Original Article

Journal of Geriatric Psychiatry and Neurology
2019, Vol. 32(6) 354-364

DOI: 10.1177/0891988719862637
journals.sagepub.com/home/jgp
SAGE

Automated Brain MRI Volumetry Differentiates Early Stages of Alzheimer's Disease From Normal Aging

Weina Zhao, MD[1,2], Yishan Luo, PhD[3], Lei Zhao, PhD[3], Vincent Mok, MD[4], Li Su, PhD[5,6], Changhao Yin, MD[2], Yu Sun, MD[1], Jie Lu, MD[7], Lin Shi, PhD[3,8], and Ying Han, PhD, MD[1,9,10,11]

Abstract

As an enrichment strategy supplemented by the diagnostic framework of subjective cognitive decline (SCD), SCD *plus* identifies features that may increase the likelihood of including future-Alzheimer's disease (AD) patients. This study aimed to identify the shared and distinct atrophy patterns between patients specified by SCD *plus* and amnestic mild cognitive impairment (aMCI, a prodromal stage of AD) and to investigate the extent that automated brain magnetic resonance imaging (MRI) volumetry can differentiate patients with SCD from normal control (NC) participants and patients with aMCI. We acquired structural MRI brain scans from 44 patients with aMCI, 40 patients with SCD (who met the major criteria of SCD *plus*), and 48 NC participants. Automatic brain segmentation was performed to quantify the volumetric measures of cognitive-relevant areas. These volumetric measures were compared across the 3 groups with analysis of variance. In addition, we performed support vector machine analyses using volumetric measures of single regions or multiple regions to further evaluate the sensitivity of automated brain volumetry in differentiating a specific group from another. The atrophy patterns in patients with aMCI and SCD were similar. Using the regional volumetric measures, we achieved high performance in differentiating aMCI and SCD from NCs (average classification accuracy [ACC] > 90%). However, the performance was not ideal when differentiating aMCI from SCD (ACC < 63%). In conclusion, patients with SCD specified by SCD *plus* presented similar atrophy patterns as patients with aMCI, which was distinguishable from NC participants. Future studies should aim to associate the atrophy patterns of SCD with possible conversion to aMCI or AD in a longitudinal design.

Keywords

subjective cognitive decline, amnestic mild cognitive impairment, Alzheimer disease, magnetic resonance imaging, brain volumetry

[1] Department of Neurology, XuanWu Hospital of Capital Medical University, Beijing, China
[2] Department of Neurology, Mudanjiang Medical University Affiliated HongQi Hospital, Mudanjiang, China
[3] BrainNow Research Institute, Shenzhen, Guangdong Province, China
[4] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong, China
[5] Department of Psychiatry, Cambridge Biomedical Campus, University of Cambridge, Cambridge, United Kingdom
[6] China-UK Centre for Cognition and Aging Research, Faculty of Psychology, Southwest University, Chongqing, China
[7] Department of Radiology, XuanWu Hospital of Capital Medical University, Beijing, China
[8] Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Shatin, Hong Kong, China
[9] Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, China
[10] Beijing Institute of Geriatrics, Beijing, China
[11] National Clinical Research Center for Geriatric Disorders, Beijing, China

Received 10/9/2018. Received revised 2/14/2019. Accepted 2/19/2019.

Corresponding Authors:
Ying Han, Department of Neurology, XuanWu Hospital of Capital Medical University, Beijing 100053, China; Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing 100053, China; Beijing Institute of Geriatrics, Beijing 100053, China; National Clinical Research Center for Geriatric Disorders, Beijing 100053, China.
Email: hanying@xwh.ccmu.edu.cn

Lin Shi, BrainNow Research Institute, Shenzhen, Guangdong Province, China; Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Shatin, Hong Kong, China.
Email: shilin@cuhk.edu.hk

Introduction

Alzheimer's disease (AD) has been associated with multiple pathophysiological processes in the brain initiated many years prior to the first onset of cognitive symptoms. As a prodromal stage of AD, amnestic mild cognitive impairment (aMCI) presents with early memory impairment relative to age-matched and education-matched healthy people and largely impacts activities of daily life.[1] Subjective cognitive decline (SCD), that is, self-perceived cognitive decline while maintaining normal performance in objective cognitive assessment,[2] has been suggested as an even earlier symptomatic disease stage of AD than aMCI.[3] Therefore, there has been increasing research interest in characterizing the functional[4,5] and structural[6-8] changes in the brains of patients with SCD to determine a better population definition for future dementia prevention trials.

With regard to structural magnetic resonance imaging (MRI) research, researchers have reported an association between brain structural deficits (eg, in the gray matter and hippocampal regions) and the onset of SCD.[7,9,10] The brain regions with atrophy in patients with SCD largely follow the AD-like atrophy pattern (notably in the medial temporal lobe), which are also present in patients with aMCI.[8] To further investigate the degree of brain volume loss among different early stages of AD, many studies applied machine learning approaches to differentiate patients with SCD or MCI from normal control (NC) participants. In these studies, differentiating aMCI from NCs[11-13] (classification accuracy >90%) was much easier than differentiating SCD from NCs[7] (classification accuracy <68%) using brain atrophy measures.

Of note, in the recent diagnostic framework of SCD proposed in 2014, SCD *plus* was supplemented as an enrichment strategy to specify features to better identify patients with SCD who have preclinical AD, including the following: (1) subjective decline in memory rather than other domains of cognition, (2) onset of SCD within the last 5 years, (3) age at onset of SCD > 60 years, (4) particular concerns (worries) associated with SCD, (5) feelings of worse performance than others of the same age-group, (6) confirmation of perceived cognitive decline by an informant, and (7) presence of the APOE ε4 genotype.[14,15] Studies that did not consider the features proposed in SCD *plus* could possibly bear the consequences of inclusion of non-AD related patients with SCD, compromising the power in statistical analyses when differentiating SCD from NCs. We hypothesized that with the implementation of SCD *plus* in defining patients with SCD, the brain volumetric measures should differentiate SCD from NCs with similar performance as when differentiating aMCI from NCs. In addition, the shared and distinct patterns of brain structural changes in SCD and aMCI as reported in the existing studies are still inconsistent due to the varied inclusion criteria of SCD and the varied measures of brain structural changes. In this regard, we proposed a study with the most recent conceptual framework of SCD with an SCD *plus* strategy to investigate the brain volumetric differences among patients with aMCI, patients with SCD, and NC participants and to test whether the brain volumetric changes in patients with SCD specified by SCD *plus* can help distinguish SCD from NCs with similar performance when distinguishing aMCI from NCs using a support vector machine (SVM; a machine learning approach for classification).

Material and Methods

Participants

One hundred thirty-two right-handed participants were recruited for this study, including 44 patients with aMCI and 40 patients with SCD from the memory clinic of the Neurology Department, Xuanwu Hospital, Capital Medical University, and 48 NC participants from the local community in Beijing who were recruited by advertisements. Normal control participants were matched in age, gender, and education. Written informed consent was obtained for all these participants. This study was approved by the Medical Research Ethics Committee of XuanWu Hospital.

