Neural Comput & Applic
DOI 10.1007/s00521-016-2451-0

ORIGINAL ARTICLE

Discriminating schizophrenia and schizo-obsessive disorder: a structural MRI study combining VBM and machine learning methods

Cumhur Tas[1,2] · Hazal Mogulkoc[1] · Gul Eryilmaz[1,3] · Isıl Gogcegoz-Gul[1,3] · Turker Tekin Erguzel[4] · Barış Metin[1,3] · Nevzat K. Tarhan[1,3]

Received: 17 December 2015 / Accepted: 1 July 2016

Abstract Schizo-obsessive disorder is characterized by the clinical syndrome in which comorbid obsessive–compulsive disorder accompanies schizophrenia. A substantial number of studies have investigated the neuropsychological and clinical differences between schizophrenia and schizo-obsessive disorder. However, the neurostructural differences between these two groups have not been adequately investigated. The aim of this study was to explore gray matter differences between schizophrenia and schizo-obsessive patients using voxel-based morphometry and support vector machines combined with feature selection algorithm. Twenty-three schizophrenia and 23 schizo-obsessive patients matched by age, gender and handedness were recruited. Clinical assessments were completed in addition to high-resolution structural MRI scanning. Group differences were investigated using contrast maps, and significant regions were subjected to a feature selection and support vector machine hybrid model. In addition, voxel-of-interest values for the commonly shared brain areas between schizophrenia and OCD reported in previous meta-analyses were also used as inputs in this step. The results showed that schizo-obsessive patients had greater gray matter densities in paracentral areas (including supplementary motor area) and middle cingulate gyrus than schizophrenia patients. These brain areas together with the fronto-subcortical areas could successfully discriminate two groups with an accuracy of 78.26 %. Our results provide the first neuroanatomical evidence that schizo-obsessive disorder and schizophrenia may be two distinct clinical entities. Based on these findings, considering schizo-obsessive disorder as a subtype of schizophrenia is discernible.

Keywords Schizophrenia · Schizo-obsessive disorder · VBM · Machine learning · Ant colony optimization

1 Introduction

Obsessive and compulsive disorder (OCD) is symptomatically characterized by the intrusive thoughts (obsessions) and repetitive behaviors (compulsions) that are carried out to prevent anxiety or distress. Around 7–46 % of schizophrenia patients experience obsessive–compulsive symptoms, and these symptoms are present in both the early and chronic stages of the illness [1]. With the support of clinical and epidemiological studies, a potential subtype called schizo-obsessive disorder has been defined, referring to schizophrenia patients who experience OCS or fulfilling the diagnostic criteria for obsessive–compulsive disorder (comorbid OCD) [2]. As a note, the main phenomenological difference between OCS and comorbid OCD in schizophrenia is mainly based on the clinical severity of OCS symptoms and deteriorating effects of these on social functioning. Despite the well-developed literature on the clinical and neuropsychological distinction of schizophrenia and schizo-obsessive patients, schizo-obsessive disorder has

✉ Cumhur Tas
cumhur.tas@uskudar.edu.tr

1 Department of Psychology, Uskudar University, Altunizade Mah. Haluk Turksoy Sk. No:14, Uskudar, 34662 Istanbul, Turkey

2 Division of Cognitive Neuropsychiatry and Psychiatric Preventative Medicine, Ruhr University, Bochum, NRW, Germany

3 NPİstanbul Neuropsychiatry Hospital, Istanbul, Turkey

4 Department of Computer Engineering, Uskudar University, Istanbul, Turkey

Published online: 12 July 2016

not been included in widely used psychiatric classification systems yet [3]. One contributing reason for this is the relative paucity of data on the neuroanatomical distinctions between schizophrenia and schizo-obsessive disorder.

Clinical and neuropsychological studies showed group differences between schizophrenia and schizo-obsessive patients in symptom severity [4], neurological soft signs [5], clinical prognosis [6] and neurocognitive capacity [7]. Interestingly, some studies reported poor global functioning [8], whereas others reported fewer symptoms and greater social functioning [9] in schizo-obsessive patients as compared with schizophrenia. These mixed results could be explained by the lack of established criteria for diagnosing schizo-obsessive disorder. For instance, Cunill et al. [10] conducted a comprehensive meta-analysis where they found that schizophrenia patients with comorbid OCD were functioning better than schizophrenia patients experiencing OCS. The authors argued that OCS in schizophrenia may be due to various reasons (i.e., side effects of some antipsychotics), whereby OCD in schizophrenia may represent a subtype in schizophrenia [8]. This notion was also supported by other studies (i.e., [11]). Regarding cognitive profile, Patel et al. [12] compared schizophrenia patients with and without OCD using a comprehensive cognitive test battery. Similar to patients with OCD, they found greater deficits only in attentional shifting for schizo-obsessive subjects compared to schizophrenia.

In terms of neuroanatomical differences, only two studies have directly compared the structural cerebral differences between schizo-obsessive and schizophrenia patients by using manual anatomical tracing. Iida et al. [13] found a greater enlargement of the lateral and third ventricle in schizophrenia patients with OCS as compared to schizophrenia without OCS. Aoyama et al. [14] found shrinkage in the left hippocampus in juvenile-onset schizophrenia patients with OCS (compared to without OCS). The latter study also found significant negative correlations with duration of illness and gray matter (GM) loss in the frontal lobe only in the schizophrenia patients experiencing OCS. As a note, schizo-obsessive disorder was not defined as comorbid OCD and schizophrenia in these two studies. Apart from these studies, a thought-provoking review suggested that schizo-obsessive disorder (as defined by comorbid OCD) may share common neural substrates with both OCD and schizophrenia [15]. The authors argued that commonly shared structures such as the caudate nucleus, orbitofrontal cortex, cingulate gyrus and the mediodorsal thalamic nucleus may be the potential candidates for a neuronal network sub serving the schizo-obsessive disorder. Ample studies have investigated the GM abnormalities in OCD and schizophrenia separately. Regarding OCD, GM loss in the fronto-subcortical pathways that include orbitofrontal cortex, anterior cingulate, caudate nucleus, globus pallidus and thalamus were commonly reported in meta-analyses [16–18]. Interestingly, GM abnormalities in the same areas were also demonstrated in schizophrenia [19, 20]. Differently, abnormalities in the prefrontal cortex, supra marginal gyrus, paracentral areas, insula, parahippocampus and amygdala were pronounced more in schizophrenia than any other psychiatric disorder [20–22].

