=

**Table 4**
Top 10% ranked gray matter (GM) morphometric features which most significantly contributed for the discrimination between first-episode schizophrenia and healthy controls.

| Gray matter region | Volumetric increase or decrease[a] | Hemisphere | MNI Coordinates (central voxel) | | | No. of Voxels |
|---|---|---|---|---|---|---|
| | | | x | y | z | |
| Anterior cingulate cortex | Increase | Right | 13 | 35.5 | 4 | 831 |
| Left frontal gyrus | Decrease | Left | −47.5 | 29.5 | 26 | 183 |
| Inferior frontal gyrus | Decrease | Right | 38 | 20 | 17.5 | 153 |
| Posterior orbital gyrus | Decrease | Right | 21 | 15 | −17 | 146 |
| Insular gyrus | Decrease | Right | 31 | 15 | −18 | 69 |
| Superior temporal gyrus | Decrease | Right | 41.5 | 14 | −15.5 | 151 |
| Insular gyrus | Decrease | Left | −35 | 13 | −14 | 412 |
| Posterior cingulate cortex | Decrease | Left | −7 | −0.5 | 52 | 140 |
| Middle temporal gyrus | Decrease | Left | −55 | −4.5 | −19.5 | 74 |
| Middle temporal, inferior temporal and fusiform gyri | Decrease | Right | 47 | −5.5 | −36 | 949 |
| Inferior temporal gyrus | Decrease | Left | −47 | −11 | −42 | 260 |
| Superior temporal gyrus | Increase | Left | −56 | −11 | −1 | 151 |
| Superior frontal gyrus and posterior cingulate cortex | Decrease | Left | −9 | −11.5 | 53 | 251 |
| Precentral gyrus | Decrease | Left | −24 | −22 | 49 | 245 |
| Postcentral gyrus | Decrease | Left | −36.5 | −23 | 48.5 | 318 |
| Precentral gyrus | Decrease | Left | −11 | −26 | 54 | 72 |
| Precentral gyrus and posterior cingulate cortex | Decrease | Left | −0.5 | −27 | 56 | 165 |
| Superior temporal gyrus (posterior portion) | Decrease | Right | 49.5 | −40.5 | 5 | 65 |
| Superior temporal gyrus (posterior portion) | Decrease | Left | −64 | −41 | 3 | 158 |
| Superior parietal lobule | Decrease | Left | −13.5 | −41.5 | 58 | 275 |
| Fusiform gyrus | Decrease | Right | 38 | −44.5 | −1 | 198 |
| Temporal-occipital junction | Decrease | Right | 40 | −56.5 | 7 | 318 |
| Temporal-occipital junction | Decrease | Left | −62 | −62.5 | −3.5 | 135 |

GM, gray matter.
[a] First-episode schizophrenia patients relative to healthy controls.

**Table 5**
Top 10% ranked white matter (WM) morphometric features which most significantly contributed for the discrimination between first-episode schizophrenia and healthy controls.

| White Matter Region/ Tract | Volumetric Increase or Decrease[a] | Hemisphere | MNI coordinates (central voxel) | | | No. of Voxels |
|---|---|---|---|---|---|---|
| | | | x | y | z | |
| Superior frontal gyrus WM | Increase | Right | 12 | 62 | 2 | 73 |
| Anterior Frontal WM[b] | Increase | Right | 37 | 44 | 4.5 | 140 |
| Anterior Frontal WM[b] | Increase | Left | −37 | 41 | −1 | 427 |
| Inferior frontal gyrus WM | Decrease | Right | 36 | 19 | 20 | 355 |
| Frontal portion of CC (body) | Decrease | Right | 16.5 | 19 | 25 | 346 |
| Inferior frontal gyrus WM | Decrease | Left | −32 | 19 | 21 | 211 |
| Inferior temporal WM[c] | Increase | Left | −46.5 | −8 | −43 | 99 |
| Superior temporal gyrus WM | Increase | Left | −55 | −11.5 | 2.5 | 318 |
| Superior parietal lobule WM | Increase | Left | −55 | −20.5 | 40.5 | 190 |
| Cuneus WM/ Occipital portion of the CC | Decrease | Left | −12 | −78 | 14 | 443 |

WM, white matter; CC, corpus callosum.
[a] First-episode schizophrenia patients relative to healthy controls.
[b] Involving the middle/ inferior frontal gyri WM and the frontal portion of the inferior fronto-occipital fasciculus.
[c] Involving the middle/ inferior temporal gyri WM and the temporal portion of the inferior longitudinal fasciculus.

70%, sensitivity = 71%, specificity = 68%). However, those results should be interpreted with caution, as the 2 first-episode psychosis groups (with continuous or episodic course) were unbalanced for 2 important confounding variables: years of education and specific diagnosis (for instance, 86% of the continuous course group patients were diagnosed as having schizophrenia compared to only 25% of the episodic course group) (Mourao-Miranda et al., 2012). Nevertheless, our SVM-classifier failed to predict 1-year outcome (remission versus non-remission) of first-episode schizophrenia patients. This might be at least partially explained by the small sample size of remitted patients' group ($n = 15$) and the subsequent risk of type II statistical errors. It should also be weighted that a follow-up of 1 year might be insufficient to reliably define outcome in schizophrenia. Also, it is interesting to notice that, when we repeated the analysis after excluding the schizophrenia patients with remitting course at follow-up, the classification performance substantially worsened (DA = 64.3%). This is probably due to loss of statistical power related to the smaller sample size.

There are a number of methodological limitations that should be weighted in the interpretation of our results. Firstly, a significant proportion of our first-episode schizophrenia patients (64.5%) were using antipsychotic medication at the day of MRI scanning. This is similar to the proportion reported in most studies that recruited samples of first-episode schizophrenia and in addition, the time of exposure for those patients who were using antipsychotic drugs was relatively short. Nevertheless, long-term antipsychotic treatment is associated with both gray and white matter reductions (Ho et al., 2011) and, thus, might have influenced our results. Secondly, comorbid substance abuse or dependence is another important confounding variable in the assessment of regional brain volumes (Colombo et al., 2012) and the fact that a substantial proportion of the patients enrolled in our study presented a positive history of substance misuse could have limited the sensitivity of the classifier to identify morphometric abnormalities specifically associated with the schizophrenia diagnosis. Finally, the present sample was acquired using two MRI scanners. However, the two scanners and acquisition protocols were identical, and a similar proportion of schizophrenia patients and healthy controls were examined in each equipment. Thus, it is unlikely that this factor might have influenced our results.

## 5. Conclusion

At the population level and using a "real world" sample of first-episode schizophrenia with comorbid substance use disorders and heterogeneous disease course, the application of a neuroanatomical pattern classifier afforded only modest discrimination between first-episode schizophrenia patients and demographically matched, next-door healthy controls recruited using an epidemiological approach.

Also, we failed to predict the 1-year prognosis (i.e., remitting versus non-remitting course) of first-episode schizophrenia.

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