The inclusion criteria for SCD were based on the recent research criteria proposed in 2014,[2] as follows: (1) self-reported experience of persistent decline in memory within the last 5 years, which was further confirmed by informants according to the strategy of SCD *plus*; (2) self-reported concerns or worries about cognitive decline (specified in SCD *plus*); (3) general normal cognition according to objective neuropsychological tests (Montreal Cognitive Assessment [MoCA] >19 for the participants with primary school education or even lower education level, >22 for those with secondary school education level, and >24 for those with university education or even higher education level; Mini-Mental State Examination [MMSE] >17 for the illiteracy participants, >20 for those with primary school education, >24 for those with junior/high school education or even higher education level); and (4) a Clinical Dementia Rating (CDR) score of 0.

The patients with aMCI were diagnosed based on the criteria proposed by Petersen in 2004,[16] which have been described in our previous studies[17,18]; that is, (1) presence of a memory complaint; (2) presence of objective memory impairment measured by MMSE, MoCA, and the auditory verbal learning test (AVLT); (3) near-normal performance on general cognition with preserved daily life activities; (4) a CDR score of 0.5; and (5) not meeting the criteria for dementia. The NC participants did not present cognitive decline complaints, and their MMSE, MoCA, and AVLT scores were within the normal range.

In addition, the participants were excluded if they had any of the following conditions: (1) other neurological disorders that could cause cognitive decline; (2) presence of infarcts, infections, or other focal injuries that were visible on MRI; (3) unable to undergo neuropsychological tests or having any contraindications to MRI scanning; (4) major depressive disorder, bipolar disorder, schizophrenia, or any other psychiatric disorders; (5) history of alcohol abuse and dependence, substance abuse, or addiction in the past 2 years; and (6) unable to complete the examinations due to other systemic diseases or

Table 1. Characteristics of the Participants.[a]

Characteristics	NC (n = 48)	SCD (n = 40)	aMCI (n = 44)	SCD vs NC, *P* Value	aMCI vs NC, *P* Value	aMCI vs SCD, *P* Value
Age, years	64.71 ± 7.69	65.08 ± 7.94	65.52 ± 7.76	1.000	1.000	1.000
Education, years	12.38 ± 4.02	12.18 ± 3.01	11.55 ± 3.26	1.000	.770	1.000
Male/female	25/23	17/23	25/19	.372	.651	.192
MMSE	28.56 ± 1.47	27.88 ± 1.70	25.55 + 3.09	.441	.001	.001
MoCA	27.27 ± 2.00	26.43 ± 2.02	21.00 ± 3.57	.408	.001	.001
CDR	0.00 ± 0.00	0.00 ± 0.00	0.46 ± 0.13	NA	.001	.001
AVLT, immediate recall scores	9.05 ± 1.71	7.84 ± 2.08	5.97 ± 1.51	.005	.001	.001
AVLT, delayed recall scores	9.77 ± 2.52	8.65 ± 3.14	4.18 ± 2.82	.195	.001	.001
AVLT, recognition scores	11.67 ± 2.85	10.84 ± 2.92	7.98 ± 3.78	.699	.001	.001

Abbreviations: CDR, clinical dementia rating; aMCI, amnestic mild cognitive impairment; AVLT, auditory verbal learning test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NA, not available; NC, normal control; SCD, subjective cognitive decline.
[a]Analysis of variance with post hoc Bonferroni test was performed for age, education, MMSE, MoCA, and AVLT (continuous variables), and Kruskal-Wallis tests with post hoc Dunn tests were performed for gender and CDR (categorical variables). The displayed *P* values were corrected for multiple comparisons.

uncertainty. All the included participants underwent brain MRI. Detailed demographics and clinical characteristics of the participants are shown in Table 1.

Image Acquisition

A 3T MRI system (Magnetom Trio Tim; Siemens, Erlangen, Germany) was used for image acquisition at the Department of Radiology, XuanWu Hospital, Capital Medical University. T1-weighted MRI scans were acquired in the sagittal plane by using a magnetization-prepared rapid acquisition gradient echo sequence with the following parameters: repetition time (TR) = 1900 ms, echo time (TE) = 2.2 ms, flip angle (FA) = 9°, inversion time = 900 ms, matrix = 256 × 256, slices = 176, thickness = 1.0 mm, and voxel size = 1 × 1 × 1 mm^3.

Image Processing

All the T1-weighted MRI scans were processed with *AccuBrain*® (BrainNow Medical Technology Limited, Shenzhen, China), an automatic brain segmentation and quantification software program based on statistical prior anatomical knowledge by experienced radiologists with 5 years of experience.[19] In detail, the segmentation of *AccuBrain* was based on a multiatlas pool that was derived from many brain MR images acquired from different scanners together with prior anatomical information from radiologists of the brain structures to be delineated. In a recent validation study based on a standard data set from the European Alzheimer's Disease Consortium—Alzheimer's Disease Neuroimaging Initiative Harmonized Protocol, where manual hippocampal segmentation references were available, *AccuBrain* achieved the best performance among the existing automatic brain segmentation tools (with a mean dice similarity coefficient of 0.89 compared with the ground truths from manual segmentation).[19] Here, we selected 18 quantified brain regions from *AccuBrain* that were cognitive-relevant for the analysis, including the lateral ventricle, third ventricle, bilateral hippocampus, amygdala, frontal lobe, occipital lobe, temporal lobe, parietal lobe, cingulate lobe, and insular areas. The volumes of these structures were divided by the intracranial volume (ICV) for each participants as a normalization process for the subsequent analyses. Here, the ICV was defined as volume within the cranium, including the brain, meninges, and cerebrospinal fluid.[20]

Statistical Analysis

We performed an analysis of variance (ANOVA) with Bonferroni post hoc tests to compare the continuous demographic characteristics and the regional brain volumetric measures among the 3 groups. Kruskal-Wallis tests with post hoc Dunn tests were performed to compare the categorical characteristics (eg, gender and CDR) of the participants in the 3 groups. Regarding the comparisons in regional brain volumes, the false discovery rate (FDR) correction with $q < .05$ was used to further adjust the *P* values generated from post hoc tests of the ANOVA for multiple comparisons regarding different brain regions.

Furthermore, we tested whether the individual volumetric measures of different brain regions or their combinations could distinguish aMCI versus NC, SCD versus NC, and aMCI versus SCD using a linear SVM with C-SVM implementation.[21,22] In detail, each of the 18 brain regional volumes was used once as an independent feature (predictor) in an SVM model to differentiate pairs of groups, and we entered all the brain volumes of 18 brain regions in another SVM model for the same classification tasks. To achieve a reliable estimation of the classification performance between pairs of groups, we performed repeated stratified nested 10-fold cross-validations with a 3-way split of data[23,24] for each of the aforementioned 19 SVM models.

For example, for the classification of SCD and NC groups (with a specific set of features as predictors), we first divided the data of the SCD group and NC group into 10 folds. We then randomly extracted 1 portion (or fold) from both groups and combined them together to make a mixed fold. In this way, the data were integrated into 10 mixed folds ($M_1, M_2, \ldots, M_{10}$),

where each fold had the same proportion of SCD and NC participants (ie, "stratified"). With this set of data, we used 1 mixed fold (eg, M_1) for testing, and the remaining 9 folds (eg, $M_2, M_3, \ldots, M_{10}$) for training and validation (ie, "nested"). Specifically, the data of the remaining 9 folds were further divided into 10 subfolds ($S_1, S_2, \ldots, S_{10}$), with 9 subfolds used for training and 1 subfold for validation. The validation process was realized during a grid search of the optimal parameter C (box constraint) for an SVM model from 2^{-10} to 2^{10}. In detail, with a specific parameter C, each subfold (S_i, $i = 1 \ldots 10$) was used once for validation and the others for training, and we evaluated the validation performance based on the average classification accuracy (ACC) and area under the curve (AUC) of the 10 validations. In this way, we searched for the optimal parameter C that maximized the ACC and AUC during validation.