The ultimate goal for comparative neuroimaging studies is to highlight potential differences in neurophysiological networks and identify biomarkers for clinical use. Recent neuroimaging methods, such as voxel-based morphometry (VBM), have become popular in this regard. One caveat is that biomarkers for clinical use should make inferences at the individual level whereby VBM analyses are conducted at the group level [23]. To overcome this issue, recent VBM studies extended their analyses by introducing their most informative features, such as the volume of interest (VOI) values to support vector machines (SVMs). SVM is a machine learning technique that uses statistical learning theory to solve multidimensional functions and is especially used for binary classification [24]. The aim of SVM is to propose an algorithm allowing the discrimination of individual samples into distinct classes. That also involves optimizing the parameters of the algorithm using both training data and evaluating its generalization performance employing the test data. Besides, nonlinear utilize a method that is referred as the "kernel trick" to find the most appropriate and easy way for mapping the original features to higher-dimensional space using some nonlinear mapping in the preprocessing steps. Therefore, the main advantage is that SVM is able to model highly nonlinear systems and provide high generalization capacity. Recent neuroanatomical studies using VBM combined with SVM have shown encouraging findings that are clinically meaningful in schizophrenia [25], autism [26] and Alzheimer's disease [27]. In these studies, VOIs or gray matter segmentation images (input features) were taken as a point in a high-dimensional space via a kernel function, and then, the data were separated into two classes (e.g., patients vs. controls) by finding a hyperplane (decision function). Despite the advantages of using SVM, one potential drawback when modeling biological systems is the noise and less informative features of the data. Therefore, selecting the optimal features in the preprocessing step is critical for the performance of SVM-based classifications [24]. Within this perspective, a nature-inspired algorithm, ant colony optimization (ACO) which has showed potential for optimizing neural signals [28], was combined with SVM for the current study. Concerning the diagnostic dilemma of distinguishing between schizophrenia and schizo-obsessive disorder, neither VBM nor SVM analyses have been used up until today.

Given all, discriminating schizophrenia and schizo-obsessive disorder is important for both clinicians and researchers as these clinical entities have different treatment

modalities and prognosis. Besides, as there is not a clear consensus in the discrimination of these clinical entities, a neuroimaging study that is combined with SVM could be very informative. Within this direction, the ultimate aim of our study was to investigate structural GM differences between schizophrenia and schizo-obsessive disorder. We further utilized an explorative approach to evaluate the discriminative power of selected neuronal structures between schizophrenia and schizo-obsessive disorder. In this step, we first used a whole brain voxel-wise analyses to observe significant group differences. Following this, VOIs for the corresponding brain areas where group differences were found and VOIs including brain regions in which neurostructural abnormalities were previously reported for schizophrenia and OCD [13–22] were subjected to ACO feature selection and SVM classification process. Specifically, this study is based on the following twofold hypothesis: First, in terms of abnormal GM volume, we predicted that schizo-obsessive patients have specific differences from schizophrenia patients. Second, our ACO-SVM analyses could present a significant accuracy to discriminate schizophrenia and schizo-obsessive patients.

2 Materials and methods

2.1 Participants

Twenty-three schizophrenia patients and 23 schizo-obsessive patients, matched on age, gender and handedness (The Edinburgh Inventory; [30]), were enrolled for this study. Patients were recruited from the outpatient department of NPIstanbul–Uskudar University Psychiatric Hospital. To ensure longitudinal certainty of the psychiatric diagnosis, we recruited patients who had regularly visited the outpatient department for at least 1 year before recruitment. The exclusion criteria were previous history of neurological disease, head injury, clinical evidence of mental retardation, the current presence of acute psychotic episode and the fulfillment of DSM-IV criteria for schizo-affective disorder or alcohol and substance dependence. Patients were diagnosed by inspecting their medical history and a clinical interview based on DSM-IV completed by an experienced psychiatrist. Patients who fulfilled diagnostic criteria for schizophrenia and OCD according to DSM-IV were defined as schizo-obsessive, similar to previous studies [10]. All patients continued to receive treatment as usual and chlorpromazine equivalent dosages (CPZ) were calculated for all patients in order to control for the medication effects [31, 32]. None of the patients were receiving clozapine, an antipsychotic that has been related to OCS symptoms in schizophrenia [33]. As a note, the antidepressant uses in the both groups were not ruled out for this study. The ethical permission was granted from the local institutional ethics committee and the written informed consents were obtained from all of the patients. The summary of sample characteristics with the statistics is given in Table 1.

2.2 Clinical assessment

An evaluation form was conducted for both groups to collect information about socio-demographic details, duration of illness, chronology of symptoms and the treatment history. The severity of general psychiatric and schizophrenic

Table 1 Demographic, clinical variables and brain volumes of the whole study group

	Schizo-obsessive			Schizophrenia				
	N	Mean	SD	*N*	*N* %	Mean	SD	*p* value
Gender								
Male	16			16	69.57			–
Female	7			7	30.43			–
Age		32.22	9.24			32.87	8.51	0.81
Duration of illness		8.52	5.67			6.00	3.18	0.07
PANSS total score		92.25	34.92			76.12	35.97	0.18
BPRS score		44.85	18.13			37.07	17.28	0.22
Yale-brown total score		33.11	8.33			–	–	–
CPZ equivalent dose		247.14	231.57			231.39	138.92	0.80
GM		638.76	63.79			629.90	67.91	0.65
WM		539.96	54.96			549.87	73.85	0.61
CSF		240.26	36.74			238.27	32.10	0.85
TIV		1418.97	129.66			1418.05	144.30	0.98

SD standard deviation, *PANSS* Positive and Negative Syndrome Scale, *BPRS* Brief Psychiatric Rating Scale, *CPZ* Chlorpromazine, *GM* gray matter volume, *WM* white matter volume, *CSF* cerebrospinal fluid, *TIV* total intracranial volume

symptoms was evaluated by the Brief Psychiatric Rating Scale (BPRS), [34] and the Positive and Negative Syndrome Scale (PANSS), [35], respectively. Schizo-obsessive patients were carefully screened for obsessive–compulsive symptoms (OCS) by a psychiatrist experienced in the diagnosis of OCD using clinical index called Yale-Brown Obsessive–Compulsive Scale (YBOCS), [36].

2.3 MRI data acquisition

Structural MRI data were collected with a SENSE eight-channel head coil on a 1.5 Tesla Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands) at NPIstanbul–Uskudar University, Istanbul, Turkey. An MPRAGE sequence (TR/TE = 8.6/4.0 s, flip angle = 8°, FOV = 240 mm, acquired voxel size = 1 mm, 150 coronal slices without gap, scan duration = 7.23 min per volume) was used to acquire high-resolution T1-weighted images of the brain. A T2-weighted axial scan and a coronal fluid-attenuated inversion recovery (FLAIR) scan were also acquired to allow for the exclusion of subjects with focal or diffuse vascular damage. Accordingly, an experienced radiologist evaluated the T2 scans and none of the subjects were excluded due to focal or diffuse vascular damage.

