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Four subgroups of Alzheimer's disease based on patterns of atrophy using VBM and a unique pattern for early onset disease

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To clarify the involvement of the posterior cingulate cortex (PCC) in Alzheimer's disease (AD), we analyzed brain volume loss by voxel-based morphometry. Forty patients with non-familial AD and 20 patients with mild cognitive impairment (MCI) were recruited and compared to 88 elderly volunteers and 40 young volunteers. Local atrophy with aging was observed bilaterally in the perisylvian opercula, anterior cingulate cortex, caudate head, dorsomedial thalamus and parahippocampal cortex. In addition to those, atrophy in AD patients was observed in the amygdala, hippocampus, subcallosal region, posterior-associated cortices and PCC. We classified AD into four subgroups according to the atrophy pattern; atrophy in the amygdala/hippocampal formations (Hipp), in the Hipp and posterior cortices, in the Hipp and PCC and in the PCC and posterior cortices (PCC/-TOPa). As a result, the probability of PCC/-TOPa was 90% for ages <65 years, whereas that of the Hipp was 100% for disease duration >36 months. PCC atrophy was found in 16 of 40 AD patients and eight of 20 MCI patients. There seemed to be two subgroups with atrophy of the PCC, the one with disease progression and the other without. The latter had characteristic features of early onset and no significant atrophy in the amygdala/anterior hippocampus. There are at least four atrophy patterns that raise doubts about a single disease entity or progression in AD. This may reflect a different hierarchical pattern of progression in patients who have atrophy in PCC and posterior cortices when compared to the Braak staging scheme.

Keywords: Voxel-based morphometry; Alzheimer's disease; Mild cognitive impairment

Introduction

Neurofibrillary tangles (NFTs) are a characteristic pathological finding of Alzheimer's disease (AD) and are associated with neuronal loss and brain volume reductions. Their regional distribution exhibits a well-defined pattern, permitting the differentiation of Braak's staging model, which is composed of 6 neuropathological stages ranging from a few NFTs in the medial temporal lobe all the way to marked NFT changes throughout the cortex, implying a hierarchical anatomical sequence (Braak and Braak, 1991). Although this model represents the broad concept of the evolution of NFT distribution, frequent order violations are also found either in qualitative or quantitative terms (Gertz et al., 1998). Bobinski et al. (1996) showed that strong correlations between MRI volumes and calculated total numbers of neurons in the hippocampus and hippocampus/subiculum region. Voxel-based morphometry (VBM), although not applicable for quantitative volume analyses such as boundary drawing methods, is a bias-free and not very time-consuming method and is useful for ascertaining atrophic changes throughout the brain. Zakzanis et al. (2003) showed that, as the disease progressed, atrophy propagated from the medial temporal lobe to the lateral temporal, parietal and frontal lobes. As shown in their report, most VBM studies supported the pathological AD staging proposed by Braak et al. (Karas et al., 2003). However, it is also true that not all cases can be explained by the single hierarchy model implied by the Braak scheme.

Involvement of the posterior cingulate cortex and precuneal cortex (PCC/PrCC) in early or preclinical stage of AD has attracted

Abbreviations: NFTs, neurofibrillary tangles; AD, Alzheimer's disease; MRI, magnetic resonance imaging; VBM, voxel-based morphometry; PCC, posterior cingulate cortex; PrCC, precuneal cortex; MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; ADRDA, Alzheimer's Disease and Related Disorders Association; CDR, Clinical Dementia Rating; WMS-R, Wechsler Memory Scale—Revised; SPM, statistical parametric mapping; BA, Brodmann area; Hipp, a group with atrophy in the amygdala/hippocampal formation; Hipp-TOPa, a group with atrophy in the amygdala/hippocampal formation and posterior cortices; Hipp-PCC, a group with atrophy in the amygdala/hippocampal formation and posterior cingulate cortex; PCC/-TOPa, a group with atrophy in posterior cingulate cortex and in the posterior cortices.

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attention recently by functional or metabolic studies. Minoshima et al. (1997) first reported that glucose hypometabolism in this region appeared very early or before the onset of AD. This phenomenon has been confirmed in many other studies. Although the hypometabolism in PCC/PrCC has been postulated to be a remote effect due to reduction in projecting fibers from the hippocampus (Matsuda et al., 2002; Meguro et al., 2001; Chetelat et al., 2003), this hypothesis seems to require more considerations. Interestingly, Scahill et al. (2002) showed atrophy of the PCC/PrCC in patients with presymptomatic stage of AD. Although their study was limited in the patients with familial type, it suggested the possibility of occurrence of neuronal degeneration in this region earlier than previously thought. In studies investigating atrophy of the PCC/PrCC in sporadic AD, several researchers did not find any atrophy in this region (Ohnishi et al., 2001; Rombouts et al., 2000; Busatto et al., 2003; Killiany et al., 2000), but some researchers found such atrophy (Frisoni et al., 2002; Baron et al., 2001; Grundman et al., 2004). Frisoni et al. (2002) found a correlation between Mini-Mental State Examination (MMSE) score and atrophy in the right inferior temporal and left PCC/PrCC, suggesting that the atrophy of the PCC/PrCC occurred as a result of disease progression. Thus, the inter-institutional discrepancies may be due to differences of the disease progression of the subjects. However, the results of those previous reports were obtained by inter-group comparison and had the possibility that the atrophy was masked in a minority of subjects. In fact, Vogt et al. (1998) showed that five subgroups of PCC neurodegeneration from no apparent neuronal loss to severe neuronal loss over 80% in most layers. Interestingly, neuronal loss in PCC was present early in the disease and the cases with severe neuronal loss in PCC had an early onset.

