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# Different patterns of gray matter atrophy in early- and late-onset Alzheimer's disease

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ABSTRACT

We assessed patterns of gray matter atrophy according to-age-at-onset in a large sample of 215 Alzheimer's disease (AD) patients and 129 control subjects with voxel-based morphometry using 3-Tesla 3D T1-weighted magnetic resonance imaging. Local gray matter amounts were compared between late- and early-onset AD patients and older and younger control subjects, taking into account the effect of apolipoprotein E. Additionally, combined effects of age and diagnosis on volumes of hippocampus and precuneus were assessed. Compared with age-matched control subjects, late-onset AD patients exhibited atrophy of the hippocampus, right temporal lobe, and cerebellum, whereas early-onset AD patients showed gray matter atrophy in hippocampus, temporal lobes, precuneus, cingulate gyrus, and inferior frontal cortex. Direct comparisons between late- and early-onset AD patients revealed more pronounced atrophy of precuneus in early-onset AD patients and more severe atrophy in medial temporal lobe in late-onset AD patients. Age and diagnosis independently affected the hippocampus; moreover, the interaction between age and diagnosis showed that precuneus atrophy was most prominent in early-onset AD patients. Our results suggest that patterns of atrophy might vary in the spectrum of AD.


## 1. Introduction

The most salient characteristic of Alzheimer's disease (AD) on magnetic resonance (MR) images is atrophy of the medial temporal lobe, including the hippocampus (Scheltens et al., 2002). Heterogeneity in patterns of atrophy has been suggested however, and age of disease onset might be one of the factors related to the distribution of atrophy (Galton et al., 2000; van der Flier et al., 2011; Whitwell et al., 2012a). The few structural imaging studies published to date on this topic have shown that gray matter (GM) atrophy in early-onset AD seems to have a predilection for brain regions other than the medial temporal lobe, more located in the posterior and frontoparietal regions of the brain (Canu et al., 2012; Frisoni et al., 2005, 2007; Ishii et al., 2005; Karas et al., 2007; Shiino et al., 2006, 2008). A former study by our group showed however that the hippocampus is similarly affected in younger and older AD patients when compared with age-matched control subjects (van de Pol et al., 2006). The available literature on this topic lacks clarity because of small sample sizes resulting in lack of power and consequently insufficiently being able to adjust for multiple testing, the absence of direct comparisons between early- and late-onset AD, and the use of different image analysis techniques (Canu et al., 2012; Frisoni et al., 2005, 2007; Shiino et al., 2006, 2008). Some studies worked with a regions-of-interest approach, therefore missing patterns of atrophy in the rest of the brain (Shiino et al., 2008). Few studies used whole-brain approaches such as voxel-based morphometry (VBM) (Ashburner and Friston, 2000) which permits comparisons of GM volume at every voxel throughout the whole brain with no specific a priori hypothesis (Frisoni et al., 2005; Karas et al., 2007; Shiino et al., 2006, 2008). An earlier study by our group addressed some of these problems, but still suffered from a small sample size and absence of an age-matched control group (Karas et al., 2007).

In addition to age at onset, apolipoprotein E (APOE) genotype has been suggested to exert regionally specific effects in the brain of AD patients (Filippini et al., 2009; Gutierrez-Galve et al., 2009; Hashimoto et al., 2001; Pievani et al., 2009). Especially in early-onset patients, APOE genotype seems to modulate the disease (van der Flier et al., 2011). In the present study we used VBM to

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detect patterns of GM atrophy in a large sample of early- and late-onset AD patients compared with age-matched control subjects, taking into account the potential modulating effect of APOE status.

## 2. Methods

### 2.1. Patients

We included 276 patients with probable AD and 140 patients with subjective complaints who visited the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc) between August 2008 and January 2011. All patients underwent a standardized 1-day assessment including medical history, informant-based history, physical and neurological examination, blood tests, neuropsychological assessment, electroencephalography and MR imaging (MRI) of the brain. Diagnoses of probable AD were made in a multidisciplinary consensus meeting according to the National Institute on Aging–Alzheimer's Association criteria (McKhann et al., 2011). The diagnosis of AD was confirmed by the presence of a presenilin 1 mutation in 3 patients and by autopsy in 1 patient.

As control subjects, we used patients who were labeled as having subjective complaints (normal clinical investigations, i.e., criteria for mild cognitive impairment not fulfilled and no major psychiatric disorder). For inclusion in the present study patients had to fulfil the following inclusion criteria: (1) availability of a T1-weighted 3-dimensional MRI scan (3DT1) at a 3.0 Tesla MRI (details see section 2.3.); (2) age between 50 and 85 years; (3) availability of APOE genotype status; and (4) availability of a Mini Mental State Examination (MMSE) score. Exclusion criteria were: (1) poor MR image quality and/or large image artifacts; (2) failure of the image segmentation pipeline (details see section 2.4.); and (3) gross brain pathology other than atrophy, including severe white matter (WM) hyperintensities (WMH). Images of 215 AD patients and 129 control subjects were available for analysis. Both groups were categorized into a younger ($<$65 years) and an older ($\geq$65 years) group. This resulted in a study sample of 95 early-onset AD patients, 120 late-onset AD patients, 97 younger and 32 older control subjects. There were 4 patients who met the criteria of posterior cortical atrophy (3 with early-onset AD [3%], 1 with late-onset AD [0.8%]) (Crutch et al., 2012b), 3 patients were diagnosed with logopenic variant primary progressive aphasia (1 with early-onset AD [1%], 2 with late-onset AD [1.6%]) (Gorno-Tempini et al., 2011).

