3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease

Liana G. Apostolova,[1,2] Ivo D. Dinov,[2,3] Rebecca A. Dutton,[2] Kiralee M. Hayashi,[2] Arthur W. Toga,[1,2] Jeffrey L. Cummings[1,4] and Paul M. Thompson[1,2]

[1]Department of Neurology, David Geffen School of Medicine, [2]Laboratory of Neuro Imaging, David Geffen School of Medicine, [3]Department of Statistics and [4]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, UCLA, CA, USA

Correspondence to: Liana G. Apostolova, MD, UCLA Alzheimer's Disease Center, 10911 Weyburn Ave., 2nd Floor, Los Angeles, CA 90095-7226, USA
E-mail: lapostolova@mednet.ucla.edu

Alzheimer's disease is the most common neurodegenerative disorder in the elderly. Amnestic mild cognitive impairment (MCI) is a relatively newly defined clinical entity that requires memory decline while activities of daily living remain intact. Most amnestic MCI patients develop Alzheimer's disease. Using an innovative surface-based hippocampal analytic technique we analysed the structural magnetic resonance hippocampal data of 31 amnestic MCI and 34 Alzheimer's disease subjects. We tested the hypothesis that Alzheimer's disease subjects have greater atrophy of the CA1, CA2 and CA3 hippocampal subfields relative to amnestic MCI subjects. 3D hippocampal maps localized the main group differences to the CA1 region bilaterally and the CA2 and CA3 region on the right (left $P = 0.0024$, right $P = 0.0002$, both corrected for multiple comparisons). Age, race, gender, education and Mini-Mental State Examination were significant predictors of hippocampal volume. Hippocampal volume was a significant predictor of clinical diagnosis. Our study suggests that as Alzheimer's disease progresses, subregional hippocampal atrophy spreads in a pattern that follows the known trajectory of neurofibrillary tangle dissemination. Novel hippocampal analytic techniques that can track the spread of hippocampal pathology in 3D with such precision are a promising research tool.

Alzheimer's disease is the most common cause of dementia worldwide. It currently affects 4.5 million Americans and is projected to affect 13.2 million by the year 2050 in the US alone (Hebert *et al.*, 2003). Mild cognitive impairment (MCI) is an intermediate cognitive state between normal ageing and dementia. MCI patients have aberrant cognitive skills but continue to function well and are capable of independent living. Scientific interest in this borderline state is on a steep rise as the annual conversion rate from MCI to dementia is 3–6 times higher than that observed in normal ageing (Petersen *et al.*, 1999; Petersen, 2000). Most MCI patients who have reached autopsy meet pathological criteria for probable or definite Alzheimer's disease (Price and Morris, 1999; Bennett *et al.*, 2005). Nevertheless MCI remains a clinically and pathologically heterogeneous state in need of more extensive definition and classification (Wahlund *et al.*, 2003). Emerging disease-modifying treatments should be used in the MCI subset with prodromal Alzheimer's disease and not in a wider population with uncertain pathology.

The hippocampus is one of the first regions affected by Alzheimer's pathology. Mild to moderate Alzheimer's disease patients have been shown to have 27% smaller hippocampal volumes relative to the normal elderly (Callen *et al.*, 2001; Du *et al.*, 2001) whereas MCI patients show an 11% reduction (Du *et al.*, 2001). In Alzheimer's disease the pathological burden spreads through the brain in a systematic fashion. Neuropathological studies have shown

that the neurofibrillary tangle pathology originates in the transentorhinal and entorhinal areas, spreads to the subiculum and CA1, and then to the CA2 and CA3 areas of the hippocampus before invading the neocortex (Arnold *et al.*, 1991; Bobinski *et al.*, 1995; Schonheit *et al.*, 2004). New, state-of-the-art 3D hippocampal analysis techniques finally allow us to demonstrate selective subregional hippocampal atrophy *in vivo* (Csernansky *et al.*, 1998; Thompson *et al.*, 2004). In this study, in addition to volumetric data, we analyse subregional morphological changes between Alzheimer's disease and the MCI groups. The sensitivity of our surface mapping techniques has been demonstrated in several neurodegenerative (Thompson *et al.*, 2003, 2004; Ballmaier *et al.*, 2004*a*), developmental (Sowell *et al.*, 2003), psychiatric (Ballmaier *et al.*, 2004*b*; Narr *et al.*, 2004) and neurological disorders (Lin *et al.*, 2005). Using the current technique our group showed that CA1 and subicular involvement in MCI are predictive of later conversion to Alzheimer's disease (Apostolova *et al.*, 2006). Based on histopathological data on Alzheimer's disease progression, we hypothesized that the differences between MCI and Alzheimer's disease subjects would be evident as more extensive spread of the atrophy to the CA1, CA2 and CA3 hippocampal subfields.

