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Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis

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Abstract

Introduction: Although mild cognitive impairment (MCI) diagnosis is mainly based on cognitive assessment, reliable estimates of structural changes in specific brain regions, that could be contrasted against normal brain aging and inform diagnosis, are lacking. This study aimed to systematically review the literature reporting on MCI-related brain changes.

Methods: The MEDLINE database was searched for studies investigating longitudinal structural changes in MCI. Studies with compatible data were included in the meta-analyses. A qualitative review was conducted for studies excluded from meta-analyses.

Results: The analyses revealed a 2.2-fold higher volume loss in the hippocampus, 1.8-fold in the whole brain, and 1.5-fold in the entorhinal cortex in MCI participants.

Discussion: Although the medial temporal lobe is likely to be more vulnerable to MCI pathology, atrophy in this brain area represents a relatively small proportion of whole brain loss, suggesting that future investigations are needed to identify the source of unaccounted volume loss in MCI.

Keywords: Mild cognitive impairment; Brain atrophy; Hippocampus; Entorhinal cortex; MRI

1. Introduction

Although Alzheimer's disease (AD) was first characterized more than 100 years ago, little concrete progress has been made toward an effective cure of this progressive disorder. Identification of mild cognitive impairment (MCI) as a prodromal phase of AD has raised hopes of the possibility of preventing or modifying progressive neurodegeneration in AD. Indeed, initial attempts at early therapeutic interventions have reported some successes in the early phase of MCI [1,2].

Clinically, MCI is defined based on the detection of cognitive decline greater than that expected at any given age and less than that observed in dementia in the context of preserved activities of daily living and the absence of other neurological disorders. However, clinical evaluation is complicated by heterogeneity in cognitive reserve and diversity in daily function. Considering that each cognitive measure is designed to target a particular brain function, selecting which cognitive measures are appropriate to assess functional decline in the MCI trajectory is a matter of concern not only for diagnostic purposes but also in the evaluation of clinical trials [3]. Besides higher uncertainty in characterizing MCI based on functional impairment [4], cognitive evaluation is not currently informative enough for demonstrating patterns of deterioration that will accurately discriminate those who will remain stable from those who will convert to AD or other dementias. Therefore, without a better understanding of the neurologic basis of the disorder, as well as the identification of structural biomarkers, reliable detection of MCI and estimation of future risk of dementia remain elusive.

Assuming that impairment in cognitive function is the result of neurodegeneration, monitoring structural brain changes may be beneficial in understanding the pathophysiology of MCI. Recent development in neuroimaging

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technologies has provided an opportunity to investigate structural biomarkers in living subjects. In the past two decades, the use of magnetic resonance imaging (MRI) to assess cerebral structure has become widespread. Most early studies have used a cross-sectional design and have suggested that, although the presence of structural differences in any particular brain area is not specific to MCI or AD (i.e. it can also be observed in "normal" aging), the pattern of regional atrophy rates and the topological progression of atrophy are quite characteristic, particularly in AD [5]. Moreover, these studies also revealed that regional atrophy rates are different in MCI and AD [6]. Consequently, identification of regionally specific atrophy rates in MCI may be beneficial for detecting the early stage of AD development, as well as evaluating the magnitude of expected structural changes in clinical trials.

Available longitudinal studies have identified a subset of brain areas that may be involved in MCI pathology. An important next step is to combine, contrast, and integrate the findings from different studies to produce normative information on regional atrophy rates, and to identify the most sensitive anatomic biomarkers characteristic for MCI. As far as we are aware, no study has systematically summarized these findings to date. Therefore, the aim of this study was to systematically review the literature concerning MCI-related structural brain changes.

2. Methodology

This systematic review was conducted based on an established methodology [7], using prespecified search terms and inclusion and exclusion criteria, and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [8].

To retrieve all references relating to longitudinal brain structural changes in MCI published in the MEDLINE database, a literature search was conducted through the PubMed portal in two stages, (1) at the beginning of the study (2) and at the end of February 2015 to update pooled data with the most recent published studies. The following search string was used for both searches; *(Brain or Cerebral or Cortical) And (Mild Cognitive Impairment Or MCI Or Cognitive disorder Or Neurocognitive disorder Or Cognitive decline Or Cognition) And (Structur* Or Volum* Or Thickness Or MRI Or Neuroimaging) And (Atrophy Or Change Or Longitudinal Or shrinkage)*. Both literal and Medical Subject Heading searches were performed. Searches were limited to studies published in English and focusing on human subjects.

2.1. Selection criteria and selection process

To be selected, studies were required to use a longitudinal methodology with two or more structural MRI scans conducted over a follow-up of 12 months or more. As MCI status defined the group being compared with healthy controls (HC), cognitive status of HC and MCI was required to be stable between all time points. Studies were required to use Peterson or Winblad criteria for MCI diagnosis. Cross-sectional, experimental, and review articles were excluded. Studies were also excluded if they had a combined total of less than 30 HC and MCI participants. All retrieved articles were first screened by title and abstract and irrelevant studies were excluded. The full text of all remaining articles was double screened by two reviewers (H.T.-J. and M.E.S.) against selection criteria.

2.2. Data extraction and structural measures

Two reviewers (H.T.-J. and M.E.S.) extracted data from all included articles and any disagreement was resolved by consensus. Data extracted consisted of (1) study design including sample source, number of participants in each group, type of structural measurement, and follow-up period; (2) participants' demographics including age, gender ratio, *APOE* ε4 ratio, years of education, dropout rate, MCI subtype for MCI groups, subjective memory complaint for HC, and handedness; (3) measurement details including number of scans, scan intervals, follow-up period, MRI parameters, segmentation method, and method of analysis; and (4) study results including areas of interest (left and right) and effect sizes (left, right, and total).

All structural measures were evaluated, and studies were categorized according to the following structural measurements; voxel-based morphometry (VBM), volumetry, tensor-based morphometry (TBM), cortical thickness, sulcal morphometry, diffusion tensor imaging (DTI), white matter hyperintensities (WMH), susceptibility weighted imaging (SWI), and other structural measures.

Studies meeting the selection criteria were assessed for quality using the Newcastle-Ottawa scale [9]. The Newcastle-Ottawa scale is an instrument for assessing the quality of studies included in a systematic review. Each study was evaluated on eight items classified into three categories including the selection of the study groups, the comparability of the groups, and the ascertainment of outcome of interest. Each quality item was awarded by a star (except two for comparability) and for each study up to nine stars in total.

2.3. Multiple reports

In the case of multiple reports for the same cohort, or any overlap of participants, an annual change rate estimate from only one publication was used in any single analysis. The most appropriate reports were selected based on recency, availability of effect size and moderators, sample size, and methodology. Studies that reported effect sizes (or provided them after contact) were the first priority and from those the most recent study with the largest sample size was selected. If there was more than one study similar in sample size and recency, the one with the highest quality rating was selected.