2.4 VBM analyses

The between-group differences in gray matter volume were analyzed by using voxel-based morphometry (VBM), [37]. Data were first processed and tested using SPM8 (Welcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB (R2010A; The MathWorks, Natick, MA, USA). Before preprocessing, the coordinate origin of each native image was manually set on the anterior commissure. All preprocessing steps were completed with the VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm.html), using default parameters. In brief, the images were bias corrected to remove MRI inhomogeneities and noise with a spatially adaptive non-local means (SANLM) filter. To further improve signal-to-noise ratio, a spatial constraint (incorporated in the segmentation procedure) was applied, based on a classical Markov random field (MRF) model. Registration to standard MNI space consisted of a linear affine transformation and a nonlinear deformation using high-dimensional DARTEL normalization [38]. Subsequently, analyses were performed on segmented gray matter (GM) and white matter (WM) images, which were multiplied by the nonlinear components derived from the normalization matrix in order to preserve actual GM and WM values locally (modulated GM and WM volumes). To check the quality of the normalization procedure, the normalized unsegmented images were visually inspected. Covariance between normalized segmented images was calculated to check for homogeneity of variance and to identify potential outliers, and none of them were excluded. Lastly, the segmented and modulated images were spatially smoothed with an 8 mm full-width-half-maximum (FWHM) Gaussian kernel. Further to this, the MarsBaR toolbox together with Automated Anatomical Labeling (AAL) templates was used to construct a volume of interest (VOI) from the original voxel in native space. Finally, partial volume estimates for gray matter were extracted within the VOI.

2.5 ACO-SVM analysis

In the current study, similar to previous studies we used VOIs as input features for SVM-ACO analysis [25, 39, 40]. Accordingly, we first calculated VOIs for brain areas that have been related to schizophrenia and OCD in the previous aforementioned literature based on our priori hypothesis (included brain regions were: bilateral amygdala, caudate, anterior–middle–posterior cingulum, parahippocampus gyrus, insula, supra marginal gyrus, thalamus, putamen, orbitofrontal cortex; 22 regions in total). These areas were selected using the WFU PickAtlas of SPM as this toolbox allows the automatic and accurate selection of ROIs based on the Talairach Daemon Database [41] (WFU PickAtlas, version 3.0.5). In addition, brain regions that are significantly different between schizophrenia and schizo-obsessive patients according to VBM analyses were also included if they were not listed in these twenty-two regions. Instead of the significant clusters, to minimize double-dipping VOIs for corresponding brain regions as a whole were included in this step.

2.5.1 Feature selection process using ant colony optimization

Although the number of regions subjected to the SVM-ACO analysis was smaller than the original number of brain voxels, measures obtained from these regions may be less effective, irrelevant and redundant for classification. Therefore, a feature selection and optimization procedure is required to select a small set of the most informative features for classification. In general, feature selection processes could be grouped under three approaches: wrapper approach, embedded approach and filter approach. Among others, wrapper approach uses a selection algorithm to make a search along the search space of all possible features and then assess each feature set by executing a classifier on the subset. It uses the prediction process as part of selection procedure, and thus, a learning method is used to evaluate the subsets according to their predictive ability [42]. Wrappers are constituted by three main components, which

are feature selection, modeling process and feature evaluation criteria (the relationship between those consecutive steps is depicted in Fig. 1). In order to extract the best subset of features, a wrapper-based approach incorporates the classifiers with stochastic optimization methods such as genetic algorithms, simulated annealing, ant colony optimization, particle swarm optimization. Among these methods, recent population-based optimization algorithms such as genetic algorithms and ACO have shown a better performance as these methods attempt to achieve better solutions by application of knowledge from previous iterations [43]. ACO algorithm developed by Dorigo et al. [44] was inspired from the behavior of real ants in forage for food (finding the shortest path between their nest and a food source) and has been successfully applied to optimization systems in the field of biomedical signaling- and EEG-based classifications [28, 29] In our study, the wrapper approach was used together with ACO optimization. According to the ACO protocol, following the error calculation steps, pheromone table was updated until the algorithm can assure diversity and converge to optimal solution. Successively, a new feature set is selected by ACO to be assigned to SVM classifier. This process loops till the stopping criterion, a non-decreasing error value for ten successive iteration or error value less than 0.02 mean squared error value, is satisfied.

Using ACO algorithm, the uninformative features (brain regions) were excluded and the weight of each selected feature was calculated between 0 and 1 based on the pheromone table of the ACO. Here, the weight for each feature in the ACO implies the relative importance of regions compared to each other across the model. Importantly, the performance of the ACO-SVM model was based on not only the SVM classifier but also the weighted feature set of ACO. These weight values for the optimized features may thus be used to reveal the discriminative potential of each brain region included in last model. As to the heuristic parameters of ACO, σ and υ are constants to trade off the relative importance of the pheromone and the heuristic information. Since many studies recommend $\sigma = 1$ and $\upsilon = 5$, we have assigned those values for the parameters, respectively. Besides, some recent studies focus on improved versions of ACO in order to eliminate the intervention of system expert and to speed up the process.

2.5.2 *Support vector machine (SVM) classifier and kernel function*

In SVM, to get a maximal margin hyperplane discriminating two classes, the selected features are implicitly mapped to a higher-dimensional space by means of a kernel function. Here, SVM with radial basis function