The study was approved by the local medical ethics committee. All patients gave written informed consent for their clinical data to be used for research purposes.

### 2.2. APOE and CSF

DNA was isolated from 10-mL blood samples in ethylenediaminetetraacetic acid. APOE genotype was determined at the Neurological Laboratory of the Department of Clinical Chemistry of the VUmc using the LightCycler APOE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). APOE data were available for all participants and were analyzed according to the presence or absence of an APOE $\varepsilon$4 allele. APOE genotype was dichotomized in $\varepsilon$4 carriers versus noncarriers. Cerebrospinal fluid (CSF) was obtained using lumbar puncture. Amyloid-$\beta_{1-42}$, total tau, and tau phosphorylated at threonine-181 (Ptau-181) were measured using sandwich enzyme-linked immunosorbent assay (Innogenetics, Gent, Belgium) (Mulder et al., 2010). CSF analyses were performed at the VUmc Department of Clinical Chemistry. Cutoff levels in our lab are as follows: amyloid-$\beta_{1-42} < 550$, total tau $> 375$, and Ptau-181 $> 52$ (Mulder et al., 2010). CSF was available for 268 subjects (early-onset AD patients: $n = 81$; late-onset AD patients: $n = 92$; young control subjects: $n = 72$; old control subjects: $n = 23$).

### 2.3. MR image acquisition and review

Imaging was carried out on a 3.0 Tesla scanner (SignaHDxt, GE Healthcare, London, UK) using an 8-channel head coil with foam padding to restrict head motion. The scan protocol includes a whole-brain 3DT1 fast spoiled gradient echo sequence (repetition time 708 ms; echo time 7 ms; flip angle, 12°; 180 sagittal slices; field of view, 250 mm; slice thickness, 1 mm; voxel size, 0.98 $\times$ 0.98 $\times$ 1 mm) which was used for VBM. In addition, our standard MRI protocol includes 3D fluid attenuated inversion recovery, dual echo, and susceptibility weighted imaging. All scans were reviewed for brain pathology other than atrophy by an experienced radiologist. WMH were rated with the Fazekas scale (Fazekas et al., 1987), a 4-point rating scale, which provides an overall impression of the presence of WMH. Subjects with a Fazekas scale score of 3 were excluded. Atrophy of the medial temporal lobe (MTA) was rated using a a 5-point visual rating scale (0 = absent to 4 = severe) based on the height of the hippocampal formation and the width of the choroid fissure and the temporal horn (Scheltens et al., 1992). Posterior atrophy (PA) was rated using a 4-point visual rating scale (0 = absent to 3 = end stage atrophy) based on the posterior cingulate and parieto-occipital sulcus and sulci of the parietal lobes and precuneus (Koedam et al., 2011).

### 2.4. Voxel-based morphometry

Digital Imaging and Communications in Medicine (DICOM) images of the fast spoiled gradient echo sequence were corrected for gradient nonlinearity distortions and converted to Nifti format. The linear transformation matrix to Montreal Neurological Institute space was calculated using FSL-FLIRT (Jenkinson and Smith, 2001) and used to place the image coordinate origin (0, 0, 0) on the anterior commissure using the Nifti s-form.

The structural 3DT1 images were then analyzed using a modified VBM pipeline in Statistical Parametric Mapping (SPM8; Functional Imaging Laboratory, University College London, London, UK) implemented in MATLAB 7.12 (MathWorks, Natick, MA, USA). In the first step, VBM automatically identified GM, WM, and CSF in all scans. Based on these segmentations the volumes (L) of GM, WM, and CSF voxels were determined separately for each scan and summed to calculate total intracranial volume (TIV). After this segmentation process the images were rigidly aligned. Next, a "DARTEL" template of the GM of all scans was created by nonlinearly aligning the GM images to a common space (Ashburner, 2007). The native GM and WM segmentations were spatially normalized to the "DARTEL" template by applying the individual flow fields of all scans, using modulation to compensate for volume changes because of compression and/or expansion. Images were smoothed using a 4 mm full width at half maximum (FWHM) isotropic Gaussian kernel. Images were visually inspected at every processing step.

Voxelwise statistical comparisons between groups were made to localize GM differences using a full factorial design which automatically models interactions between the factors. We used diagnosis (AD patients vs. control subjects) and age ($<$65 vs. $\geq$65 years) as factors with independent levels with unequal variance, using absolute threshold masking with a threshold of 0.2 and implicit masking. Sex and TIV were entered as covariates. To avoid the arbitrary dichotomization of age, we additionally used an analysis of covariance model with diagnosis (AD patients vs. control subjects) as a factor with independent levels with unequal variance, using absolute threshold masking with a threshold of 0.2 and implicit