SHORT REPORT

Structural correlates of early and late onset Alzheimer's disease: voxel based morphometric study

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J Neurol Neurosurg Psychiatry 2005;**76**:112–114. doi: 10.1136/jnnp.2003.029876

Objective: To examine the brain structural correlates of age at onset in patients with Alzheimer's disease.
Methods: We studied nine patients with early onset (age ⩽65 years), nine with late onset (age >65) Alzheimer's disease (EOAD and LOAD, respectively) of mild-moderate severity, and 26 controls who were stratified into younger (YC, age ⩽65, n=9) and older (OC, age >65, n=17) subjects. The patients were closely matched for clinical severity: 3/2/3/1 patients had clinical dementia rating of 0.5/1/2/3, respectively, in both the groups. High resolution magnetic resonance images of the brain of the EOAD and YC groups and the LOAD and OC groups were compared on a voxel by voxel basis with statistical parametric mapping to detect areas specifically atrophic.
Results: The patients with EOAD showed greater neocortical atrophy at the temporoparietal junction while the patients with LOAD showed greater hippocampal atrophy. The results could not be accounted for by the apolipoprotein E genotype.
Conclusions: Since genetic factors are believed to play a relevant pathogenetic role in EOAD and environmental factors in LOAD, genetic and environmental factors may differentially predispose the neocortical and limbic areas to the development of Alzheimer's neuropathology.

Whether or not sporadic early and late onset Alzheimer's disease (EOAD and LOAD, respectively) are variants of the same disease or two distinct entities is still unknown. Research on the topic has focused on clinical, neuropsychological, and functional and structural imaging features.

A higher prevalence of language impairment or other neocortical functions[1–3] and faster progression has been reported in EOAD,[3 4] but others have failed to confirm these findings.[5] Functional imaging with single photon emission computed tomography (SPECT) and positron emission tomography (PET) has more consistently reported more severe perfusional and metabolic deficits in the temporoparietal areas in EOAD,[6–8] although only one recent study has found differences in the medial temporal regions.[8] The few structural imaging studies published to date have shown greater grey matter atrophy in EOAD. An early computed tomography (CT) study reported atrophy in patients with EOAD but did not compare this with its topographical distribution in LOAD.[9] Similar results were later replicated in a magnetic resonance imaging (MRI) study.[10] In a serial CT study, Kono and colleagues[4] found that progression of cerebral atrophy was greater in patients with EOAD but again they did not study the localisation of the atrophy. Similar results were found in an MRI study by Woo *et al*.[11]

In the present study we examined the brain structural correlates of age at onset in patients with EOAD and LOAD to identify specific patterns of grey matter atrophy. We used MR based, voxel based morphometry (VBM), a computerised and largely automated algorithm that allows assessment of structural changes throughout the whole brain with no specific a priori hypothesis.[12]

METHODS

Participants and assessment

The patients for this study were selected from a group of 29 patients with NINCDS-ADRDA[13] probable AD described in previous reports.[14] Age at onset was estimated from the caregiver's report of memory disturbances exceeding the episodic forgetfulness that might be regarded as usual for the patient or of other disturbances (language, praxis, orientation, visuospatial skills) that proved to be clearly related to the disease.[14] None of the EOAD patients had a family history suggestive of autosomal dominant disease, although a few had one or two affected relations. Neuropsychological testing was carried out as previously described.[15 16]

The 26 control subjects were relatives of the patients (mostly spouses) without cognitive deficits. All patients and controls were right handed. Apolipoprotein E (ApoE) genotyping was carried out as previously described.[17] Written informed consent was obtained from both the patients and their primary caregivers or the control subjects. No compensation was provided. The study was approved by the local ethics committee.

Of the original 29 patients with AD, nine were 65 years or younger at disease onset (EOAD). Of these, 3, 2, 3, and 1 had clinical dementia rating (CDR)[18] of 0.5, 1, 2, and 3, respectively. From the other 20 (LOAD) patients, nine were selected to match the EOAD group on the CDR scale on a 1:1 basis. When more than one matching patient with LOAD was available, the one with the closest matching Mini Mental State Examination (MMSE) was chosen. Controls were stratified into younger (YC, age ⩽65, n = 9) and older (OC, age >65, n = 17) and compared with the patients with EOAD and LOAD, respectively, in the VBM analysis.

Magnetic resonance imaging

Both the patients and controls underwent high resolution sagittal T1-weighted volumetric MRI as previously described.[19] Intracranial volume was measured by manual tracing on 3.9 mm thick coronal slices from anterior to posterior. The average intraclass correlation coefficient was 0.983 (95% C.I. 0.932 to 0.996, p<0.0005).

