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ORIGINAL PAPER

Association between fully automated MRI-based volumetry of different brain regions and neuropsychological test performance in patients with amnestic mild cognitive impairment and Alzheimer's disease

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Abstract Fully automated magnetic resonance imaging (MRI)-based volumetry may serve as biomarker for the diagnosis in patients with mild cognitive impairment (MCI) or dementia. We aimed at investigating the relation between fully automated MRI-based volumetric measures and neuropsychological test performance in amnestic MCI and patients with mild dementia due to Alzheimer's disease (AD) in a cross-sectional and longitudinal study. In order to assess a possible prognostic value of fully automated MRI-based volumetry for future cognitive performance, the rate of change of neuropsychological test performance over time was also tested for its correlation with fully automated MRI-based volumetry at baseline. In 50 subjects, 18 with amnestic MCI, 21 with mild AD, and 11 controls, neuropsychological testing and T1-weighted MRI were performed at baseline and at a mean follow-up interval of 2.1 ± 0.5 years ($n = 19$). Fully automated MRI volumetry of the grey matter volume (GMV) was performed using a combined stereotactic normalisation and segmentation approach as provided by SPM8 and a set of pre-defined binary lobe masks. Left and right hippocampus masks were derived from probabilistic cytoarchitectonic maps. Volumes of the inner and outer liquor space were also determined automatically from the MRI. Pearson's test was used for the correlation analyses. Left hippocampal GMV was significantly correlated with performance in memory tasks, and left temporal GMV was related to performance in language tasks. Bilateral frontal, parietal and occipital GMVs were correlated to performance in neuropsychological tests comprising multiple domains. Rate of GMV change in the left hippocampus was correlated with decline of performance in the Boston Naming Test (BNT), Mini-Mental Status Examination, and trail making test B (TMT-B). The decrease of BNT and TMT-A performance over time correlated with the loss of grey matter in multiple brain regions. We conclude that fully automated MRI-based volumetry allows detection of regional grey matter volume loss that correlates with neuropsychological performance in patients with amnestic MCI or mild AD. Because of the high level of automation, MRI-based volumetry may easily be integrated into clinical routine to complement the current diagnostic procedure.

Keywords MRI volumetry · Dementia · Alzheimer's disease · Mild cognitive impairment · Neuropsychology

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. In the last years, great efforts have been made to develop biomarkers that allow early diagnosis of AD, also in the clinical stage of amnestic mild cognitive impairment (aMCI). Apart from cerebrospinal fluid (CSF) biomarkers, MRI-based volumetry has been proposed as a promising biomarker allowing early detection of structural changes such as loss of grey matter volume (GMV). In most studies, volumetry of the structures of the medial temporal lobe (MTL, i.e., hippocampus,

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amygdala) has been assessed for its diagnostic value in AD or amnestic MCI [1–5]. The observed structural changes or changes in GMV seen in dementia may account for deficits observed in neuropsychological domains. Medial temporal lobe GMV has been related to a reduction of neuropsychological performance, especially in memory tasks in aMCI and AD patients [3, 4, 6]. Not surprisingly, most studies to date focus on hippocampal and amygdala volume. Thus, little is known on the relationship between GMV in cortical lobes and performance in neuropsychological tests of patients with MCI or AD.

In the present retrospective study, we used a newly developed fully automated method for the measurement of GMV in frontal, temporal, occipital, and parietal lobes as well as in the hippocampal area for both brain hemispheres separately. The method is based on automated segmentation of high-resolution T1-weighted MRI and volumes of interest (VOIs) predefined in a computer atlas of the brain. GMVs were tested for correlation with neuropsychological performance scores in 21 patients with mild AD, 18 patients with amnestic MCI and 11 controls. Apart from this, we studied longitudinal data, which were available for a subset of patients, and associated the rate of neuropsychological performance loss (a) to baseline GMVs and (b) to rates of regional GMV loss.

Methods

Patients

Fifty subjects were included retrospectively, 18 with amnestic MCI, 21 with mild dementia of the Alzheimer type and 11 controls. Longitudinal data with a single follow-up assessment were available from 19 of the subjects. Both, baseline and follow-up assessment included a clinical workup, neuropsychological testing, and MRI-scanning. The study was performed between May 2003 and July 2007. Out-patients of the "Memory Clinic" of the Department of Psychiatry and Psychotherapy of the University of Hamburg Medical Centre and their accompanying relatives were asked to participate in the study. Inclusion criteria were: age between 45 and 95 years, mild dementia due to AD or amnestic MCI.

