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Alzheimer's & Dementia 10 (2014) 99–108

Alzheimer's & Dementia

Gray matter atrophy pattern in elderly with subjective memory impairment

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Abstract

Background: Individuals with subjective memory impairment (SMI) report worsening of memory without impairment in cognitive tests. Despite normal cognitive performance, they may be at higher risk of cognitive decline compared with individuals without SMI.

Methods: We used a discriminative function (a support vector machine) trained on an independent data set of 226 healthy control subjects and 191 patients with probable Alzheimer's disease (AD) dementia to characterize the baseline gray matter patterns of 24 individuals with SMI and 53 control subjects. We tested for associations of these gray matter patterns with SMI presence, cognitive performance at baseline, and cognitive decline at follow-up.

Results: Individuals with SMI showed greater similarity to an AD gray matter pattern compared with control subjects without SMI. In addition, episodic memory decline was associated with an AD gray matter pattern in the SMI group.

Conclusions: Our results indicate a link between the gray matter atrophy pattern of patients with AD and the presence of SMI. Furthermore, multivariate pattern recognition approaches seem to be a sensitive method for identifying subtle brain changes that correspond to future memory decline in SMI.

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Keywords: Prediction; Cognitive decline; Subjective memory impairment; Magnetic resonance imaging; Pattern recognition; Early diagnosing

1. Introduction

Individuals with subjective memory impairment (SMI) report declining memory without measurable cognitive deficits. Whether individuals with SMI are at greater risk of both cognitive decline and the development of mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia still remains an area of controversy. Although some studies demonstrate an increased risk for those with SMI [1,2], others found no relation between SMI and cognitive

J. Peter and L. Scheef contributed equally to this paper.

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

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http://dx.doi.org/10.1016/j.jalz.2013.05.1764

performance or cognitive decline (see Aschenbrenner and colleagues [3] for an overview). Specifically, a cross-sectional study [4] found that subjective memory complaints reported in the memory complaint questionnaire [5] were not associated with cognitive measures. A recent study by Reid and colleagues [6] found the Memory Complaint Questionnaire (MAC-Q) to be influenced greatly by affective status and not to be a useful screening tool of memory impairment. One longitudinal study [7] found that more severe memory complaints reported in the memory function questionnaire [8] were not associated with cognitive measures but with lower mood and greater global psychological distress after 5 years of follow-up. Subjects who developed cognitive impairment over 5 years reported more complaints at baseline, but this relationship was not statistically significant.

The lack of a general definition of SMI and the existence of several terms (e.g., subjective memory complaints, subjective memory impairment, subjective cognitive impairment) complicates the comparability of results across studies. In addition, there is no general guideline of how to measure SMI. Nevertheless, research on SMI and the investigation of longitudinal cognitive development of those individuals is of substantial clinical relevance. The identification of those individuals with SMI who will show progressive cognitive decline would be of major benefit for future dementia prevention strategies because AD-related pathological processes begin decades before the onset of symptoms of dementia [9]. SMI may, therefore, indicate the first changes in cognition, corresponding to a very subtle alteration at the pre-MCI stage of AD, and thus may be a clinical indicator for predementia and pre-MCI biomarker-based detection of AD [10].

So far, a number of studies have reported cross-sectional biomarker evidence for AD in SMI [11–15]. The first longitudinal studies have been published recently [16–18]. Stewart and colleagues [18] found an association between longitudinal changes in hippocampal volume in nondemented individuals with subjective reports of memory impairment in a population-based sample, but subjects with MCI were not excluded from the study. Selnes and colleagues [17] found that structural connectivity of the medial temporal lobe, measured using Diffusion Tensor Imaging DTI, outperformed cerebrospinal fluid biomarkers in the prediction of cognitive decline in a combined subjective cognitive impairment/MCI group. In a study on SMI only, Scheef and colleagues [16] found a weak (nonsignificant) association between a smaller right hippocampal gray matter volume and subsequent cognitive decline. Recently, an increased risk of conversion to both MCI and AD dementia in subjects with SMI and cerebrospinal fluid evidence for AD has been reported [19].

In the current study, we evaluated the association between gray matter patterns and cross-sectional as well as longitudinal cognitive performance in individuals with SMI and control subjects. The same sample as in the study by Scheef and colleagues [16] was used to clarify whether the prediction of memory decline can be improved by multivariate structural whole-brain data analyzed using support vector machine (SVM) algorithms. These automated methods are unbiased [20] because they are independent from subjective judgments [21]. They learn to identify a disease-specific pattern of gray matter changes from training data. Similar to other studies in AD [22] or in healthy elderly [23], we reduced magnetic resonance imaging (MRI) data to a single variable (decision value [DV]). We adopted an approach that was applied previously to healthy aging [12] by using healthy elderly and AD patients to define a spectrum ranging from healthy to AD. The DV effectively codes the location of each individual magnetic resonance (MR) image on this spectrum, with negative values indicating a pattern similar to healthy control subjects and positive values indicating a pattern similar to AD. A DV close to 0 represents the transition state between both.