Here, the ACC was the number of correctly classified samples divided by the total number of samples. The AUC was the area under the receiver operating characteristics (ROC) curve, where the ROC curve was obtained by plotting the true-positive rates versus the false-positive rates for all possible thresholds of the estimated posterior probability of each sample to be predicted.[25,26] The value of AUC varies from 0.5 representing no discrimination to 1.0 representing perfect discrimination in a classification.[27] On the one hand, the ACC depended on the selected threshold (ie, the predicted class labels in SVM), whereas the AUC considered all possible thresholds based on probability estimations, thus providing a sense of ranking for each sample rather than a simple class label.[25] On the other hand, the AUC also suffered from some drawbacks such as ignoring the goodness-of-fit of the model[28]; therefore, it was not recommended as an independent measure of model performance.[29] As both the ACC and AUC are widely used in neuroimaging-based classification studies of prodromal AD stages,[13] we considered both as outcome measures for a reliable evaluation of the model performance and an easier comparison with previous studies.

The parameter C that achieved the best performance in validation was treated as the optimal parameter to retrain the model with the data that combined the training set and validation set (ie, $S_1, S_2, \ldots, S_{10}$ or $M_2, M_3, \ldots, M_{10}$). The resulting model was used to predict the class labels of the testing set (ie, M_1) that was never used for training or validation. Of note, each of the 10 mixed folds (M_i, $i = 1, 2, \ldots, 10$) were once held apart for testing while the remainder were used for training and validation, and we recorded the generated ACC and AUC of the 10 evaluations on unseen data. The aforementioned stratified nested cross-validation was further performed 20 times (ie, "repeated") regarding random partitions of the data for the mixed 10-folds ($M_1, M_2, \ldots, M_{10}$), and the classification performance in testing was evaluated by the average ACC and AUC of the resulting 200 independent evaluations. The repeated random partitions of the data and full use of each fold for testing helped to minimize the effect of the random variation on the evaluation of model performance.[30] Regarding the classification of MCI versus NC and MCI versus SCD, the analysis procedure was similar.

Results

The demographic characteristics of the participants are shown in Table 1. Age, gender, and education level were matched for the 3 groups (NC, SCD, and aMCI; $P > .05$ for each group comparison). When comparing the SCD and NC groups, there were no significant differences in MoCA and MMSE. Additionally, the patients with SCD had significantly lower immediate recall scores of AVLT than the NC participants ($P = .005$). In addition, patients with aMCI had significantly lower MMSE, MoCA, and AVLT, and higher CDR than the NC group and SCD group ($P < .001$).

The results from the ANOVA with post hoc Bonferroni tests and FDR correction are shown in Table 2, and the trends of the volumetric differences among the 3 groups were indicated from the error bars, as shown in Figures 1–3. Most of the predefined brain regions showed significant volumetric differences between the aMCI and NC groups and between SCD and NC groups (corrected $P < .05$). There was a significant volumetric difference in the lateral ventricle for aMCI versus NC but not for SCD versus NC. Regarding the comparison between aMCI and SCD, only the volume ratios of the right hippocampus, left amygdala, and left temporal lobe showed a weak difference (corrected $P < .10$), where patients with aMCI had more severe atrophy than patients with SCD in these structures.

The binary classification performance for the 3 groups of participants are provided in Table 3, and the models with relatively good performance (ACC > 80% in any binary classification) are also shown in Figure 4. Regarding the classification of aMCI versus NC and SCD versus NC, the SVM models that included the volume ratios of multiple brain regions as predictors (model 19) achieved better performance than the models that only considered the volume ratio of an individual region as the predictor (model 1 $\sim$ model 18). In the SVM models with multiple brain regions considered, the performance of the classification between SCD and NC (ACC: 94.51%, AUC: 0.9776) was as good as that of the classification between aMCI and NC (ACC: 95.90%, AUC: 0.9924). In addition, 2 SVM models with individual volumetric features (left occipital lobe and right temporal lobe) also achieved high performance (ACC > 90%, AUC > 0.90) in the classifications of aMCI versus NC and SCD versus NC.

When it came to the classification between aMCI and SCD, the ACC was generally less than 63% and the AUC was less than 0.71. The SVM model that included the volumetric measures of multiple brain regions (ACC = 54.95%, AUC = 0.6080) performed no better than several models with individual volumetric features (eg, bilateral hippocampus, bilateral amygdala, and left temporal lobe).

Discussion

In this study, we investigated the volumetric difference of typical brain regions among patients with SCD, who were specified by SCD *plus*, patients with aMCI, and NC participants. The brain regions with significant volumetric differences found

Table 2. Comparison of Brain Volume Ratios in NC participants and Patients With SCD and aMCI.

Region	NC Mean ± SD	SCD Mean ± SD	aMCI Mean ± SD	SCD vs NC Corrected[a] *P* Value	aMCI vs NC Corrected, *P* Value	aMCI vs SCD Corrected, *P* Value
Lateral ventricle	0.0150 ± 0.0067	0.0161 ± 0.0059	0.0191 ± 0.0085	1.0000	.0287	.4346
Third ventricle	0.0019 ± 0.0005	0.0021 ± 0.0005	0.0021 ± 0.0005	.4668	.1148	1.0000
Hippocampus L	0.0031 ± 0.0004	0.0024 ± 0.0003	0.0022 ± 0.0003	1.36E-18	1.50E-25	.1318
Hippocampus R	0.0033 ± 0.0003	0.0025 ± 0.0003	0.0023 ± 0.0003	4.49E-20	8.12E-28	.0900
Amygdala L	0.0014 ± 0.0002	0.0011 ± 0.0001	0.0010 ± 0.0001	1.01E-09	2.82E-17	.0900
Amygdala R	0.0016 ± 0.0002	0.0013 ± 0.0002	0.0012 ± 0.0002	1.58E-08	1.56E-15	.1022
Frontal lobe L	0.0543 ± 0.0027	0.0522 ± 0.0025	0.0517 ± 0.0022	6.26E-04	7.16E-06	1.0000
Frontal lobe R	0.0550 ± 0.0028	0.0528 ± 0.0028	0.0529 ± 0.0027	6.49E-04	0.0012	1.0000
Occipital lobe L	0.0288 ± 0.0020	0.0242 ± 0.0019	0.0238 ± 0.0018	3.29E-20	1.12E-23	1.0000
Occipital lobe R	0.0236 ± 0.0017	0.0205 ± 0.0015	0.0199 ± 0.0016	6.48E-15	1.41E-19	.8258
Temporal lobe L	0.0390 ± 0.0022	0.0345 ± 0.0025	0.0330 ± 0.0025	6.57E-14	6.51E-22	.0900
Temporal lobe R	0.0408 ± 0.0027	0.0345 ± 0.0023	0.0333 ± 0.0024	5.38E-21	1.67E-27	.3180
Parietal lobe L	0.0280 ± 0.0019	0.0279 ± 0.0022	0.0278 ± 0.0025	1.0000	1.0000	1.0000
Parietal lobe R	0.0278 ± 0.0017	0.0282 ± 0.0019	0.0282 ± 0.0022	1.0000	1.0000	1.0000
Cingulate lobe L	0.0102 ± 0.0008	0.0086 ± 0.0007	0.0086 ± 0.0005	1.14E-19	1.18E-19	1.0000
Cingulate lobe R	0.0111 ± 0.0007	0.0095 ± 0.0007	0.0093 ± 0.0006	3.45E-19	1.87E-23	.9288
Insular L	0.0048 ± 0.0004	0.0044 ± 0.0003	0.0043 ± 0.0005	1.68E-04	1.15E-07	.8420
Insular R	0.0053 ± 0.0004	0.0048 ± 0.0004	0.0047 ± 0.0004	1.33E-07	3.68E-09	1.0000

