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BIOLOGICAL PSYCHIATRY - ORIGINAL ARTICLE

Classification of schizophrenia using feature-based morphometry

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Abstract The objective of this study was to use a combined local descriptor, namely scale invariance feature transform (SIFT), and a non linear support vector machine (SVM) technique to automatically classify patients with schizophrenia. The dorsolateral prefrontal cortex (DLPFC), considered a reliable neuroanatomical marker of the disease, was chosen as region of interest (ROI). Fifty-four schizophrenia patients and 54 age- and gender-matched normal controls were studied with a 1.5T MRI (slice thickness 1.25 mm). Three steps were conducted: (1) landmark detection and description of the DLPFC, (2) *feature* vocabulary construction and *Bag-of-Words* (BoW) computation for brain representation, (3) SVM classification which adopted the *local* kernel to implicitly implement the feature matching. Moreover, a new weighting approach was proposed to take into account the discriminant relevance of the detected groups of features. Substantial results were obtained for the classification of the whole dataset (left side 75%, right side 66.38%). The performances were higher when females (left side 84.09%, right side 77.27%) and seniors (left side 81.25%, right side 70.83%) were considered separately. In general, the supervised weighed functions increased the efficacy in all the analyses. No effects of age, gender, antipsychotic treatment and chronicity were shown on DLPFC volumes. This integrated innovative ROI-SVM approach allows to reliably detect subjects with schizophrenia, based on a structural brain marker for the disease such as the DLPFC. Such classification should be performed in first-episode patients in future studies, by considering males and females separately.

Keywords Neuroimaging · MRI · Support vector machine · Dorsolateral prefrontal cortex · Shape morphometry

The preliminary results of this study were presented at the XI Conference of the Italian Association for Artificial Intelligence (AIxIA), Reggio Emilia, Italy, December 9–12, 2009. The dataset used in this work is part of a larger database kept by the Research Unit on Brain Imaging and Neuropsychology (RUBIN) at the Department of Public Health and Community Medicine-Section of Psychiatry and Clinical Psychology of the University of Verona.

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Introduction

Computational neuroanatomy using magnetic resonance imaging (MRI) has been used consistently in schizophrenia to detect specific morphological abnormalities of the brain in comparison with normal subjects (Giuliani et al. 2005). In general two methods are routinely used, i.e. the region of interest (ROI) analysis or the voxel-based morphometry (VBM) (Ashburner and Friston 2000). The ROI methods are focussed on specific brain regions which are manually traced by expert operators. The VBM considers the whole brain after a normalization procedure which maps the current brain onto a standard reference, namely the *stereotaxic* space, allowing a voxel-by-voxel comparison. Both methods have reported some consistent findings such as cortical atrophy, particularly of the prefrontal cortex, with related ventricular enlargement, shrinkage of the hippocampus and of the superior temporal gyrus, and reduction of the cerebral asymmetry (Andreone et al. 2007a; Arnone et al. 2008; Bellani et al. 2010a; Fornito et al. 2009; Kempton et al. 2010). However, neither technique enables patients with schizophrenia to be classified automatically, based on the brain's features. In this perspective, apart from standard volumetric methods (Ashburner and Friston 2000; Baiano et al. 2008), few studies have applied innovative approaches to detect schizophrenia based on the brain characteristics (Fan et al. 2007; Gerig et al. 2001; Koutsouleris et al. 2009; Yoon et al. 2007). Specifically, Gerig et al. (2001) proposed a ROI-based morphometric analysis by defining spherical harmonics and a 3D skeleton as shape descriptors, i.e. the shape descriptor-based approach was successfully compared to classical volumetric techniques. Yoon et al. (2007) utilized a support vector machine (SVM) to classify cortical thickness, which was measured by calculating the Euclidean distance between linked vertices on the inner and outer cortical surfaces. Fan et al. (2007) combined deformation-based morphometry with SVM, capturing multivariate relationships across various anatomical regions. Finally, Koutsouleris et al. (2009) performed a whole brain SVM analysis, detecting the dimensionality of MR images by the optimal number of uncorrelated principal components obtained by principal component analysis (PCA). Several cortical and subcortical areas across the two hemispheres were found to characterize patients with schizophrenia, at-risk subjects and unaffected family members (Davatzikos et al. 2005; Fan et al. 2007, 2008; Koutsouleris et al. 2009; Yoon et al. 2007). However, with the exception of the preliminary study by Gerig et al. (2001), these reports were not driven by a priori hypothesis and did not consistently detect any specific structural markers. Also, they applied multivariate whole brain techniques, thus being limited by the analysis of an immense dimensional space in relatively small samples.

