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Defining Multivariate Normative Rules for Healthy Aging using Neuroimaging and Machine Learning: An Application to Alzheimer's Disease

Ailton Andrade de Oliveira[a], Maria Teresa Carthery-Goulart[a], Pedro Paulo de Magalhães Oliveira Júnior[b], Daniel Carneiro Carrettiero[c], João Ricardo Sato[a,b,*] and for the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Center of Mathematics, Computation and Cognition, Universidade Federal do ABC, Santo André, Brazil*
[b]*NIF-LIM44, Department of Radiology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*
[c]*Center of Natural and Human Sciences, Universidade Federal do ABC, Santo André, Brazil*

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Abstract.
Background: Neuroimaging techniques combined with computational neuroanatomy have been playing a role in the investigation of healthy aging and Alzheimer's disease (AD). The definition of normative rules for brain features is a crucial step to establish typical and atypical aging trajectories.
Objective: To introduce an unsupervised pattern recognition method; to define multivariate normative rules of neuroanatomical measures; and to propose a brain abnormality index.
Methods: This study was based on a machine learning approach (one class classification or novelty detection) to neuroanatomical measures (brain regions, volume, and cortical thickness) extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI)'s database. We applied a ν-One-Class Support Vector Machine (ν-OC-SVM) trained with data from healthy subjects to build an abnormality index, which was compared with subjects diagnosed with mild cognitive impairment and AD.
Results: The method was able to classify AD subjects as outliers with an accuracy of 84.3% at a false alarm rate of 32.5%. The proposed brain abnormality index was found to be significantly associated with group diagnosis, clinical data, biomarkers, and future conversion to AD.
Conclusion: These results suggest that one-class classification may be a promising approach to help in the detection of disease conditions. Our findings support a framework considering the continuum of brain abnormalities from healthy aging to AD, which is correlated with cognitive impairment and biomarkers measurements.

Keywords: Dementia, neurodegeneration, neuroimaging, normative, outliers, pattern recognition, support vector machines

*Correspondence to: João Ricardo Sato (CMCC), Universidade Federal do ABC, Av. dos Estados, 5001, Bairro Bangu, Santo André, SP, CEP 09210-580, Brasil. Tel.: +55 11 49968437; E-mail: joao.sato@ufabc.edu.br.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

INTRODUCTION

Due to its low invasiveness and high discrimination power between tissues, magnetic resonance imaging (MRI) has been considered a powerful tool for the investigation of disorders in the central nervous system. Structural imaging experienced a considerable advance in the last years with deep gray matter volumetry [1–3], cortical surface modelling [4], and

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voxel-based morphometric analysis of T1 images [5].

The utilization of machine learning techniques in neuroimaging data analysis has increased substantially in the last decade. These techniques are suitable both to extract patterns from a multivariate perspective and to classify subgroups by obtaining prediction labels for new observations. One of the most popular methods is support vector machine (SVM) [6–8]. However, a great amount of studies still focus on classification problems with two classes, usually discriminating patients under a very specific condition from healthy subjects. A promising alternative is the construction of normative rules aimed at defining characteristic patterns of a given population (e.g., healthy subjects) rather than seeking a discriminating pattern. Thus, assuming we have a large sample of healthy (typical) subjects, novelty detection methods have the potential to identify individuals with abnormal brains as outliers. The search for characteristic patterns might be portrayed as an issue of data description in the machine learning literature [9–11].

Normative databases of neuroimaging data are becoming a promising approach for the evaluation of neuroanatomical features [12, 13]. However, there are few studies employing non-supervised classifiers to neuroimaging data. One-Class Support Vector Machine (OC-SVM) is a non-supervised variant of SVM classifiers which focus on the detection of outliers. Hardoon and Manevitz [14] applied these techniques to non-clinical functional MRI data to identify the execution of a motor task based on brain activity patterns. Similarly, Sato et al. [15], on a proof of concept study, have built a normative database of functional connectivity patterns by also using an OC-SVM in a laterality experiment. Song and Wyrwicz [16] have used an OC-SVM classifier to detect active voxels. The basic idea of OC-SVM is that abnormality may occur in very different ways. Therefore, the main concern is to identify deviant patterns from typical ones (used to train the machine).

