ELSEVIER

Neurobiology of Aging 33 (2012) 242–253

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment

Carrie R. McDonald[a,b,*], Lusineh Gharapetian[b], Linda K. McEvoy[b,c], Christine Fennema-Notestine[a,b], Donald J. Hagler, Jr.[b,c], Dominic Holland[b,c], Anders M. Dale[b,c,d], and the Alzheimer's Disease Neuroimaging Initiative[1]

[a] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA
[b] Multimodal Imaging Laboratory, University of California, San Diego, La Jolla, CA, USA
[c] Department of Radiology, University of California, San Diego, La Jolla, CA, USA
[d] Department of Neurosciences, University of California San Diego, La Jolla, CA, USA

Received 5 January 2010; received in revised form 2 March 2010; accepted 21 March 2010

Abstract

We investigated the relationship between regional atrophy rates and 2-year cognitive decline in a large cohort of patients with mild cognitive impairment (MCI; $n = 103$) and healthy controls ($n = 90$). Longitudinal magnetic resonance image (MRI) scans were analyzed using high-throughput image analysis procedures. Atrophy rates were derived by calculating percent cortical volume loss between baseline and 24 month scans. Stepwise regressions were performed to investigate the contribution of atrophy rates to language, memory, and executive functioning decline, controlling for age, gender, baseline performances, and disease progression. In MCI, left temporal lobe atrophy rates were associated with naming decline, whereas bilateral temporal, left frontal, and left anterior cingulate atrophy rates were associated with semantic fluency decline. Left entorhinal atrophy rate was associated with memory decline and bilateral frontal atrophy rates were associated with executive function decline. These data provide evidence that regional atrophy rates in MCI contribute to domain-specific cognitive decline, which appears to be partially independent of disease progression. MRI measures of regional atrophy can provide valuable information for understanding the neural basis of cognitive impairment in MCI.

Keywords: Cognitive decline; Cortical thinning; Executive dysfunction; Naming; Semantic fluency; Verbal memory

1. Introduction

Although episodic memory deficits are the hallmark feature of mild cognitive impairment (MCI), deficits in other cognitive domains are present in a large number of patients. In particular, mild anomia (Blackwell et al., 2004; Storandt et al., 2002) and reductions in semantic fluency (for a review, see Taler and Phillips, 2008) develop in many patients with MCI, suggesting impaired lexical-semantic processing. In addition, a subset of patients with MCI show significant executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency (Belleville et al., 2007; Chang et al., 2009). What has not been established is whether these domain-specific cognitive deficits in MCI are secondary to global brain atrophy versus progressive atrophy within specific neocortical regions. Medial temporal lobe atrophy is prominent in patients with Alzheimer's disease (AD), but there is increasing evidence that atrophy is widespread even in preclinical AD

* Corresponding author at: Multimodal Imaging Laboratory, Suite C101, 8950 Villa La Jolla Drive, La Jolla, CA 92037, United States. Tel.: +1 858 534 2678.

E-mail address: camcdonald@ucsd.edu (C.R. McDonald).

[1] Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. Complete listing of ADNI investigators available at http://www.loni.ucla.edu/ADNI/Data/ADNI_Authorship_List.pdf.

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2010.03.015

(Fennema-Notestine et al., 2009; McEvoy et al., 2009). Therefore, delineating the magnetic resonance imaging (MRI) correlates of domain-specific cognitive decline could lead to an improved understanding of the neural basis of cognitive impairment in MCI.

There is an emerging literature describing baseline structural MRI correlates of cognitive impairment in MCI, AD, and mixed patient samples (Apostolova et al., 2008; Galton et al., 2001; Grossman et al., 2004; van der Flier et al., 2005). The most reliable and well-documented finding is an association between impaired verbal memory and medial temporal lobe atrophy that is particularly robust for hippocampal and entorhinal regions (see Ries et al., 2008 for a review). Hippocampal and entorhinal atrophy have been shown to predict conversion to AD (Jack et al., 1999; 2000; 2005; Killiany et al., 2002; Evoy et al., 2009), as well as memory decline in MCI and AD (Cardenas et al., 2009; Mungas et al., 2001). Therefore, this relationship is the most frequently studied and the medial temporal lobes are the most common targets for region of interest MRI analyses in MCI.