In this study, we aimed at automatically classifying schizophrenia by applying a ROI-based machine learning approach (Duda et al. 2001) within the dorsolateral prefrontal cortex (DLPFC), a reliable structural marker for schizophrenia (Potkin et al. 2009; Prasad et al. 2007; Yoon et al. 2008). This technique utilizes a few, significant landmarks to detect and characterise local region descriptors. The novelty therefore consists in characterising brain abnormalities in terms of intra-ROI local patterns which are not necessarily spatially coherent, using consistent neuroanatomical features for the disease. The underlying hypothesis consists in relaxing the common constraint that morphological anomalies appear at the same voxel location for the entire population. Therefore, a new *kernel* of a SVM was designed to compare a pair of brains represented by an unordered set of features. The proposed method is inspired by the *Bag-of-Words* (*BoW*) (Cruska et al. 2004) paradigm which implicitly implements feature matching within the SVM framework (Grauman and Darrell 2007). Finally, a weighting function was introduced to define the relevance of the detected features, namely the *visual words*, in discriminating between patients and controls.

Materials and methods

Sample

Fifty-four patients suffering from schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, (DSM-IV) (American Psychiatric Association 1994) were recruited from the South Verona Psychiatric Case Register (Amaddeo et al. 1997, 2009) (Table 1). The register includes information about patients residing in the epidemiologically defined catchment area of South Verona (with a population of approximately 100,000 inhabitants) and treated by the South Verona Community-based Mental Health Service (CMHS) and related clinics. Diagnostic evaluation was based on the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC-SCAN) (World Health Organisation 1992). These assessments were conducted by trained clinical psychologists with extensive experience of using the SCAN, as previously described (Andreone et al. 2007b), who were blind to diagnosis. The Italian version of the SCAN was edited by our group (World Health Organisation 1996) and our investigators attended specific courses held by official trainers on how to administer this scale. The inter- and intra-rater reliability of the IGC-SCAN assessments was monitored by regular quality control meetings. Diagnostic validity was further confirmed by clinical consensus by two qualified psychiatrists. The patients' psychopathology was rated using the Brief Psychiatric Rating Scale (BPRS, 24-item version) (Ventura et al. 2000). Information about age of onset, duration of

Table 1 Demographic features of the subjects

	Healthy controls ($N = 54$)	Patients with schizophrenia ($N = 54$)
Age (years)	39.19 ± 10.05	37.96 ± 10.90
Gender (females/males)	25/29	19/35
Race	Caucasian	Caucasian
Duration of illness (years)		12.53 ± 10.04
AP Lifetime treatment (years)		10.77 ± 9.23
CPZ-equivalent dose (mg)		241.91 ± 176.29
BPRS total scores		47.20 ± 20.95

Healthy controls and patients with schizophrenia did not significantly differ for age or gender ($p > 0.05$)

AP antipsychotic, *CPZ* chlorpromazine

illness, and number of hospital admissions was obtained during an interview and from medical records. Fifty-four matched healthy individuals without any personal lifetime history of DMS-IV Axis I disorders, recruited from the same catchment area, were also studied (Table 1). Exclusion criteria for all participants were (a) alcohol or substance abuse within the preceding 6 months, as defined by the DSM-IV (b) any current major medical or neurological illness, (c) history of traumatic head injury with loss of consciousness, (d) DSM-IV axis I comorbidity**.** Additional exclusion criteria for comparator subjects were (a) any self-reported history of psychiatric disorders in first-degree relatives (b) any prescribed medication.

The study was approved by the Ethics Committee of the Azienda Ospedaliera of Verona. All the participants provided their signed informed consent, having understood the nature and purpose of the study after it was explained to them.