In addition to the structural MRI marker, other known predictors of cognitive decline were included in the statistical models. These additional predictors were episodic memory as the most severely and earliest affected cognitive domain in AD and MCI [24], which is also considered a proxy for future dementia [25], as well as age, gender, education, and the apolipoprotein E (*APOE*) genotype (e.g., [19,26,27].

2. Methods

2.1. Participants

Individuals with SMI (n = 24) were recruited from the memory clinic of the Clinical Treatment and Research Center for Neurodegenerative Disorders, Department of Psychiatry and Neurology, University Hospital Bonn (Bonn, Germany). The fact of being referred to the memory clinic and a standard question served to identify those with SMI. To be classified as SMI, subjects had to answer the questions "Do you feel like your memory is becoming worse?" with "Yes, and this worries me" instead of one of the other options ("No" or "Yes, but this does not worry me"). In addition, SMI status had to be verified by significant others to increase the validity of reported memory decline [28]. The informants were the spouses or close relatives (usually, those who accompanied the individual to the memory clinic). Furthermore, the onset of SMI had to be within the past 10 years to exclude chronic "memory complainers."

Healthy control subjects (n = 53) without SMI and normal cognitive performance were recruited from the general population. The SMI group and the control group did not differ in terms of gender, age, education or *APOE* ε4 distribution (see details in Table 1). For all participants, normal cognitive functioning was defined by the Consortium to Establish a Registry of Alzheimer's Disease neuropsychological battery [29], using German age-, gender-, and education-adjusted norms [30]. None of the participants scored less than 1.5 standard deviations on any of the subtests of the

Table 1
Sociodemographic characteristic of the full sample

Characteristic	Controls	SMI	*P* value
n	53	24	
Male/female	18/35	6/18	$\chi^2 = 0.62$; $P = .59$ (ns)
Age, years	67.1 ± 6.1	66.0 ± 7.1	$t = 0.65$; $P = .52$ (ns)
Education, years	14.9 ± 3.6	14.9 ± 2.8	$t = 0.04$; $P = .99$ (ns)
APOE ε4 status, n, %	11 (21.2)	7 (29.2)	$\chi^2 = 0.58$; $P = .45$ (ns)
Follow-up interval, months	34.4 (14.2)	34.2 (11.0)	$t = 0.58$; $P = .958$ (ns)
Decision values	−0.6 ± 0.5	−0.3 ± 0.4	$t = 2.42$; $P = .02$

Abbreviations: SMI, subjective memory impairment; ns, not significant; *APOE*, apolipoprotein E. n, number

NOTE. Higher decision values indicate a greater similarity to an Alzheimer's disease gray matter atrophy pattern. Mean values with 1 standard deviation are reported.

Consortium to Establish a Registry of Alzheimer's Disease battery.

Exclusion criteria were (*i*) current neurological or severe medical disease; (*ii*) medication that may interfere with cognition, including any psychotropic medication; and (*iii*) any other detectable cause of memory impairment. Current and lifetime psychiatric disorders were assessed with the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition [31] and the Beck's Depression Inventory [32]. Subjects with a current psychiatric disorder or with one in the past were excluded, with the exception of a single depressive episode more than 10 years ago, which was reported by 2 patients with SMI and 4 control subjects. The *APOE* genotype [33] was determined in all participants. The study protocol was approved by the ethical committee of the medical faculty of the University of Bonn. All participants provided written informed consent.

2.2. Longitudinal cognitive testing

Both diagnostic groups were monitored longitudinally to assess their cognitive course over time. The neuropsychological battery at baseline and at three follow-up-visits included the German Verbal Learning and Memory Test (VLMT [34]), the Trail Making Test A and B (TMT A/B [35]), and a lexical 2-minute verbal fluency task [36]. The latter was applied to test speed and executive functions (see Table 2 for baseline sores). There were no significant group differences between the SMI and control subjects in any test of the baseline neuropsychological battery, although individuals with SMI scored slightly lower on all tests and needed slightly more time for the TMT (see Table 2 for details).

Table 2
Baseline performance on neuropsychological battery

Neuropsychological test	Controls	SMI	*P* value, *t* test
Verbal memory score	85.2 ± 16.1	78.2 ± 22.6	.18
Trail Making Test A	43.1 ± 12.4	42.8 ± 13.4	.92
Trail Making Test B	97.7 ± 37.3	103.8 ± 58.1	.58
Verbal fluency	10.4 ± 4.4	8.7 ± 4.6	.14

Abbreviation: SMI, subjective memory impairment.