Diagnoses were established by a trained psychiatrist (S.A., M.E. or H.J.) after neuropsychological testing, psychiatric and neurological assessment as well as a standard radiological examination of morphological cranial MRI scans according to DSM-IV criteria and international research criteria. Exclusion criteria were insufficient command of the German language or moderate to severe dementia. All patients who participated in the study signed an informed consent form prior to assessment, which was approved by the local ethics committee.

Neuropsychological testing

The neuropsychological test battery consisted of the mini-mental state examination (MMSE), Trail making test A (TMT-A) and B (TMT-B), Boston naming test (BNT), Wechsler memory scale immediate (WMS IR) and delayed recall (WMS DR), CERAD wordlist immediate (WL IR) and delayed recall (WL DR), CERAD constructive praxis immediate (CP IR) and delayed recall (CP DR), and clock drawing test (CDT). The testing was performed by a trained neuropsychologist who was blinded to the diagnosis as well as to the results of MRI.

At follow-up, only MMSE was performed in the complete subsample of 19 patients, whereas full neuropsychological testing was performed in 13 patients only, because of advanced dementia in the remaining 6 patients.

Image acquisition and post-processing

For image acquisition, a Siemens Symphony 1.5 T was used deploying a 3D T1-weighted magnetisation prepared rapid gradient echo (MPRAGE) sequence with a TR of 1,820 ms, a TE of 3.93 ms, a TI of 1,100 ms, and a flip angle of 12 degree. Pixel size was 1.0 mm and slice thickness was 1.0 mm.

MR images were segmented and stereotactically normalised to the MNI (Montreal Neurological Institute) space using a combined segmentation and registration approach as implemented in the SPM8 software package (release April 2009; Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) based on the work of Ashburner and Friston [7]. Prior tissue probability maps for grey matter(GM), white matter (WM), and cerebrospinal fluid (CSF) were deployed (downloaded from http://www.cyceron.fr/web/free_access_software.html) to assist segmentation and registration, which were generated from a population of 662 healthy elderly subjects aged between 63 and 75 years [8]. Maps feature an isotropic resolution of 1.0 mm matching the resolution of the image to be segmented.

For all analyses of the present study, we used the default settings of the unified segmentation engine. A mixture of Gaussians to model intensity distributions of GM, WM, CSF, and 1—GM—WM—CSF was deployed. The number of Gaussians was 2, 2, 2, and 4, respectively. Further parameters were: 25 mm for the cutoff of three-dimensional discrete cosine transform basis function for spatial warping, very light regularisation (0.0001), and 60 mm width for the Gaussian smoothness of intensity bias field.

The unified segmentation approach yields three stereotactically normalised tissue maps with a voxel volume of 1 mm^3. The Jacobian of the transformation field was applied locally to ensure that the volume is preserved after stereotactical normalisation.

Volumetry

For volumetry, all voxel intensities of the stereotactically normalised GM map within a predefined mask were summed up. Binary masks with an isotropic resolution of 2 mm for the frontal, parietal, occipital, and temporal lobe, separately for both hemispheres, were derived from a lobe atlas in MNI space published by Fonov et al. [9]. Masks for the ventricles were derived from the prior CSF probability map with a 30 % wider margin to accommodate the great variety of ventricle sizes. Hippocampus masks for the left and right side were taken from a toolbox developed by Eickhoff et al. [10]. They comprise the CA and FD substructures as defined in by Amunts et al. [11] and feature an isotropic resolution of 1 mm (Fig. 1).

MRI-based volumetry was performed fully automatically and, therefore, was fully user-independent. Computation time for a single data set was less than four minutes on an Intel Core 2 Duo CPU with 3.33 GHz and 8 GB RAM.

Statistical analysis

Between-group comparisons with respect to continuous variables were performed using an univariate ANOVA