Magnetic resonance imaging acquisition

The MRI scans were acquired using a 1.5 T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B. All the participants were provided with earplugs to reduce acoustic noise and their head was placed in a comfortable head holder to keep it steady in order to minimize movement artefacts. Initially, exploratory T1-weighted images (TR = 450 ms, TE = 14 ms, flip angle = 90°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 384 × 512) were obtained to verify the subject's head position and the quality of the image. A coronal 3D MPR sequence was acquired (TR = 2,060 ms, TE = 3.9 ms, flip angle = 15°, FOV = 176 × 235, slice thickness = 1.25 mm, matrix size = 270 × 512, TI = 1,100) to obtain 144 images covering the entire brain.

Automatic classification analysis

The proposed method was based on three main steps: (1) landmark detection and description, (2) *feature* vocabulary construction and computation, (3) SVM classification.

Landmark point detection and description

A *landmark* or *feature* is a set of points that can be clearly differentiated from its neighbouring image points. In this paper, we employed the Difference of Gaussians (DoG) point detector (Lowe 2004) which is robust to image-translation, -rotation and -scale. This implies that a landmark can be detected without requiring an explicit registration procedure. Moreover, the region of influence of each landmark (i.e., the *neighbourhood*) was also estimated with this technique. In general, a wider region was adaptively defined for homogeneous areas and viceversa. Therefore, for each landmark the scale invariance feature transform (SIFT) descriptor (Lowe 2004) was applied to characterize its local neighbourhood. In practice, the pixels of the landmark's neighbourhood are encoded into a multidimensional feature vector which effectively and concisely describes the local area. A pair of successive slices from the DLPFC, with the extracted landmarks and their region of influence are reported in Fig. 1. Slice thickness of 1.25 mm was utilized. Then the most characteristic patches in terms of strong local pattern variations were selected from each brain. Here, the main idea was to verify whether there were brain anomalies among those variations.

Feature vocabulary construction

After the landmark detection was completed, each brain was represented by a set of unordered feature vectors. Moreover, such sets generally appeared with different cardinalities. In order to compare a pair of brains, the *Bag-of-Words* (BoW) approach was introduced (Cruska et al. 2004). The set of feature vectors coming from all brains was clusterized by employing the k-means clustering technique (Duda et al. 2001). According to the BoW paradigm, the centroids of the clustering were referred as *visual words* or *feature prototypes* (Cruska et al. 2004). Indeed, the set of visual words provides a quantization of the feature space, i.e., the so called *feature vocabulary*. Then, each set of feature vectors observed on each brain was transformed into a histogram that counted the frequency of occurrence of such feature prototypes (Cruska et al. 2004). In order to obtain this, each feature vector of a brain was compared with all the visual words and was associated to the closest one. The outputted histogram became the descriptor of the brain. The set of landmark points of the DLPFC extracted from the whole dataset is

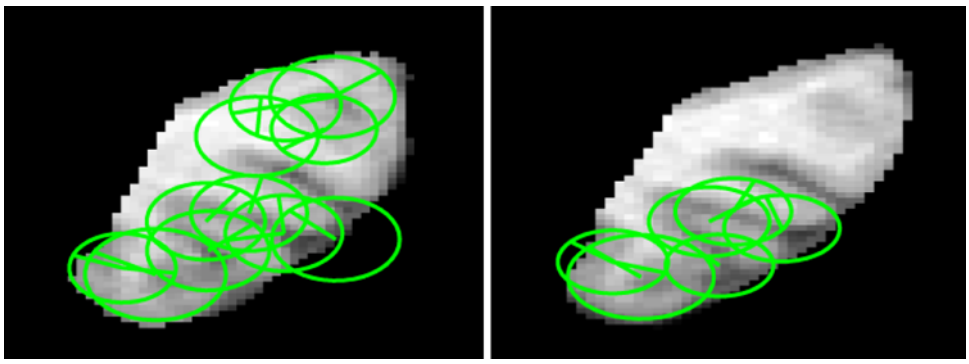

Fig. 1 Two succeeding slices from the dorsolateral prefrontal cortex (DLPFC). Landmark points are identified by *green ellipsoids* and represent *feature* that can be clearly differentiated from its neighbouring image points. The region of influence of a landmark is represented by the set of pixel inside its ellipsoid; in general, a wider region is adaptively defined for homogeneous areas and viceversa

shown in Fig. 2. Each landmark is coloured according to its closest visual words. In this fashion, similar landmarks are associated to the same visual word and visualized with the same colour.