Material and methods
Patients
Our study analyzed the data of 31 MCI and 34 probable Alzheimer's disease patients according to the restrictions and policies of the UCLA Institutional Review Board. Demographic information on the subjects is detailed in Table 1. The standard diagnostic work-up included physician interview, general and neurological examination, Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), tests of general intellectual functioning (Wechsler Adult Intelligence Scale—3rd edition (Wechsler, 1981), verbal memory [California Verbal Learning Test—2nd edition (Delis *et al.*, 1987)] and Wechsler Memory Scale—3rd edition: Logical Memory (Wechsler, 1987), visuospatial function [Rey–Osterrieth Complex Figure test—copy (Corwin and Bylsma, 1993)], visual memory [Wechsler Memory Scale—3rd edition: Visual reproduction (Wechsler, 1987) and Rey–Osterrieth Complex Figure test—delayed recall (Corwin and Bylsma, 1993)], language [Boston Naming Test (Kaplan *et al.*, 1983) and Controlled Oral Word Association Test (Benton and Hamsher, 1989)],

attention [Wechsler Adult Intelligence Scale—3rd edition: digit symbol, Trails A (Kelland *et al.*, 1992)], and executive function [Trails B (Kelland *et al.*, 1992), the Stroop test (Stroop, 1935) and the Wisconsin Card Sorting Test (Berg, 1948)]. All patients received the full diagnostic work-up except for seven Alzheimer's disease patients with MMSE scores below 18 who were unable to undertake formal neuropsychological evaluation. Diagnosis was determined by consensus decision with neurologists, psychiatrists and neuropsychologists participating and was based on the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association criteria for Alzheimer's disease (McKhann *et al.*, 1984) and the Petersen criteria for MCI (Petersen *et al.*, 2001). Additional inclusion criteria were age 55–90 years, no evidence of concurrent general medical condition of sufficient severity to impact cognition, no history of drug or alcohol abuse, and no concurrent psychiatric or other neurological illness. We excluded subjects whose baseline images were acquired >6 months from the date of neuropsychological evaluation and those with conditions precluding safe performance of MRI.

Imaging data acquisition and analysis
The imaging data were collected on a 1.5 T Signa MRI scanner (Milwaukee, WI) with the following protocol: 3D spoiled gradient echo, gapless coronal acquisition perpendicular to the long axis of the hippocampus, TR 28 ms, TE 6 ms, FOV 220 mm, 256 × 192 matrix, slice thickness 1.5 mm. MRI scans were rotated and globally scaled to match the ICBM53 average brain imaging template using a 9-parameter linear transformation (Collins *et al.*, 1994). Image intensity non-uniformities were eliminated with a regularized tricubic B-spline approach (Shattuck *et al.*, 2001). The hippocampi were traced on gapless coronal slices following a detailed well-established protocol with high intra- and inter-rater reliability (Narr *et al.*, 2001; Pantel *et al.*, 2000) by one researcher (L.G.A.) blinded to subjects' age, gender and diagnosis. When boundaries were ambiguous, a standard neuroanatomical atlas was consulted (Duvernoy, 1988). Traces included the hippocampus proper, dentate gyrus and subiculum. Intra-rater reliability was established by blinded retracing of 14 hippocampi a year later. It yielded an intra-rater reliability coefficient, for volume measurements, of 0.987. Region of interest (ROI) volumetric data were extracted and analysed statistically.

Hippocampal contours were split into top and bottom components and transformed into 3D parametric surface mesh models (Thompson *et al.*, 2004) normalizing the spatial frequency of the digitized surface points within and across brain slices. A medial core (i.e. a curve threading down the centre of the hippocampus) was computed. Hippocampal radial distance

Table 1 Demographic characteristics

Variable	Alzheimer's disease	MCI	Test statistics	Test score	*P*-value
Age (years)	76.2 (8.3) range 52–89	73.7 (7.4) range 57–84	Student's *T*	$t_o = 1.284$	0.21
Gender (M:F)	15:19	15:16	Proportion	$z_o = -0.345$	0.73
Education (years)	14.0 (2.1) range 12–19	16.23 (2.7) range 12–20	Wilcoxon rank sum	$w_o = 773.0$	**<0.001**
Race (W:AA:A)	29:1:4	26:2:3	$\chi^2_{df=2}$	$x^2_o = 1.18$	0.55
MMSE	20.9 (6.3) range 4–29	28.2 (1.6) range 23–30	Wilcoxon rank-sum	$w_o = 977.5$	**<0.001**