Regarding clinical applications, there was a recent re-analysis using OC-SVM on data from a study which had previously used a two-class SVM [17] to classify healthy controls and patients with unipolar depression. In this study, subjects were exposed to faces with emotional expression and classification was based on the standard global brain activation in response to these stimuli. However, since the sample was small, even combining unipolar depression patients who responded to treatment to those that did not, data was insufficient to train a two-class SVM. As a result, the study did not obtain significant predictions about the response to treatment. By using OC-SVM [18], the authors found a significant correlation between the scores obtained from OC-SVM and patients' scores in the Hamilton Rating Scale for Depression. In addition, they were also able to identify two subgroups associated with the future response to treatment. A study by Sato et al. [15] on attention deficit and hyperactivity disorder is another example of OC-SVM usefulness in neuroimaging data analysis. The authors applied OC-SVM to the functional connectivity between precuneus/(posterior cingulate) and dorsal anterior cingulate cortex and abnormal connectivity patterns were found for attention deficit and hyperactivity disorder. A more recent study [19] foresaw the application of OC-SVM for the definition of normative rules as a promising method, considering large-scale multicentric neuroimaging datasets.

With the trend of increasing life expectancy, we face a growing impact of neurodegenerative diseases such as Alzheimer's disease (AD) [20]. AD is a neurodegenerative disorder of progressive nature that impairs neuronal function leading to gradual degradation in functional, cognitive and behavioral aspects ultimately rendering subjects into total dependency for even the most basic activities of daily living. Although controversial, the most accepted etiological hypothesis is the so-called "Amyloid Cascade Hypothesis" [21, 22], which considers amyloid-β deposits found during histopathological examination of the affected brains to be the disease's main cause; however, there are alternative hypotheses, e.g., age-dependent hypothesis which considers neuroinflammation and altered state of brain cells as consequences of an initial injury [23]. Considerable advances have been made in the understanding of the underlying neural basis of AD. However, as a definitive biomarker is not available yet, the clinical diagnosis of this disease can be only probabilistic, even in the case of typical AD [24]. According to currently accepted consensus recommendations, in order to fulfill the criteria for probable AD, an individual must present clinically with an early and significant episodic memory impairment and at least one supportive biomarker criteria. These biomarkers might be structural brain changes visible on MRI with early and extensive involvement of the medial temporal lobe, molecular neuroimaging changes seen with positron emission tomography (PET) with hypometabolism or hypoperfusion in temporoparietal areas, and changes in cerebrospinal fluid biomarkers [24]. Research of other biomarkers is still needed to contribute for the diagnosis of the disease at the earliest possible phase so that

available therapeutic approaches can be more effective [24].

In this study, we applied OC-SVM to the public MRI data from the project Alzheimer's Disease Neuroimaging Initiative (ADNI) [25]. This initiative has acquired images from subjects with AD, subjects with mild cognitive impairment (MCI), and healthy control subjects. The utilization of supervised machine learning methods has shown a promising potential to explore the ADNI database. Stonnington et al. [26] applied relevance vector regression to predict individual clinical scores based on morphological features extracted from structural MRI. Further studies have investigated the potential of machine learning methods to explore MCI progression and possible conversion to the AD to AD [27–29]. In a more technical study, Chu et al. [30] have tested automated feature selection methods (*t*-test filtering and recursive feature elimination) in group classification and have not found a significant improvement in accuracy. Recently, Casanova et al. [31] proposed a risk score for AD by using regularized logistic regression.

Previous methods proposed in the literature focused on the discrimination between patients with AD and healthy controls and the prediction of progression to AD. From a multivariate perspective, there is no description of a typical pattern or normative rules to MRI data. In the present study, using an automated method and OC-SVM we extracted morphometric features (cortical thickness and volumetric information) from the images to define normative rules based on healthy subjects. As a byproduct of this approach, an abnormality scale was obtained, providing quantitative indication that a prospective patient can be considered atypical based on his/her age and neuroanatomical measures. Finally, we illustrate how this brain abnormality score is associated to clinical data, biomarkers, and also prognosis.

MATERIAL AND METHODS

Image database

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression to MCI and to early AD. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, see ADNI's Progress Report and Future Plans [32] and http://www.adni-info.org.