The relationship between feature prototypes and morphological abnormalities due to schizophrenia was tentatively captured. For each cluster of features its discriminative *relevance* was measured by counting the occurrences for each group separately. In particular, the following weighting function was defined for each *visual word*:

$$w_i(n_p^{c_i}, n_c^{c_i}) = \begin{cases} 1.5 & \text{if} \quad \left\| n_p^{c_i} - n_c^{c_i} \right\| \geq \Delta \\ 0.5 & \text{otherwise} \end{cases} \tag{1}$$

where c_i is the ith centroid (i.e., the visual word, $i = 1, \ldots, K$), $n_p^{c_i}$ and $n_c^{c_i}$ are the percentages of patients and controls in c_i, and Δ is a heuristic constant. In this way, clusters composed by a clear majority of the population (i.e. patients or controls) were considered to be more discriminant for the classification.

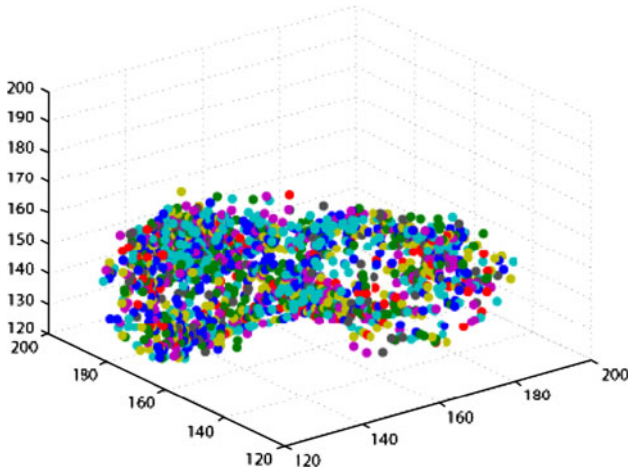

Fig. 2 Clusterized feature vectors are shown. The centroids of the clustering are referred as visual words (or feature prototypes) and each point is *coloured* according to its *visual word*. Similar landmarks are associated to the same visual word and therefore are visualized with the same colour

Support vector machine classification

SVMs (Brurges 1998) are powerful classifiers which have reliably been used for schizophrenia (Fan et al. 2007). Note that usually a SVM requires a fixed length vector which characterizes *globally* the subject to be classified. Here, however, due to the BoW representation, a subject (i.e., a brain) was encoded by a set of local features. In particular, the novelty consisted in employing a suitable *kernel function* to implicitly implement the feature matching. Such kernels are generally referred to as *local* kernels or *matching* kernels (Grauman and Darrell 2007).

In order to construct a BoW histogram of a new brain, we compared each of the extracted features with the visual words w.r.t. the visual vocabulary by counting the number of features assigned to each visual word. The BoW representation h^A for brain A was obtained in this way.

In detail, the kernel function was defined as:

$$K\left(h^A, h^B\right) = \sum_{i=1}^{K} w_i \min(h_i^A, h_i^B) \tag{2}$$

Where h_i^A denotes the count of the ith bin of the histogram h^A with K bins, and w_i is computed from Eq. 1. Such a kernel was called a weighted *histogram intersection* function and was shown to be a valid kernel (Grauman and Darrell 2007). Histograms were assumed to be normalized such that

$$\sum_{i=1}^{K} h_i = 1$$

As observed by Grauman and Darrell (2007), the proposed kernel implicitly encoded the point-to-point

matching, since corresponding features were likely to belong to the same histogram bin. Indeed, the histogram intersection function counted the number of feature matching, which are intermediated by the visual words. More in detail, since two points are declared as being a 'match' if both are associated to the same visual word, the *tolerance* of matching (i.e. the maximum error matching of a pair of points) is bounded by the size of cluster associated to the visual word.