M: male; F: female; W: white; AA: African American; A: Asian.

measures (i.e. the distance from the medial core to the surface) were estimated and recorded at each corresponding surface point. These values were used to generate individual distance maps that were combined across subjects to produce group average distance maps allowing for comparison of surface morphology between the groups (Thompson *et al.*, 2004). The resulting maps are essentially a measure of hippocampal thickness at each surface point. To ensure that our findings were not biased by spatial scaling to the Imaging Consortium for Brain Mapping (ICBM) space (e.g. adjusting for inter-individual differences in the global brain scale) we reverted the individual distance maps back to native space and created a second set of native space group average distance maps. A schematic representation of these methods can be found in Apostolova *et al.* (2006).

Statistical analyses

Both the ICBM space and the native space hippocampal maps were analysed. The group average maps were statistically compared using linear regression (Fig. 1, middle row) and correlation analyses between radial distance and clinical diagnosis (Fig. 1, bottom row). The radial atrophy significance maps were adjusted for multiple comparisons using permutation-based statistics with a threshold of $P < 0.01$. This statistical method first defines the area of the map with suprathreshold values (e.g. $P < 0.01$) and then compares it in 100 000 iterations to the suprathreshold area of 100 000 statistical null distributions where the disease variable (e.g. Alzheimer's disease versus MCI) is randomly assigned to the study subjects, while keeping the total number of subjects with each diagnosis the same (Thompson *et al.*, 2004).
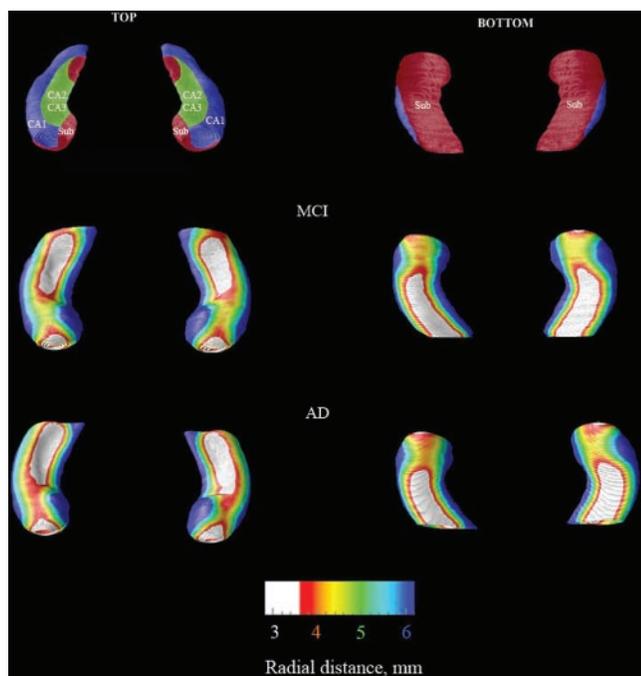

Fig. 1 Group average radial distance maps in Alzheimer's disease (bottom row) and MCI subjects (middle row). The top row is a schematic representation of the hippocampal subfields mapped onto a representative hippocampal surface [definitions based on Duvernoy (1988) and West and Gunderson (1990)].

Predictors of hippocampal volume and clinical diagnosis were analysed with backward stepwise multiple linear regression and backward stepwise multiple logistic regression, respectively. The significance threshold for removing predictor variables (with poor goodness-of-fit) was set at 0.15. Age, race, gender, education and MMSE and their interactions were included as independent variables in both models. Hippocampal volume was included as an additional predictor in the logistic regression model. Separate logistic regression models with and without MMSE, and with MMSE dichotomized using a cut-off of 24, were also developed. This cut-off is clinically used as an arbitrary guide for the possibility of dementia.

Results

The demographic characteristics of both groups are listed in Table 1. We compared demographic variables between the groups using parametric (for non-skewed distribution) and non-parametric tests (for skewed distribution). As expected, the Alzheimer's disease subjects had significantly lower MMSE scores. They were relatively less educated than the amnestic MCI subjects.