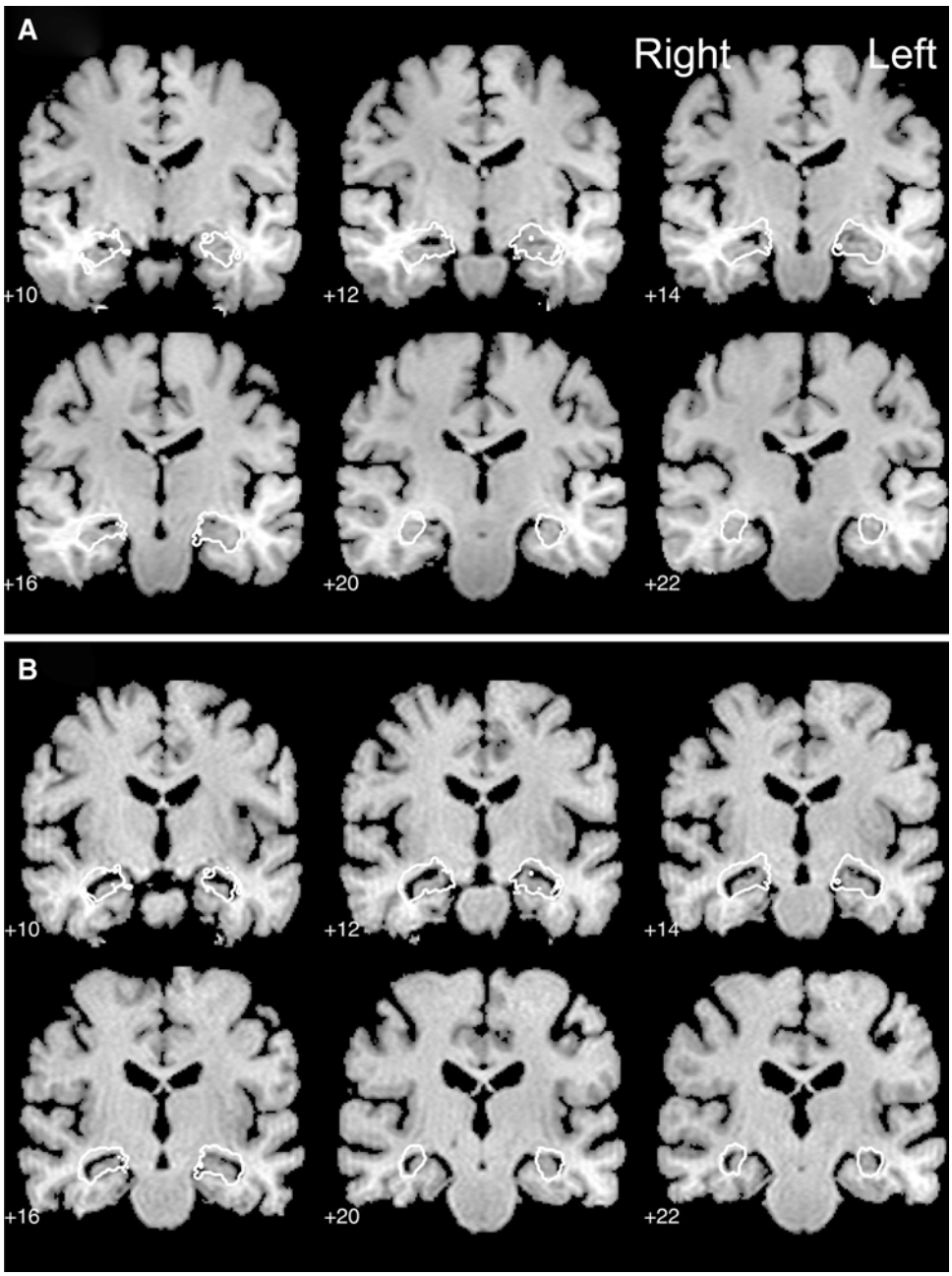

Fig. 1 Coronal view of two patients with *left* and *right* hippocampus mask (*white contours*) in MNI space (after stereotactical normalisation of brain images): **a** female amnestic MCI patient aged 67 years and **b** female AD patient of the same age

analysis. The Levene-test was performed to assess the equality of variances. The Scheffé post hoc test was used to assess differences between the three diagnostical groups if variances were equal, otherwise the Tamhane test was used. For dichotomous variables, the Chi-square test was applied. Correlations between parameters of MRI volumetry and neuropsychological test scores were calculated using Pearson correlation coefficient. Additionally, Benjamini-Hochberg-correction was performed to control for multiple testing for correlations at baseline. Data analysis was performed using the SPSS software package (version 16.0.1, SPSS Inc., Chicago, IL. USA).

Results

Study population and neuropsychological testing at baseline

Demographics and results of neuropsychological testing at baseline are summarised in Table 1. Twenty-one patients with AD, 18 patients with amnestic MCI and 11 controls without dementia, MCI or memory deficits were included. The age and gender distribution did not differ significantly, although the control group had the lowest mean age, followed by the amnestic MCI group and the AD group.

Neuropsychological test results were compared between the groups. AD patients exhibited the most severe neuropsychological deficits, especially in verbal memory tasks for complex verbal material (WMS immediate and delayed recall) and word list (CERAD word list immediate and delayed recall), a non-verbal memory task (CERAD constructive praxis delayed recall; CP DR), verbal fluency (VF), and cognitive speed (TMT-A). AD patients also had significantly lower MMSE scores than controls. With a mean MMSE score of 26.2, only patients with mild AD were assessed in our study.

Only for CERAD word list immediate and delayed recall (WL IR, WL DR) and CP DR amnestic MCI patients scored different from controls, while the MMSE for MCI patients (mean 27.2 points) was not statistically different from controls.