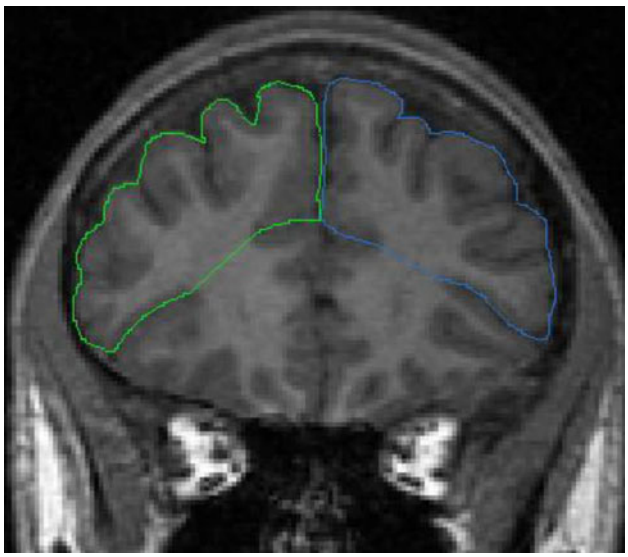

Fig. 3 Dorsolateral prefrontal cortex tracing. The superior border of the DLPFC was the superior frontal sulcus, the inferior border was the upper border of the Sylvian fissure posteriorly and the horizontal ramus of the Sylvian fissure anteriorly; the lateral boundary was the edge of the brain, and the medial boundary was the line connecting the most medial point of the superior frontal sulcus with the Sylvian fissure/horizontal ramus

Dorsolateral prefrontal cortex landmarks

All imaging data were analyzed using the BRAINS2 software developed at the University of Iowa. The superior border of the DLPFC was the superior frontal sulcus, the inferior border was the upper border of the Sylvian fissure posteriorly and the horizontal ramus of the Sylvian fissure anteriorly. The lateral boundary was the edge of the brain, and the medial boundary was the line connecting the most medial point of the superior frontal sulcus with the Sylvian fissure/horizontal ramus (Fig. 3). The tracing started anteriorly to the posterior border of the genu and ended at the anterior border of the horizontal ramus of the Sylvian fissure, as per a previously published technique (Prasad et al. 2005). A rater who was blind to the subjects' identity traced all the scans, after reaching intra-class correlation coefficients (ICCs) >0.90 (0.92 for left DLPFC, 0.98 for right DLPFC) with another rater by blindly tracing 10 randomly selected scans. The volumes (ml) were obtained by summing the volumes of all relevant slices and were expressed in cm^3. Intracranial volume (ICV) was traced in the coronal place along the border of the brain and included the cerebrospinal fluid, dura mater, sinus, optic chiasma, brainstem, and cerebral and cerebellar matter. The inferior border did not extend below the base of the cerebellum. An inter-rater reliability of 0.97 was achieved for the ICV measurements.

Results

Landmark extraction was obtained using the SIFT implementation available from http://vision.ucla.edu/vedaldi. Then feature points were properly clusterized in order to obtain the *visual words*. The Matlab (http://www.mathworks.com) version 7.4 of the *K*-mean algorithm was used

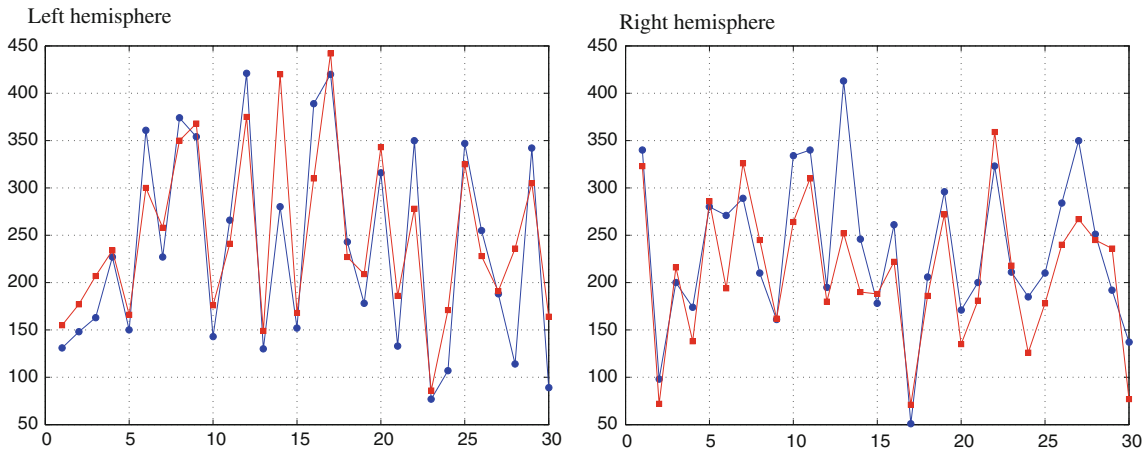

Fig. 4 Histogram of word occurrences for the whole dataset for the left and right hemispheres. Patients with schizophrenia are marked in *red*, healthy controls in *blue*