NOTE. Mean values with 1 standard deviation are reported.

The VLMT assesses learning and recall of a 15-item word list, which is presented five times. Four subscores were derived from the VLMT: (*i*) immediate recall (sum of recalled words within trials 1–5), (*ii*) immediate recall after interference (a list of new, distracter words in trial 6), (*iii*) delayed recall after 30 minutes (trial 7), and (*iv*) recognition (hits less false alarms). Assuming that a single summary measure would be the most stable marker for memory performance, an exploratory and confirmatory factor analysis of the four subscores (summed raw values) was performed. Factor solutions for one to five factors were extracted with oblique rotations and compared using the Kaiser-Guttmann criteria [37], the scree test [38], the Fürntratt criterion [39], and a comparison of goodness-of-fit indices. Following conventions, calculated χ^2 values are expected to be nonsignificant ($P > .05$) for relevant factors, because a nonsignificant value implies a small discrepancy between an observed and implied covariance matrix. In addition, absolute fit indices, root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) were expected to be $P < .04$, and a comparative fit index of more than 0.90 to be in the acceptable range. The factor analysis identified one single episodic memory factor with an almost ideal model fit (n = 77, $\chi^2 = 0.254$, $df = 2$, comparative fit index = 1.000, RMSEA = 0.000, 90% confidence interval $P = .000$–0.110, and SRMR = 0.004). The results of the χ^2 test indicated that the chosen model was suitable for these data, and RMSEA and SRMR values well below 0.04 indicated excellent model fit. Confirmatory factor analysis was performed to validate the model. Fixing the factor variance to one and allowing free loadings on the factor yielded a confirmation with our sample. This finding is in line with previous investigations by the authors of the VLMT [40]. We therefore added up the four scores mentioned earlier into one robust verbal memory score for cross-sectional and longitudinal analyses.

2.3. Follow-up visits

Participants of the SMI group returned after 14 ± 3.0 months, 32.5 ± 6.1 months, and 45.1 ± 5.6 months for follow-up visits. Participants in the control group returned

after 15.5 ± 2.9 months, 33.3 ± 6.1 months, and 41.7 ± 4.1 months for follow-up visits. In the SMI group, 22 subjects had at least one follow-up, 16 had two follow-up visits, and 11 had three follow-ups. In the control group, 45 participants had at least one follow-up, 36 had two follow-ups, and 15 had three follow-up visits. Follow-up rates did not differ between the SMI and control groups (χ^2 [3] = 2.67, not significant). There were no significant differences between dropouts and participants still remaining in the study with regard to age, gender, and years of education.

2.4. Imaging

All subjects were scanned at baseline on as 3-T MRI scanner (Philips Achieva, Philips, Best, Netherlands), equipped with an eight-channel SENSE head coil. Sequence parameters were as follows: T1-weighted three-dimensional turbo field echo; SENSE reduction factor 2.5 in the anteroposterior direction and 1.5 in the right–left direction; echo time, 3.6 ms; repetition time, 7.6 ms; flip angle, 8°; field of view, 256 × 256 mm^2; matrix size, 320 × 320; number of slices, 170; slice thickness, 0.8 mm; and spatial resolution, 0.8 × 0.8 × 0.8 mm^3. Up to three structural data sets were acquired for each subject. These data sets were averaged to optimize the signal-to-noise ratio. The mean image volumes entered the processing pipeline as outlined next.

2.5. Preprocessing

Image preprocessing was done using statistical parametric mapping software (SPM 8). The unified segmentation algorithm [41] was used in combination with a nonlinear image warping approach (DARTEL [42]). Unified segmentation estimates the tissue segmentation based on a probabilistic Gaussian mixture model including prior knowledge of a priori probability for every tissue class from a template. The process estimates jointly the nonlinear registration to the prior tissue probability maps (TPMs), the segmentation, and intensity nonuniformity resulting from field inhomogeneity. Default processing parameters were used for segmentation. DARTEL was used to warp more accurately the gray matter TPMs (GM-TPMs) into a common template space. This included a segmentation (parameters estimated during the unified segmentation step) and initial resampling to 1.5-mm isotropic resolution. The study-specific population template was built from the GM-TPMs of the training set. During this process, the initial template was built by averaging the TPMs of the population, estimating nonlinear mapping from all individual TPMs to the average, and warping all individual TPMs into that common template space. This process was repeated six times, and for every iteration taking the average of the warped TPMs as a new template and gradually decreasing the internal smoothing kernel size, thus getting gradually crisper templates. All training and test GM-TPMs were warped into the same space as the training data, which were derived from a subset of the Alzheimer's Disease Neuroimaging Initiative (ADNI) and which has been used in a previous study [43]. Gray matter volume normalization by modulation with the Jacobian determinant was used to compensate for local changes in volume (compression or extension).