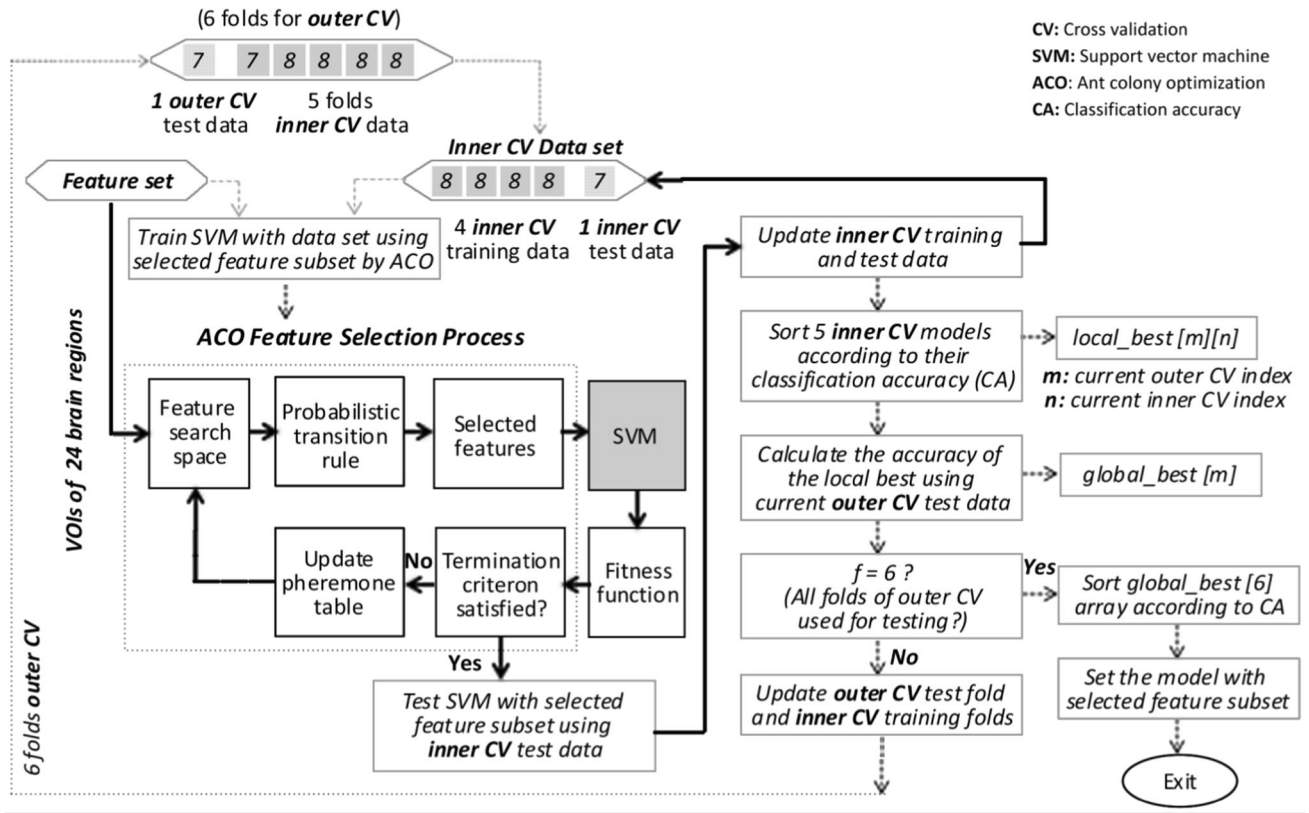

Fig. 1 Flowchart of nested *k*-fold cross-validation with classification and feature selection (ACO) process

(RBF) kernel that non-linearly maps samples into a higher-dimensional space was used. RBF was selected over a linear kernel firstly because recent neuroimaging studies have demonstrated that RBF-SVM have significantly outperformed linear SVM [45]. Secondly, nonlinear classifiers may state to high-level feature conjunctions in a way that they differed from their response to individual features [46, 47]. The cost (C) parameter and RBF kernel hyper-parameter (δ) were fixed and set as 0.1 and 0.001, respectively, in our study.

2.5.3 Cross-validation process

The validation outcome of ACO-SVM model was evaluated with *k*-fold cross-validation a commonly used procedure in previous neuroimaging studies [25–27, 47, 48]. Importantly, cross-validations were conducted in a nested manner (nested *k*-fold CV). Based on recent studies, this procedure was selected to strictly control the information leak between the training and test data and to get a totally unbiased estimate of classification accuracy [24, 47–51]. In brief, the idea behind nested *k*-fold CV is to divide the dataset into k scattered subsets, just as used in the *k*-fold CV method. In addition, a separate *k*-fold CV within the $k-1$-fold during training is performed [51]. As a note, our *k*-fold nested cross-validation consisted of two cross-validation (CV) procedures (the inner and outer CV) wrapped around each other. Here, the inner CV (fivefold) was used for model training and generation, while the outer CV (sixfold) evaluates the performance of the models generated. Accordingly, the data were first split into six parts using stratified sampling. Onefold was reserved for outer CV and the remaining fivefold were used for training process in the inner CV. In the inner CV cycle, five models were generated at the end. Following the inner CV loop, one reserved outer CV test fold was swapped with one of the folds of five training folds so that the models generated by the inner CV process could be tested by completely different test data for each outer CV cycle. The best model was selected based on minimum error on training data from entire set of generations, performance classification parameter and fitness value. The details of *k*-fold nested CV procedure together with feature selection and classification process are illustrated in Fig. 1. The accuracy of the classifier was measured by the proportion of observations that were correctly classified into schizophrenia or schizo-obsessive group ((True positive + True negative)/(True positive + True negative + False positive + False negative) * 100)). In addition to accuracy, sensitivity, specificity and AUC values were also calculated. SVM-ACO analyses were conducted with open source (libSVM; http://www.csie.ntu.edu.tw/~cjlin/libsvm/) and in-house codes in MATLAB.

2.6 Data analysis

Demographics and scores on clinical evaluations were compared between groups with independent samples *t* tests. We analyzed the data in the following three steps. Firstly, the overall intracranial volume (TIV) was calculated as the total sum of the volumes of GM, WM and CSF. The differences of GM, WM and TIV between subjects and controls were compared with independent samples *t* tests. The statistical threshold was set to 0.05 in this step (*p* value). Secondly, for the GM analysis, modulated GM images in each group were subjected to a voxel-wise *t* test analysis in SPM8 with covariation for TIV and duration of illness. To control for errors due to multiple statistical testing, the results were estimated with a cluster level threshold of $p < 0.05$, with voxel-level threshold of $p < 0.001$ and a minimum cluster size (k) of 99 voxels, using the AlphaSim software (http://www.restfmri.net/forum/REST_V1.4), which applied Monte Carlo simulation (parameters: individual voxel $p = 0.001$; rmm = 2.5; 5.000 simulations). Importantly, the use of this approach is legitimized in ample VBM studies and the FWE correction may be too conservative for our explorative study [52]. In the third step, extracted VBM features were subjected to the SVM-ACO model to identify the discrimination accuracy and selected features.

3 Results

In preliminary analysis, we did not find any differences in the BPRS and PANSS score of the schizophrenia and schizo-obsessive patients. Besides, the GM, WM and CSF volumes did not differ between groups (see Table 1 for details).

3.1 Voxel-wise whole brain difference between schizo-obsessive versus schizophrenia patients

Testing the regional GM density between schizophrenia and schizo-obsessive patients showed two clusters of decreased GM in the schizophrenia group. The cluster sizes, t-values, Brodmann areas and MNI coordinates for these areas are given in Table 2. Accordingly, the first cluster comprised from two peak voxels: the right paracentral lobule and right supplementary motor area that also includes the middle portion of right cingulate cortex. The second cluster comprised left supplementary motor area including the left middle cingulate (see Fig. 2 for illustration). Lastly, testing the gray matter loss in schizo-obsessive as opposed to schizophrenia patients did not show significant brain region differences.