Abbreviations: L, left; aMCI, amnestic mild cognitive impairment; NC, normal control; R, right; SCD, subjective cognitive decline; SD, standard deviation.
[a]The *P* values shown here were generated from an analysis of variance with post hoc Bonferroni corrections and are further adjusted with FDR correction for the multiple brain regions involved in comparisons.

in patients with aMCI compared to NC participants were generally reproduced in patients with SCD. In detail, atrophy in the bilateral hippocampus, amygdala, frontal lobe, occipital lobe, temporal lobe, cingulate lobe, and insular region was found in both patients with aMCI and SCD. All these atrophy patterns found in patients with aMCI were in line with the previous studies.[31-34] Atrophy of the hippocampus, amygdala, frontal lobe, and temporal lobe in patients with SCD has also been reported,[10,35,36] and the remaining atrophy patterns in patients with SCD identified in our study coincided with the region-specific alterations of memory processing found in a functional MRI study.[37] In addition, we found relatively larger ventricle structures in patients with aMCI than NC participants (which was reported previously)[38] but not in patients with SCD. For the first time, we compared the volumetric difference of predefined brain regions between patients with aMCI and SCD. In general, there were no significant volumetric differences between the 2 groups for the predefined brain regions, which was in line with a previous study using a density map-based (voxel-based morphometry) approach.[8] We only identified relatively more severe atrophy in patients with aMCI than patients with SCD ($P < .10$ after FDR correction) in the bilateral hippocampus, amygdala, and left temporal lobe (Table 2, Figures 1 and 2). These results, together with the enlarged ventricles found in patients with aMCI but not in patients with SCD, may provide further evidence to support SCD as a transitional period between normal aging and aMCI before possible progression to AD.[4,39]

Additionally, we investigated the severity or sensitivity of brain volumetric changes in differentiating the 3 groups from one another. In the classification analyses, we achieved very high accuracy to distinguish aMCI from NC and SCD from NC when using the volumetric information of multiple brain regions as features (with ACC > 94% and AUC > 0.97 in both classifications). These results outperformed the existing studies that used predefined region-based methods to classify aMCI versus NC (ACC < 90%, AUC < 0.93)[40,41] and the studies that achieved the best performance in aMCI versus NC classification by using the density map-based approach (ACC = 90%) and cortical surface-based approach (AUC = 0.95).[11,40] More importantly, we also achieved much better performance than a recent study that also used a predefined region-based approach to distinguish SCD from NC (ACC < 68%),[7] which was observed either in our model with the volume ratios of multiple brain regions as the predictors or in the several other models that use the volume ratio of a single region as the predictor (Figure 4). In fact, for the first time, we demonstrated that automated MRI volumetry could differentiate SCD from NC with a very similar performance to that of differentiating aMCI from NC. In addition, we also applied the volumetric measures to distinguish aMCI from SCD, and none of the models achieved ideal classification performance as that of aMCI versus NC and SCD versus NC, which was in line with the general similar atrophy pattern between aMCI and SCD, identified in the group comparison analysis.

Of note, we applied a robust approach for parameter tuning and evaluation of the classification performance of the SVM models, that is, the repeated nested cross-validations[23,24] that used a 3-way split of the data set to keep the test data set unseen during model training. This method helped to achieve reliable

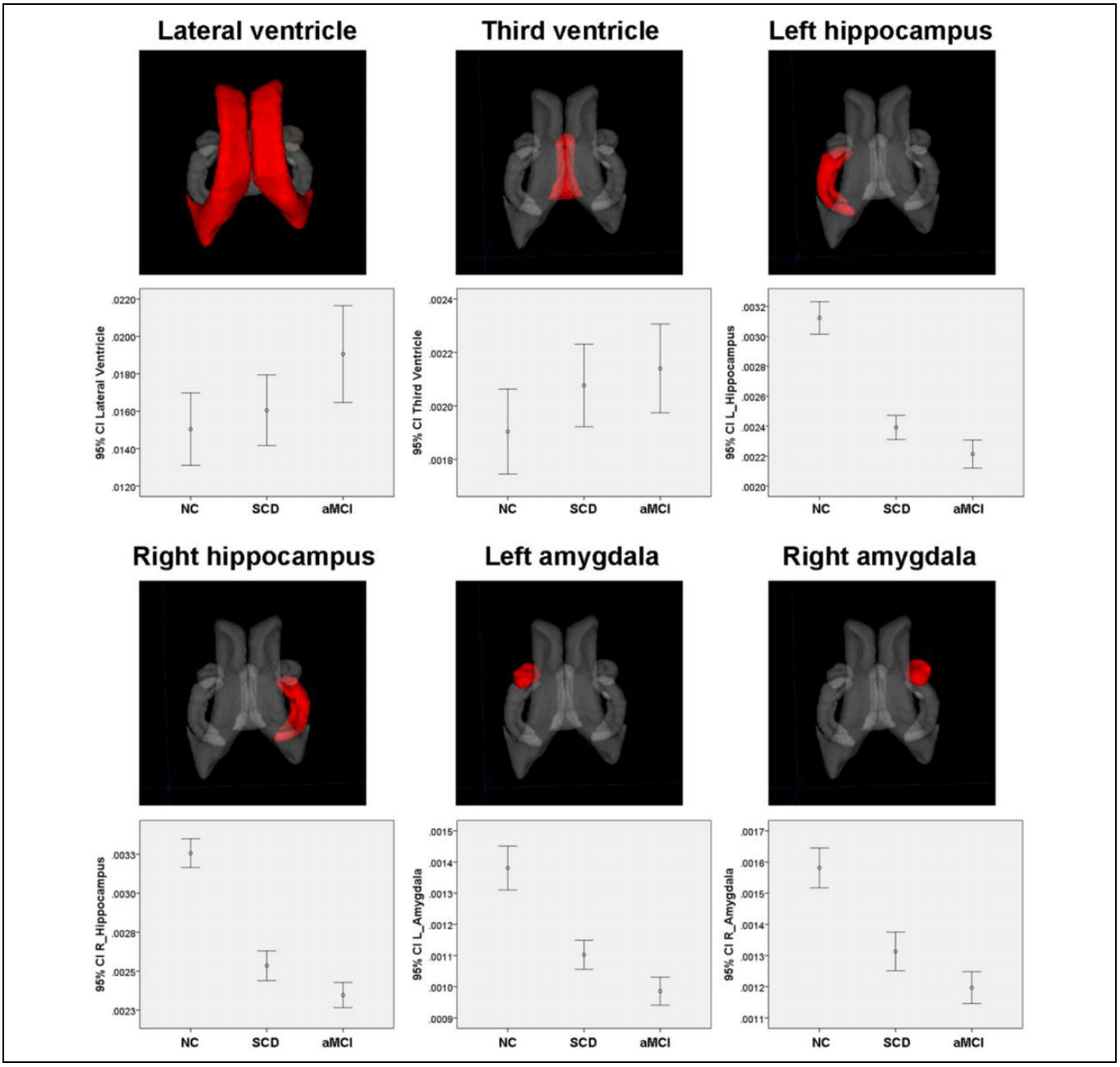

Figure 1. Error bars for the volume ratios of subcortical structures. Three-dimensional illustrations for the segmented brain structures are also provided.