Hippocampal radial atrophy maps

The group average radial distance maps are shown in Fig. 1. The native space hippocampal radial atrophy significance and correlation maps are shown in Fig. 2. The global scaling factors from native to ICBM space did not differ between the two groups (mean scaling factor Alzheimer's disease = 1.41, SD = 0.15; MCI = 1.41, SD = 0.18; independent samples *t*-test $t = 0.037$, $P = 0.97$). The ICBM space maps and the corresponding permutation-corrected P values were very similar to the native space maps, so they are not further reported here. After correction for multiple comparisons with permutation threshold of $P < 0.01$, the hippocampal maps were highly significant (*Left*: dorsal hippocampal surface $P = 0.00036$, ventral surface $P = 0.0044$, both regions combined: $P = 0.0024$; *right*: dorsal hippocampal surface $P = 0.00027$, ventral surface, $P = 0.0002$, both regions combined: $P = 0.00024$). A schematic of subregional hippocampal anatomy in 3D was prepared in consultation with two well-established sources (Duvernoy, 1988; West and Gundersen, 1990) (Fig. 2, *top*). We observed significantly greater atrophy in hippocampal areas corresponding to the CA1 bilaterally and the CA2 and CA3 areas on the right in Alzheimer's disease relative to amnestic MCI.

Volumetric results

We first examined the data for correlations between the variables controlling for diagnosis. As expected, MMSE correlated positively with left hippocampal volume (partial $r = 0.42$, $P < 0.001$) and right hippocampal volume (partial $r = 0.29$, $P < 0.021$). Subjects from non-white racial backgrounds had smaller hippocampi ($r = -0.27$, $P = 0.031$). Females had lower education relative to males ($r = -0.45$;
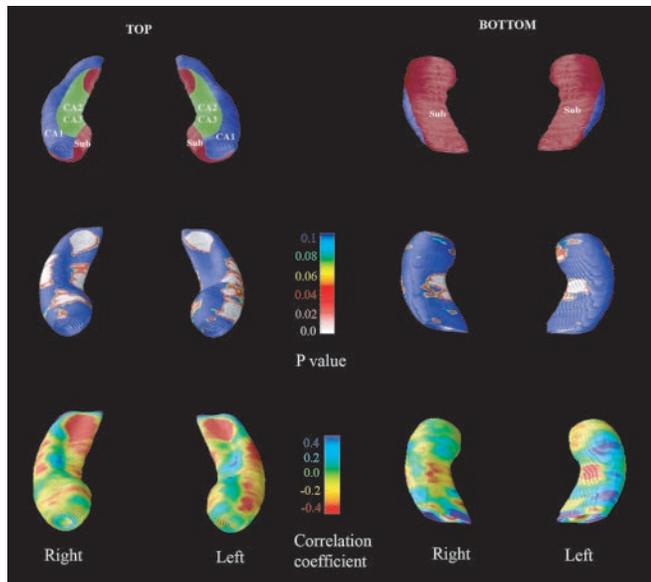
Fig. 2 Statistical 3D maps of hippocampal radial atrophy in native space. As in Fig. 1 the top row is a schematic representation of the hippocampal subfields mapped onto a representative hippocampal surface [definitions based on Duvernoy (1988) and West and Gunderson (1990)]. The significance maps (*middle row*) are the result of a 3D-surface-based logistic regression analysis and show the regions where hippocampal atrophy is significantly associated with diagnosis of Alzheimer's disease (as opposed to MCI). The correlation maps (*bottom row*) show the regional strength of the association between hippocampal atrophy and clinical diagnosis with positive correlations showing an association with diagnosis of Alzheimer's disease.

Table 2 Backward stepwise linear models regressing hippocampal volume on all other variables and their pairwise interactions

	Left hippocampus*		Right hippocampus**	
	t	P	t	P
Age	2.32	0.024	3.17	0.002
Race	Removed	>0.15	2.46	0.017
Gender	−2.29	0.026	−2.83	0.006
Education	−2.57	0.013	−2.42	0.019
MMSE	2.68	0.01	3.56	0.001
Age × MMSE	−2.12	0.039	−3.05	0.003
Education × gender	2.12	0.035	2.6	0.012
Race × MMSE	−1.92	0.06	−2.85	0.006

*Left hippocampal multiple linear regression model $F = 6.53$, $P < 0.0001$.
**Right hippocampus multiple linear regression model $F = 6.05$, $P < 0.0001$.

$P < 0.0001$). There was no hippocampal asymmetry (paired *t*-test comparing left and right hippocampal volume: Alzheimer's disease $t = -1.4$, $P = 0.17$; MCI $t = -0.08$, $P = 0.93$). Alzheimer's disease patients had significantly smaller hippocampal volumes relative to amnestic MCI (independent *t*-test: left $t = -4.5$, $P < 0.0001$, right $t = -4.4$, $P < 0.0001$).