MRI-based volumetry at baseline

Comparing volumetric measures at baseline between controls, MCI, and AD patients, we found that AD patients had higher volumes of the total CSF compartment and of the left ventricle (Table 2). Apart from that, left and right hippocampal volumes were significantly decreased in AD patients compared to controls. The volume of the left hippocampus was lower in AD patients than MCI patients.

Table 1 Study population and results of the neuropsychological testing

	Controls ($n = 11$)		aMCI ($n = 18$)		AD ($n = 21$)		p (ANOVA)
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	67.6	5.7	70.6	6.0	72.8	6.7	NS
Gender (f/m)	7/4		12/6		12/9		NS
Neuropsychological parameters							
Mini-mental state examination (MMSE)	28.6	0.9	27.2	2.5	26.2^{+++}	2.0	0.011
Wechsler Memory Scale immediate recall (WMS IR)	19.9	7.5	16.1	7.4	$10.4^{++},*$	5.9	0.002
Wechsler Memory Scale delayed recall (WMS DR)	17.0	7.6	10.4	8.1	5.1^{+++}	5.5	0.0002
Verbal fluency (words/min) (VF)	24.4	5.9	19.6	5.2	16.5^{++}	6.6	0.005
Boston naming test (BNT)	14.2	0.9	13.4	2.0	13.1	2.9	NS
CERAD word list immediate recall (WL IR)	20.4	5.6	15.1^{++}	2.4	$11.8^{++++},*$	3.3	0.000001
CERAD word list delayed recall (WL DR)	7.6	2.2	4.5^{++}	2.2	$2.0^{++++},**$	1.5	<0.000001
CERAD constructive praxis immediate recall (CP IR)	9.8	1.5	10.2	0.9	9.2	1.7	NS
CERAD constructive praxis delayed recall (CP DR)	8.9	2.3	5.8^{+}	3.5	4.7^{++}	2.4	0.001
Clock drawing test (CDT)	1.5	1.0	1.7	1.0	2.0	1.2	NS
Trail making test A (s) (TMT-A)	40.6	16.4	48.8	14.7	$65.0^{+},*$	22.4	0.002
Trail making test B (s) (TMT-B)	119.2	70.4	144.5	58.8	166.2	64.6	NS

Between-group differences were calculated using ANOVA analysis. Post hoc Scheffé procedure was used for all variables apart from "MMSE" and "CERAD constructive praxis immediate recall" where Tamhane test were used due to unequally distributed variances as assessed by the Levene-test

AD Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *ns* not significant

* $p < 0.05$, ** $p < 0.005$ versus aMCI group, $^{+}$ $p < 0.05$, $^{++}$ $p < 0.005$, $^{+++}$ $p < 0.0005$, $^{++++}$ $p < 0.00005$ versus control group (p values derived from Scheffé-procedure or Tamhane test, respectively)

Table 2 MR volumetric measures (mean and standard deviation, SD) and results of the ANOVA analysis of MRI volumetric measures

	Controls ($n = 11$)		aMCI ($n = 18$)		AD ($n = 21$)		p (ANOVA)
	Mean	SD	Mean	SD	Mean	SD	
Total GMV (ml)	590.7	51.4	580.6	59.7	559.1	58.9	NS
Total WMV (ml)	454.6	40.8	448.2	58.9	454.0	50.3	NS
Total volume CSF compartment (ml)	435.2	124.5	436.3	85.8	516.6	100.8	0.03
Ventricular volume left (ml)	23.4	10.0	23.8	9.0	33.0	15.6	0.04
Ventricular volume right (ml)	23.9	10.3	24.5	9.7	33.0	15.0	NS
GMV frontal left (ml)	87.2	8.7	87.5	11.0	82.2	9.0	NS
GMV frontal right (ml)	91.3	9.8	91.5	12.5	86.9	9.1	NS
GMV pariatal left (ml)	40.4	4.8	39.6	4.0	37.2	4.3	NS
GMV parietal right (ml)	43.4	4.9	42.0	5.0	39.8	4.5	NS
GMV occipital left (ml)	27.3	2.9	26.8	3.4	25.1	3.1	NS
GMV occipital right (ml)	27.5	3.1	26.3	3.5	25.8	3.5	NS
GMV temporal left (ml)	67.4	5.5	65.4	8.1	60.9	8.5	NS
GMV temporal right (ml)	70.2	6.5	68.7	9.3	66.3	7.7	NS
GMV hippocampal left (ml)	3.0	0.4	2.7	0.4	$2.3^{+++,*}$	0.4	0.00004
GMV hippocampal right (ml)	3.0	0.4	2.7	0.5	2.4^{++}	0.4	0.002

Post hoc Scheffé procedure was used for all variables, *AD* Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *GMV* grey matter volume, *WMV* white matter volume, *CSF* cerebrospinal fluid, ns, not significant

* $p < 0.05$, *** $p < 0.0005$ versus MCI group, $^{+}$ $p < 0.05$, $^{++}$ $p < 0.005$, $^{+++}$ $p < 0.0001$ versus control group

No significant volumetric differences were observed between the three groups for the remaining brain regions (Table 2).