In the current study, we considered the structural MRI from 814 subjects who participated in ADNI's first phase (ADNI-1, without processing errors in freesurfer recon-all pipeline, more information about the protocol and ethical issues can be found at http://adni-info.org/). The demographic information of this sample is described in Table 1. Clinical data (Mini-Mental State Examination, MMSE [33]; and Clinical Dementia Rating, CDR [34], global and sum of boxes), genotypic information (ApoE) and biomarkers (tau protein and amyloid-β, lumbar puncture, see Shaw et al. [35]) were also used in the analyses. Finally, we also considered information about the conversion from MCI to AD (at the last assessment of the subject, in a maximum period of 36 months) in further analyses.

Table 1
Demographic information of the sample used in this study

Gender	Diagnosis	Age	Frequency	Relative frequency
Male	C	<60	0	0%
		60–70	5	4.20%
		71–80	87	73.11%
		>80	27	22.69%
	MCI	<60	7	2.75%
		60–70	42	16.47%
		71–80	128	50.19%
		>80	78	30.59%
	AD	<60	1	1.00%
		60–70	22	22.00%
		71–80	41	41.00%
		>80	36	36.00%
Female	C	<60	0	0%
		60–70	1	0.92%
		71–80	85	77.98%
		>80	23	21.10%
	MCI	<60	4	2.86%
		60–70	35	25.00%
		71–80	61	43.57%
		>80	40	28.57%
	AD	<60	5	5.49%
		60–70	11	12.09%
		71–80	49	53.85%
		>80	26	28.57%

C, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease.

Imaging processing

Neuroanatomical measures of the subjects were obtained from their structural MRI files by using the standard recon-all pipeline of FreeSurfer software version 4.5.0 (freely available at http://surfer.nmr.mgh.harvard.edu/fswiki/). The output of this processing includes neuroanatomical measures from brain regions based on an automated segmentation and parcellation procedures. Further information about recon-all pipeline can be found in referred literature [4, 36–38]. In this study, we considered measures of average thickness of cortical structures and volumetric information of cerebellar and subcortical structures. These two measures were considered because they are the most intuitive/interpretable ones that could be extracted from parcellated brain regions. Note that in the case of subcortical structures, cortical thickness cannot be estimated and thus the volume was extracted. Other possible anatomical measures are curvature, Jacobian or gyrification, which are more complex features with difficult interpretation of findings.

One-class SVM

OC-SVM is an unsupervised learning method originally proposed by Schölkopf [39]. This method determines a boundary for identifying the subjects of a target population, once the variables of interest and a large sample of "examples" subjects are available. After training, observations (subjects) unseen by the classifier are then automatically labeled as either typical or atypical (outliers). Given a training data set consisting of N observations (e.g., MRI brain images) of dimension d (the number of input variables), i.e., $D = \{x_1..x_N\} \subset \Re^d$, the goal is to find the most compact region containing most of the observations belonging to the typical class.

ν-OC-SVM based on a Radial Basis Function (RBF) as kernel is one of the most used methods. This function is given by $k(\vec{u}, \vec{v}) = \exp(-\gamma(\vec{u}, \vec{v})^2)$, where gamma is a constant and $\vec{u}$ and $\vec{v}$ are vectors. The basic idea is to project the data (neuroanatomical features) onto a hypersphere and then determine the hyperplane furthest from the origin enclosing most of the data (see Fig. 1). In other words, a mapping function Φ receives the characteristics (in this case, the anatomical brain measures such as cortical thickness) of an observation (subject) at the input space (the space of brain anatomical measurements), projecting this observation onto a hypersphere (a sphere defined in a space greater than 3 dimensions; in this case, we have several dimensions