Table 2 Summary of peak differences for areas with greater gray matter density in schizo-obsessive compared to schizophrenia patients

Clusters	Regions	Brodmann area	Cluster size	Peak voxel coordinates (MNI)			Peak voxel *t*-value
				x (mm)	*y* (mm)	*z* (mm)	
Cluster 1	Right paracentral lobule	6	120	11	−34	54	4.00
	Right supplementary motor area/right middle cingulum	5/24		9	−24	49	3.45
Cluster 2	Left supplementary motor area/left middle cingulum	32/24	101	−9	9	46	3.83

Results were AlphaSim corrected (=<0.05 FWE; extent threshold = 99 voxels; $df = 1.42$)

MNI Montreal Neurological Institute

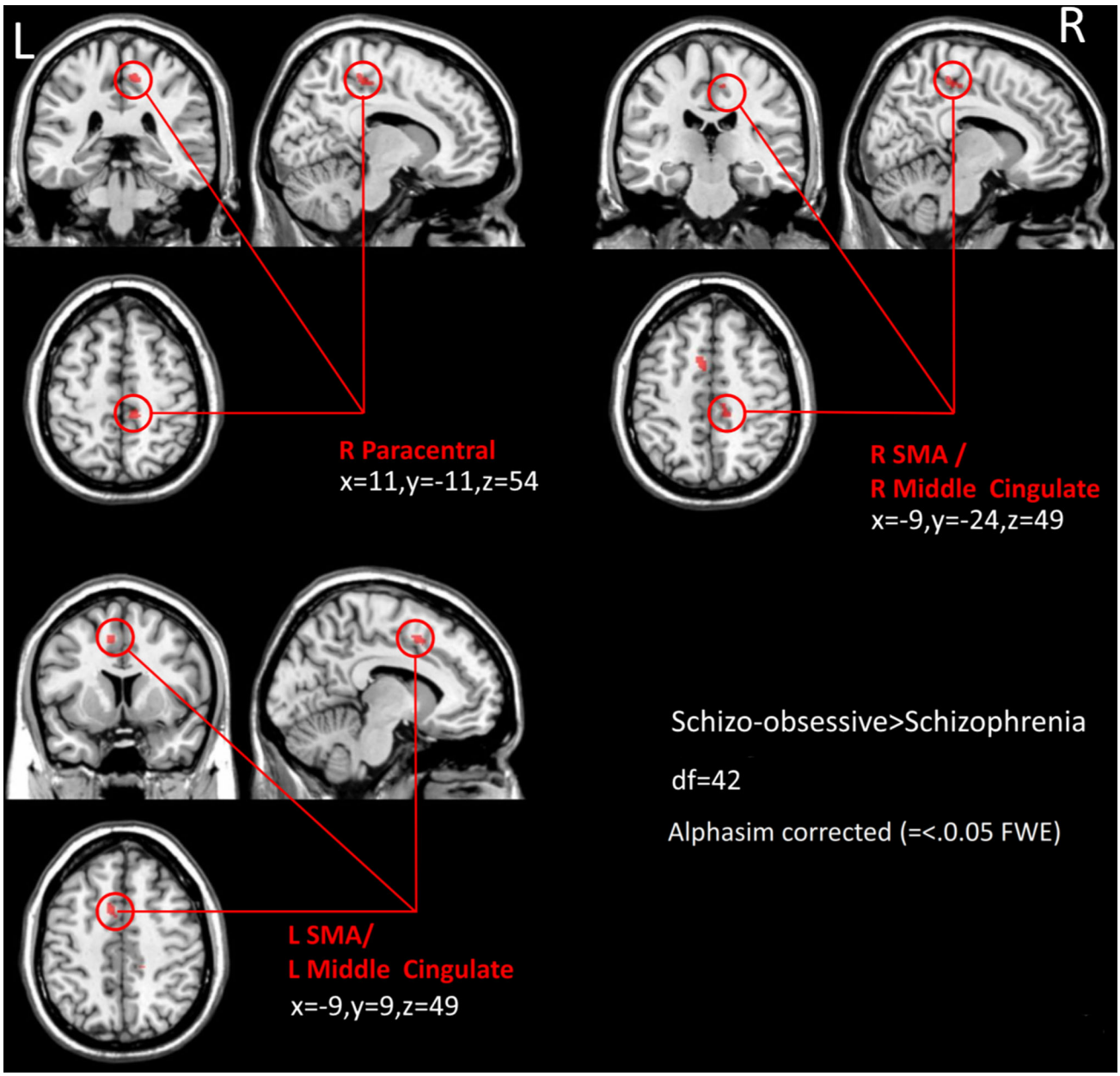

Fig. 2 Areas with greater gray matter density in schizo-obsessive compared to schizophrenia patients. SPM{*t*} statistically significant regions (using AlphaSim correction for multiple comparisons) superimposed on a T1 brain template image (*L* left, *R* right)

3.2 Results of the ACO process

Together with the bilateral GM differences in the paracentral areas, in total twenty-four regions were subjected to the SVM-ACO model. Following the ACO process, eighteen brain regions were selected and subjected to the SVM model as inputs (bilateral parahippocampus, left putamen, right amygdala, right supra marginal gyrus, left posterior cingulate were excluded). Regarding the discrimination potential between the patient groups, left and right thalamus, right caudate, left and right anterior, middle cingulum, right posterior cingulum, left supramarginal area and left paracentral lobule (including supplementary motor areas) were fully weighted, whereas left orbitofrontal cortex (weight value: 0.97), right orbitofrontal cortex (weight value: 0.74), right putamen (weight value: 0.84), left amygdala (weight value: 0.74), right (weight value: 0.58) and left insula (weight value: 0.65) and right paracentral lobule (weight value: 0.97) had estimated weights less than 1.

3.3 SVM-ACO model performance

Regarding, the classification results and accuracy values, our hybrid model could discriminate patients of schizo-obsessive and schizophrenia with a considerably high accuracy (78.26 %), sensitivity (0.79), specificity (0.78) and an acceptable area under curve value (AUC) in the ROC analyses (0.79; see ROC curve in Fig. 3). Accordingly, the model correctly classified 18 patients (over 23) in the schizo-obsessive group. P-values for accuracy, sensitivity, specificity and AUC were below 0.01. Kappa value for the current model was 0.57. Lastly, the mean duration of illness was regressed to the decision values of the final model and we did not observe any noteworthy effect on the SVM model ($p > 0.05$).

Here, the diagonal line represents the change level. The area under the diagonal is 0.5 unit square and AUC = 0.5 means the chance discrimination that curve located on diagonal line in ROC space. The minimum AUC should be considered a chance level, i.e., AUC = 0.5.