Correlation of regional volumes and neuropsychological parameters at baseline

The volumes of different brain regions were correlated with the results of the neuropsychological tests using Pearson correlation corrected for age and gender (Table 3). To correct for multiple testing and reduce the false discovery rate, Benjamini-Hochberg procedure was applied resulting in an uncorrected p value of 0.013 to be significant at the 5 % level. Only significant results following this approach are shown in Table 3.

Different patterns of correlations were observed. The MMSE score, as a measure of global cognition, significantly correlated with total grey matter volume, occipital left, parietal right, and both-sided frontal GMVs. Left hippocampal GMV correlated with memory tasks (WMS IR, WMS DR, WL IR, WL DR). GMV in the temporal lobe was related to language tasks (BNT, VF), while frontal, parietal, and occipital GMVs were significantly correlated to tests comprising multiple domains such as executive functions, cognitive speed, and visuoconstruction (TMT-A, TMT-B, and CDT). Parietal right GMV as well as both-sided occipital GMVs correlated with the score in constructive praxis. TMT-A, TMT-B, and CDT also correlated with total grey matter volume.

Correlation of baseline MRI volumetric measures and change of neuropsychological test scores over time

Follow-up data were available from a total of 19 patients (AD $n = 8$, amnestic MCI $n = 11$) with a mean follow-up time of 2.1 ± 0.5 years. Follow-up MRI scans were available from 16 patients. From the 11 patients with amnestic MCI, 6 (54.5 %) converted to AD at follow-up, while 5 still met the criteria of amnestic MCI. The differences (Δ) between the different volumetric and neuropsychological parameters were calculated by subtracting the respective value at baseline from the follow-up value. Several volumetric measures at baseline were correlated with the change of neuropsychological test scores over time as shown in Table 4. We observed the strongest correlations between CSF volume at baseline and the decrease of performance over time for the delayed recall of the CERAD wordlist, and hippocampal left volume and the change over time of TMT-B score (Table 4). Among others, a significant correlation was seen between initial hippocampal volume and decline in MMSE score per year (Table 4; Fig. 1).

Correlations of the change of brain regional volumes and change of neuropsychological test scores over time

To assess whether cognitive decline is paralleled by a change of GMV in specific brain regions, we normalised the change of grey matter volumes and the change

Table 3 Correlations of Grey matter volumes (GMV) of different brain regions with the results of the neuropsychological tests in patients with AD and amnestic MCI using Pearson correlation ($n = 39$)

		Global/ multiple domains	Memory				Language		Cognitive speed		Executive function/ visuoconstruction	
		MMSE	WMS IR	WMS DR	WL IR	WL DR	VF	BNT	TMT-A	TMT-B	CP	CDT
Total GMV	*r*	0.472	–	–	–	–	–	–	−0.455	−0.530	–	−0.436
	p	0.005	–	–	–	–	–	–	0.007	0.002	–	0.009
GMV frontal left	*r*	0.431	–	–	–	–	0.455	–	−0.473	−0.529	–	–
	p	0.010	–	–	–	–	0.007	–	0.005	0.002	–	–
GMV frontal right	*r*	0.492	–	–	–	–	0.414	–	−0.503	−0.578	–	–
	p	0.003	–	–	–	–	0.013	–	0.003	0.001	–	–
GMV parietal left	*r*	–	–	–	–	–	–	–	−0.450	−0.465	–	−0.482
	p	–	–	–	–	–	–	–	0.007	0.006	–	0.004
GMV parietal right	*r*	0.431	–	–	–	–	–	–	−0.461	−0.506	0.422	−0.594
	p	0.010	–	–	–	–	–	–	0.006	0.003	0.011	0.000
GMV occipital left	*r*	0.447	0.463	–	–	–	–	–	−0.531	−0.550	0.483	−0.481
	p	0.007	0.006	–	–	–	–	–	0.002	0.001	0.004	0.004
GMV occipital right	*r*	–	–	–	–	–	–	–	–	−0.499	0.446	–
	p	–	–	–	–	–	–	–	–	0.003	0.008	–
GMV temporal left	*r*	–	–	–	0.452	–	0.598	0.584	–	–	–	–
	p	–	–	–	0.007	–	0.0004	0.0004	–	–	–	–
GMV temporal right	*r*	–	–	–	–	–	–	–	−0.412	–	–	–
	p	–	–	–	–	–	–	–	0.013	–	–	–
GMV hippocampal left	*r*	–	0.549	0.506	0.451	0.641	–	–	–	–	–	–
	p	–	0.001	0.003	0.007	0.00009	–	–	–	–	–	–