A backward stepwise multiple linear regression model was used to examine the relation between hippocampal volume and clinical diagnosis while controlling for age, race, gender, education, MMSE and their interactions. Both the right and left hippocampal multiple linear regression models were highly significant (left hippocampus $F = 6.53$, $P < 0.0001$; right hippocampus $F = 6.05$, $P < 0.0001$). MMSE, education, age, gender and the interaction terms between age and MMSE, and between education and gender, were significant predictors in both models. Race and its interaction with MMSE were significant predictors in the right hippocampal model. The interaction between race and MMSE reached a trend-level for significance in the left hippocampal model (Table 2).

Backward stepwise multiple logistic regression models were used to examine the relation between clinical diagnosis and hippocampal volume while controlling for age, race,

gender, education and their interactions. We developed separate models with and without MMSE and one where MMSE was dichotomized with a cut-off of 24. Separate models were developed for the left, right and combined (left plus right) hippocampal volumes. The overall accuracy for each model was estimated (Table 3).

In the models without MMSE, hippocampal volume was a powerful predictor of clinical diagnosis ($P = 0.001$ for left, right and combined hippocampal volume). Education was a significant predictor in the left and right hippocampal models. The interaction between age and race was a significant predictor of clinical diagnosis in the left hippocampal model.

In the logistic models with MMSE as a continuous variable, hippocampal volume was no longer a significant predictor of clinical diagnosis. Education, gender and the interactions between age and race, race and gender and gender and MMSE were significant diagnostic predictors in the model including the left hippocampal volume. Perhaps surprisingly, education was the only significant diagnostic predictor in the models including the right hippocampal volume and the combined hippocampal volume.

In the logistic model where the predictor MMSE was dichotomized at 24, hippocampal volume was the sole significant predictor for differentiating Alzheimer's disease and amnestic MCI.

Discussion

As Alzheimer's disease progresses, the neurofibrillary pathology engulfs the hippocampal structure in a highly selective and orderly fashion. After spreading from the entorhinal cortex to the subiculum it affects the CA1 hippocampal subfield, and later the CA2, CA3 and finally the CA4 subfields (Schonheit *et al.*, 2004). A previous work by Bobinski *et al.* (1995, 1997) has looked into the differences between post-mortem hippocampal subfield volume

Table 3 Classification accuracy for backward stepwise logistic models regressing clinical diagnosis (Alzheimer's disease versus MCI) on other variables

Hippocampal variable in the logistic model	MMSE variable in the logistic model	χ^2	P	Accuracy % overall (Alzheimer's disease/MCI)	Significant predictors		
					Variables	Wald	P
Left hipp volume	Excluded	41.5	<0.0001	84.6 (91.2/77.4)	Left hipp	11.2	0.001
					Education	5.8	0.016
					Age × race	4.8	0.028
					Race	3.6	0.06*
Right hipp volume		31.1	<0.0001	78.5 (82.4/74.2)	Right hipp	11.7	**0.001**
					Education	8.5	**0.004**
Combined hipp volume		40.2	<0.0001	83.1 (85.3/80.6)	Combined hipp	11.8	0.001
					Education	3.2	0.073*
Left hipp volume	Continuous	70.7	<0.0001	92.3 (91.2/93.5)	Education	4.6	0.033
					Gender	4.2	0.04
					Age	3.3	0.069*
					Age × race	4.6	0.033
					Race × gender	4.4	0.036
					Gender × MMSE	4.1	0.042
Right hipp volume		71.4	<0.0001	92.3 (91.2/93.5)	Education	4.1	**0.042**
Combined hipp volume		71.2	<0.0001	92.3 (91.2/93.5)	Education	4.5	0.034
					Combined hipp	2.7	0.098*
Left hipp volume	Dichotomized (cut-off 24)	57.6	<0.0001	89.2 (85.3/93.5)	Left hipp	6.8	0.009
					Age × gender	3.0	0.081*
Right hipp volume		51.9	<0.0001	86.2 (85.3/87.1)	Right hipp	5.9	**0.015**
Combined hipp volume		55.7	<0.0001	86.2 (85.3/87.1)	Combined hipp	7.1	0.008
					Age × race	3.4	0.066*

Hipp = hippocampus; × = denotes interaction between two variables.
*Trend for significance.