4 Discussions and conclusions

The first goal of this paper was to explore the GM differences between patients with schizo-obsessive disorder and schizophrenia. The second goal was to explore the discriminative power of these differences using ACO-SVM hybrid model. Our results showed significantly greater GM densities for schizo-obsessive patients in bilateral paracentral areas, including supplementary motor area and middle cingulate. In addition, these areas, together with the brain regions sharing common anatomical substrates with OCD and schizophrenia (i.e., orbitofrontal cortex, thalamus), could discriminate these two groups with a considerably high accuracy.

In light of these findings, relatively preserved GM density in supplementary motor area and middle cingulate cortex in schizo-obsessive patients may indicate that schizo-obsessive disorder represents a subtype of schizophrenia with similar psychotic symptoms, yet with different neurostructural abnormalities. Reductions in the GM density in the paracentral lobule, including

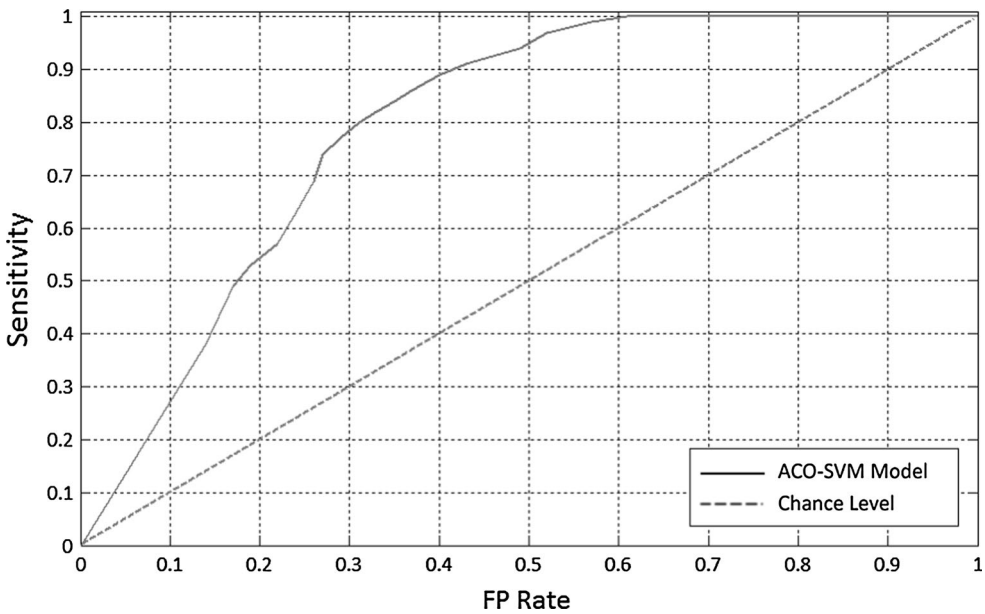

Fig. 3 ROC curve for the SVM and ACO hybrid model used for VOI-based classification. *FP* false positive

supplementary motor area, have been commonly reported previously in schizophrenia patients as compared to healthy individuals [52]. Furthermore, studies in prodromal schizophrenia demonstrated GM loss in supplementary motor area even before the first psychotic episode [53]. In addition to this, a recent study found that GM reductions in supplementary motor area were positively associated with increased psychotic symptoms in schizophrenia [54]. In general, the paracentral lobule, including supplementary motor area, has a key role in motor control and is responsible for sending and receiving inputs to and from the somatosensory projections of the thalamus, basal ganglia and other cortical motor areas [55, 56]. Moreover, middle cingulate cortex is essential for action initiation and is related to multiple prefrontal, parietal and premotor areas in the execution of self-initiated movements [57, 58]. Accumulating evidence supports the progenitor role of these three brain areas in the planning and complex decision making processes [59] that are significantly impaired in schizophrenia and OCD. Taken as a whole, these demonstrated differences led us propose that the disrupted neuronal synchrony in early somatosensory integration, action execution and observation may have a dominant role in schizophrenia, whereas an alternative and possibly less severe pathway may pave the ground for the development of schizo-obsessive disorder. Several authors consider OCD and schizophrenia as two entities having a single continuum. One functional difference that has been demonstrated in OCD in schizophrenia is the different degrees of impairments demonstrated in dorsolateral (DLPFC) and ventromedial prefrontal cortex (VMPFC). Accordingly, the network that includes impairments in VMPFC more than DLPFC may result with OCS in schizophrenia whereby, a greater DLPFC could explain the psychotic symptoms [15–19]. Although we could not find GM differences in DLPFC in the current study, studies investigating functional activities between DLPFC and VMPFC in schizophrenia and schizo-obsessive disorder may support such explanation.

The ACO-SVM approach in this study classified schizophrenia and schizo-obsessive patients with a high overall accuracy. Accordingly, the discriminative role of paracentral areas, orbitofrontal cortex, cingulate cortex and subcortical structures between schizophrenia and schizo-obsessive patients in this study may support our assumption that these disorders should be considered as separate entities. As a note, this study used a hybrid model that selected more informative VOI-based features first, and then classified the subjects benefiting from the feature subset. This may be one possible reason why we found greater accuracy as compared with other VBM studies using only SVM in schizophrenia [60]. It should also be noted that, based on the literature, some brain regions that were not evident in the conventional VBM analysis were introduced as additional features together with the significant brain regions found in the first step. Most of these features have survived from the analyses steps and introduced in last ACO-SVM model. Taken together, the ACO-SVM approach in this study could be useful as a supplementary multivariate analysis method in conjunction with the univariate VBM analyses.

Whether schizo-obsessive disorder should be classified under obsessive–compulsive or schizophrenia spectrum disorder is under debate [2]. According to our results, we did not show differences in the GM areas such as prefrontal (i.e., DLPFC; [20]) and temporal areas (i.e., TPJ; [19]) which were specific to schizophrenia in the previous studies comparing schizophrenia with other psychiatric disorders (i.e., [22]). Moreover, there has been a debate in the literature on whether deficits in orbitofrontal cortex, cingulate cortex and subcortical structures (i.e., thalamus, putamen and amygdala) are specific to the brain–behavioral models of OCD, or in contrast, abnormalities in these brain regions are common for both schizophrenia and OCD. However, we are not able to make any contribution to this debate as we did not have an OCD group in our study. In the literature, only one VBM study compared the GM volumes of OCD and schizophrenia patients and found greater orbitofrontal cortex loss in schizophrenia [61]. A suggestion for future studies could be to investigate the associations between the neuropsychological profile and structural brain abnormalities between OCD, schizophrenia and schizo-obsessive patients. Despite all, based on our findings, it could be suggested that schizo-obsessive disorder may be classified under the umbrella of schizophrenia spectrum disorders, rather than OCD. (i.e., [1, 62]). One main limitation of this study is that all patients were under medication, and it is evident that antipsychotics may also contribute to the development of OCS [29]. Besides, the effect of antidepressant use over the GM density was not controlled in this study. As a note, we controlled the effects of antipsychotics and did not find any group differences in the calculated mean CPZ equivalents. Another potential limitation is that there was a trend toward a significant difference in the duration of illness between the two groups. We controlled this issue by including the mean duration of illness variable as a nuisance covariate in our statistical model. Lastly, almost all brain regions whose GMVs were used as inputs in the SVM analyses were a priori selected based on the previous meta-analyses. Only paracentral lobule was found to be significant in the VBM analyses and was also included into the SVM analyses. Therefore, it could be argued that a slightly less conservative approach was used to control double-dipping for the current study.