Only statistically significant results for a false discovery rate (FDR) under 5 % (nominal $p \leq 0.013$) according to Benjamini-Hochberg correction are displayed

AD Alzheimer's disease, *aMCI* amnestic mild cognitive impairment, *MMSE* Mini-mental state examination, *WMS IR* Wechsler memory scale logic memory immediate recall, *WMS DR* Wechsler memory scale logic memory delayed recall, *WL IR* CERAD word list immediate recall, *WL DR* CERAD word list delayed recall, *CP DR* CERAD constructive praxis delayed recall, *VF* verbal fluency, *BNT* Boston naming test, *TMT-A* tral making test A, *TMT-B* trail making test B, *CP* CERAD constructive practice, *CDT* clock drawing test

Table 4 Pearson correlation of grey matter volumes (GMV), ventricular volumes and total cerebrospinal fluid volume at baseline with the change of the neuropsychological test scores normalised to time in 19 patients followed up longitudinally

		Global/multiple domains	Language	Memory				Executive function/ visuoconstruction	
		ΔMMSE/year	ΔVF/year	ΔWMS IR/ year	ΔWMS DR/ year	ΔWL IR/ year	ΔWL DR/ year	ΔTMT-B/ year	ΔCP DR/ year
CSF volume	*r*	–	0.52	–	–	0.50	0.72	–	–
	p	–	0.03	–	–	0.03	0.001	–	–
Ventricular volume left	*r*	–	0.57	–	–	–	–	−0.56	–
	p	–	0.01	–	–	–	–	0.02	–
Ventricular volume right	*r*	–	0.56	–	–	–	–	−0.48	–
	p	–	0.02	–	–	–	–	0.04	–
GMV temporal left	*r*	–	–	–	−0.65	–	–	–	–
	p	–	–	–	0.022	–	–	–	–
GMV temporal right	*r*	–	–	–	–	–	–	–	0.52
	p	–	–	–	–	–	–	–	0.03
GMV hippocampal left	*r*	−0.49	–	−0.56	–	–	–	0.63	–
	p	0.03	–	0.03	–	–	–	0.004	–

Only statistically significant ($p < 0.05$) results are displayed

MMSE Mini-mental state examination, *VF* verbal flusncy, *WMS IR* Wechsler memory scale logic memory immediate recall, *WMS DR* Wechsler memory scale logic memory delayed recall, *WL IR* CERAD word list immediate recall, *WL DR* CERAD word list delayed recall, *TMT-B* trail making test B, *CP DR* CERAD constructive praxis delayed recall

of neuropsychological parameters to the time interval between the respective examinations and studied the correlation between the two observables.

We found several correlations between the annual loss rate of regional brain volumes and the annual rate of change of neuropsychological parameters (Table 5). These correlations show that decline of cognitive function goes along with loss of brain regional volume.

The strongest correlation was found between the rate of left hippocampal GMV loss and the rate of performance decrease with regard to the Boston naming test (ΔBNT/year, Fig. 2). ΔBNT also strongly correlated with left frontal GMV loss. There were also significant correlations between the loss of MMSE points and GMV loss in the left and the right hippocampus (Table 5). TMT-A was strongly correlated with global measures, such as total GMV loss and change of CSF volume as well as GMV loss in multiple brain regions.

Discussion

The present study demonstrates correlations between regional GMVs and neuropsychological test performance both in cross-sectional and longitudinal analyses in a population of amnestic MCI and patients with mild AD.

As expected, we observed differences in neuropsychological test performance between healthy controls, MCI patients, and AD patients at time of the baseline examination. However, the relatively high baseline MMSE scores of AD and MCI patients indicate that there were mainly mildly affected patients included in our study (Table 1). In terms of baseline MRI volumetric measures, there were significant differences mainly in left and right hippocampal GMV between controls, MCI, and AD patients in line with early disease. Nonetheless, we were able to demonstrate strong correlations between neuropsychological test performance and GMV in many assessed brain regions in an expected manner. The topographic allocation of correlations is in accordance with the assumption of where different cognitive domains are supposed to be represented on the cerebral cortex (Table 3). Relevant correlations were found between left hippocampal volume and memory tasks, between left temporal lobe and language tasks as well as between executive functions (TMT-B) and cognitive speed (TMT-A) and frontal, parietal, and occipital volumes. Visuoconstruction (CP) was associated with both-sided occipital and right parietal volumes. The MMSE as a global measure of cognitive function was correlated with total GMV, frontal, parietal (right), and occipital (left) volumes, while the CDT, also a commonly applied screening test for AD, correlated significantly with total GMV and parietal and occipital (left) GMVs.