2.6. Generation of DVs

The individual MRI data were reduced to a single variable (DV) by applying a multivariate pattern recognition method. Intuitively, the DV is a scalar that characterizes individual MR images on a scale ranging from healthy to progressed AD. Technically, it is the distance of the testing image to the separating hyperplane of a classifier. The decision boundary was obtained by an SVM [44], which is supervised in a sense that it deducts a classification rule from training data. Related methods have been found to predict individual cognition in subjects with AD and MCI [45], and they have been used successfully to detect those with MCI who will convert later to dementia [46,47] or those healthy elderly who will convert to MCI [48].

A linear SVM, implemented as a *C*-SVM in LibSVM software [49] was chosen. Data used to train the SVM were obtained from the ADNI database as described in our previous work [43]. In brief, we included 226 healthy control subjects and 191 subjects with probable AD using the cost parameter that yielded the highest cross-validation accuracy (accuracy, 86.7%). In addition, we determined voxels that contributed most to the classification of the training data set.

The trained classifier was applied to each MRI data set of the study to obtain the DVs, which are similar to the Spatial Pattern of Abnormality for Recognition of Early Alzheimer's disease (SPARE) index and the Structural Abnormality index (STAND) score used in other classification studies [22,48]. A detailed description of the DV can be found elsewhere [44].

2.7. Modeling of cross-sectional and longitudinal association of DV with group and cognitive performance

Structural equation modeling was used for data analysis (MPlus 6.12).

2.8. Treatment of time-invariant covariates

The following steps were followed for each association analysis in the model-fitting process: We first started with an unconditional model, estimating the dependent variables without covariates (model 1 → basic model). We then added age, years of education, *APOE* ε4 status, and gender as covariates (model 2 → model including time-invariant covariates). To reduce the complexity of the final model, only variables significant at least at a trend level ($P < .1$) remained in the final model, which is in line with the proposed scheme of Nesselroade [50]. Because a significant amount of

residual variance remained after adding covariates to the model, a final model that included the DV as a predictor variable was generated, given that it yielded the highest model fit. We report only those results for the final model (model 3 → final model with DV as predictor).

2.9. Cross-sectional group comparison

The association of DV (dependent variable) with group (SMI and control subjects) and with the covariates remaining in the final model was examined. In addition, a receiver–operating characteristic (ROC) curve was carried out to test the discriminative accuracy of the DV regarding SMI and control subjects (see Fig. 1 for data analysis overview).

2.10. Cross-sectional analyses of the association of DV with cognitive performance

In further cross-sectional models, associations between memory score (as extracted from the VLMT) as well as TMT A/B and verbal fluency scores with DV and covariates that remained in the final model were tested. The models were both calculated across all subjects and for each group separately within multigroup models.

2.11. Longitudinal growth curve modeling of cognitive decline

Growth curve modeling with linear growth factors is a particularly useful approach of structural equation modeling for longitudinal data. Growth curve modeling was applied because it accommodates irregular numbers of follow-up information per subject using the full information maximum likelihood method under a missing at random assumption [51]. Individually varying times between observations were included by estimating random effects models, with time as a random variable.

We tested for associations between memory decline over time (with slope as the dependent variable) and DV as a predictor, handling time-invariant covariates as described earlier. Multigroup modeling was used to examine the associations between cognitive changes and DV in both groups separately (see Fig. 1 for data anlysis overview).

2.12. Estimation method and fit indices

The indices Akaike information criterion (AIC), sample size-adjusted Bayesian information criterion (BIC), and RMSEA were used to describe model fit. The maximum likelihood with robust standard errors (MLR) and χ^2 were