This study provides preliminary evidence that schizo-obsessive disorder may represent a unique subtype in

schizophrenia spectrum. A necessary follow-up to this research is the replication of these findings in larger samples using multivariate neuroimaging approaches and alternative input features (VOIs, cortical thickness, fMRI activations, manual tracing). Lastly, identifying specific neuroanatomical differences in schizo-obsessive patients using feature selection and SVM could also have clinical importance in predicting prognosis and treatment response in the long-term follow-up for our patients.

Acknowledgments Uskudar University Research Council and NPIstanbul Neuropsychiatry Hospital funded the sample collection and MRI scans (No. NPI-120814).

References

1. Poyurovsky M, Hramenkov S, Isakov V, Rauchverger B, Modai I, Schneidman M, Fuchs C, Weizman A (2001) Obsessive–compulsive disorder in hospitalized patients with chronic schizophrenia. Psychiatry Res 102:49–57
2. Bottas A, Cooke RG, Richter MA (2005) Comorbidity and pathophysiology of obsessive–compulsive disorder in schizophrenia: Is there evidence for a schizo-obsessive subtype of schizophrenia? J Psychiatry Neurosci 30:187–193
3. Braff DL, Ryan J, Rissling AJ, Carpenter WT (2013) Lack of use in the literature from the last 20 years supports dropping traditional schizophrenia subtypes from DSM-5 and ICD-11. Schizophr Bull 39:751–753
4. Berman I, Sapers BL, Chang HH, Losonczy MF, Schmildler J, Green AI (1995) Treatment of obsessive–compulsive symptoms in schizophrenic patients with clomipramine. J Clin Psychopharmacol 15:206–210
5. Sevincok L, Akoglu A, Topaloglu B, Aslantas H (2004) Neurological soft signs in schizophrenic patients with obsessive–compulsive disorder. Psychiatry Clin Neurosci 58:274–279
6. Nechmad A, Ratzoni G, Poyurovsk M, Meged S, Avidan G, Fuchs C, Bloch Y, Weizman R (2003) Obsessive–compulsive disorder in adolescent schizophrenia patients. Am J Psychiatry 160:1002–1004
7. Michalopoulou PG, Konstantakopoulos G, Typaldou M, Papageorgiou C, Christodoulou GN, Lykouras L, Oulis P (2014) Can cognitive deficits differentiate between schizophrenia with and without obsessive–compulsive symptoms? Compr Psychiatry 55:1015–1021
8. Cunill R, Huerta Ramos E, Castells X (2013) The effect of obsessive–compulsive symptomatology on executive functions in schizophrenia: a systematic review and meta-analysis. Psychiatry Res 210:21–28
9. Tibbo P, Kroetsch M, Chue P, Warneke L (2000) Obsessive–compulsive disorder in schizophrenia. J Psychiatr Res 34:139–146
10. Cunill R, Castells X, Simeon D (2009) Relationships between obsessive–compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. J Clin Psychiatry 70:70–82
11. Üçok A, Ceylan ME, Tihan AK, Lapçin S, Ger C, Tükel R (2010) Obsessive compulsive disorder and symptoms may have different effects on schizophrenia. Prog Neuro-Psychopharmacol 35:429–433
12. Patel DD, Laws KR, Padhi A, Farrow JM, Mukhopadhaya K, Krishnaiah R, Fineberg NA (2010) The neuropsychology of the schizo-obsessive subtype of schizophrenia: a new analysis. Psychol Med 40:921–933
13. Iida J, Matumura K, Aoyama F, Iwasaka H, Hirao F, Sakiyama S (1998) Cerebral MRI findings in childhood-onset schizophrenia, comparison of patients with prodromal obsessive–compulsive symptoms and those without symptoms. Recent Prog Child Adolesc Psychiatry 2:75–83
14. Aoyama F, Iida J, Inoue M, Iwasaka H, Sakiyam S, Hata K, Kishimoto T (2000) Brain imaging in childhood- and adolescence-onset schizophrenia associated with obsessive–compulsive symptoms. Acta Psychiatr Scand 102:32–37
15. Gross Isseroff R, Hermesh H, Zohar J, Weizman A (2003) Neuroimaging communality between schizophrenia and obsessive compulsive disorder: A putative basis for schizo-obsessive disorder? World J Biol 4:129–134
16. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET (2008) Integrating evidence from neuroimaging and neuropsychological studies of obsessive–compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav R 32:525–549
17. Rotge JY, Guehl D, Dilharreguy B, Tignol J, Bioulac B, Allard M, Burbaud P, Aouizerate B (2009) Meta-analysis of brain volume changes in obsessive–compulsive disorder. Biol Psychiatry 65:75–83
18. Rotge JY, Langbour N, Guehl D, Bioulac B, Jaafar N, Allard M, Aouizerate B, Burbaud P (2010) Gray matter alterations in obsessive–compulsive disorder: an anatomic likelihood estimation meta-analysis. Neuropsychopharmacology 35:686–691
19. Bor E, Fornito A, Radu J, Walterfang M, Seal M, Wood SJ, Yücel M, Velakoulis D, Pantelis C (2011) Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res 127:46–57
20. Fusar-Poli P, Radua J, McGuire P, Borgwardt S (2011) Neuroanatomical maps ofpsychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. Schizophr Bull 38:1297–1307
21. Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E, Fox PT (2008) Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biol Psychiatry 64:774–781
22. McIntosh AM, Job DE, Moorhead TW, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2004) Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. Biol Psychiatry 56:544–552
23. Orrù G, Pettersson-Yeo W, Marquand AF, Sartori G, Mechelli A (2012) Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review. Neurosci Biobehav R 36:1140–1152
24. Lemm S, Blankertz B, Dickhaus T, Müller KR (2011) Introduction to machine learning for brain imaging. Neuroimage 56:387–399
25. Liu Y, Teverovskiy L, Carmichael O, Kikinis R, Shenton M, Carter CS, Stenger VA, Davis S, Aizenstein H, Becker J, Lopez O, Meltzer C (2004) Discriminative MR image feature analysis for automatic schizophrenia and Alzheimer's disease classification. In: Barillot C, David H, Hellier R, Pierre (eds) Medical image computing and computer-assisted intervention—MICCAI2004 7th international conference. Springer, Saint-Malo, pp 393–401
26. Ecker C, Rocha-Rego V, Johnston P, Mourao-Miranda J, Marquand A, Daly EM, Brammer MJ, Murphy C, Murphy DG (2010) Investigating the predictive value of whole-brain structural MR scans in autism: a pattern classification approach. NeuroImage 49:44–56