estimation of the generalization abilities of the classification models and to minimize the bias and variation in the metrics of model estimation based on our study cohort. As several classification models (aMCI vs NC and SCD vs NC) with a single predictor (ie, the volume ratio of a single region) in this study also outperformed the existing studies; these ideal classification performances may derive from the patient inclusion criteria and the brain segmentation tool that we used. First, we applied the recently proposed strategy SCD *plus* and only included the patients who had worries about their memory decline with informant confirmation of their memory decline.[2] These inclusion criteria potentially screened for the inclusion of patients with more severe cognitive deficits and a higher possibility of AD conversion in our study compared to the other studies investigating brain atrophy of SCD, in which informant confirmation and/or worries about the memory decline for the diagnosis of SCD were missing.[7,12] In fact, the patients with SCD with worries about their cognitive decline were at much higher risk of conversion to AD and thus might have more severe brain atrophy than the patients with SCD without worries.[15] These findings were important, as the patients with SCD identified with the recent concept of

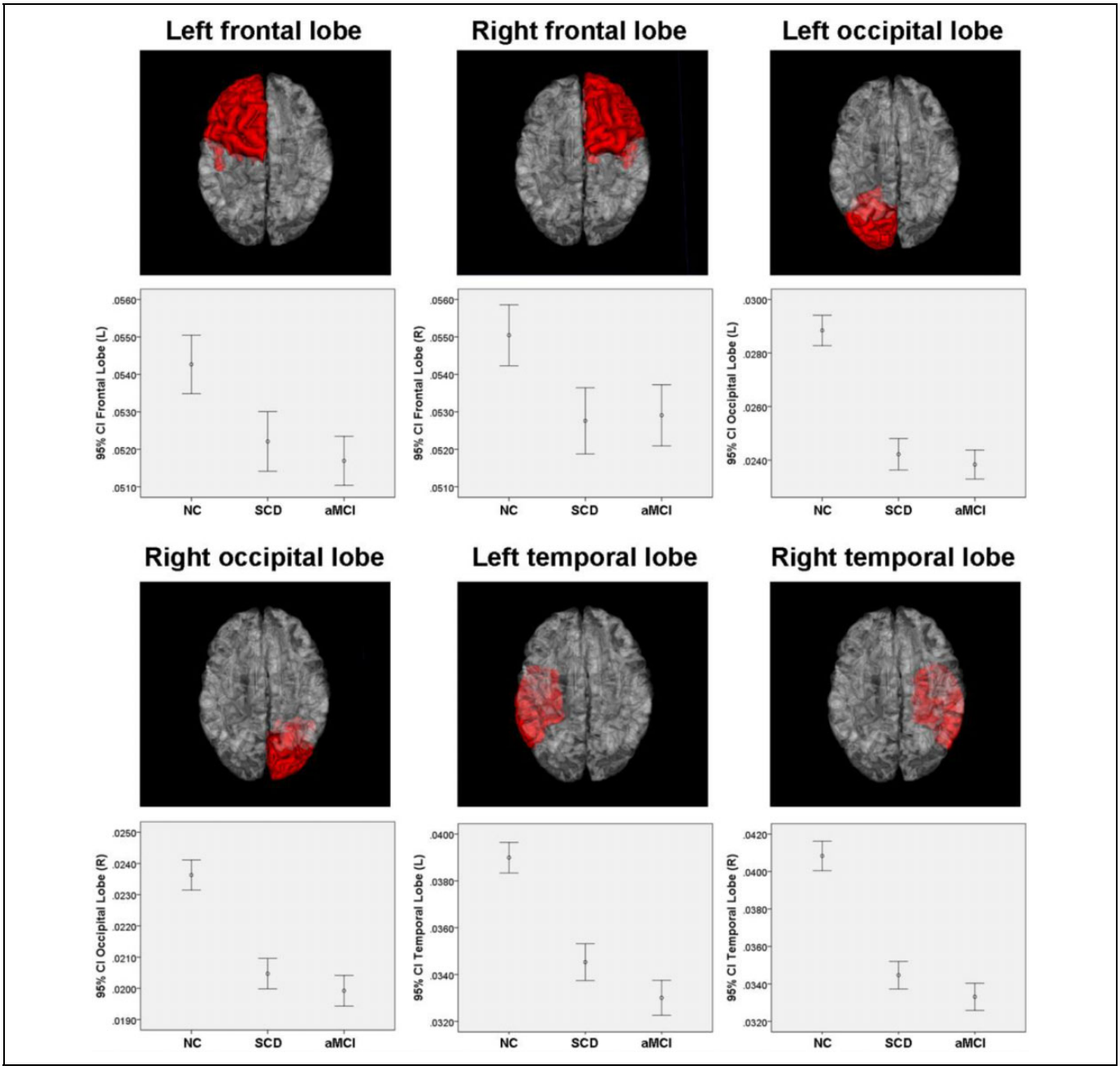

Figure 2. Error bars for the volume ratios of bilateral frontal, occipital, and temporal lobes. Three-dimensional illustrations for these segmented brain structures are also provided.

SCD *plus* in our study (which indicated higher risk of conversion from SCD to AD) would be of more clinical interest. Furthermore, as the degree of cognitive deficits in the patients with aMCI (as measured by MMSE) was similar to most of the studies that investigated the classification of aMCI versus NC,[11,12,41] the enhanced classification performance of aMCI versus NC (as well as SCD vs NC) in our study may also result from the brain segmentation tool (*AccuBrain*) that we used, which has presented the highest accuracy in hippocampus segmentation to date among the existing automated image processing tools.[19] In fact, when using the hippocampus volume as the only predictor in the classifications of aMCI versus NC and SCD versus NC, a previous study had an AUC of less than 0.68,[7] whereas in our study, the AUC was more than 0.95. Furthermore, this result indicated that with the help of an accurate and robust automatic brain segmentation tool, the predefined region-based approach (using volumetric information of either individual or multiple brain regions) can achieve comparable sensitivity in measuring brain structural changes with density map-based and cortical surface-based approaches and even better performance in differentiating aMCI and SCD from NC.

