Shifting regional atrophy rates in the progression from normal aging to Alzheimer's disease quantified by Fluid registration

J. D. Sluimer[1], W. M. van der Flier[2], G. B. Karas[1], R. A. van Schijndel[3], J. Barnes[4], R. G. Boyes[4], K. S. Cover[5], S. D. Olabarriaga[6,7], N. C. Fox[4], P. Scheltens[2], H. Vrenken[1,5], and F. Barkhof[1]

[1]Department of Radiology, VU University Medical Center, Amsterdam, Netherlands, [2]Department of Neurology, VU University Medical Center, Amsterdam, Netherlands, [3]Department of Informatics, VU University Medical Center, Amsterdam, Netherlands, [4]Dementia Research Centre, Institute of Neurology, University College London, London, United Kingdom, [5]Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, Netherlands, [6]Department of Medical Physics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [7]Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background: Alzheimer's disease (AD), the most common form of dementia, develops gradually. Patients with mild cognitive impairment (MCI) have an isolated memory deficit, but do not fulfill criteria for dementia. MCI is often seen as a transitional stage for AD. On MRI, atrophy of the medial temporal lobe has been observed in both AD and MCI. Whole brain atrophy rates, as determined from repeated MRI, distinguish patients with AD and MCI from controls[1]. Atrophy rates in specific brain regions, may yield even more specific information on the development of the disease.

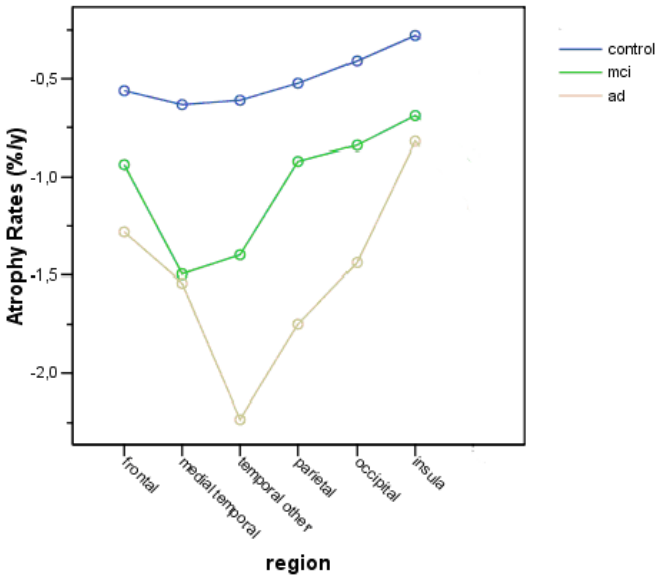
Aim: To determine the rate of brain atrophy in six regions in MCI and AD in comparison with a group of controls.

Subjects and Methods: We included 64 patients with AD, 44 patients with MCI, and 34 controls, who underwent identical MR imaging at two timepoints (average interval 1.8 years (sd 0.7; range 0.9-4.2y)). Clinical information is given in the **Table**.

MR imaging was performed using a Siemens Magnetom Impact system operating at 1.0 T. 3D-MPrage imaging was performed of 168 coronal slices with 1.5mm slice thickness, a 250mm rectangular field-of-view and 256 matrix, with TR/TE/TI = 15/7/300 ms. To pre-process images for analysis, for each subject, images were first bias-corrected using N3 software[2], then the images from the two timepoints were co-registered to a halfway position, using the skull-based scaling constraint as implemented in the SIENA software[3]. Residual bias field differences between the two timepoints were then removed as described by Lewis and Fox[4]. A brain mask was extracted from the resulting images using BET[5] and registration of a standard mask using FLIRT[6]. To analyse tissue changes over time, a nonlinear registration between the resulting images from the two timepoints was then performed using Fluid software[7] with 2000 iterations. Visual inspection of the results confirmed that in all cases the registration had worked well. Brain tissue was separated from non-brain using FAST[8]. Finally, by co-registering the AAL mask[9] to the individual data, tissue deformation between the two timepoints was then calculated from the average Jacobian determinants in six pre-defined regions: frontal, medial temporal, temporal (excluding medial temporal), parietal, occipital, and insula. The data analysis required around 1,200 computing hours, and was performed in the grid infrastructure provided by the Virtual Laboratory for e-Sciences project (www.vl-e.nl).

Table Demographics and clinical variables by diagnostic group

	Controls	MCI	AD
N of subjects	34	44	64
Age, y m(sd)	67 (9)	71 (6)	67 (8)
Sex, w/m	16 / 18	21 / 23	38 / 26
MMSE baseline m(sd)	28 (2)	26 (3)	22 (5)
MR scan interval, y m(sd)	1.9 (0.9)	1.9 (0.7)	1.7 (0.6)
Regional atrophy rates, %/y m(sd)			
Frontal	-0.6 (0.7)	-0.9 (0.7)	-1.3 (0.8)
Medial temporal	-0.6 (0.7)	-1.5 (0.7)	-1.5 (0.7)
Temporal (minus medial temporal)	-0.6 (0.5)	-1.4 (0.8)	-2.2 (1.0)
Parietal	-0.5 (0.5)	-0.9 (0.7)	-1.7 (0.9)
Occipital	-0.4 (0.4)	-0.8 (0.6)	-1.4 (1.0)
Insula	-0.3 (0.7)	-0.7 (0.6)	-0.8 (0.8)



Results: The **Table** and **Figure** show that for MCI patients, the highest atrophy rates were observed in the (medial) temporal lobe, where atrophy rates were comparable to those of AD patients. With progression of the disease the atrophy seems to spread through the brain, as AD patients show even higher atrophy rates in the remaining part of the temporal lobe, and atrophy rates in the frontal, parietal and occipital lobes were additionally increased in comparison to patients with MCI. ANOVA for repeated measures with region as within subjects factor, group as between subjects factor, and age and sex as covariates, showed a significant main effect of group ($p<0.001$), main effect of region ($p<0.001$), and an interaction between group and region ($p<0.001$).

Conclusion: These data illustrate how atrophy seems to spread through the brain while the disease progresses. In MCI, the temporal lobe shows the greatest atrophy rate. In AD patients, the medial temporal lobe shows an atrophy rate comparable to MCI, while the remaining part of the temporal lobe demonstrates an even higher rate of atrophy. Moreover, atrophy also accelerates in parietal and occipital lobes.

References: [1]JD Sluimer *et al.*, Radiology *in press*; [2]JG Sled *et al.*, IEEE Trans Med Imaging 1998;17:87-97; [3]SM Smith *et al.*, Neuroimage 2002;17:479-489; [4]EB Lewis *et al.*, Neuroimage 2004;23:75-83; [5]SM Smith *et al.*, Human Brain Mapping 2002;17:143-155; [6]M Jenkinson *et al.*, Neuroimage 2002;17:825-841; [7]PA Freeborough *et al.*, J Comput Assist Tomogr 1998;22:838-843; [8]Y Zhang *et al.*, IEEE Trans Med Imaging 2001;20:45-57; [9]N Tzourio-Mazoyer *et al.*, Neuroimage 2002;15:273-289.

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