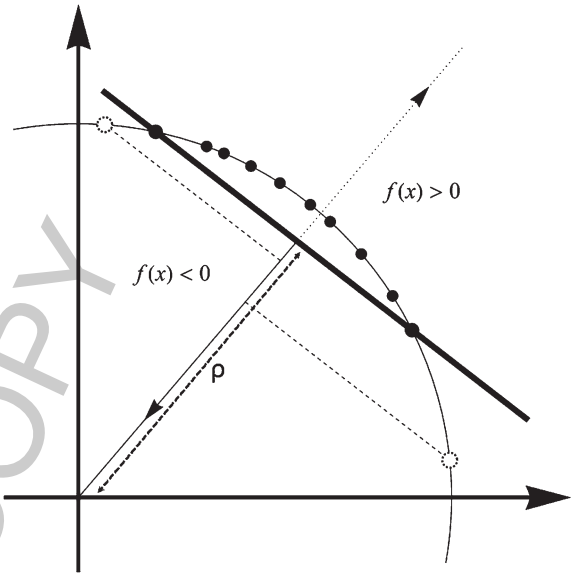

Fig. 1. ν-OC-SVM abnormality score and its relation with the decision function. The white dots represent points not recognized as typical ones (outliers) $f(\mathbf{x})$ are negative for outliers. ρ: distance between the hyperplane and the origin of the hyperplane that separates most of the data from the origin.

because we are considering the anatomical information of more than 3 brain regions) in a space called feature space. The idea of transforming the data from the input space to the feature space is to facilitate the discrimination of the data that cannot be easily classified in the input space, but this might be accomplished at the feature space. After the data is projected on the hypersphere (see Fig. 1), the problem is to define what can be considered at typical observation. In the v-OC-SVM, the method tries to find a hyperplane in which the proportion of (1–v) of the projected observations are above this hyperplane. A hyperplane is the extension of the concept of a plane for spaces greater than 3 dimensions, described by an intercept and a linear combination (hyperplane coefficients) of its coordinates. When doing the mathematical calculations, one may notice the so called "kernel trick", in which the function Φ does not need to be specified, but only an approximation of its dot product (a property of functions), the so called kernel function. The main advantage of using kernel functions is that, under some conditions (Mercer conditions), the same kernel can approximate the dot products of several distinct Φ functions, allowing generalizability.

As described previously, the v-OC-SVM method requires the pre-specification of parameter ν, which determines what fraction of the typical data (type I Error) will be classified as atypical [40]. Further

details about this method can be found in the referred literature.

In this work, we applied the dual formulation of ν-OC-SVM obtained by the method of Lagrange multipliers (a well-established approach in numerical optimization theory, which aims to minimize/ maximize an objective function subject to some constraints, further details can be found in [39]). By using this mathematical framework, the problem of separating the origin from the data (described previously) is equivalent to minimize an objective function given by:

$$\min_{a} \sum_{i\ j} \alpha_i \alpha_j k(\mathbf{x}_i,\ \mathbf{x}_j),$$

where α_i's are coefficients, k is the kernel function (e.g., radial basis function) and x_i are the feature values of each individual (e.g., brain anatomical features of the subject j). This minimization is constrained to the following conditions:

$$0 \leq \alpha_i \leq \frac{1}{\nu N} \sum_{i} \alpha_i = 1.$$

Then, the separating hyperplane coefficients w and the distance of this hyperplane from the origin ρ can be calculated by using the formulas:

$$w = \sum_{i} \alpha_i \Phi(\mathbf{x}_i),$$

$$\rho = \sum_{i} \alpha_j k(x_i,\ x_j); \quad \text{where } i \text{ is such that } \alpha_i > 0,$$

Where Φ is the mapping function from the input space to the feature space. The numerical implementation of the solution of this problem is technically complex and it is out of the scope of this study. Further details about these procedures are described in [39]).

In addition, given w (separating hyperplane coefficients) and ρ (distance from the origin) as above, it can be shown that the decision function

$$f(\mathbf{x}) = (w \cdot \Phi\ (\mathbf{x})) - \rho$$

is positive for most of the examples in the training data set (typical). When negative, its value represents an outlier (atypical observation) as shown in Fig. 2. In other words, the role of the decision function is to attribute a value for each new observation (set of brain anatomical characteristics of a novel subject). The sign of this value defines the predicted label for this observation (typical or atypical, given a normative data used to train OC-SVM). In this study, a positive value of the decision suggests that the subject belongs to the typical healthy aging group. Conversely, negative values indicate possible deviations from this "normal" pattern, such as mild cognitive impairment or AD.