estimates and subfield neuronal counts in groups of normal elderly and terminal Alzheimer's disease patients. They found significantly greater CA1, CA2, CA3 and subiculum atrophy in the severe Alzheimer's disease relative to the cognitively normal patients. The more severely affected Alzheimer's disease patients (e.g. those that were mute and immobile) had significantly lower neuronal counts in the CA1, CA2, CA4 and the subiculum relative to normal controls while the less severely affected Alzheimer's disease patients (e.g. those that were not yet mute and immobile) had lower neuronal counts only in the CA1 and subiculum area relative to normal controls. (Bobinski et al., 1995, 1997)

Using the present technique for 3D modelling of the hippocampus our group recently showed that amnestic MCI patients who later convert to Alzheimer's disease show greater subiculum and CA1 atrophy (e.g. atrophy along the lateral and ventral hippocampal surfaces) than those who do not (Apostolova et al., 2006). Identical morphometric hippocampal differences were reported by another group comparing normal control and very mild Alzheimer's disease patients (CDR = 0.5) (Wang et al., 2006).

In this study we have moved on to compare amnestic MCI and mild Alzheimer's disease patients. We were able to demonstrate that mild Alzheimer's disease patients have significantly greater atrophy of the lateral hippocampal area bilaterally corresponding to the CA1 hippocampal subfield, and the top portion of the right hippocampus corresponding to the CA2 and CA3 subfields relative to amnestic MCI patients. These findings are in agreement with the pathological observations (Bobinski et al., 1995, 1997; Schonheit et al., 2004).

Although it would have been interesting to include a normal control group, the volumetric and shape differences between normal elderly and MCI are beginning to be more firmly established (Csernansky et al., 2000, 2005; Wang et al., 2003). Hippocampal volumes distinguish Alzheimer's disease and MCI from normal ageing with relatively high sensitivity and specificity, but do poorly in differentiating MCI from Alzheimer's disease (Kantarci et al., 2002). In this study we added 3D maps to the ROI technique to highlight the regional hippocampal differences between Alzheimer's disease and MCI.

We found that MMSE score had a strong positive correlation with hippocampal volume and was the most significant predictor of hippocampal volume along with age, gender (smaller volume in females) and education. The observed strength of MMSE correlation with hippocampal volume (partial $r = 0.42$) is very similar to the MMSE/hippocampal volume correlations seen in other Alzheimer's disease studies ($r = 0.35$–0.47) (Jack et al., 2002, 2004). Our data show a negative association between education and hippocampal volume (i.e. patients with higher education tended to have smaller hippocampal

volumes). This finding agrees with the cognitive reserve hypothesis that posits that education along with social attainment, and social, mental and physical activity, provide a buffer against cognitive impairment perhaps through maintenance and/or formation of efficient neural networks (Stern, 2002). Thus for the same level of cognitive impairment highly educated patients are expected to have greater hippocampal atrophy.

Within the logistic models the relationships among clinical diagnosis, MMSE and hippocampal volume were complex. All models were highly significant. As we predicted hippocampal atrophy is a very powerful diagnostic predictor. However, when MMSE is entered into the model as a continuous variable the hippocampal predictive power dissipates. This phenomenon is likely to be caused by the splitting of the effect between two predictors (MMSE and hippocampal volume) that are in a tight causal relationship with one another. Indeed, after we dichotomized MMSE at 24—a frequently used arbitrary cut-off for the possibility of dementia, hippocampal volume regained its predictive power.

The strengths and limitations of our study should be recognized. As we only included amnestic MCI subjects, our findings may not be applicable for the non-amnestic MCI subtype. The between-group difference in education is another limitation. Our MCI group had on average two more years of education relative to the Alzheimer's disease group. This difference, although small, was statistically significant. Based on the cognitive reserve hypothesis such a difference should lead to reduction of the observed effect size in a study like ours as education and hippocampal volume are thought to have an inverse association (e.g. between two otherwise identical MCI or Alzheimer's disease patients the one with more education will be expected to show more severe hippocampal atrophy). The strengths of our study lie in its sample size, the spatial precision of our technique and its ability to portray the changes in 3D.

Using a surface modelling hippocampal technique our study shows that hippocampal atrophy in Alzheimer's disease is not a uniform but a subregion-specific process that closely follows the known anatomical trajectory of the neurofibrillary tangles. Our anatomical precision in visualizing Alzheimer's disease progression in 3D at the subregional level of the hippocampus shows promise for cross-sectional and longitudinal epidemiological and therapeutic studies.

Acknowledgements

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