Correlations of the volume of certain brain structures with cognitive function have been described previously, but in few studies only fully automated MRI volumetry has been applied and has mostly been restricted to the assessment of hippocampus, amygdalae, temporal horn, or whole brain volumes [3, 4].

Table 5 Correlation of the change of grey matter volumes and the change of neuropsychological parameters both normalised for the observation time ($n = 15$)

		Global/ multiple domains	Memory		Cognitive Speed	Executive function/ visuoconstruction	
		ΔMMSE/year	ΔBNT/year	ΔCP DR/year	ΔTMT-A/year	ΔTMT-B/year	ΔCDT/year
Δtotal GMV/year	*r*	–	0.682	–	−0.70	–	–
	p	–	0.007	–	0.004	–	–
ΔCSF volume/year	*r*	–	−0.55	–	0.68	–	–
	p	–	0.04	–	0.005	–	–
ΔGMV frontal left/year	*r*	–	0.69	0.65	−0.66	–	0.55
	p	–	0.007	0.01	0.008	–	0.04
ΔGMV frontal right/year	*r*	–	–	0.74	–	–	0.60
	p	–	–	0.02	–	–	0.02
ΔGMV parietal left/year	*r*	–	0.58	–	−0.66	–	
	p	–	0.03	–	0.007	–	–
ΔGMV occipital left/year	*r*	–	0.68	0.55	−0.64	–	–
	p	–	0.07	0.04	0.01	–	–
ΔGMV occipital right/year	*r*	–	0.63	–	−0.72	–	–
	p	–	0.02	–	0.003	–	–
ΔGMV temporal left/year	*r*	0.59	0.65	0.60	–	–	–
	p	0.02	0.01	0.02	–	–	–
ΔGMV temporal right/year	*r*	0.59	–	–	–	–	–
	p	0.02	–	–	–	–	–
ΔGMV hippocampal left/year	*r*	0.79	0.90	–	−0.70	–	–
	p	0.001	0.00002	–	0.006	–	–
ΔGMV hippocampal right/year	*r*	0.66	–	–	–	−0.62	–
	p	0.007	–	–	–	0.01	–

Only statistically significant ($p < 0.05$) results are displayed

MMSE Mini-mental state examination, *BNT* Boston naming test, *CP DR* CERAD constructive praxis delayed recall, *TMT-A* trail making test A, *TMT-B* trail making test B, *CDT* clock drawing test

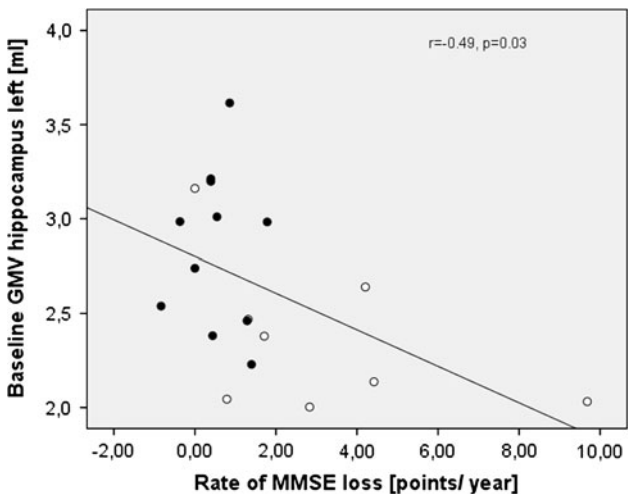

Fig. 2 Scatter plot of hippocampal volume at baseline versus prospective decline in MMSE score/year in patients with Alzheimer's disease (*open circle*) and amnestic MCI patients (*filled circle*). The *black line* indicate regression curve for the whole population

In most studies, correlations were found between hippocampal volume and memory tasks [3, 12, 13], while other studies did not confirm such a relationship [14]. Some studies report a stronger correlation between left hippocampal volume than right hippocampal volume [12, 13] with performance in memory tasks. This is in line with our finding of a strong correlation of the left hippocampal GMV with memory tasks (Table 3). The side difference may explain the relatively weak correlations [3] or no correlation [14] found in case total hippocampal volumes were tested for correlation with memory performance.