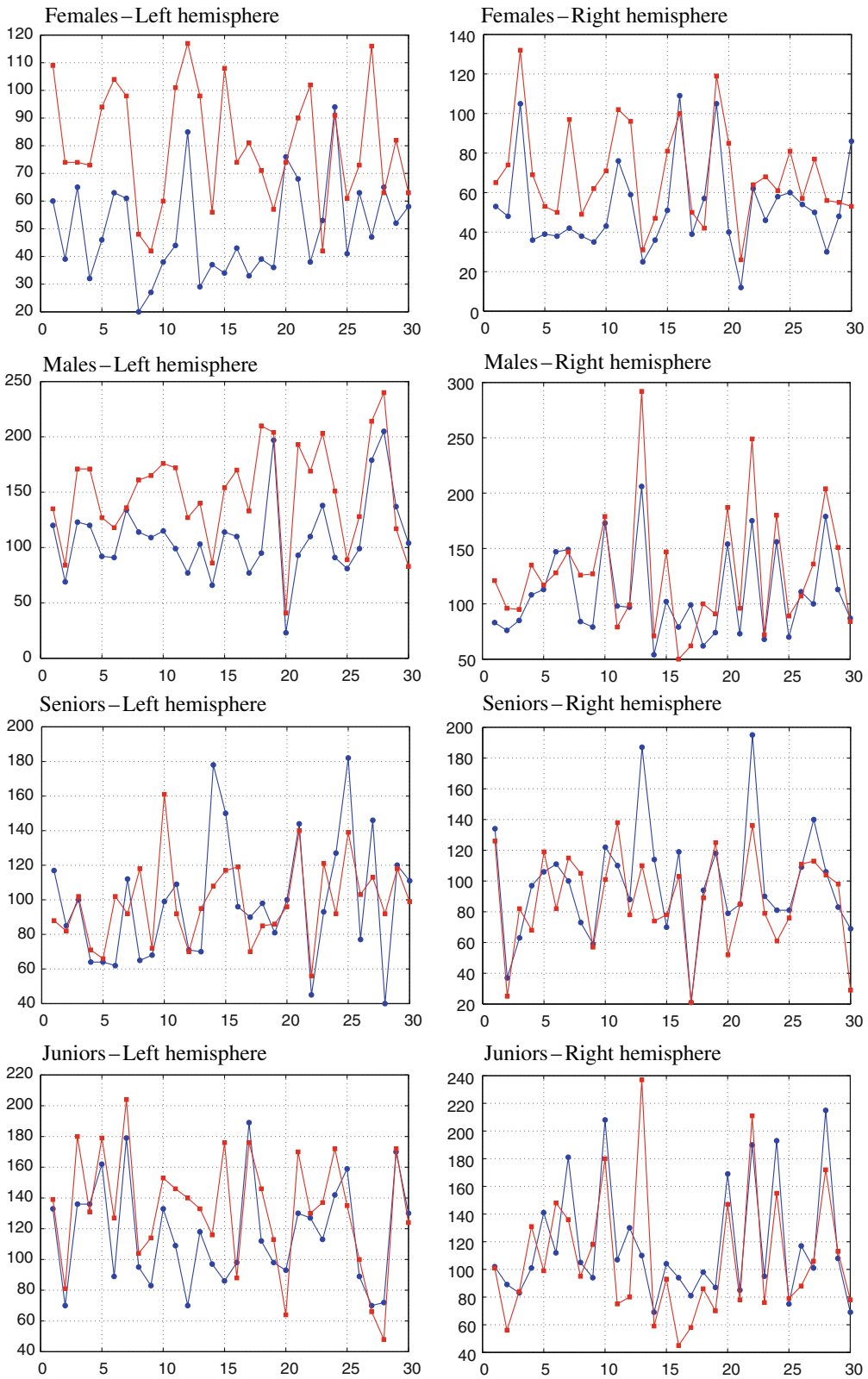

Fig. 5 Word relevance for patients with schizophrenia (*red*) and healthy controls (*blue*), stratified by gender and age