27. Magnin B, Mesrob L, Kinkingnéhun S, Pélégrini-Issac M, Colliot O, Sarazin M, Dubois B, Lehéricy S, Benali H (2009) Support vector machine-based classification of Alzheimer's disease from whole-brain anatomical MRI. Neuroradiology 51:73–83
28. Erguzel TT, Ozekes S, Tan O, Gultekin S (2014) Feature selection and classification of electroencephalographic signals an artificial neural network and genetic algorithm based approach. Clin EEG Neurosci. doi:10.1177/1550059414523764
29. Huang CL (2009) ACO-based hybrid classification system with feature subset selection and model parameters optimization. Neurocomputing 73:438–448
30. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113
31. Rijcken CA, Monster TB, Brouwers JR (2003) Chlorpromazine equivalents versus defined daily doses: How to compare antipsychotic drug doses? J Clin Psychopharmacol 23:657–659
32. Kroken RA, Johnsen E, Ruud T, Wentzel-Larsen T, Jørgensen HA (2009) Treatment of schizophrenia with antipsychotics in Norwegian emergency wards, a cross-sectional national study. BMC Psychiatry 9:24
33. Doyle M, Chorcorain AN, Griffith E, Trimble T, O'Callaghan E (2014) Obsessive compulsive symptoms in patients with Schizophrenia on clozapine and with obsessive compulsive disorder: a comparison study. Compr Psychiatry 55:130–136
34. Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812
35. Kay SR, Flszbein A, Opfer LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261
36. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS (1989) The Yale-Brown obsessive compulsive scale: I. Development, use, and reliability. Arch Gen Psychiatry 46:1006–1011
37. Ashburner J, Friston KJ (2000) Voxel-based morphometry—the methods. NeuroImage 11:805–821
38. Ashburner J (2007) A fast diffeomorphic image registration algorithm. NeuroImage 38:95–113
39. Lao Z, Shen D, Xue Z, Karacali B, Resnick SM, Davatzikos C (2004) Morphological classification of brains via high-dimensional shape transformations and machine learning methods. Neuroimage 21:46–57
40. Fung G, Stoeckel J (2007) SVM feature selection for classification of SPECT images of Alzheimer's disease using spatial information. Knowl Inf Syst 11:243–258
41. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19:1233–1239
42. Kohavi R, John GH (1997) Wrappers for feature subset selection. Artif Intell 97:273–324
43. Li Y, Wang G, Chen H, Shi L, Qin L (2013) An ant colony optimization based dimension reduction method for high-dimensional datasets. J Bionic Eng 10:231–241
44. Dorigo M, Gambardella LM (1997) Ant colony system: a cooperative learning approach to the traveling salesman problem. IEEE Trans Evol Comput 1:53–66
45. Song S, Zhan Z, Long Z, Zhang J, Yao L (2011) Comparative study of SVM methods combined with voxel selection for object category classification on fMRI data. PLoS One 6(2):e17191
46. Norman KA, Polyn SM, Detre GJ, Haxby JV (2006) Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cognit Sci 10:424–430
47. Misaki M, Kim Y, Bandettini P, Kriegeskorte N (2010) Comparison of multivariate classifiers and response normalizations for pattern-information fMRI. NeuroImage 53:103–118
48. Douglas PK, Lau E, Anderson A, Head A, Kerr W, Wollner M, Cohen MS (2013) Single trial decoding of belief decision making from EEG and fMRI data using independent components features. Front Hum Neurosci 7:392
49. Krstajic D, Buturovic LJ, Leahy DE, Thomas S (2014) Cross-validation pitfalls when selecting and assessing regression and classification models. J Cheminform 6:1–15
50. Japkowicz N, Shah M (2011) Evaluating learning algorithms: a classification perspective. Cambridge University Press, Cambridge
51. Varma S, Simon R (2006) Bias in error estimation when using cross-validation for model selection. BMC Bioinform 7:91
52. Exner C, Weniger G, Schmidt-Samoa C, Irle E (2006) Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. Schizophr Res 84:386–396
53. Voets NL, Hough MG, Douaud G, Matthews PM, James A, Winmill L, Webster P, Smith S (2008) Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. NeuroImage 43:665–675
54. Stegmayer K, Horn H, Federspiel A, Razav N, Bracht T, Laimböck K, Strik W, Dierks T, Wiest R, Müller TJ (2014) Supplementary motor area (SMA) volume is associated with psychotic aberrant motor behaviour of patients with schizophrenia. Psychiatry Res Neuroimaging 223:49–51
55. Goldberg G (1985) Supplementary motor area structure and function: review and hypotheses. Behav Brain Sci 8:567–588
56. Jürgens U (1984) The efferent and afferent connections of the supplementary motor area. Brain Res 300:63–81
57. Hoffstaedter F, Grefkes C, Caspers S, Roski C, Palomero-Gallagher N, Laird AN, Fox PT, Eickhoff SB (2013) The role of anterior midcingulate cortex in cognitive motor control. Hum Brain Mapp 35:2741–2753
58. Vogt BA, Berger GR, Derbyshire SW (2003) Structural and functional dichotomy of human midcingulate cortex. Eur J Neurosci 18:3134–3144
59. Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G (2005) Grasping the intentions of others with one's own mirror neuron system. PLoS Biol 3:79
60. Gould IC, Shepherd AM, Laurens KR, Cairns MJ, Carr VJ, Green MJ (2014) Multivariate neuroanatomical classification of cognitive subtypes in schizophrenia: a support vector machine learning approach. Neuroimage Clin 18:229–236
61. Riffkin J, Yücel M, Maruff P, Wood SJ, Soulsby B, Olver J, Pantelis C (2005) A manual and automated MRI study of anterior cingulate and orbito-frontal cortices, and caudate nucleus in obsessive–compulsive disorder: comparison with healthy controls and patients with schizophrenia. Psychiatry Res Neuroimaging 138:99–113
62. Rajkumar RP, Reddy Y, Kandavel T (2008) Clinical profile of "schizo-obsessive" disorder: a comparative study. Compr Psychiatry 49:262–268