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Neurobiology of Aging 28 (2007) 1062–1069

NEUROBIOLOGY OF AGING

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Imaging markers of mild cognitive impairment: Multivariate analysis of CBF SPECT

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Received 9 February 2006; received in revised form 19 April 2006; accepted 3 May 2006
Available online 5 July 2006

Abstract

This study aimed to investigate cross-sectional and longitudinal changes of regional cerebral blood flow (rCBF) in preclinical dementia using single photon emission computed tomography (SPECT). SPECT and cognitive function were investigated in 39 mild cognitive impairment (MCI) subjects and 20 age-matched controls. All subjects were followed longitudinally 19 months on average, 16 MCI subjects progressed to Alzheimer's disease (AD), who were retrospectively defined as progressive mild cognitive impairment (PMCI) at baseline and 23 MCI subjects remained stable and were defined as stable mild cognitive impairment (SMCI) at baseline. SPECT was performed both at the initial investigation and at follow-up. Image data were analyzed using multivariate analysis, SPM and volume of interest (VOI)-based analysis. Significant covariate patterns were derived, which differentiate among PMCI, SMCI and controls at baseline as well as describe the longitudinal progression of PMCI. The combined SPECT and neuropsychology increased the diagnostic accuracy of PMCI at baseline. SPECT and neuropsychological testing can be used objectively for both baseline diagnosis and to monitor changes in brain function during very early AD.

Keywords: Single photon emission computed tomography (SPECT); Mild cognitive impairment (MCI); Alzheimer's disease (AD); Neuronal network; Ordinal trends analysis (OrT); Cognitive function

1. Introduction

Mild cognitive impairment (MCI) is conceptualized as a boundary state between aging and dementia [1]. The term refers to individuals whose memory or other cognitive abilities are not normal, but do not meet conventional criteria for dementia. Most of the MCI subjects will progress to dementia, especially Alzheimer's disease (AD), at a rate of 10–15% per year, as compared to the normal aging who convert at a rate of 1–2% per year [15].

The current MCI research mainly concerns the early diagnosis of dementia and pharmacologic intervention. Thus, a thorough understanding of genesis and natural history of Alzheimer disease is necessary, which will lead to a number of potential clinical applications, including the diagnosis, treatment, and prevent of the onset and progression of the disease. Single photon emission computed tomography (SPECT) has been shown to be useful for the diagnosis of AD

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doi:10.1016/j.neurobiolaging.2006.05.017

[9]. Reduced regional cerebral blood flow (rCBF) in parietal lobe and parieto-temporal association cortex are the typical findings in early AD. In MCI, SPECT has also been shown to be able to predict conversion to AD. A decreased rCBF in parietal lobe, posterior cingulate and precuni was found to be related to the future development of dementia [10,11,13]. Regarding to the longitudinal rCBF changes of MCI, selective rCBF reduction was observed in the left hippocampus and parahippocampus gyrus [13]. Concerning the neuropsychological evaluation, MCI had impaired cognitive function at baseline and declined significantly faster concerning episodic memory, semantic memory and perceptual speed during the follow-up, but working memory was spared [3].

In brain imaging data analysis, multivariate analysis techniques have recently received increasing attention. The technique is based upon principal component analysis (PCA), which evaluates correlation of activation across brain regions. Scaled subprofile model (SSM) analysis is one type of multivariate analyses and could be applied in the cross-sectional study to identify the covariate pathological brain networks in diseased groups. Ordinal trends (OrT) analysis is the method of choice in the analysis of neuroimaging data from experiments with parametric designs involving two or more task condition [6,8]. It focuses on neural processes for which the associated covariance patterns exhibit ordinal trends, i.e., the subject scores increase monotonically with changes in experimental conditions or at different time points. While originally developed for the study of time series fMRI data, this approach can also be used to model the specific network changes that occur in PET and SPECT studies of disease progression, as well as serial imaging studies of treatment effects and medication washout in the resting condition.

The results of multivariate analysis can be more easily interpreted as a signature of neuronal networks. Univariate approaches, on the other hand, cannot directly address functional connectivity in the brain. The multivariate approach can also result in greater statistical power when compared with univariate techniques, which are forced to employ very stringent, and often overly conservative, corrections for voxel-wise multiple comparisons. Multivariate techniques also lend themselves much better to prospective application of results from the analysis of one dataset to entirely new datasets. Multivariate techniques are thus well placed to provide information about mean differences and correlations with behavior, similarly to univariate approaches, with potentially greater statistical power and better reproducibility checks.

Based on this background, we aimed to examine the natural history of MCI using SPECT and neuropsychology and evaluated baseline differences and longitudinal progression of MCI. SSM analyses were applied in SPECT data among the groups of PMCI, SMCI and normal controls at the initial investigation, and OrT analysis was performed in PMCI and SMCI, both separately and combined, to model the disease progression. Neuropsychological tests were correlated with covariate pattern expression.

2. Patients and methods

2.1. Subjects

Thirty-nine MCI subjects and twenty controls were evaluated. The MCI subjects were selected from those individuals consecutively investigated for suspected dementia at the Geriatric Clinic, Karolinska University Hospital. The control subjects were recruited through advertisements in the press, the Swedish Pensioner Society and a Driving and Aging project.

All subjects underwent SPECT and neuropsychological examination at the initial investigation. The MCI subjects were followed clinically for an averaged interval of 18.7 ± 8.7 months. The subjects underwent a second clinical evaluation as well as neuropsychological and SPECT examination. Sixteen MCI subjects progressed to AD. The MCI subjects were retrospectively diagnosed as progressive mild cognitive impairment (PMCI) at baseline. Twenty-three subjects remained stable, which were retrospectively diagnosed as stable mild cognitive impairment (SMCI) at baseline. The baseline values of PMCI, SMCI and controls did not differ at baseline with respect to age (PMCI: 61.6 ± 7.2 (years), SMCI: 58.7 ± 9.5 (years), controls: 61.3 ± 8.0 (years), $p = 0.4853$), gender (PMCI (f/m): 8/8, SMCI (f/m): 14/9, controls (f/m): 13/7, $p = 0.6485$) and follow-up time (PMCI: 18.9 ± 8.6 months, range: 9–41 months; SMCI: 18.5 ± 9.0 months, range: 9–39 months, $p = 0.8741$). No subjects received either psychotropic medication or an acetylcholinesterase inhibitor likely to influence the results of SPECT scanning.

2.2. Diagnosis

Subjects who were diagnosed as MCI performed at least 1.5 S.D. below average for their age on at least one neuropsychological test, but did not fulfill the diagnostic criteria for dementia according to DSM-IV criteria [18] and did not have evidence of impairment in social or occupational functioning. Other medical conditions likely to explain the cognitive impairment were excluded during the clinical examination, which included a routine MRI scan. PMCI and SMCI are retrospective diagnostic terms based on the clinical follow-up. PMCI referred to the MCI subjects who converted to dementia according to the DSM-IV criteria during the follow-up. Whereas, SMCI was defined as the subjects who still did not fulfill the criteria for dementia according to DSM-IV during the observation time.

2.3. Neuropsychological tests

All subjects were examined by an experienced psychologist in five cognitive domains using nine psychological tests. The five cognitive domains evaluated were episodic memory, semantic memory, visuospatial function, attention and general cognitive function. The nine psychological tests included