In the present study, we wanted to examine whether there was variability of the atrophy in this brain region. Moreover, we assumed that the atrophy in some cases in this region would appear much earlier than at the staging proposed by Braak et al. In order to investigate this hypothesis, we compared AD patients individually with age-matched healthy elderly subjects. We prepared a normal standard of the brain from healthy elderly subjects and aimed to (1) clarify the differences between cerebral atrophy due to normal aging and AD; (2) identify the variability of cerebral atrophy in patients with AD by examining their brains individually; and (3) ascertain whether atrophy of the PCC exists before the onset of dementia or during the mild cognitive impairment (MCI) stage.

Methods

Subjects

The present study was based on a retrospective cohort study. The cohort of patients was the patients registered as outpatients of the Neurological and Cerebrovascular Disease Center from January 1, 2002, to June 30, 2005. All patients with impaired memory complaint underwent careful history taking and physical and neurological examinations, including tests of mental status. Serum electrolyte levels, hepatic, renal and thyroid function and vitamin B_{12} levels were also routinely assessed. Screening for depression was conducted by means of a brief instrument (self-rating depression scale) and by interviews with family members regarding any depressive symptoms. Patients with a history of epilepsy, severe head injury or gross hearing deficit and those with modified Hachinski Ischemic score ≥5 or MRI evidence of lacunar or other vascular lesions were excluded from the study.

We selected 40 patients with mild to moderate AD (19 men, 21 women; age range=55–82 years; mean age=71.1+9.7 years) who exhibited none of the above exclusion criteria and had clinical diagnoses of probable AD on the basis of the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) and of Diagnostic and the dementia criteria of the Statistical Manual of Mental Disorders—Fourth Edition. Amnestic MCI patients (Grundman et al., 2004) who met the following 4 criteria at the first visit were selected (20 patients, 10 men, 10 women, age range 49–77 years; mean age=67.7+9.0 years): (1) neither possible nor probable NINCDS or ADRDA AD criteria were met at initial consultation; (2) MMSE score was above 23; (3) Clinical Dementia Rating (CDR) score was 0.5, with at least 0.5 in the memory domain; and (4) selective impairment of delayed recall was apparent with no apparent loss in general cognitive, behavioral or functional status; presented with subjective forgetfulness or forgetfulness that alerted their spouses. Impairment of delayed recall was assessed with the Wechsler Memory Scale—Revised (WMS-R) test in accordance with Alzheimer's Disease Cooperative Study.

Control groups of normal elderly subjects (n=88, age >60 years) and normal young subjects (n=40) were also studied. Left-handed and ambidextrous individuals were excluded from the present study. Elderly subjects in the control group were free of symptoms suggestive of physical or mental disorder, and no such disorders were evident from general medical questioning or neurological examination. They had an MMSE score of ≥27, CDR=0 and a Hachinski Ischemic score of <4. No subject in this group was taking any class of psychotropic medication. The normal young subjects were recruited from the students of our medical school. All patients and their representatives and control subjects were informed by a written consent form that had been approved by the Institutional Review Board of our University. A summary of the demographic and clinical characteristics of the subjects is given in Table 1.

All MR studies were performed with a 1.5-T MR scanner (Signa Lx, General Electric Medical Systems, Milwaukee, WI). After routine MR imaging for diagnostic evaluation of exclusion criteria (to exclude other causes of dementia) three-dimensional T1-weighted MR imaging was performed using spoiled gradient-recalled acquisition that provided high anatomical resolution and good gray/white matter contrast for subsequent segmentation and VBM. The acquisition parameters were as follows: 9.1 ms/1.9 ms/2 (TR/TE/excitation) to give contiguous slices of 1.4 mm thickness

Table 1
Demographics and clinical findings of the subjects

	Control—young	Control—elderly	AD	MCI
Number	40	88	40	20
Gender (M/F)	16/24	40/48	19/21	10/10
Age (years)	24.5+2.1	68.7+8.7	71.1+9.7	67.7+9.0
MMSE	–	29.09+1.47*	18.03+3.91*	26.80+1.88*

AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.
* Significant difference among three groups (P<0.001, Kruskal–Wallis test).