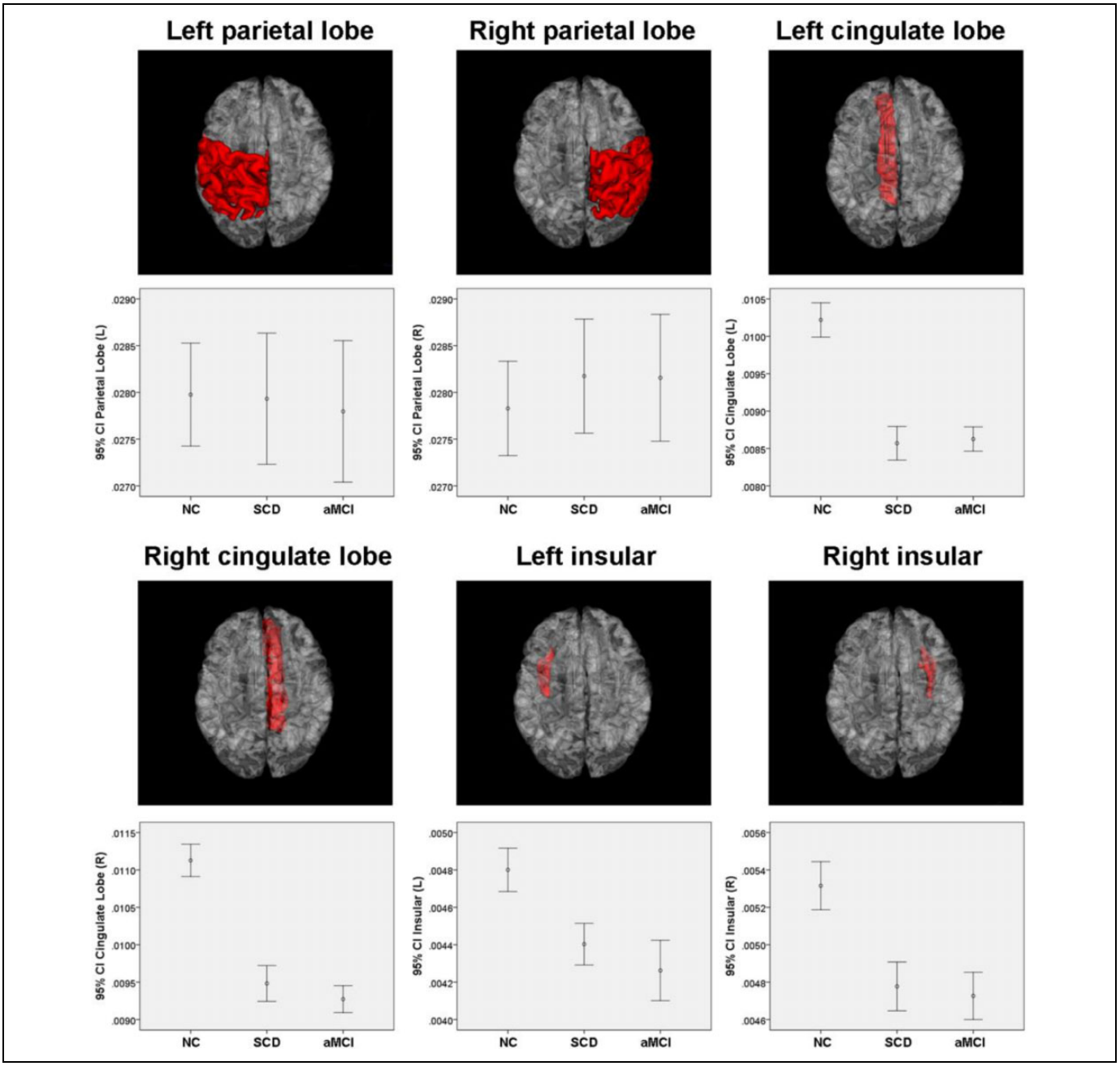

Figure 3. Error bars for the volume ratios of bilateral parietal lobe, cingulate lobe, and insular gyrus. Three-dimensional illustrations for these segmented brain structures are also provided.

There are several limitations in this study that should be considered. First, the sample size in our study was relatively small for each group of participants (aMCI, SCD, and NC), which indicated that the results from our study might not be generalizable to a cohort with significantly different demographic characteristics. Future studies with a larger sample size could combine MRI volumes and general demographic characteristics to achieve more generalizable results in clinical practice. Second, detailed neuropsychological tests were not available in our study cohort to comprehensively evaluate the cognitive functioning of the participants. In addition, the SCD group in this study met 4 of the 7 features of SCD *plus* but not all of the features as proposed in the consensus paper on SCD in preclinical AD.[2] For example, the information about the presence of the APOE ε4 genotype was not available for the patients with SCD. However, the validation of the proposed features of SCD *plus* is still ongoing, and which item to reject remains an open question.[14] In fact, this study confirmed that by using part of the features of SCD *plus* (ie, subjective decline in memory rather than other domains of cognition, onset of SCD within the last 5 years, particular concerns or worries associated with SCD, and confirmation of perceived cognitive

Table 3. Accuracies and AUCs of SVM Models.[a]

Model	Regional Feature Involved	aMCI vs NC		SCD vs NC		aMCI vs SCD	
		ACC	AUC	ACC	AUC	ACC	AUC
1	Lateral ventricle	0.5953	0.6327	0.5065	0.5128	0.5474	0.6048
2	Third ventricle	0.5832	0.6147	0.5658	0.6112	0.4929	0.5038
3	Hippocampus L	0.8514	0.9712	0.7737	0.9572	0.6236[f]	0.6999[f]
4	Hippocampus R	0.8369	0.9922	0.8144	0.9630	0.6046[f]	0.6887[f]
5	Amygdala L	0.7923	0.9689	0.7013	0.8919	0.5807	0.7057[f]
6	Amygdala R	0.7939	0.9537	0.7090	0.8748	0.5844	0.7013[f]
7	Frontal lobe L	0.6699	0.7607	0.6615	0.7153	0.5040	0.5075
8	Frontal lobe R	0.6267	0.6866	0.6719	0.7129	0.4715	0.4099
9	Occipital lobe L	0.9344	0.9710	0.9026	0.9751	0.5335	0.5573
10	Occipital lobe R	0.8551	0.9562	0.8282	0.9193	0.5369	0.5750
11	Temporal lobe L	0.8534	0.9608	0.7960	0.9053	0.6243[f]	0.6642[f]
12	Temporal lobe R	0.9349	0.9657	0.9028	0.9528	0.5610	0.6249
13	Parietal lobe L	0.4920	0.4743	0.5233	0.4031	0.4667	0.4160
14	Parietal lobe R	0.5291	0.5470	0.5480	0.5543	0.4662	0.3392
15	Cingulate lobe L	0.8572	0.9568	0.8027	0.9424	0.4894	0.4948
16	Cingulate lobe R	0.8135	0.9646	0.7909	0.9356	0.5585	0.5847
17	Insular L	0.6546	0.7997	0.6495	0.7780	0.5115	0.5820
18	Insular R	0.7272	0.8428	0.7237	0.8113	0.4917	0.5113
19	All features above	0.9590[b]	0.9924[c]	0.9451[d]	0.9776[e]	0.5495	0.6080

Abbreviations: ACC, average classification accuracy; AUC, area under the curve; L, left; aMCI, amnestic mild cognitive impairment; NC, normal control; R, right; SCD, subjective cognitive decline; SVM, support vector machine.

