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Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment

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Recent research has shown an increased rate of conversion to dementia in subjects with mild cognitive impairment (MCI) compared to controls. However, there are no specific methods to predict who will later develop dementia. In the present study, 22 controls and 56 MCI subjects were followed on average for 37 months (max. 60 months) and studied with magnetic resonance imaging (MRI) at baseline to assess changes in brain structure associated to later progression to dementia. Voxel-based morphometry (VBM) was used to investigate gray matter atrophy. During the follow-up, 13 subjects progressed to dementia. At baseline, no differences were detected in age or education between the control and MCI subjects, but they differed by several neuropsychological tests. The stable and progressive MCI subjects differed only by CDR sum of boxes scores and delayed verbal recall, which were also significant predictors of conversion to dementia. At the baseline imaging, the MCI subjects showed reduced gray matter density in medial temporal, temporoparietal as well as in frontal cortical areas compared to controls. Interestingly, the progressive MCI subjects showed atrophy in the left temporoparietal and posterior cingulate cortices and in the precuneus bilaterally, and a trend for hippocampal atrophy when compared to the stable MCI subjects. We conclude that widespread cortical atrophy is present already two and a half years before a clinical diagnosis of dementia can be set.

Keywords: Mild cognitive impairment; Alzheimer's disease; Voxel-based morphometry; Magnetic resonance imaging; Conversion to dementia

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in older age, affecting millions of elderly subjects world-wide and causing remarkable costs to the society. Mild cognitive impairment (MCI) is considered as a possible intermediary state between healthy aging and AD (Petersen et al., 1995). Although previous studies have shown an increased rate of conversion to dementia (6–25%) (Petersen et al., 2001) in MCI, some of the MCI subjects will remain stable or even improve during follow-up (Gauthier et al., 2006). Currently, no specific methods are available to predict who will develop dementia. Thus, biomarkers that would help in identifying MCI subjects likely to convert to dementia are under extensive investigation. With the prospects of developing agents that modify the course of AD instead of the currently available symptomatic treatment, early identification of subjects that will progress to AD would be of extreme importance.

In vivo magnetic resonance imaging (MRI) is a promising noninvasive tool in the search of biomarkers for the detection of early AD. The first AD-related neuropathological changes appear in the medial temporal lobe (MTL) substructures (Braak and Braak, 1991), and atrophy of the hippocampus and entorhinal cortex has also been

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; GM, gray matter; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTL, medial temporal lobe; PMCI, progressive mild cognitive impairment; SMCI, stable mild cognitive impairment; VBM, voxel-based morphometry.

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detected in subjects with MCI and AD in comparison to controls cross-sectionally (Juottonen et al., 1999; Killiany et al., 2002; Pennanen et al., 2004). Previous longitudinal studies assessing MRI volumetric measures have shown that the baseline atrophy (Korf et al., 2004) or atrophy rate (Jack et al., 2004) of the MTL structures is greater in subjects that will later convert to AD or dementia in general. However, the region of interest-based approaches used in the aforementioned studies are time-consuming as they rely on manual outlining, and also depend on the tracers' expertise which makes it difficult to compare results across laboratories.

More developed analysis techniques such as voxel-based morphometry (VBM), which provide means to assess the atrophy of the whole-brain in an automated manner, may prove more useful in the investigation of structural changes in relation to aging and early AD. A recent VBM study demonstrated that aging affects the gray matter density in the prefrontal, medial temporal and striatal cortices whereas longitudinal cognitive decline is related to atrophy in the posterior parietal, medial temporal and prefrontal cortices (Tisserand et al., 2004). Cross-sectional VBM studies comparing MCI subjects to controls have shown atrophy of the MTL, temporal neocortex, thalamus and the cingulate gyrus (Chetelat et al., 2002; Karas et al., 2004; Pennanen et al., 2005) whereas longitudinal studies investigating MCI converters and non-converters with VBM have detected atrophy in frontoparietal and MTL regions (Bozzali et al., 2006) as well as in the posterior medial parietal cortices (Chetelat et al., 2005). The subjects in these longitudinal studies were, however, recruited through memory clinics, thus representing a selected sample of subjects seeking help for memory problems.