Although the correlation of hippocampal volume and memory tasks has been described in numerous studies for AD patients, there are only few papers describing the correlation of atrophy in brain regions other than hippocampus and medial temporal lobe with neuropsychological deficits in AD patients [15, 16]. However, volumetric assessment of other brain regions may be interesting, since in AD and other dementing disorders brain regions other than medial temporal lobe may

be affected and may account for the clinical presentation of the neurodegenerative disease including deficits esp. in language, visuoconstruction and executive functions.

Pantel et al. correlated regional atrophy patterns with neuropsychological domains derived by a factor analysis of different neuropsychological test scores and first described a correlation between regional atrophy and distinct neuropsychological functions in patients with moderate AD (mean MMSE 16.8 ± 6.4) [15]. Correlations were found for the GMV of the right amygdale/hippocampus complex with reproduction of visual material, for the GMV of the left temporal and parietal lobes with naming and praxia, for the whole brain GMV with psychomotor speed and selective attention, and for the GMV of the left frontal lobe with verbal fluency [15]. In an earlier study, hippocampal volume was correlated with memory tasks, and temporal volume was correlated with speech tasks, while no correlations were found between the assessed neuropsychological parameters and frontal lobe volume [16]. In these studies, only patients with moderate but not mild dementia or amnestic MCI were included.

The results of our study confirm and expand these results as we found correlations going beyond the well-known correlations between hippocampal volumes and memory tasks and left temporal volume and performance in verbal tests (BNT) in AD patients (Table 3).

In the longitudinal part of the study, we were able to establish correlations between GMV of several brain regions at baseline with the rate of decline of neuropsychological performance over time (Table 4). A striking correlation was found between left hippocampal GMV and rate of MMSE decline. Thus, left hippocampal GMV may serve as a predictor of global cognitive decline in patients with amnestic MCI and AD (Fig. 2). We also observed that the rate of volume loss in several brain regions paralleled the rate of the loss of neuropsychological performance, with the strongest correlation between the BNT, a naming task, and left hippocampal GMV (Table 5; Fig. 3). These findings suggest a close relationship between structural changes (GMV) and function (neuropsychological performance) in patients with AD and amnestic MCI, but need confirmation from larger longitudinal studies.

There are several limitations of our study that need to be addressed in future studies. Since the study design was observational and retrospective, the proportion of patients completing the follow-up visit and undergoing a second MRI-scan was relatively low, which may have biased our results. In future studies larger samples should be observed in prospective study protocols. The overall low number of participants may account for a preliminary character of our findings; further questions such as the correlation of cerebrospinal fluid biomarkers for AD and GMV or the value of automated MRI volumetry in the prediction of AD from amnestic MCI should be addressed in larger studies.

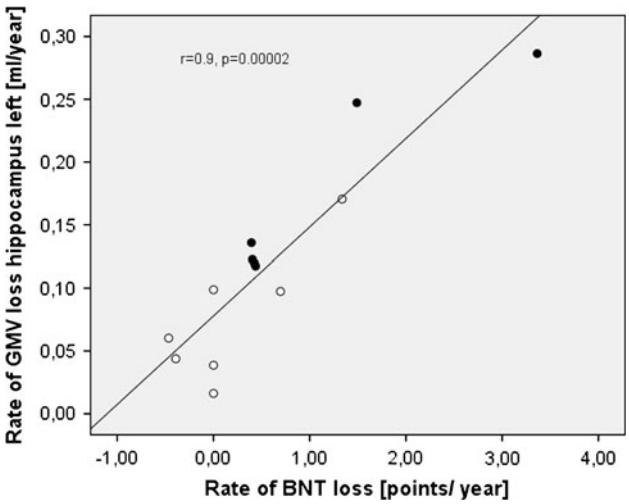

Fig. 3 Scatter plot of the longitudinal change of *left* hippocampal *grey* matter volume versus the change of Boston naming test scores per year (ΔBNT/year) in Alzheimer's disease (*open circle*) and amnestic MCI patients (*filled circle*). The *black line* indicates the regression curve

Most studies to date have performed manual or semi-automated segmentation of brain structures, which is time-consuming and prone to intra- and inter-rater variability depending on the experience and expertise of the raters [2, 6, 13, 15, 16] and hence not suitable for daily clinical routine. However, this study confirms and extends existing results deploying a fully automated MR-based volumetry.

In conclusion, fully automated MRI-based volumetry seems to be a promising approach to study regional grey matter volume and rate of grey matter loss in patients with early AD and MCI in a routine clinical setting. Prospective studies including healthy elderly controls are warranted to assess the prognostic value of this volumetric approach as a possible biomarker for very early neurodegeneration.

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Conflict of interest L.S. is an employee of jung diagnostics GmbH where automated MRI-based volumetry was performed blinded for diagnosis. The other authors (S.A., R.B., M.E., J.T.L, H.J.) do not report any conflicts of interest or financial involvement with BBS medical services.

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