Abbreviations: ApoE, apolipoprotein E; CDR, clinical dementia rating (scale); CT, computed tomography; EO/LOAD, early onset/late onset Alzheimer's disease; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography; VBM, voxel based morphometry

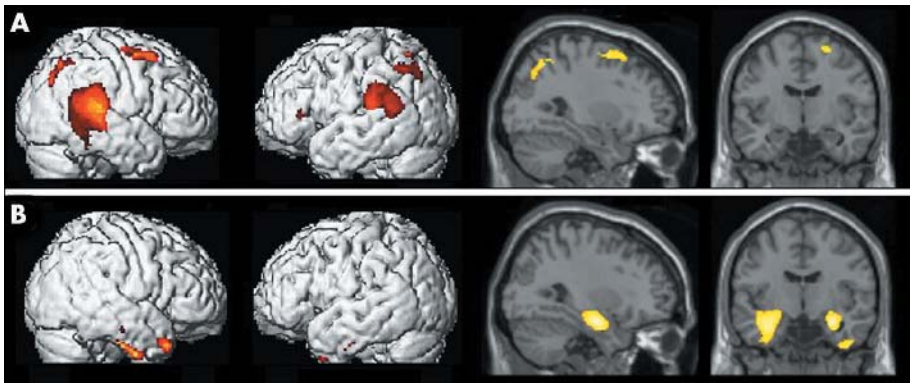

Figure 1 Regions of atrophy in (A) patients with early onset Alzheimer's disease compared with younger controls and in (B) patients with late onset Alzheimer's disease compared with the older controls, with p<0.05 corrected for multiple comparisons. Intracranial volume and sex were included as confounding covariates. Atrophy in patients with early onset involved the temporoparietal junction and the right middle and left inferior frontal gyri (A); those with late onset showed more atrophy in the hippocampus bilaterally and anterior part of the temporal and fusiform gyri (B).

Voxel based morphometry preprocessing

This has been described in detailed in previous reports[19] and a detailed flow chart is available at http:\\centroalzheimer.supereva.it\additional-data.doc.[20] Briefly, MR images were processed with SPM99 following an optimised protocol including (*a*) generation of a customised template, (*b*) generation of customised prior probability maps, and (*c*) the main VBM steps: normalisation of the original MR images, segmentation of normalised images, cleaning of grey matter images, modulation of grey matter images, and smoothing of modulated images.

Statistical analysis

A ''single subject: conditions and covariates'' model was used. Intracranial volume and sex were included as nuisance covariates. Regions specifically atrophic in EOAD and LOAD were detected by contrasting EOAD with YC and LOAD with OC, thresholding the resulting T maps at p<0.05 corrected for multiple comparisons.

RESULTS

The patients with EOAD and the YC did not differ with regard to age (mean (SD), range: 62 (7), 53–70 *v* 61 (4), 54–64; p = 0.34), sex (78% *v* 89% women; p = 0.53), education (7 (SD 2) *v* 8 (4); p = 0.49), and ApoE ϵ4 allele (22% *v* 6%; p = 0.35). They differed with regard to MMSE (18 (5) *v* 30 (1); p<0.005). The patients with LOAD when compared with the OC group, showed a trend towards older age (78 (4) 74–86 *v* 74 (6) 66–86; p = 0.085), had higher ϵ4 allele frequency (39% *v* 13%; p = 0.071), and had significantly different MMSE (20 (5) *v* 29 (2); p<0.005) and intracranial volume (ICV) (1056 (76) *v* 1160 (106) ml; p = 0.03). Patients with EOAD when compared with the patients with LOAD had lower MMSE (18 (5) *v* 20 (5); p<0.005) and shorter disease duration (2.8 (2.1) *v* 4.1 (2.8)), but this difference did not reach statistical significance (p = 0.26). The mean age at onset was 59 (6) and 73 (5) (p<0.005), respectively.

Patients with EOAD performed less well than the patients with LOAD on non-verbal tasks of constructional apraxia (Rey–Osterrieth figure (copy) 4.8 (11.1) *v* 20.7 (13.5); p = 0.03, Mann–Whitney U test) and reasoning (Raven's coloured progressive matrices 12.8 (6.7) *v* 22.1 (4.1); p = 0.04), while the two groups were not significantly different on the verbal and non-verbal memory tasks as well as verbal fluency tasks.

Figure 1A and table 1 show that patients with EOAD had greater atrophy than YC in the temporoparietal cortex. The most significant voxel—that is, the voxel with the highest z score, was in the right temporoparietal junction, and the widest cluster was in the left parietal regions. A relatively small and less significant cluster was located in the head of the hippocampus. In contrast, in the patients with LOAD the largest and most significant clusters of atrophy were located in the hippocampus bilaterally, and smaller and less significant clusters were located in the inferior temporal neocortex (fig 1B and table 1).

To take into account the effect of ApoE polymorphism on brain morphology, the analysis was re-run including the presence of at least one ϵ4 allele as a nuisance covariate, but the results did not change appreciably.