[a]The mean values of the ACC and AUC generated with a 20-times stratified nested 10-fold cross-validation are displayed here. Models 1 to 18 only included an individual regional volume as the predictor of the model, and model 19 included all the regional volumes from Model 1 to 18 as predictors in the model. Paired sample t-tests were used to compare the model performance measures acquired from the 200 evaluations during the testing procedure.

[b]Significantly higher than Model 9 and Model 12 with $P < 0.01$ and the other models with $P < 0.001$.

[c]Similar with Model 4 ($P = 0.587$) but significantly higher than the other models with $P < 0.001$.

[d]Significantly higher than all the other models with $P < 0.001$.

[e]Similar with Model 9 ($P = 0.372$) but significantly higher than the other models with $P < 0.001$.

[f]Significantly higher than Model 19 with $P < 0.001$.

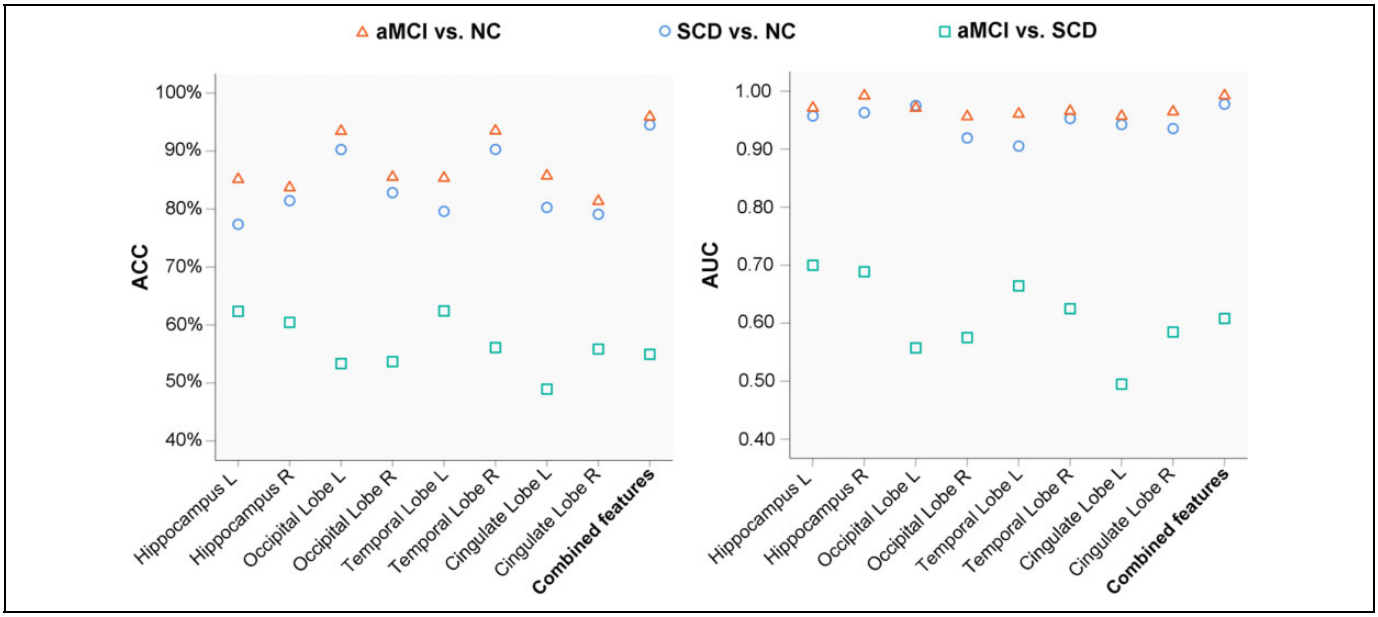

Figure 4. Performance of SVM models for classifications of aMCI versus NC, SCD versus NC, and aMCI versus SCD. Regarding the models with individual regional features as predictors, only the models that have ACC >80% in the classification of aMCI versus NC or SCD versus NC are displayed. The model of "combined features" indicates the one with all the volumetric measures of 18 brain regions as a predictor. aMCI indicates amnestic mild cognitive impairment; L, left; R, right; NC, normal control; SCD, subjective cognitive decline; SVM, support vector machine.

decline by an informant), we could also include patients with SCD with more severe brain atrophy (ie, indicating higher risk of AD conversion) than the previous studies that did not apply SCD *plus* features. The impact of the other features of SCD *plus* still needs to be validated in the future. Furthermore, we did not include patients with SCD who failed to match the major features of SCD *plus* (eg, patients without concerns or worries about their SCD) as an additional reference group; therefore, a direct comparison in brain atrophy was not available between the patients with SCD with and without SCD *plus* features. Finally, this study was based on cross-sectional data, and the follow-up data of the subjects were not available regarding their potential conversion from SCD to aMCI/AD or aMCI to AD. As not all participants identified as SCD or aMCI will have further progression, future studies should aim to investigate the atrophy patterns of the converters (patients who converted from SCD to aMCI/AD or from aMCI to AD at follow-ups) and whether automated MRI volumetry can help identify the participants with higher risk of subsequent conversion.[15]

In conclusion, we identified the shared and distinct atrophy patterns between patients with SCD and aMCI using automated volumetric measures of predefined brain regions, and the patients with SCD were identified, as proposed recently, by using the strategy of SCD *plus*. The brain atrophy of several temporal lobe structures found in patients with aMCI was less severe or absent in patients with SCD, which provided further evidence about the transitional role of SCD between NC and aMCI prior to further progression to AD. In addition, we further demonstrated that atrophy in patients with SCD (with worries of cognitive decline and informant confirmation as specified by SCD *plus*) was severe enough to differentiate them from NC participants using the predefined region-based approach, and the classification performance was similar to that of aMCI versus NC. The results of the study need to be validated with a larger sample size, and future efforts should aim to investigate the prediction power of automated MRI volumetry in the conversion from SCD to aMCI or AD.

Authors' Note

Weina Zhao and Yishan Luo are joint first authors. Weina Zhao and Yishan Luo contributed to the main body of the manuscript. Ying Han and Lin Shi conceptualized, designed, supervised the study, and approved the final version of the manuscript. Yu Sun and Jie Lu contributed to the study design and data collection. Lei Zhao contributed to data analysis and manuscript preparation. Vincent Mok, Changhao Yin, and Li Su provided clinical advice and comments on the draft. All the authors interpreted the data, provided important feedback, and revised the manuscript.

Acknowledgments

The authors thank the Family Planning Commission of Shunyi District Beijing and Alzheimer's Research UK (ARUK-SRF2017B-1), Addenbrooke's Charitable Trust, Alzheimer's Society, and The Lewy Body Society for their support.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Lin Shi is the director of BrainNow Medical Technology Limited. Yishan Luo and Lei Zhao are employees of BrainNow Medical Technology Limited.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article was supported by the National Key Research and Development Program of China (2016YFC1306300, 2016YFC0103000), the National Natural Science Foundation of China (Grant No. 31371007, 81571755, 81430037, 61633018, 6150332, 81771795, 81601454, 81522021), the Beijing Municipal Government (PXM2019_026283_000002), the Beijing Nature Science Foundation (7161009), the Beijing Municipal Science & Technology Commission (Z161100002616020), and the Fundamental and Clinical Cooperative Research Program of Capital Medical University (16JL-L08).