Data analysis

We applied OC-SVM to the neuroanatomical features (volumes of the cerebellum and subcortical structures and cortical thicknesses) extracted by FreeSurfer (115 features, Desikan Atlas [41], see Supplementary Material). Gender and age effects were previously removed from the data by considering the residuals of multiple regression using these two variables as regressors. For each brain region and the whole sample, a linear model was fitted considering the anatomical measurement of this region as a response variable and gender and age as predictor variables. The residual, i.e., the difference between actual and predicted anatomical measurement was used for further analysis. This procedure was carried out in order to reduce possible effects of age and gender in OC-SVM analysis. Although the site of acquisition (or scanner) could also be included as covariate, we prefer not to use this variable in order to keep the generalizability of the method. Otherwise, the application of the proposed method to the data of an unseen site would require an "in-site" large database for normalization purposes.

We then trained OC-SVM considering half of the healthy sample (training data) and then tested in the other half and also the MCI and AD sample (test data). This analysis was carried out by using the software GNU R Project [42] version 2.15.3 and the package e1071 [43] based on library LIBSVM [44]. In the present study, since the sample is large, we split the healthy controls (228 subjects) sample in training and test set (114 subjects in each set), for validation. Gamma parameter was then selected in order to keep the false alarm rate of the test set as close as possible as ν, in order to avoid overfitting. It is important to highlight that we used only half of the healthy subjects in OC-SVM training. Thus, patients' data were never used to tune the parameters. We set ν values at 0.3 (so the expected rate of type I error is 30%) and fixed the kernel gamma parameter at 0.001 (after tuning). It is important to emphasize that the specification of ν parameter is arbitrary. In this study, we set v at 0.3 because given our sample size it allows a reliable validation of the predicted and observed false alarm rate (which must be 30%). Since the test set is composed of 114 control subjects, we expect 34.2 subjects to be wrongly assigned as atypical. Ideally, ν should be as close as possible to zero. However, if the false alarm