Table 2 Classification rate for healthy controls and patients with schizophrenia

Experiment	Healthy controls (*n*)	Patients with schizophrenia (*n*)	Left		Right	
			Weight score (%)	Raw score (%)	Weight score (%)	Raw score (%)
Whole dataset	54	54	75.00	62.93	66.38	59.48
Females	25	19	84.09	77.27	77.27	72.73
Males	29	35	60.00	44.62	67.69	50.77
Seniors	23	25	81.25	73.52	70.83	64.12
Juniors	31	29	71.67	55.27	63.33	51.18

Senior subjects are ≥40 years and juniors are <40 years

n number

by fixing $K = 30$. Therefore, the *relevance* of each visual word was computed by obtaining the weighs w_i (Fig. 3). Also, in order to take into account the intra-class variability, the whole dataset was stratified by sex (males and females) and age (subjects <40 years, and subjects ≥40 years) (Fig. 4, 5).

The classification is shown in Table 2. Scores were obtained by leave-one-out cross validation (Duda et al. 2001). In general, a dramatic improvement was observed when weights were applied. Substantial results were obtained for the classification of the whole dataset (left hemisphere 75%, right hemisphere 66.38%). Moreover, performances increased when only females (left side 84.09%, right side 77.27%) and only seniors (left side 81.25%, right side 70.83%) were taken into consideration.

Interestingly, DLPFC volumes significantly inversely correlated with length of illness on the right side (Spearman's rho coefficient $= -0.43$, $p = 0.001$) with a trend for significance on the left one (Spearman's rho coefficient $= -0.23$, $p = 0.10$). In contrast, no significant correlations were found between antipsychotic lifetime treatment or dosages and bilateral DLPFC volumes (partial correlation analyses controlling for length of illness, $p > 0.05$). Age did not show any significant association in both control and schizophrenia group with DLPFC volumes (Spearman's correlation, $p > 0.05$). Moreover, DLPFC size did not significantly differ between patients treated with typical and atypical antipsychotics and between chronic and non-chronic schizophrenia patients separated in accordance to mean of length of illness (GLM multivariate with age, gender, and ICV as covariates, $p > 0.05$). Finally, schizophrenia patients did not show any significant differences for DLPFC volumes when males and females (GLM multivariate with age, and ICV as covariates, $p > 0.05$) and junior and senior individuals were compared (GLM multivariate with gender, and ICV as covariates, $p > 0.05$). Age, length of illness, BPRS scores, and antipsychotic lifetime treatment did not differ between female and male schizophrenia subjects and between patients treated with typical and atypical antipsychotic drugs (student *t* test, $p > 0.05$).

Discussion

This study showed that our innovative approach integrating ROI and SVM techniques allows to consistently classify subjects with schizophrenia. In particular, a reliable neuroanatomical marker for the disease such as the DLPFC was chosen and the Bag-of-Words (BoW) paradigm was applied. The designed kernel was able to compare local regions localized in the DLPFC without imposing spatial constraint among them. Local features were encoded by multivariate descriptors which allowed for a greater versatility in capturing anatomical variations. The results were promising, since satisfactory scores were observed in the analysis of the whole dataset (up to 75%), being higher when the subjects were stratified by sex and age (84% for females and 81% for older subjects). Prior studies using automatic classification strategies for schizophrenia have reported similar rates, ranging between 75 and 90% (Fan et al. 2011; Ince et al. 2008; Ingalhalikar et al. 2010; Pohl and Sabuncu 2009). In particular, Koutsouleris et al. (2009) have shown that pattern classification may be a valuable tool to detect psychosis event at the early stages of the illness. With regard to females with schizophrenia, prior MRI studies found increased probabilistic distribution of gray matter (Yoon et al. 2005) and higher classification accuracy (Fan et al. 2007). Similarly, older patients were better classify than younger individuals with schizophrenia. In this context, sexual dysmorphism and aging effects may have a significant interaction with the disease processes (Frazier et al. 2008; Granholm et al. 2000), possibly resulting in a better detection of the disease when SVM techniques are applied. Although age, chronicity, illness severity, and duration of treatment may in part explain male/female differences, in our sample men and women patient groups did not differ for those variables. Finally, the left hemisphere was classified with higher accuracy, which is consistent with prior pattern classification studies focused on cortical thickness (Yoon et al. 2007), potentially supporting the relevance of reduced laterality in schizophrenia (Bellani et al. 2009a, 2010b; Ribolsi et al. 2009).