The present VBM study investigated whole-brain structural changes associated to later conversion to dementia. Fifty-six MCI subjects and 22 controls, deriving from a randomly selected population-based cohort, were included in the study. Structural MRI scans were acquired at baseline, and the subjects were followed up to 60 months with clinical examination and neuropsychological testing. Recently, it was shown in the same study sample that hippocampal volume (assessed by manual outlining) is a significant predictor of conversion, whereas white matter lesions are not associated with conversion (Tapiola et al., in press). The present study expands on the previous work by associating the clinical follow-up data of the MCI subjects to the evaluation of whole-brain structural changes related to progression to dementia. Moreover, we also investigated correlations between those neuropsychological tests that predicted dementia and gray matter density in controls and MCI subjects. We hypothesized that MCI subjects would at baseline present widespread cortical atrophy compared to controls. Furthermore, we hypothesized that those MCI subjects converting to dementia during the follow-up would at baseline show more extensive atrophy than stable MCI subjects. In particular, atrophy in progressive MCI subjects was expected to be found in the medial temporal regions and in the posterior cingulate cortex and precuneus, which presumably are the areas affected in the MCI stage according to the knowledge on the distribution of AD-related neuropathological changes (Braak and Braak, 1991) and considering MCI as early-stage AD (Morris et al., 2001).

Materials and methods

Subjects

The present study included 22 controls (age range 63–80) and 56 MCI subjects (age range 64–81). Both the controls and MCI subjects were recruited from two distinct population-based longitudinal studies running at the Brain Research Unit, University of Kuopio during 1997–2004. The first cohort was a random sample of 1,150 persons (age range 60–76) drawn from a population register including all the subjects living in the city of Kuopio as well as in nursing facilities (Hanninen et al., 2002; Tervo et al., 2004). Eighteen subjects had either died or moved out of the area before the evaluation, and out of the 1132 eligible subjects 71.6% (806 subjects) participated in the study. The second study group was derived from a large population-based random sample within the framework of the North Carelia Project and FINMONICA (Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular disease) originally studied in the 1970s and 1980s (Kivipelto et al., 2001). A randomly selected subgroup of 2000 subjects from this sample was invited for re-examination and altogether 72.5% (1449 subjects) were re-evaluated in 1998. Consecutive MCI subjects fulfilling the diagnostic criteria for MCI used in the cohorts, and not having any other neurological or psychiatric diseases or medication affecting cognition were included in the MRI study. The controls were identified as cognitively normal in the cohorts, and they did not have any neurological or psychiatric disorders or psychoactive medication. The study was approved by the Ethics Committee of Kuopio University Hospital, and informed written consent was acquired from all the subjects.

Neuropsychological testing

In both cohorts, the follow-up visits consisted of a structured interview including CDR scale (Hughes et al., 1982), demographic information, medical history, current medication, history of smoking and alcohol consumption, and a subjective assessment of memory disturbances and depression as well as a clinical examination. Unlike during the first and second follow-up visits of the first cohort, during the third follow-up it was also possible to include an informant interview due to the smaller amount of subjects to be assessed. The informants were interviewed to corroborate the subject's memory complaints, and they also completed the CDR interview. The neuropsychological testing in the first cohort included the following tests: *Memory:* Visual Reproduction Test (immediate and delayed recall) from the Wechsler Memory Scale (Russel, 1975), Logical Memory Test (immediate and delayed recall) from the Wechsler Memory Scale-Revised (Wechsler, 1987), Word List Recall (immediate and delayed recall) from the CERAD Neuropsychological Assessment Battery (Morris et al., 1989), Delayed Recall of the Constructional Praxis from CERAD (Morris et al., 1989), NYU Paragraph Recall (immediate and delayed recall) (Kluger et al., 1999); *Language:* Abbreviated (15 items) Boston Naming Test (Kaplan et al., 1991), vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981); *Attention and executive function:* Verbal Fluency Test (Borkowski et al., 1965; Butters et al., 1987), Trail Making Test parts A and C (Reitan, 1958); *Visuospatial skills:* Constructional Praxis from CERAD (Morris et al., 1989), Block Design from the WAIS-R (Wechsler, 1981); *Global Functioning:* Clock Drawing Test (Morris et al., 1989), Mini-Mental State Examination (MMSE) (Folstein et al., 1975). According to the national guidelines in Finland, the subjects have not been opted to perform the backwards spelling task in the MMSE assessment and the scoring for the corresponding section is based solely on the seven subtraction task.