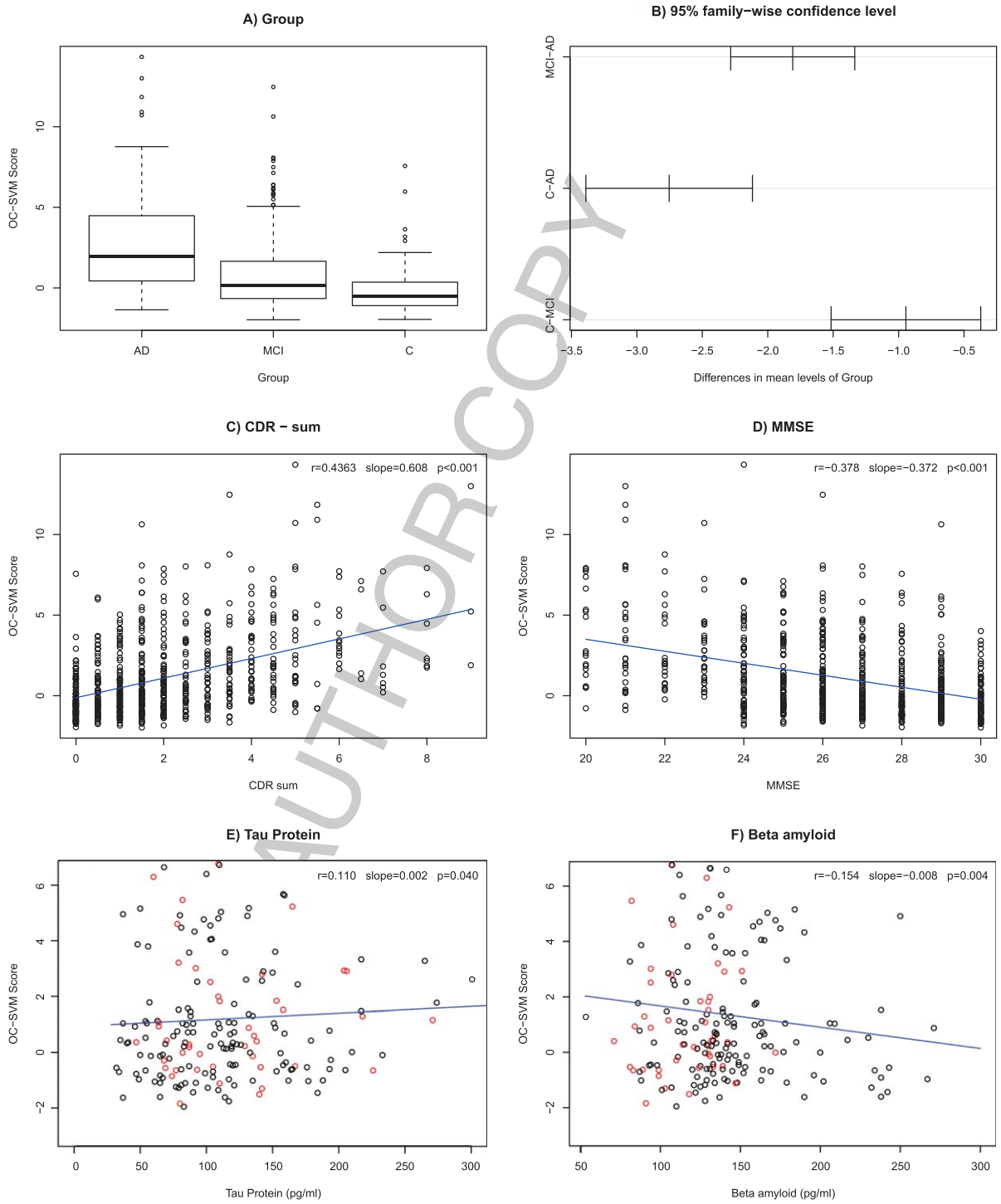

Fig. 2. A) Box-plots of abnormality scores (negative values of the decision function) across diagnostic groups (in the test set). The greater is the score the greater is the deviation from the typical brain pattern. Note that most subjects in AD group were pointed out as being abnormal. As expected, most subjects in MCI group were between controls and AD group. B) Confidence Intervals for differences of abnormality scores by diagnostic condition obtained through Tukey's HSD *post-hoc* test. C, D) Scatter-plots between abnormality scores and MMSE/CDR sum-of-boxes. E, F) Scatter-plot of abnormality scores and tau protein and amyloid-β concentration, respectively. The subjects depicted in red are APOE4 genotype carriers. C, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease.

rate was too small, we would have too few occurrences for a validation whether the expected and observed rates are close (e.g., if $\nu = 0.05$ the expected false alarm rate would be only 5.7 subjects). However, since the main feature of our proposal is the development of an abnormality score and not a categorical labeling, the score are not strongly affected by slight changes gamma, because most changes will be only in the cut-off of the decision value (for the categorization).

For a new subject, if the decision value $f(\mathbf{x})$ is negative, it implies that the subject is considered an outlier. If positive, the subject is considered typical. Thus, the negative value of the decision function $-f(\mathbf{x})$ might be considered as a measure of brain abnormality [19]. The higher is this measure, the higher is the deviation from the typical pattern. All statistical analyses were based solely on the test data, i.e., controls from the training set were excluded in order to avoid double dipping. The accuracy in each group (controls, MCI and AD) was calculated and the abnormality scores were then compared using one-way ANOVA. Associations with clinical (CDR global and sum of boxes), and biomarker data (tau protein and amyloid-β concentration) were carried out using the one-way ANOVA and Spearman's correlation tests, respectively.

RESULTS

All results were based solely on the analysis of the test sample, in order to avoid double dipping. The accuracy in each class (controls labeled by OC-SVM as non-outliers and patients classified as outliers) is presented in Table 2. Note that the accuracy in the healthy control group (specificity) is close to 70% as expected ($1 - \nu$, where ν was previously set to 0.3). Box-plots describing the abnormality scores (negative values of the decision function f(x)) are shown in Fig. 2. ANOVA test indicates that the mean abnormality score is significantly different between groups (AD, MCI, and controls, $p < 0.001$). We applied Tukey's HSD *post-hoc* tests and all group pair wise differences were statistically significant with $p < 0.001$. As expected, the largest difference in the abnormality score was between healthy controls and AD patients as depicted in Fig. 2.

Table 2
Accuracy (in the test set) of the classification at each group

Group	Accuracy (%)
Healthy controls	67.5% (specificity)
Mild cognitive impairment (MCI)	54.4% (sensitivity for MCI)
Alzheimer's disease (AD)	84.3% (sensitivity for AD)

In addition, significant differences (one-way ANOVA, $p < 0.001$) were found in the mean abnormality score across CDR-global groups (low, mid and high). Complementary, we found a positive correlation between the OC-SVM abnormality score and the CDR-sum-of-boxes (Spearman's rho = 0.463, $p < 0.001$) and a negative correlation with MMSE (Spearman's rho = −0.378, $p < 0.001$). Significant correlations were also found between the abnormality score and both tau (Spearman's rho = 0.110, $p < 0.04$) and amyloid-β (Spearman's rho = −0.154, $p < 0.004$) concentration. Finally, the mean abnormality score of MCI individuals with future conversion to AD was greater than the mean of abnormality score of the subjects without conversion (one-way ANOVA, $p < 0.001$).