References

1. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262-1270.
2. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):844-852.
3. Luck T, Luppa M, Matschinger H, Jessen F, Angermeyer MC, Riedel-Heller SG. Incident subjective memory complaints and the risk of subsequent dementia. *Acta Psychiatr Scand*. 2015;131(4):290-296.
4. Lopez-Sanz D, Bruna R, Garces P, et al. Functional connectivity disruption in subjective cognitive decline and mild cognitive impairment: a common pattern of alterations. *Front Aging Neurosci*. 2017;9:109.
5. Colijn MA, Grossberg GT. Amyloid and Tau biomarkers in subjective cognitive impairment. *J Alzheimers Dis*. 2015;47(1):1-8.
6. Striepens N, Scheef L, Wind A, et al. Volume loss of the medial temporal lobe structures in subjective memory impairment. *Dement Geriatr Cogn Disord*. 2010;29(1):75-81.
7. Rogne S, Vangberg T, Eldevik P, Wikran G, Mathiesen EB, Schirmer H. Magnetic resonance volumetry: prediction of subjective memory complaints and mild cognitive impairment, and associations with genetic and cardiovascular risk factors. *Dement Geriatr Cogn Dis Extra*. 2016;6(3):529-540.
8. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology*. 2006;67(5):834-842.
9. Stewart R, Dufouil C, Godin O, et al. Neuroimaging correlates of subjective memory deficits in a community population. *Neurology*. 2008;70(18):1601-1607.
10. Peter J, Scheef L, Abdulkadir A, et al. Gray matter atrophy pattern in elderly with subjective memory impairment. *Alzheimers Dement*. 2014;10(1):99-108.
11. Davatzikos C, Fan Y, Wu X, Shen D, Resnick SM. Detection of prodromal Alzheimer's disease via pattern classification of magnetic resonance imaging. *Neurobiol Aging*. 2008;29(4):514-523.

12. Desikan RS, Cabral HJ, Hess CP, et al. Automated MRI measures identify individuals with mild cognitive impairment and Alzheimer's disease. *Brain*. 2009;132(pt 8):2048-2057.
13. Rathore S, Habes M, Iftikhar MA, Shacklett A, Davatzikos C. A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages. *Neuroimage*. 2017;155:530-548.
14. Molinuevo JL, Rabin LA, Amariglio R, et al. Implementation of subjective cognitive decline criteria in research studies. *Alzheimers Dement*. 2017;13(3):296-311.
15. Wolfsgruber S, Kleineidam L, Wagner M, et al. Differential risk of incident Alzheimer's Disease dementia in stable versus unstable patterns of subjective cognitive decline. *J Alzheimers Dis*. 2016;54(3):1135-1146.
16. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.
17. Han Y, Wang J, Zhao Z, et al. Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: a resting-state fMRI study. *Neuroimage*. 2011;55(1):287-295.
18. Li Y, Wang X, Li Y, et al. Abnormal resting-State functional connectivity strength in mild cognitive impairment and its conversion to Alzheimer's disease. *Neural Plast*. 2016;2016: 4680972.
19. Abrigo J, Shi L, Luo Y, et al. Standardization of hippocampus volumetry using automated brain structure volumetry tool for an initial Alzheimer's disease imaging biomarker. *Acta Radiol*. 2018;60(6):769-776. 284185118795327.
20. Whitwell JL, Crum WR, Watt HC, Fox NC. Normalization of cerebral volumes by use of intracranial volume: implications for longitudinal quantitative MR imaging. *Am J Neuroradiol*. 2001; 22(8):1483-1489.
21. Cortes C, Vapnik V. Support-vector networks. *Mach Learn*. 1995; 20(3):273-297.
22. Chang C-C, Lin C-J. LIBSVM: a library for support vector machines. *ACM Trans Intell Syst Technol*. 2011;2(3):1-27.
23. Casanova R, Whitlow CT, Wagner B, et al. High dimensional classification of structural MRI Alzheimer's disease data based on large scale regularization. *Front Neuroinform*. 2011;5(22):22.
24. Krstajic D, Buturovic LJ, Leahy DE, Thomas S. Cross-validation pitfalls when selecting and assessing regression and classification models. *J Cheminform*. 2014;6(1):10.
25. Huang J, Ling CX. Using AUC and accuracy in evaluating learning algorithms. *IEEE Trans Knowl Data Eng*. 2005;17(3): 299-310.
26. Khandoker AH, Palaniswami M, Karmakar CK. Support vector machines for automated recognition of obstructive sleep apnea syndrome from ECG recordings. *IEEE Trans Inf Technol Biomed*. 2009;13(1):37-48.
27. Nam B-H, D'Agostino RB. Discrimination index, the area under the ROC curve. In: Huber-Carol C, Balakrishnan N, Nikulin MS, Mesbah M, eds. *Goodness-of-Fit Tests and Model Validity*. Berlin, Germany: Springer; 2002:267-279.
28. Vaughan I, Ormerod S. The continuing challenges of testing species distribution models. *J Appl Ecol*. 2005;42(4):720-730.
29. Lobo JM, Jiménez-Valverde A, Real R. AUC: a misleading measure of the performance of predictive distribution models. *Glob Ecol Biogeogr*. 2008;17(2):145-151.
30. Moradi E, Pepe A, Gaser C, Huttunen H, Tohka J, Alzheimer's Disease Neuroimaging Initiative. Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. *Neuroimage*. 2015;104:398-412.
31. Kovacevic S, Rafii MS, Brewer JB, Alzheimer's Disease Neuroimaging Initiative. High-throughput, fully automated volumetry for prediction of MMSE and CDR decline in mild cognitive impairment. *Alzheimer Dis Assoc Disord*. 2009;23(2):139-145.
32. Hamalainen A, Tervo S, Grau-Olivares M, et al. Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *Neuroimage*. 2007;37(4):1122-1131.
33. McEvoy LK, Fennema-Notestine C, Roddey JC, et al. Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. *Radiology*. 2009;251(1):195-205.
34. Kakeda S, Korogi Y. The efficacy of a voxel-based morphometry on the analysis of imaging in schizophrenia, temporal lobe epilepsy, and Alzheimer's disease/mild cognitive impairment: a review. *Neuroradiology*. 2010;52(8):711-721.
35. Verfaillie SC, Tijms B, Versteeg A, et al. Thinner temporal and parietal cortex is related to incident clinical progression to dementia in patients with subjective cognitive decline. *Alzheimers Dement*. 2016;5:43-52.
36. Perrotin A, La Joie R, de La Sayette V, et al. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: differential affective and imaging correlates. *Alzheimers Dement*. 2017;13(5):550-560.
37. Wang XN, Zeng Y, Chen GQ, et al. Abnormal organization of white matter networks in patients with subjective cognitive decline and mild cognitive impairment. *Oncotarget*. 2016;7(31): 48953-48962.
38. Carmichael OT, Kuller LH, Lopez OL, et al. Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia. *Alzheimer Dis Assoc Disord*. 2007;21(1):14-24.
39. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry*. 2010;67(4):414-422.
40. Sørensen L, Igel C, Liv Hansen N, et al. Early detection of Alzheimer's disease using MRI hippocampal texture. *Hum Brain Mapp*. 2016;37(3):1148-1161.
41. Chincarini A, Bosco P, Calvini P, et al. Local MRI analysis approach in the diagnosis of early and prodromal Alzheimer's disease. *Neuroimage*. 2011;58(2):469-480.