The DLPFC was used for brain classification in this study based on the evidence that it is a reliable anatomical marker of schizophrenia (Bellani et al. 2009b; Lopez-Garcia et al. 2006). In particular, the DLPFC (Broadmann areas 9 and 46) is part of the frontal–subcortical neural circuitry that modulates mood and emotional processing (Gray et al. 2002; Lopez-Garcia et al. 2006). It is connected with higher order association centres in the temporal and parietal lobe and is involved in working memory and executive functions (Cabeza and Nyberg 2000; Smith and Jonides 1999). As far as schizophrenia is concerned, several in vivo magnetic resonance imaging (MRI) and neuropsychological findings have clearly shown that DLPFC plays a crucial role in the pathophysiology of the disease (Cannon et al. 2005; Meyer-Lindenberg and Weinberger 2006). In particular, DLPFC may in part sustain deficits of working memory, context processing, and learning in schizophrenia (Brambilla et al. 2007, 2011; MacDonald and Carter 2003), which may be improved after cognitive training along with DLPFC activation (Haut et al. 2010). However, it should be mentioned that, although the DLPFC is a key structure (Glahn et al. 2005), it has clearly been shown that a complex neural network sustains the neurobiology of schizophrenia (Corradi-Dell'acqua et al. 2011; Kaymaz and van Os 2009) and that possibly different pathological processes may relate to particular subgroups (Fornito et al. 2009), based for instance on specific psychopathological dimensions (i.e. negative, positive, and disorganization symptoms) (Goghari et al. 2010). The use of combined ROI and SVM approaches might therefore consider other specific structural markers to further automatically characterize the disease, such as the anterior cingulate, the hippocampus, the superior temporal gyrus and the corpus callosum, which have consistently been found to be altered in schizophrenia (Baiano et al. 2007; Brambilla et al. 2005).

It should be noted that our findings may have partially been limited by the administration of antipsychotic drugs or by length of illness. However, no effects of the duration of treatment, dosages, or type of antipsychotics were found on the volumes of the DLPFC. Also, chronically ill and non-chronically ill patients had comparable DLPFC size. In regards of our tracing landmarks for detecting DLPFC, we followed the method suggested by (Prasad et al. 2005) which greatly includes Brodmann's areas 9 and 46. However, it should be considered that there is a large inter-individual and inter-hemispheric anatomical variability in the DLPFC boundaries in humans (Rajkowska and Goldman-Rakic 1995b). Therefore, for some subjects part of other areas (i.e. 8 and 10) may possibly have been included in the tracing. The DLPFC indeed comprises the Brodmann's areas 9 and 46 predominantly but also a few transitional areas: 9–8, 9–45, 46–10, and 46–45 (Rajkowska and Goldman-Rakic 1995a). As a result, different landmarks and measurement procedures have generally been used (Crespo-Facorro et al. 1999; Sanches et al. 2009; Tisserand et al. 2002) and up to date there is still no "in vivo" gold standard technique to delimit this region in humans. In general, it should also be kept in mind that the role of SVM remains at the moment an ancillary diagnostic tool which tentatively improve the ability to diagnose patients with schizophrenia and that will probably never substitute the expertise of the clinical psychiatrist. Nonetheless, SVM techniques represent a very promising tool for clinical and research psychiatry and other sequences may be useful to further classify schizophrenia such diffusion weighted imaging or functional magnetic resonance imaging, as recently shown (Ingalhalikar et al. 2010; Ulas et al. 2011; Yang et al. 2010). Pattern classification has also satisfactory been used in other neuropsychiatric conditions, such as autism (Ingalhalikar et al. 2010) and Alzheimer's disease (Plant et al. 2010).

In conclusion, this study showed that the DLPFC can be used as a brain structural marker to detect subjects with schizophrenia using an integrated innovative ROI-SVM approach. Similar investigations should be carried out in first-episode patients, considering males and females separately since they may express differential patterns of DLPFC neuropathology.

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Conflict of interest None.

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