In summary, as expected, healthy controls were labeled as the most typical, patients with AD presented the most abnormal brains, and MCI individuals ranged mostly between these two extremes. Moreover, the abnormality score was associated not only with clinical data but also with biomarker measures. Lastly, high levels of brain abnormality scores in MCI were also associated with future conversion to AD.

DISCUSSION

A promising alternative use of SVM is the construction of normative rules, using one-class SVM variant to characterize the typical set of neuroanatomical features and its response over previously unseen data to decide whether the subject's neuroanatomical measures correspond to a typical example or to an outlier. A potential application to the diagnosis of medical conditions is to train a one-class classifier with data from healthy subjects in order to have the outlier outcome of the classifier as an indication of an adverse condition. Although the classification accuracy could be higher by using a two-class SVM instead of OC-SVM, a key advantage of the proposed method is that the pathological group is solely defined by a deviation from the typical pattern. Thus, *a priori* selection or high weighting of specific regions (crucial to discriminate specific diseases) is not necessary. Moreover, our normative rules were based solely on half of the healthy volunteers' sample. Thus, conceptually, the same rules might be used in the case of other diseases and not only AD.

To illustrate this approach, we chose the structural MRI images from the database maintained by the ADNI whose primary goal has been to test whether serial MRI, PET, other biological markers and clinical

and neuropsychological assessment can be combined to measure the progression of MCI to early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

Our approach was developed from a perspective that AD progresses in a continuum and thus, brain changes also occur on a continuum. Therefore possible transitions may occur from health aging through MCI and then to AD states. One of the most important issues in AD severity measurement, which motivates the proposal of an abnormality score, is placing an individual on this continuum based on objective neurobiological measures. In the current study, we have extracted neuroanatomical measures with FreeSurfer software from the structural MRI data of the ADNI project. We used a random half of the healthy participants of the ADNI dataset as the training data of a ν-OC-SVM classifier and tested its outcome against the other half of healthy subjects and the MCI and AD subjects. The classifier, despite being trained only with healthy subjects, appears to have detected a gradation between healthy subjects and the severity of the MCI and AD subjects. The abnormality scores were different among groups with statistical significance and Tukey's HSD *post-hoc* tests have shown that the difference between healthy subjects and AD patients was greater than the difference between healthy subjects and individuals with MCI (Fig. 2). In addition, more than three quarters of AD subjects had an abnormality score greater than zero, suggesting that the outlier detection was correct (Fig. 2). MCI subjects were those in which the classifier had the lowest accuracy (Table 2), and it is an expected finding given that the difference between MCI and controls is smaller than between MCI and AD subjects (Fig. 2). On top of that, it is also compatible with the fact that the cognitive performance (and thus, brain integrity) of MCI subjects is in between healthy subjects and AD patients [45]. Moreover, the OC-SVM abnormality score was found to be correlated with CDR (global and sum-of-boxes) and biomarker measures (tau protein and amyloid-β concentration), reinforcing the robustness of the proposed method. From a prognosis perspective, our findings also suggest that high abnormality scores may be a potential feature to identify MCI patients more likely to progress to AD.

As expected, the best accuracy found in the analyzed scenario occurs among AD subjects, for which OC-SVM labeled 84.3% of them as outliers. This is smaller than the reported accuracy found using supervised machine-learning techniques [46] that reported values greater than 90%. Furthermore, it is important to emphasize that although the ν-OC-SVM classifier was able to find a characteristic pattern for the training data set (that we chose to be comprised of only healthy subjects), this classifier is not characterizing the healthy state. It obtains a representation for what is typical given this particular training data set. Westman et al. [47] were able to combine the ADNI dataset with the European AddNeuroMed (http://www.innomed-addneuromed.com/) suggesting that the dataset can be extended to others as long as the MRI captures had followed the same protocol. In this sense, we used the ADNI database only as an illustrative dataset for the proposed method.