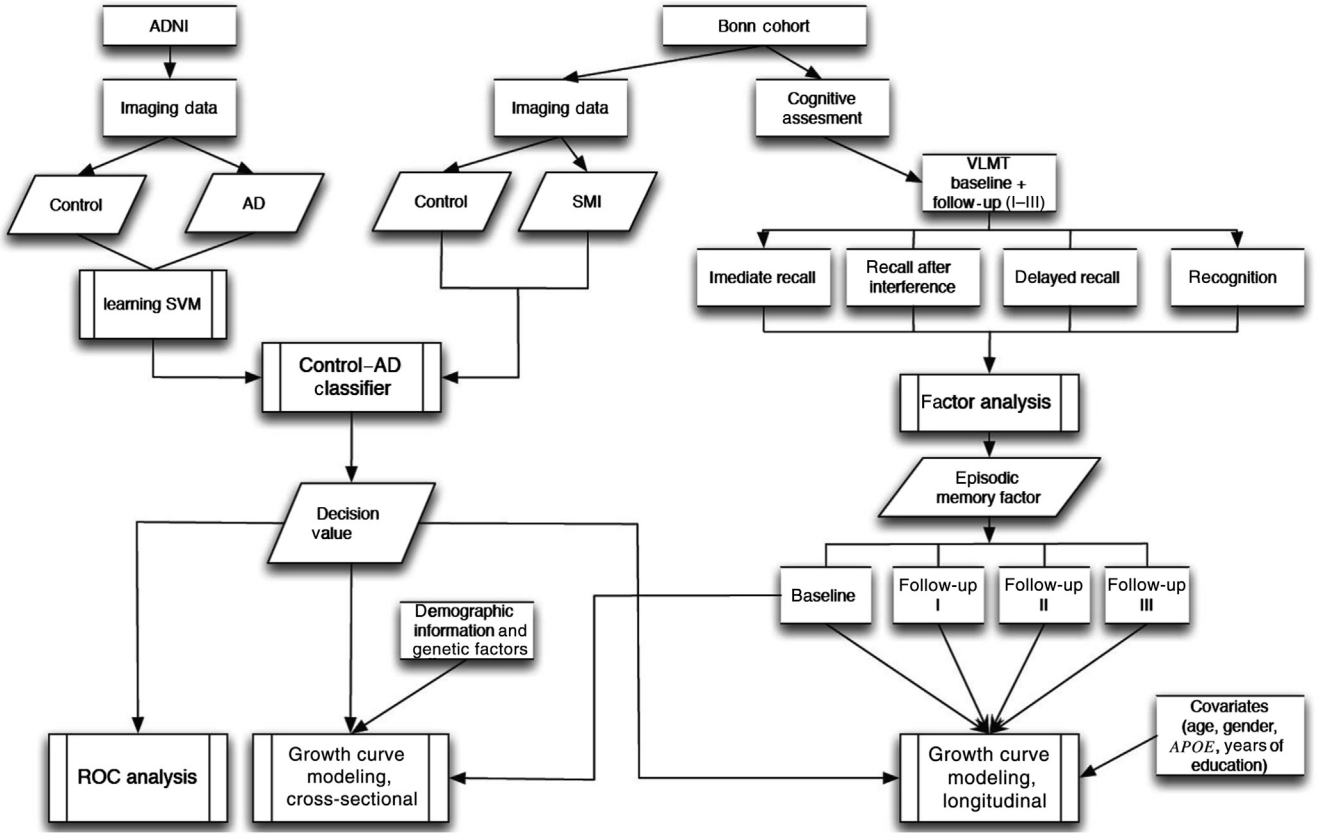

Fig. 1. Data analysis overview. ADNI, Alzheimer's Disease Neuroimaging Initiative; AD, Alzheimer's disease; SMI, subjective memory impairment; VLMT, Verbal Learning and Memory Test; SVM, support vector machine; ROC, receiver–operating characteristic; *APOE*, apolipoprotein E.

used for model estimation, allowing robust estimation even if the assumption of normal distribution was challenged. We report maximum likelihood parameter estimates, which can be interpreted as partial regression coefficients, and significance values (P values). For longitudinal random models, usual fit indices (e.g., RMSEA) are not available; therefore, only the AIC and the sample size-adjusted BIC were applied.

3. Results

3.1. Cross-sectional group comparison

The final model (model 3) achieved an almost ideal fit (n = 77; AIC, 50.873, sample size-adjusted BIC, 46.022; RMSEA = 0.000). Age (standardized estimate, 0.595, $P < .001$) and *APOE* genotype (standardized estimate, −0.244, $P < .003$) remained as significant covariates (older age and presence of an *APOE* ε4 allele being associated with a greater DV) and, together with group membership (SMI, control subjects: standardized estimate, −0.249, $P = .002$), explained 49.1% of variance in the DV.

As shown in Table 1, the DV differed statistically significant between SMI individuals and control subjects, with SMI showing greater similarity to an AD brain.

The area under the curve of the ROC analysis for the discrimination between SMI and control subjects using DV was 0.67 (95% confidence interval, 0.54–0.81; $P = .005$; Fig. 2). Figure 3 illustrates voxels that were most informative to classify AD and healthy control subjects, and therefore contribute to the classification of SMI individuals and control subjects. The voxels were mostly distributed in the hippocampal and parahippocampal areas.

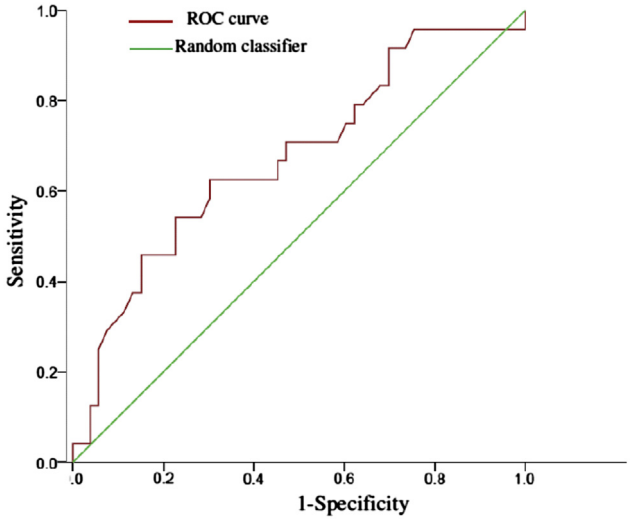

Fig. 2. Receiver–operating characteristic (ROC) curve of classifying individuals with SMI and controls by decision value.

3.2. Association of DV with cognitive performance at baseline

The model fit of the final model including the DV (n = 77; AIC, 636.388; sample size-adjusted BIC, 632.281; RMSEA = 0.000) outperformed both the unconditional model (AIC, 656.147; sample size-adjusted BIC, 654.505) and the model with significant covariates except the DV (AIC, 638.822; BIC, 650.476). The DV predicted baseline episodic memory across all subjects (standardized estimate, −0.248; $P = .01$). With increasing DV, memory performance was reduced. Years of education (standardized estimate, 0.336; $P = .001$) and gender (standardized estimate, −0.389, $P < .0001$) had additional effects, with better educated and female participants performing best. In the multigroup model, the association between DV and memory was significant in the control group (standardized estimate, −0.334; $P = .005$) and was of similar size and reached the level of a statistical trend toward significance in the SMI group (standardized estimate, −0.297, $P = .058$). The same covariates contributed significantly in the separate analyses. Figure 4 displays the association of DV with memory performance at baseline in both groups. There was no significant prediction of baseline speed and executive function performance (neither TMT nor verbal fluency) by DV.

3.3. Association of the DV with memory decline

The model fit of the final model including DV (n = 77; AIC, 1787.283; sample size-adjusted BIC, 1810.591) outperformed both the fit of the unconditional model (AIC, 1801.801; sample size-adjusted BIC, 1822.778) and the model with significant covariates except the DV (AIC, 1794.117; sample size-adjusted BIC, 1819.755). With increasing DV, memory declined more (three measurement points [baseline plus two follow-ups]: estimate, −0.272; $P = .023$; and four measurement points [baseline plus three follow-ups]: estimate, −0.292; $P = .008$). Figure 5 displays the association of DV with memory performance in both groups at the last follow-up visit. Only gender was retained as a covariate in the final model, with women showing less memory decline than men (estimate, −0.416; $P = .001$). In the analogous multigroup analysis, memory decline variance explained by DV was significant in the SMI group over three measurement points (estimate, −0.406; $P = .012$), but not in the control group (estimate, −0.163, $P = .385$). Over four measurement points, the association between DV and memory decline in the SMI group no longer remained significant. The loss of significance is attributable to the increased standard error of the memory slope estimate, resulting from the small number of subjects with four measurement points. There was no significant association of DV with speed or executive functions (TMT and verbal fluency) over time for three or four time points.

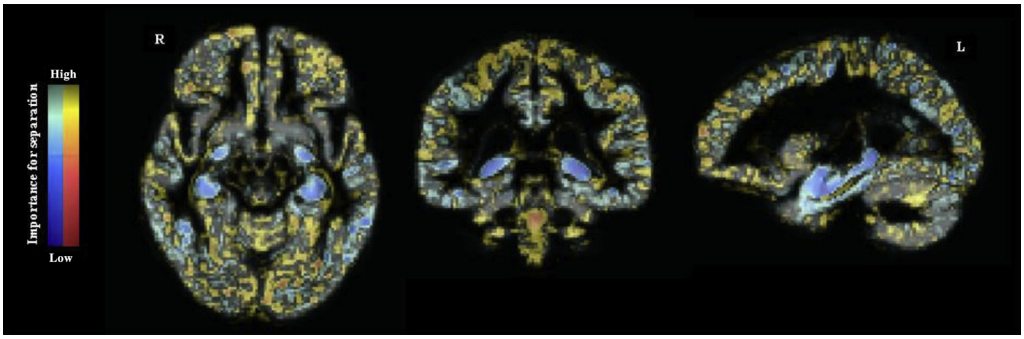

Fig. 3. Illustration of the most relevant voxels for discrimination between Alzheimer's disease (AD) dementia and healthy control subjects as identified by the trained classifier. Gray background represents the gray matter template of the training sample. Cold colors indicate regions where decreased gray matter contribute toward identification of a test sample as having AD dementia whereas warm colors indicate regions where increased gray matter contribute toward identification of a test sample as having AD dementia. The model was obtained with Alzheimer's disease Neuroimaging Initiative healthy control subjects (n = 226) vs. probable AD dementia (n = 191). R, right; L, left.

4. Discussion

The aim of our study was to evaluate the association of SMI with an AD-like gray matter atrophy pattern. In addition, we investigated the association of cross-sectional as well as longitudinal cognitive performance with this gray matter atrophy pattern in individuals with SMI and in control subjects.

An SVM based on a training set of AD dementia patients and control subjects derived from an independent data set was used to reduce the entire MRI gray matter information to one single variable (DV) that expresses similarity to an AD brain. Voxels most relevant for the classifier to separate patients with AD and healthy control subjects were predominantly distributed in the hippocampus and parahippocampus. In earlier studies, similar regions have been identified to discriminate AD from other neurodegenerative diseases [21] and to display volume reduction in subjects with SMI [11,13].

The DV differed significantly between SMI and control subjects, with SMI subjects showing greater similarity to an AD brain. ROC analysis revealed a relatively low, but

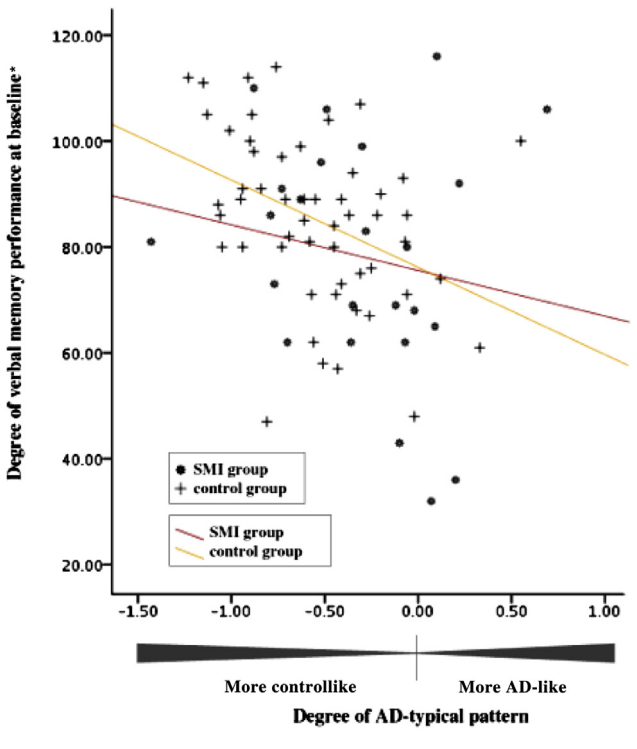

Fig. 4. Association between baseline verbal memory score and degree of similarity to an Alzheimer's disease (AD) gray matter atrophy pattern. SMI, subjective memory impairment. *Higher scores indicate better performance.

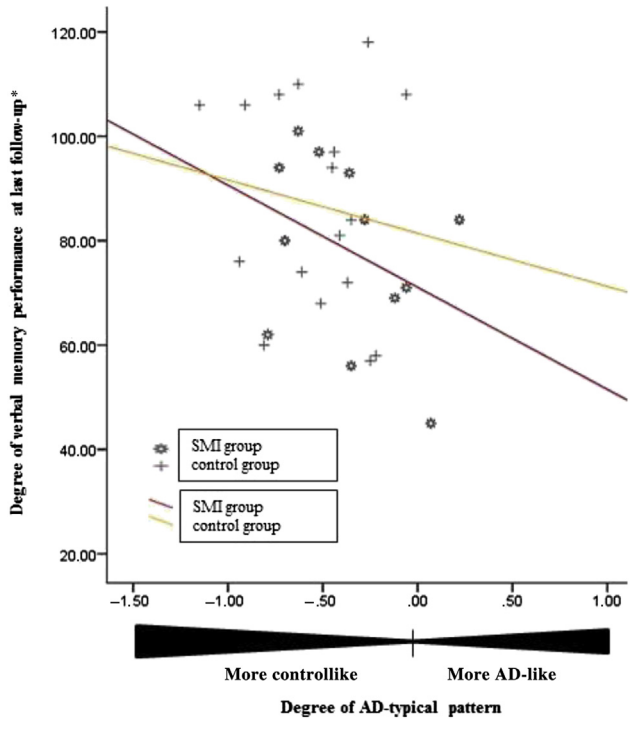

Fig. 5. Association between verbal memory score at last follow-up and degree of similarity to an Alzheimer's disease (AD) gray matter atrophy pattern. SMI, subjective memory impairment. *Higher scores indicate better performance.

nevertheless significant, discrimination accuracy (area under the curve, 0.67).