DISCUSSION

We have shown that patients with early onset Alzheimer's disease have greater temporoparietal atrophy and patients with late onset Alzheimer's disease greater medial temporal

Table 1 Atrophic regions in patients with early onset Alzheimer's disease compared with the younger controls and in patients with late onset Alzheimer's disease compared with the older controls (p<0.05 corrected for multiple comparisons)

Cluster size k	Region	Stereotactic coordinates (mm) x	y	z	z score
EOAD patients *v* younger controls					
1180	R superior temporal gyrus	60	−30	16	5.91
	R supramarginal gyrus	60	−48	20	5.38
	R middle temporal gyrus	62	−44	−6	4.86
1740	L precuneus	−30	−68	42	5.58
	L superior parietal lobule	−22	−64	56	5.23
	L superior parietal lobule	−32	−56	50	5.23
307	R middle frontal gyrus	28	2	60	5.13
	R middle frontal gyrus	28	16	60	5.13
502	L postcentral gyrus	−58	−30	20	5.10
	L superior temporal gyrus	−60	−50	14	4.68
94	L hippocampus (head)	−34	−20	−20	4.67
20	L inferior frontal gyrus	−44	32	6	4.60
4	R fusiform gyrus	52	−42	−22	4.33
LOAD patients *v* older controls					
1168	L hippocampus (head)	−32	−16	−22	5.87
522	R hippocampus (head)	30	−8	−20	5.67
	R hippocampus (body)	32	−30	−6	4.40
177	R inferior temporal gyrus	46	−4	−44	5.19
	R inferior temporal gyrus	46	−14	−38	4.85
	R inferior temporal gyrus	52	−20	−34	4.77
110	R superior temporal gyrus	40	22	−34	4.95
15	L superior temporal gyrus	−24	12	−46	4.74
6	R inferior temporal gyrus	66	−18	−20	4.39
5	L inferior temporal gyrus	−52	−14	−32	4.38

L, left; R, right.

atrophy than controls. These data suggest that age at onset is associated with the region where the disease strikes in the brain. Since genetic factors are believed to play a relevant role in EOAD even when known mutations cannot be found, while LOAD is believed to be mainly due to environmental factors, these results lead to the hypothesis that genetic and environmental factors may predispose topographically different regions of the brain to AD pathology.

The interpretation of the structural patterns in EOAD and LOAD should be addressed separately. In LOAD, the higher frequency of ϵ4 might explain the finding of greater medial temporal lobe atrophy as patients carrying the ϵ4 allele have smaller hippocampi[21] and tend to have disproportionate impairment of memory.[22] However, accounting for the effect of ApoE genotype in our analysis did not alter the results, indicating that the effect of age at onset on the loss of hippocampal volume is not mediated by the ApoE genotype. Alternatively, the age associated changes known to take place in the medial temporal lobe[23] may result in lower functional—and structural—reserve in these areas thus predisposing older patients to development of symptoms related to medial temporal lobe damage, as suggested by some neuropathological studies.[23]

More intriguing is the interpretation of the selective neocortical involvement in EOAD. Genes play a relevant role in EOAD,[24] and yet unknown genetic factors might confer neocortical regions greater susceptibility to AD. This hypothesis is consistent with the twin studies of Thompson and colleagues, who showed that frontal, linguistic, and parieto-occipital areas (including the temporoparietal cortex) are under strict genetic control, with 95–100% of the variance being attributable to genetic factors.[25] On the contrary, the hippocampus is genetically controlled to a lesser degree, with genes explaining only about 40% of the variance of hippocampal volumes.[26] These observations suggest that genetic factors may drive the susceptibility to developing AD lesions in the neocortex in young age, while environmental factors might exert a similar effect on medial temporal lobe structures at older age.

Some limitations of this study should be borne in mind. First, we do not know whether the participants of this study were carriers of certain mutations. Although none of the patients with EOAD had a family history suggestive of autosomal dominant AD, we cannot exclude that some had mutations of APP, PS1, or PS2. Secondly, the history of specific clinical features of dementia (such as early language or visuospatial disturbances) was not collected in a structured way, thus preventing correlations with patterns of structural impairment. Thirdly, it can be problematic to interpret the results of VBM in areas of high anatomical variation such as the medial temporal lobe due to imperfect registration. Lastly, our EOAD group was small, and replication of our findings in studies with larger groups is necessary.

ACKNOWLEDGEMENTS

Cristina Geroldi, MD, PhD, Roberta Rossi, PsyD, and Lorena Bresciani, PsyD, gave useful suggestions.

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The study was supported by the Research Council for Health of the Academy of Finland, EVO grants 5772720 from the Kuopio University Hospital, and Maire Taponen Foundation.

Competing interests: none declared

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Received 8 October 2003
In revised form 22 April 2004
Accepted 23 April 2004

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