Although the findings of this study reinforced the association between the biomarkers and the brain abnormalities, the molecular scenario in AD progression is still an open question. The presence of amyloid-β deposits forming plaques in AD brain could not be an initiating event but rather a consequence of several primary changes such as, impaired microvascular function [48], decline in brain metabolic activity [49], age-dependent neuroinflamatory process [23], or increased oxidative stress [50], demonstrating that the amyloid cascade hypothesis that has guided much of the AD research for more than 25 years [51, 52] is still under development. In addition to that, several amyloid-independent mechanisms might lead to AD (for review, see [53]). The main limitation is that the amyloid-β levels and plaques is not necessarily a marker of the dementia. Plaques are abundant in cognitively healthy older individuals. Thus, the amyloid-β peptide is not necessarily the cause or unique factor in AD etiology. These results support the claim that amyloid-β should not be considered a harbinger of cell death but rather a protective response to insult (for a review, see [54]). Actually, the process that leads to amyloid-β deposit is correlated with tau pathology, which is more directly related to dementia. Tau pathology correlates better than amyloid-β pathology to cognitive impairment in AD human patients [55]. Furthermore, mutation in the tau gene causing frontotemporal dementia and Parkinsonism linked to chromosome 17 [56] suggests that tau dysfunction without amyloid-β pathology is sufficient to cause neuronal death leading to clinical dementia. On the other hand, studies in AβPP transgenic mice have shown that tau is essential to promote amyloid-β toxicity [57] and also has the ability to rescue premature mortality [58]. Taken together, these results point out that tau and amyloid-β play different roles in AD.

Moreover, although we have not found associations between ApoE genotype and brain abnormality, the role of ApoE as an integral and pathological part of amyloid cascade hypothesis should be analyzed with caution. Figure 2E and F suggests that dementia severity is not strongly related to the APOE4 genotype, since all dementia patients go through a similar degenerative process. However, APOE4 subjects may have an earlier degeneration and represent a higher proportion of the patients [59]. Controversial findings on the function of ApoE on amyloid-β levels illustrate the uncertainty of its role in AD etiology (for review, see [60]). Some studies have demonstrated that ApoE has no effect on amyloid-β production [61, 62] and that even APOE4 allele was not associated with CSF biomarkers levels such as amyloid-$\beta_{1\text{-}42}$, T-tau and P-tau [63]. Others have shown ApoE as an amyloid-β partner [64, 65] with an amyloid-β catalytic function [66]. Further, other studies have suggested that ApoE has an amyloid-β clearance function [67]. The exact role of ApoE in AD pathology still remains unknown. Despite its strong genetic association with AD, the ApoE ε4 allele is neither necessary nor sufficient for AD progression [68]. It has also been suggested that ApoE receptors, rather than ApoE itself, may be responsible for the modulation of amyloid-β production [69, 70]. Our proposed brain abnormality index was not found to be significantly associated to ApoE ε4 allele demonstrating that the function of ApoE as an AD biomarker should be carefully evaluated.

As limitations of the present approach, we mention the use of only a Gaussian kernel; not considering years of education and the use of medication. As AD prevalence increases with age and it is not the same between genders [71] here, gender and age effects [72] were previously removed from the data by considering the residuals of multiple regression. However, this assumes linearity and other more sophisticated methods could also have been applied.

It is important to consider that we are illustrating the application of neuroimaging and machine learning on the definition of normative rules. The choice of the neuroimaging data from the ADNI project or the classifier as ν-OC-SVM with Gaussian kernel does not imply that the approach is restricted to this particular combination. In fact, further studies can explore other data sets and other set-ups for the classifier. In addition, we believe that the accuracy can be improved by including other modalities beyond neuroanatomical features extracted from MRI since there are encouraging results involving multimodal classification [73].

CONCLUSIONS

One-class support vector machines have been shown to be a promising tool for the development of normative databases from neuroimaging data. In the current study, we demonstrated that this approach could be used to measure brain abnormality and to suggest possible conversion from MCI to AD. Complementary, our findings confirm that subjects with mild cognitive impairment have brains with structural features in between the two groups and that the degree of brain abnormality is also reflected in clinical assessment and biomarkers' levels.

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