Studies of lexical-semantic processing are fewer in number, but there is evidence linking impaired naming and semantic fluency to atrophy within a number of neocortical regions. Impaired visual naming has been linked to medial temporal lobe atrophy in a sample of healthy elderly, MCI, and AD (van der Flier et al., 2005). In a study of patients with AD and MCI who later converted to AD, impaired visual naming and semantic fluency were associated with left parietal, and bilateral frontal, temporal lobe, and anterior cingulate atrophy (Apostolova et al., 2008). Although there was considerable overlap in the regional atrophy associated with impairment on each task, reduced semantic fluency showed a stronger correlation with left inferior parietal and supramarginal atrophy, whereas reduced naming showed a stronger correlation with atrophy in left inferior temporal cortex. These studies provide evidence that language impairments in MCI and/or AD are linked to atrophy within a number of perisylvian regions, but that naming and semantic fluency have partially unique neuroanatomical substrates.

Structural MRI studies of executive functioning in MCI are scarce, but there are data suggesting that atrophy within frontal, cingulate, and temporal lobe regions contribute to executive dysfunction. In particular, dorsolateral and medial frontal lobe volume loss has been associated with poorer composite scores derived from measures of fluency, set-shifting, and response inhibition in MCI (Cardenas et al., 2009). Neocortical thinning in dorsolateral frontal, posterior cingulate, and lateral temporal lobe regions has also been associated with impaired set-shifting and working memory performance (Chang et al., 2009), and decreases in left dorsolateral and medial gray matter concentration has been detected in patients with a dysexecutive subtype of MCI (Pa et al., 2009). These data support previous literature implicating dorsolateral prefrontal regions in executive functioning, but also suggest that executive dysfunction in MCI may be more complex, relying on the integrity of a number of other frontal and posterior cortical regions.

To date, only a handful of studies have employed longitudinal MRI for understanding the relationship between atrophy rates and cognitive decline in MCI. Whole brain atrophy rates have been associated with decline on measures of global cognition (Evans et al., 2010; Sluimer et al., 2008), verbal memory (Jack et al., 2004), and set-shifting performance (Evans et al., 2010). Total cortical gray matter and hippocampal atrophy has been linked to memory and executive functioning decline in MCI (Mungas et al., 2005), and temporal lobe atrophy rates have been linked to both verbal memory decline and overall disease progression in MCI (Leow et al., 2009).

These studies provide compelling evidence for a relationship between atrophy rates and cognitive decline in MCI. However, most existing studies have relied on baseline imaging or have evaluated longitudinal changes in whole brain atrophy or a very limited number of regions, providing a snapshot into critical structure-function relationships. Furthermore, many studies have included mixed MCI/AD/healthy control samples, precluding an analysis of whether the structure-function relationships are general in nature or unique to diagnosis. Therefore, the degree to which regional neocortical atrophy rates are related to domain-specific cognitive decline in MCI has not been fully evaluated.

In this study, we investigate the relationship between regional neocortical atrophy rates and domain-specific cognitive decline in a large, well-characterized group of patients with MCI. We evaluate whether atrophy rates obtained over a 2-year period are related to memory, language, and executive function decline over the same time interval in MCI, and whether the atrophy patterns associated with decline in each cognitive domain are spatially unique from the pattern associated with increasing disease severity. Based on the existing literature, we predicted that left medial temporal lobe atrophy would be associated with verbal memory decline, whereas dorsolateral frontal lobe atrophy would be related to executive functioning decline in MCI. We hypothesized that atrophy rates within left perisylvian regions would be associated with naming and semantic fluency decline in patients with MCI, but that left temporal lobe atrophy would contribute to naming decline, whereas left temporoparietal atrophy would contribute to semantic fluency decline.

2. Methods

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging