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Measuring Global Brain Atrophy with the Brain Volume/Cerebrospinal Fluid Index: Normative Values, Cut-Offs and Clinical Associations

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Key Words

Global brain atrophy · Atrophy index · Magnetic resonance imaging · Normative values · Cut-off · Alzheimer's disease · Mild cognitive impairment · Normal aging · Cerebrospinal fluid biomarkers · Cognition

Abstract

Background: Global brain atrophy is present in normal aging and different neurodegenerative disorders such as Alzheimer's disease (AD) and is becoming widely used to monitor disease progression. ***Summary:*** The brain volume/cerebrospinal fluid index (BV/CSF index) is validated in this study as a measurement of global brain atrophy. We tested the ability of the BV/CSF index to detect global brain atrophy, investigated the influence of confounders, provided normative values and cut-offs for mild, moderate and severe brain atrophy, and studied associations with different outcome variables. A total of 1,009 individuals were included [324 healthy controls, 408 patients with mild cognitive impairment (MCI) and 277 patients with AD]. Magnetic resonance images were segmented using FreeSurfer, and the BV/CSF index was calculated and studied both cross-sectionally and longitudinally (1-year follow-up). Both AD patients and MCI

Camila Orellana and Daniel Ferreira contributed equally to the study.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (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 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.

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patients who progressed to AD showed greater global brain atrophy compared to stable MCI patients and controls. Atrophy was associated with older age, larger intracranial volume, less education and presence of the ApoE ε4 allele. Significant correlations were found with clinical variables, CSF biomarkers and several cognitive tests. ***Key Messages:*** The BV/CSF index may be useful for staging individuals according to the degree of global brain atrophy, and for monitoring disease progression. It also shows potential for predicting clinical changes and for being used in the clinical routine.

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Introduction

Brain atrophy is observed in normal aging and different neurodegenerative disorders. Measurements of global brain atrophy are becoming widely used to monitor progression of diseases such as Alzheimer's disease (AD), as well as a marker of neurodegeneration [1].

Several methods have been proposed for evaluating global brain atrophy. Visual ratings such as the Global Cortical Atrophy Scale [2, 3] and the Brain Atrophy and Lesion index [4] are quick and easy to use, hence have strong potential to be implemented in the clinical routine. However, they might be subjected to interrater disagreement and require training or experience. Recently, multivariate methods and machine learning algorithms based on high-dimensional structural magnetic resonance imaging (MRI) data provide much richer information about brain morphology and have high diagnostic performance [5]. However, they are extremely sophisticated. An alternative is the use of automated MRI methods that are able to capture signs of brain atrophy. FSL and FreeSurfer packages are the most utilized methods in recent research for measuring brain atrophy [6–8]. Siena [9] and SienaX [10] are part of FSL and have been extensively used to measure global brain atrophy. Although FreeSurfer does not include any measurement of global brain atrophy, the brain volume/cerebrospinal fluid index (BV/CSF index) has previously been used to investigate global brain atrophy [11, 12]. The BV/CSF index is fast, and easy to calculate and interpret. Importantly, the index has the potential to be generated using computed tomography (CT) images, the most widely available imaging technique in primary health care, where most of the dementia evaluations take place [13]. Therefore, the index could also measure disease severity based on brain atrophy in CT images. However, the BV/CSF index has not been validated in a large cohort yet.

All methods mentioned above have identified a gradient of global brain atrophy of AD > mild cognitive impairment (MCI) > healthy controls [4, 14–18]. Some studies have investigated associations with CSF biomarkers and cognition [4, 14, 15, 18–30]. However, an important limitation that obstructs the use of measurements of global brain atrophy in clinical practice is the lack of normative values for interpretation. The aims of the current study were to (1) test the ability of the BV/CSF index to detect global brain atrophy in healthy controls, MCI and AD patients, both at baseline and at the 1-year follow-up; (2) investigate the influence of key confounding variables such as age, gender, education, ApoE ε4 status, intracranial volume (ICV) and the cohort used; (3) provide normative values and cut-offs for mild, moderate and severe global brain atrophy, and (4) study associations with commonly used clinical measures, core CSF biomarkers of AD and a wide range of cognitive tests.

Materials and Methods

Subjects

A total of 1,009 subjects were included in this study: 324 healthy controls, 408 MCI patients and 277 AD patients. The MCI patients were classified as MCI converters (n = 79) if they fulfilled diagnostic criteria of AD at the 1-year follow-up (MCI-C), or as MCI stable cases (n = 329) if they remained stable (MCI-S). Subjects were recruited from two different cohorts: the AddNeuroMed study (n = 330) [31] and the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (n = 679) [32]. AddNeuroMed is part of the InnoMed European Union FP6 programme and was designed to develop and validate novel surrogate markers in AD. The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations. The project was established to develop standardized imaging techniques and biomarker procedures in healthy controls, MCI and AD patients. The data were obtained from the ADNI database (adni.loni.usc.edu, PI: Michael M. Weiner). Both AddNeuroMed and ADNI were approved by institutional review boards at each site.

Participant recruitment and eligibility criteria were very similar in the two cohorts. AD diagnosis was based on NINCDS-ADRDA and DSM-IV criteria for probable AD, a Mini Mental State Examination (MMSE) score between 20 and 26, and a total Clinical Dementia Rating (CDR) [33] score of 0.5 or above. MCI diagnosis required an MMSE score between 24 and 30, memory complaints, normal activities for daily living, a total CDR score of 0.5, and a Geriatric Depression Scale (GDS) score of ≤5. For the healthy controls, the inclusion criteria were an MMSE score between 24 and 30, a total CDR score of 0, and a GDS score ≤5. All these diagnoses were made without the use of MRI scans. No significant neurological or psychiatric illness, no significant unstable systemic illness or organ failure, and no history of alcohol or substance abuse or dependence were required for all the participants.

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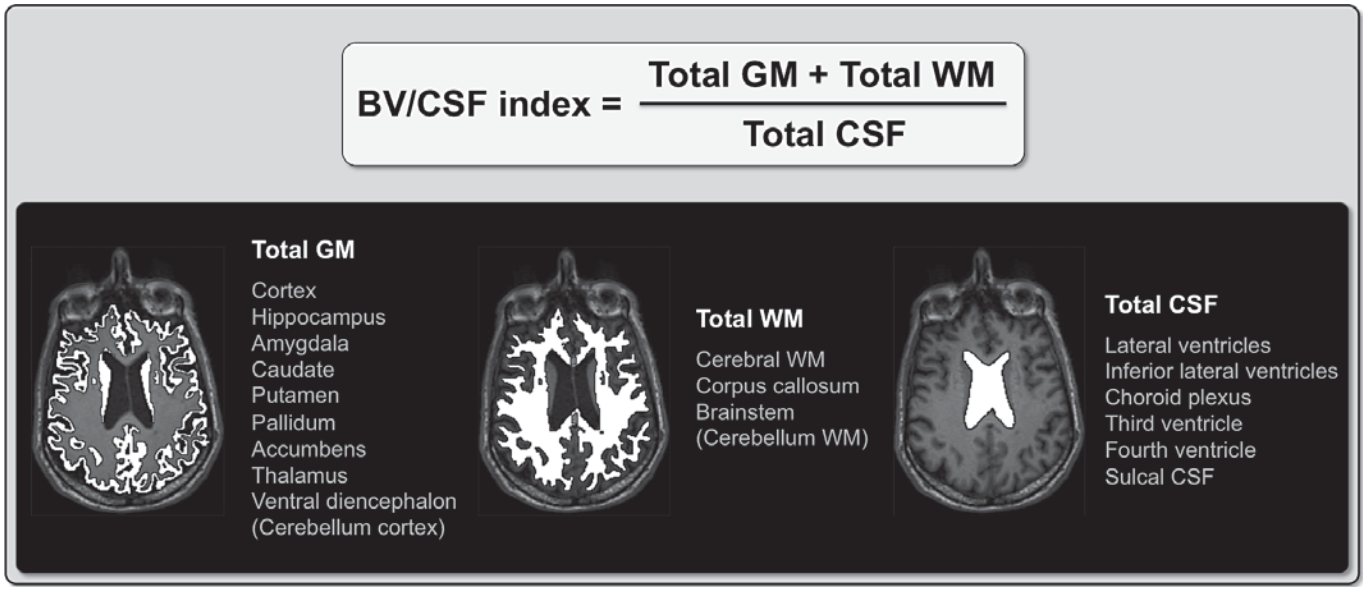

Fig. 1. BV/CSF index. Total grey matter (GM) volume, total white matter (WM) volume and total cerebrospinal fluid (CSF) volume were automatically segmented with FreeSurfer 5.3.0 (see white areas in the magnetic resonance pictures) and include the regions or structures listed below the headers. Two versions of the index can be calculated: one including the cerebellum and another one excluding this structure. Results for the version excluding the cerebellum are presented in online supplementary tables 4–7 and supplementary figure 1.

MRI and the BV/CSF Index

The MRI acquisition protocol used in AddNeuroMed was designed to be compatible with the one applied in ADNI [34]. The high-resolution sagittal 3-dimensional T1-weighted MPRAGE sequence (voxel size $1.1 \times 1.1 \times 1.2$ mm^3) was selected for this study and processed with FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). Besides the cross-sectional stream, images were processed using the longitudinal stream [35] to measure changes at the 1-year follow-up. A template image was created for each participant using information from time point 1 (baseline) and time point 2 (1-year follow-up) [36]. Image processing was then initialized with common information from the template, significantly increasing reliability and statistical power (see online suppl. table 1; for all online supplementary material, see www.karger.com/doi/10.1159/000442443 for full details and references). Data management and image processing were done through the Hive Database system [37], which is a web-based application that facilitates management, sharing and processing of large imaging data sets. Cortical and subcortical volumetric segmentations were obtained, and the BV/CSF index was calculated as detailed in figure 1. Lower values of the BV/CSF index indicate greater atrophy. An estimation of the total ICV was also obtained from FreeSurfer.

Demographic Variables and Outcome Measures

The key demographic variables age, gender and years of education were included for the analyses. Disease severity was assessed with the CDR scale (global and sum of boxes: CDR-SOB). Depressive symptomatology was evaluated with the GDS. Cognitive performance was assessed with the MMSE, Alzheimer's Disease Assessment Scale (ADAS-Cog), Auditory Verbal Learning Test (AVLT), Boston Naming Test (BNT), Clock Test, Digits Span Test, WAIS-R Digit Symbol Substitution Test, Trail-Making Test (TMT) and Category Fluency Test (animals and vegetables). Further details and references for clinical and cognitive tests are reported elsewhere for the ADNI cohort [32]. ApoE ε4 status was also included to assess genetic risk, and CSF levels of amyloid-β ($A\beta_{42}$) and total tau proteins were included to investigate amyloid deposition and neurodegeneration, respectively.

Statistical Analysis

ANOVA and mixed ANCOVA were used to compare means. The Pearson correlation was conducted to study relationships between variables. Multiple linear regression (backwards) was performed in order to investigate the influence of demographic and clinical variables on the BV/CSF index. Performance of the BV/CSF index and suggested cut-offs for discriminating between AD patients and controls was evaluated by means of (a) sensitivity and specificity values calculated from true- and false-positive/negative values, and (b) analyses for testing and assessing the area under the curve (AUC) of the receiver-operating characteristic (ROC) curve and 95% confidence intervals. A p value of 0.05 was considered significant, and the Bonferroni correction for multiple comparisons was applied in all principal and post hoc analyses. All the analyses were performed using SPSS 22.0 for Mac.

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Table 1. Demographics, clinical variables and the BV/CSF index

	CTL (n = 324)	MCI-S (n = 329)	MCI-C (n = 79)	AD (n = 277)	p
AddNeuroMed/ADNI, n	108/216	89/240	21/58	112/165	–
Age, years	75.0±5.8	75.1±6.8	74.2±6.7	75.8±6.9	0.298
Gender, % female	50	38	41	55[b]	<0.001
Education, years	14.3±4.4	13.9±4.7	13.9±4.1	12.0±4.8[a, b]	<0.001
ApoE ε4, % carriers	27	47[a]	65[a, b]	61[a, b]	<0.001
ICV, dm^3	1.52±0.16	1.55±0.17	1.55±0.15	1.52±0.18	0.017
MMSE	29.1±1.1	27.1±1.7[a]	26.6±1.8[a]	22.3±3.7[a–c]	<0.001
BV/CSF index	24.46±11.56	20.46±9.20[a]	17.78±7.66[a]	16.54±7.82[a, b]	<0.001

Values in the table represent means ± SD except for AddNeuroMed/ADNI, where numbers of participants are presented, as well as for gender and ApoE ε4 carriers, where percentage is presented. For MMSE, n = 996. CTL = Controls. Bonferroni correction for 7 comparisons: $p < 0.007$; [a] significantly different from CTL; [b] significantly different from MCI-S; [c] significantly different from MCI-C.

Results

The demographic and clinical characteristics of the four study groups are shown in table 1. Significant between-group differences were found for gender, years of education, ApoE ε4 status and MMSE.

Influence of Demographic and Clinical Variables on the BV/CSF Index

The multiple linear regression model showed that a lower BV/CSF index was associated with older age (β = –0.427), larger ICV (β = –0.351), lower education (β = 0.138) and presence of the ApoE ε4 allele (β = –0.099; $F_{4, 1,004} = 107.202$; $p < 0.001$; $R^2 = 0.30$). There were no significant associations between the BV/CSF index and both gender and cohort (AddNeuroMed vs. ADNI).

BV/CSF Index across Diagnostic Groups: Cross-Sectional and Longitudinal Analyses

The BV/CSF index can be used to study differences in brain volume at a certain time point (e.g. baseline), as well as brain atrophy over time. ADNI patients with available MRI data as well as clinical and cognitive evaluations both at baseline and 1-year follow-up were selected for these analyses (n = 624). The mixed ANCOVA showed a significant interaction between diagnosis (controls vs. MCI-S vs. MCI-C vs. AD) and time (baseline vs. 1-year follow-up; $F_{3, 614} = 5.566$; $p = 0.001$), accounting for the confounding effect of age, ICV and ApoE ε4 status (fig. 2). There was a clear gradient of atrophy with AD and MCI-C patients evidencing a comparable degree of atrophy, but significantly greater than the one found in MCI-S and controls. MCI-S patients also showed significantly more atrophy than the controls ($F_{3, 614} = 27.538$; $p < 0.001$) (online suppl. table 2). Significant brain atrophy changes were observed between baseline and 1-year follow-up ($F_{1, 614} = 109.663$; $p < 0.001$). This finding was modulated by diagnostic group: the AD and MCI-C groups showed greater atrophy over 1 year (magnitude of the effect: $\eta^2_{par} > 0.60$) as compared with MCI-S and controls ($\eta^2_{par} < 0.40$). This corresponds with a percentage of change in the BV/CSF index equal to 10% in AD and 9% in MCI-C patients, as compared with a percentage of change of 6% in MCI-S and 4% in controls.

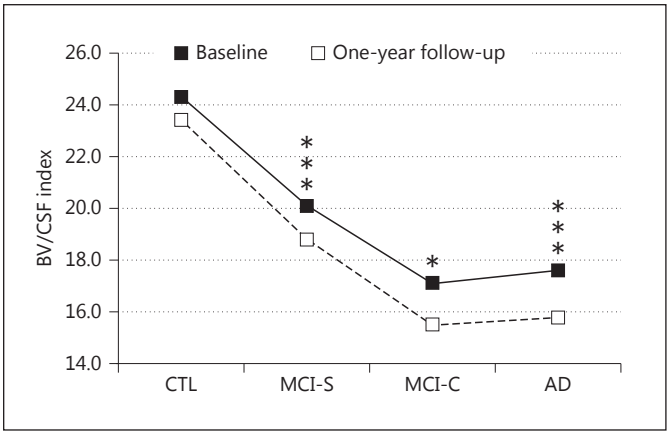

Fig. 2. Effect of diagnosis and time on the BV/CSF index. Sample size: 191 controls (CTL), 239 MCI-S, 62 MCI-C and 129 AD patients. * $p < 0.05$; *** $p < 0.001$.

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Table 2. Correlation between BV/CSF index and clinical variables, CSF biomarkers, and cognition

	BV/CSF index (BL) × clinical variables (BL)	BV/CSF index (BL) × clinical variables (change)	BV/CSF index (change) × clinical variables (change)
MMSE	0.225	0.178	0.142
CDR-SOB	–0.259	–0.185	*–0.087*
$A\beta_{42}$ (pg/ml)	*0.142*		
T-tau (pg/ml)			
AVLT Learning	0.314		0.109
AVLT Delayed	0.253		
AVLT Recognition	0.200		
BNT	0.149	*0.094*	*0.123*
Clock test (drawing)	0.188		*0.128*
Digits forward			0.096
Digits backward	0.161		*0.096*
WAIS-R digit symbol substitution	0.301	*0.092*	0.145
TMT-A	–0.151		
TMT-B	–0.245		
Category fluency (animals)	0.213		*0.086*

Only significant correlations are presented in the table. Bonferroni correction for 15 tests: $p < 0.003$ (in italics, p values between 0.05 and 0.003). The sample size is n = 624 in all the analyses except for $A\beta_{42}$ and T-tau (n = 336). T-tau = Total tau protein; BL = baseline; change = difference between 1-year follow-up and baseline.

Association with Clinical Variables, CSF Biomarkers and Cognition

ADNI patients with available MRI data as well as clinical and cognitive evaluations both at baseline and 1-year follow-up were selected for these analyses (n = 624). CSF data were available for 345 individuals. A lower BV/CSF index at baseline was correlated with worse performance in MMSE, CDR-SOB, AVLT, BNT, clock test drawing, digits backwards, TMT and category fluency (animals) at baseline. There was also a trend for an association between lower BV/CSF index at baseline and lower CSF $A\beta_{42}$ levels ($p = 0.009$, did not pass the Bonferroni correction; table 2). When CSF $A\beta_{42}$ and tau levels were stratified into normal or abnormal using previously published cut-offs for the ADNI cohort [38], participants with abnormal CSF $A\beta_{42}$ had a significantly lower BV/CSF index at baseline ($t_{166, 617} = 2.924$; $p = 0.004$).

Cognitive performance at the 1-year follow-up was then subtracted from cognitive performance at baseline in order to study longitudinal changes in cognition. A lower BV/CSF index at baseline correlated with longitudinal changes in MMSE and CDR-SOB, with a trend for BNT and digit symbol ($p = 0.018$ and 0.021, respectively).

Finally, values of the BV/CSF index at the 1-year follow-up were also subtracted from values at baseline in order to study brain atrophy over 1 year. Atrophy using the BV/CSF index was correlated with longitudinal changes in MMSE, AVLT learning, digits forward and digit symbol. There was also a trend for an association between atrophy and longitudinal changes in CDR-SOB, BNT, clock test drawing, digits backward and category fluency (animals; p values between 0.05 and Bonferroni correction 0.003). Complementary correlation analyses were performed in order to investigate associations with other frequently used clinical and cognitive measures (online suppl. table 3). Greater brain atrophy correlated with more depressive symptomatology and worse performance in ADAS-Cog, clock test copying and category fluency (vegetables).

Cut-Off for the BV/CSF Index

The ROC analysis showed that the BV/CSF index as continuous variable achieved an AUC of 72.9 for the separation between AD patients and controls. The value providing higher accuracy was identified (BV/CSF index = 17.22) and was used to classify individuals in normal and abnormal global brain atrophy (table 3, unadjusted cut-off). This new dichotomized variable showed an AUC of 66.7 (sensitivity = 64.6; specificity = 68.8). Based on the results obtained in the regression analyses presented

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Table 3. Associations between different degrees of global brain atrophy and diagnostic groups and key outcome variables

	No atrophy	Mild atrophy	Moderate atrophy	Severe atrophy	p
Unadjusted cut-off					
Group size, n	539	160	155	155	–
Diagnosis, % CTL/MCI-S/MCI–C/AD	69/57/39/35	16/13/25/17	7/19/19/20	8/12/17/28	<0.001
Age, years	73.4±6.4	76.3±6.5[a]	77.5±5.8[a]	78.2±5.6[a, b]	<0.001
Gender, % female	59	15	14	12[a]	0.001
Education, years	13.6±4.6	13.9±4.6	12.8±5.0	13.4±4.7	0.153
ApoE ε4 status, % carriers	42	53	48	50	0.039
MMSE	27.2±3.0	26.3±3.6[a]	25.5±3.4[a]	24.8±4.3[a, b]	<0.001
CDR	0.4±0.3	0.5±0.4[a]	0.6±0.4[a, b]	0.7±0.5[a, b]	<0.001
$A\beta_{42}$, pg/ml	177.9±58.1	160.2±45.6	163.4±58.8	153.3±50.1[a]	0.017
T-tau, pg/ml	97.7±54.2	102±57.6	91.1±43.7	83.7±55.7	0.308
Age-adjusted cut-off					
Group size, n	456	187	184	182	–
Diagnosis, % CTL/MCI-S/MCI–C/AD	65/47/29/25	14/22/22/20	13/16/25/25	8/16/24/30	<0.001
Age, years	75.7±6.0	74.6±7.0	74.7±6.9	75.1±6.8	0.149
Gender, % female	53	18	15[a]	15[a]	<0.001
Education, years	13.8±4.5	13.4±4.9	13.3±4.8	13.2±4.7	0.456
ApoE ε4 status, % carriers	39	50	55[a]	49	0.001
MMSE	27.3±2.9	26.5±3.4[a]	25.6±3.8[a]	24.8±3.9[a, b]	<0.001
CDR	0.3±0.3	0.5±0.4[a]	0.6±0.5[a]	0.7±0.5[a, b]	<0.001
CSF $A\beta_{42}$, pg/ml	180.3±56.3	179.6±60.4	148.4±46.0[a, b]	155.4±52.4[a]	<0.001
CSF T-tau, pg/ml	95.3±53.5	98.5±56.1	102.5±53.2	85.9±52.1	0.373

Sample size in all the analyses is n = 1,009 except for MMSE (n = 996), CDR (n = 995), and $A\beta_{42}$ and T-tau (n = 345). Values in the table represent means ± SD except for group size, where numbers of participants are presented, as well as for diagnosis, gender and ApoE ε4 carriers, where percentage is presented. CTL = Controls; T-tau = total tau protein. Bonferroni correction for 9 tests: $p < 0.0055$. [a] Significantly different from no atrophy; [b] significantly different from mild atrophy; [c] significantly different from moderate atrophy.

above, we decided to evaluate the influence of different demographic and clinical factors on this *unadjusted cut-off*. We first studied the performance of the unadjusted cut-off in different age decade ranges: 55–64 years; 65–74 years; 74–84 years, and 85–95 years (the 55- to 64-year group includes a 53-year-old and a 54-year-old participant). ROC analyses were performed for each decade, and cut-offs providing the highest AUC value were combined in order to create a single cut-off, the *age-adjusted cut-off*. This new cut-off achieved an increased AUC value of 70.1 (sensitivity = 75.1; specificity = 65.1). We also wanted to study the effect of ICV and years of education on this age-adjusted cut-off. By using median values, the sample was stratified in four groups according to high (≥14 years) and low (<14 years) education, and large (≥1.52 dm^3) and small (<1.52 dm^3) ICV. Results showed that the age-adjusted cut-off was robust and stable across education and ICV groups (AUC values around 70.0).

Normative values for interpretation of the BV/CSF index are provided in figure 3 for three different degrees of global brain atrophy: mild, moderate, and severe. Table 3 shows that more advanced degrees of brain atrophy were associated with increased disease severity, older age, male gender, presence of the ApoE ε4 allele and lower CSF $A\beta_{42}$ levels.

Discussion

Brain changes in AD have been extensively documented, with acceleration in global and regional atrophy contributing to disease progression [39]. Alzheimer patients have greater brain atrophy than MCI patients, and both have greater atrophy than cognitively normal controls [4, 15–18, 40]. The gradient of global brain atrophy was reflected by the BV/CSF index (AD > MCI-C > MCI-S > controls). Interestingly, we found a significant interaction showing faster atrophy over 1 year in AD and MCI-C patients as compared with MCI-S patients and controls. Previous studies have investigated global brain atrophy in

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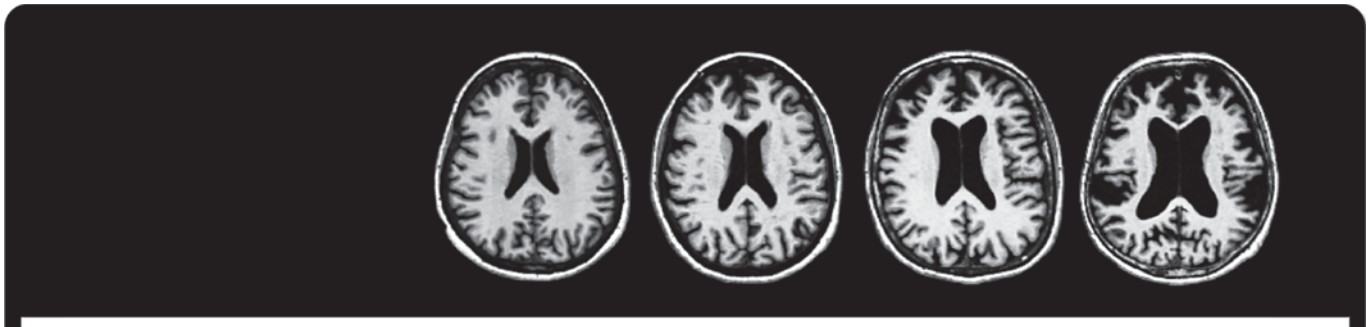

		Normal atrophy	Mild atrophy	Moderate atrophy	Severe atrophy
Unadjusted cut-off		>17.22	≤ 17.22	≤ 14.38	≤ 11.21
Age-adjusted cut-off	55-64 years	> 37.86	≤ 37.86	≤ 25.17	≤ 17.57
	65-74 years	> 24.07	≤ 24.07	≤ 18.25	≤ 14.14
	75-84 years	> 15.08	≤ 15.08	≤ 12.87	≤ 10.23
	85-94 years	> 15.56	≤ 15.56	≤ 12.57	≤ 10.67

Fig. 3. Normative values for interpretation of the BV/CSF index. Using the unadjusted cut-off and the age-adjusted cut-off, abnormal values of the BV/CSF index were stratified into three different degrees of global brain atrophy according to percentile 100 (mild atrophy), percentile 66 (moderate atrophy) and percentile 33 (severe atrophy). Raw and age-adjusted normative values were calculated. The age decade range of 55–64 years includes a 53-year-old and a 54-year-old individual. Magnetic resonance images are provided for 4 individuals (all 65 years old) as examples of different degrees of global brain atrophy (normal atrophy, BV/CSF index = 38.19; mild atrophy, BV/CSF index = 23.54; moderate atrophy, BV/CSF index = 16.28; severe atrophy, BV/CSF index = 8.61). Normal atrophy = Degree of global brain atrophy within the normal range according to the unadjusted cut-off and the age-adjusted cut-off.

AD, MCI and control groups [15–20, 22, 23], but the only study that tested for the same interaction did not find a significant effect [19].

A lower BV/CSF index at baseline correlated with increased disease severity and global cognitive impairment, in line with previous studies [4, 14, 15, 19–23]. Further, the index also correlated with domain-specific cognitive measurements at baseline. The strongest correlations were obtained for learning in episodic memory (AVLT) as well as attention/processing speed (WAIS-R Digit Symbol Substitution Test). Impairment in episodic memory is the main hallmark in the typical presentation of AD [41]. Impairment in executive functions, language and visuospatial functions has also been described in AD and is now included in the current diagnostic criteria of the disease [41]. Several studies also point at impairment in attention and processing speed [42], probably due to reduced white matter integrity [43]. The BV/CSF index correlated with functions beyond episodic memory, suggesting that the index reflects the effect of processes leading to both global brain atrophy and disease-specific regional atrophy. Although regional atrophy in the medial temporal lobe is the main finding in AD and causes memory impairment [44], atrophy in other brain regions such as the frontal lobe and posterior cortex is also frequently reported [45, 46]. Therefore, measurements that account for atrophy in brain regions other than the medial temporal lobe are important in AD [41].

A lower BV/CSF index at baseline was also associated with increased amyloid pathology in the brain (i.e. CSF $A\beta_{42}$ levels). Previous studies have frequently focused on the hippocampus and have shown both positive [40, 47] and negative results [48]. Nevertheless, Pittsburgh com-

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pound B PET studies have consistently found widespread amyloid pathology accompanied by structural brain changes [for a review, see 49]. Hence, the BV/CSF index might reflect global brain atrophy paralleling widespread amyloid pathology as described in Pittsburgh compound B PET studies.

Of note, the BV/CSF index does not only reflect an association between reduced brain volume and clinical variables, CSF biomarkers, and cognition at baseline, but was also able to predict clinical progression at the 1-year follow-up. To our knowledge, the association between clinical variables, CSF biomarkers or cognition, and measurements of global brain atrophy such as the Global Cortical Atrophy Scale and the Brain Atrophy and Lesion index has not been tested longitudinally. We have recently introduced a disease severity index derived from a multivariate method [15]. In line with the present study, this severity index showed an association with MMSE, ADAS-Cog, CDR-SOB and ApoE ε4 status, both cross-sectionally and longitudinally [15, 20]. Another severity index, the SPARE-AD index, showed that older healthy individuals with an increased AD-like pattern of atrophy at follow-up had reduced MMSE and memory performance (California Verbal Learning Test) [22]. Global brain atrophy measured by Siena has also been shown to correlate with worse cognitive performance (MMSE, episodic memory and category fluency) [14, 18, 23, 50, 51], as well as reduced $A\beta_{42}$ and increased tau levels in the CSF [51].

In the present study, greater global brain atrophy was significantly associated with older age, larger ICV, lower education and presence of the ApoE ε4 allele [45, 52–56], while gender and the cohort used did not have any significant effect, as previously reported [54, 55, 57, 58]. To the best of our knowledge, this is the only study investigating the influence of all these confounding factors on global brain atrophy in the same sample. This is crucial in order to understand the relationship between confounding factors and their importance. Other strengths of the current study are inclusion of the largest sample to date in a study of global brain atrophy in AD, provision of normative data and cut-off values for interpretation of different degrees of global brain atrophy (fig. 3) and investigation of numerous cognitive and clinical measures.

Some limitations should also be recognized. Longitudinal analyses were limited to a follow-up of 1 year. Structural MRI and CSF biomarkers normally achieve higher diagnostic performance with longer follow-up periods [59, 60]. Although we obtained an acceptable AUC value (70%) for discriminating AD patients from healthy controls, previous studies on AddNeuroMed and ADNI cohorts have reported higher diagnostic performance using a multivariate index and visual ratings of atrophy in the medial temporal lobe [15, 45]. Nonetheless, other measurements such as the Brain Atrophy and Lesion index have achieved AUC values of 70% or less [4]. Finally, the proposed cut-offs should be tested in population-based cohorts, since particularly the ADNI is a highly selected cohort and might not be completely representative of the general population [61, 62].

In conclusion, the BV/CSF index is suitable for measuring global brain atrophy. Its association with key clinical measures, amyloid pathology and cognition highlights its clinical utility. Given its simplicity, it has potential for being used in the clinical routine. Automated methods for MRI analysis are becoming more available to the clinicians [30]. The BV/CSF index has been tested using FreeSurfer in this study. However, it works more as a concept that could be implemented on any other image analysis tool providing separated volumes for brain (grey + white matter) and CSF. Some of these software packages are being used in the clinical workup at present [6, 63]. In addition, the BV/CSF index could even be implemented on CT images, the most widely available imaging technique in clinical settings [13].

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