Given that the ADNI data used here as an entirely independent training set were acquired with different scanner hardware and MR sequences, our results speak to the stability of pattern recognition methods across sites and indicate robust differences of the structural brain pattern between SMI and control subjects.

Similarity to an AD brain, as indicated by the DV, was associated with poorer episodic memory. This association was observed across all subjects and within each group, although this effect only reached a trend toward statistical significance ($P = .058$) in the SMI group, most likely because of the limited sample size. Our data extend earlier studies with similar findings in healthy individuals, in subjects with MCI, and in subjects with AD dementia using voxel-based morphometry and related methods [45,52] to individuals with SMI.

The finding of an association of cognitive performance with an AD gray matter atrophy pattern in the control group is of particular interest because it suggests that anatomic similarity to an AD brain is related significantly to memory functioning, even at stages without SMI. In agreement with this finding, a study by Rentz and colleagues [53] with cognitively normal elderly revealed a correlation between the degree of amyloid deposition in the brain as measured with positron emission tomography and poorer memory performance assessed with a highly challenging memory task. This suggests that cognitively normal elderly subjects with asymptomatic preclinical AD may be detected with sensitive neuropsychological markers.

Of substantial relevance is the prediction of future cognitive decline in SMI. In our study, the DV predicted episodic memory decline significantly in SMI participants. To our knowledge, this is the first association of an MR biomarker of AD with memory decline in an SMI sample. In our recent publication with a region of interest-based approach in the same sample, we observed an association of memory decline with gray matter volume of the right hippocampus only at a trend level [16]. This suggests that the use of whole-brain information by the DV is superior to single, preselected target regions. The DV did not predict measures of speed and executive function in our study (neither at baseline nor at follow-up). In contrast to markers of episodic memory (i.e., VLMT), those are not considered predictors for future dementia [25] and indicate the specificity of our findings.

Our study is limited by the small sample sizes and the irregular numbers and intervals of follow-up visits, which we addressed by applying growth curve modeling approaches. In addition, we did not focus on conversion to dementia. The required observational time periods would have extended up to 10 years in samples that start at the SMI stage.

In summary, our study indicates a link between an AD-like gray matter atrophy pattern and the presence of SMI as well as an association of future episodic memory decline and an AD-like brain in subjects with SMI. This suggests that structural MRI in conjunction with fully automated multivariate pattern recognition methods is sensitive to brain changes already in a stage without clinical signs of memory impairment.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (KL 2415/2-1), the Dr. Kübler-Chicken Foundation of the University of Freiburg, the Alzheimer Forschungsinitiative, and the German Competence Network on Dementia funded by the German Federal Ministry for Education and Research (grant O1GI 0102).

RESEARCH IN CONTEXT

1. Systematic review: A literature search was conducted via PubMed using the terms "subjective memory impairment MRI" and "subjective cognitive impairment MRI" for reports published before November 10, 2012.
2. Interpretation: Early diagnosing of dementia is one of the major topics in research today. Therefore, the use of pattern recognition methods has gained a lot importance during past years. Our results support subjective memory impairment as a very early manifestation of Alzheimer's disease (AD), and multivariate pattern recognition approaches as a sensitive method for the identification of subtle brain changes that correspond to the preclinical stages of AD.
3. Future directions: Our study indicates the combination of earliest symptomatic signs and highly sensitive disease markers as promising for the identification of individuals for future intervention in preclinical AD. In future research, early diagnosing should also be focused on healthy elderly people. This is supported by our finding of an association of cognitive performance and AD gray matter atrophy pattern in control subjects because it suggests that anatomic similarity to an AD brain is related significantly to memory functioning even in normal aging.

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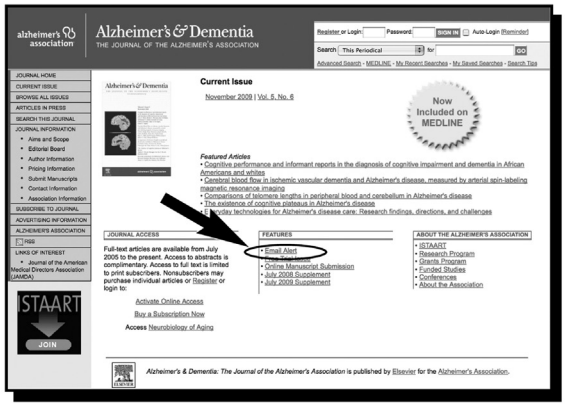

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