Localized hippocampus measures are associated with Alzheimer pathology and cognition independent of total hippocampal volume

Owen Carmichael[a,b,*], Jing Xie[b], Evan Fletcher[a], Baljeet Singh[a], Charles DeCarli[a], and the Alzheimer's Disease Neuroimaging Initiative

[a] *Department of Neurology, School of Medicine, University of California, Davis, Davis, CA, USA*
[b] *Graduate Group in Computer Science, School of Engineering, University of California, Davis, Davis, CA, USA*

Abstract

Hippocampal injury in the Alzheimer's disease (AD) pathological process is region-specific and magnetic resonance imaging (MRI)-based measures of localized hippocampus (HP) atrophy are known to detect region-specific changes associated with clinical AD, but it is unclear whether these measures provide information that is independent of that already provided by measures of total HP volume. Therefore, this study assessed the strength of association between localized HP atrophy measures and AD-related measures including cerebrospinal fluid (CSF) amyloid beta and tau concentrations, and cognitive performance, in statistical models that also included total HP volume as a covariate. A computational technique termed localized components analysis (LoCA) was used to identify 7 independent patterns of HP atrophy among 390 semiautomatically delineated HP from baseline magnetic resonance imaging of participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Among cognitively normal participants, multiple measures of localized HP atrophy were significantly associated with CSF amyloid concentration, while total HP volume was not. In addition, among all participants, localized HP atrophy measures and total HP volume were both independently and additively associated with CSF tau concentration, performance on numerous neuropsychological tests, and discrimination between normal, mild cognitive impairment (MCI), and AD clinical diagnostic groups. Together, these results suggest that regional measures of hippocampal atrophy provided by localized components analysis may be more sensitive than total HP volume to the effects of AD pathology burden among cognitively normal individuals and may provide information about HP regions whose deficits may have especially profound cognitive consequences throughout the AD clinical course.
© 2012 Elsevier Inc. All rights reserved.

Keywords: Hippocampus; Alzheimer's disease; Morphometry; Biomarkers; Shape analysis

1. Introduction

The Alzheimer's disease (AD) pathological process is hypothesized to begin with the overproduction and aggregation of amyloid beta in the brain, followed by the development of neurofibrillary tau pathology in a stereotypical chronological and spatial progression (Braak and Braak, 1991; Hardy and Selkoe, 2002). According to this schema, neurofibrillary pathology appears first in the transentorhinal region, followed by entorhinal cortex and the CA1 subfield of the hippocampus (HP), finally extending into the CA4 and subiculum HP subfields. It is hypothesized that neurofibrillary pathology in these regions eventually causes neuronal dysfunction and death that leads to impaired memory function, which is the cognitive hallmark of early disease. Measures of medial temporal atrophy from structural magnetic resonance imaging (MRI), including total HP volume, are therefore believed to be sensitive to early AD pathology and the cognitive decline that presumably results from it (Barkhof et al., 2007; Bobinski et al., 1996, 2000; Bourgeat et al., 2010; Csernansky et al., 2004; deToledo-Morrell et al., 2007; Gosche et al., 2002; Jack et al., 2002; Jagust et al., 2008; Silbert et al., 2003; Whitwell et al., 2008).

* Corresponding author at: Center For Neuroscience, 1544 Newton Court, Davis, CA, 95618, USA. Tel.: +1 530 754 9657; fax: +1 530 754 5036.

E-mail address: ocarmichael@ucdavis.edu (O. Carmichael).

Total HP volume, however, is limited in its ability to account for the complex organization of the HP as a collection of functionally interconnected subfields; most investigators combine the contributions of CA1–4, subiculum, dentate gyrus, and possibly other subfields into an overall HP volume measure. Because these regions are damaged differentially by AD-related neurofibrillary pathology, total HP volume may reflect a mix of damaged and healthy subregions early in the AD course.

Partly for this reason, a number of methods for measuring localized HP subregions have been developed. Early efforts measured areas of slices oriented perpendicular to the longitudinal HP axis (Laakso et al., 2000). Another approach measured, at thousands of HP surface points, the "thickness" of the HP in terms of distance from the surface to a central HP axis (Frisoni et al., 2008). Another method performed high-dimensional warping of HP to a common anatomical template, followed by statistical analysis of the warping using principal components analysis (PCA) (Csernansky et al., 2005). By relating spatially variable HP measures to clinical diagnosis of AD, AD risk factors, and other markers, these methods have suggested that a characteristic spatial progression of HP neuronal loss may be detectable in vivo from structural MRI (Csernansky et al., 2005; Laakso et al., 2000; Morra et al., 2009; Thompson et al., 2004; Wang et al., 2009; Xie et al., 2009).

These methods for localized HP structure measurement have been limited, however, in their ability to provide measures that integrate HP surface measurements over local neighborhoods, while at the same time being concise and sensitive to AD-related changes. The HP slicing approach loses information about the possibly complex spatial pattern of HP change by collapsing all of the information in an entire slice down to single measurement of surface area. The thickness approach conversely provides the user with thousands of highly localized measurements that do not reduce to a concise set of numbers summarizing broader patterns. The PCA approach does summarize the subject-to-template deformation into a concise set of spatial patterns, but these patterns are not anatomically constrained and therefore typically cover multiple disconnected regions. The biological information contained within each spatial pattern can therefore be difficult to interpret (Alcantara et al., 2007).

Conversely, localized components analysis (LoCA) provides anatomically constrained information related to structure of the HP (Alcantara et al., 2007, 2009). Like the PCA approach, it attempts to condense HP shape characteristics into a small number of measurements, each of which describe the structure of a set of HP surface points. Unlike the PCA approach, however, each of the LoCA measurements describes a single, spatially localized neighborhood. We have previously shown that this method can provide sensitive measurements of biologically relevant subregional changes to a variety of brain structures, including the HP (Harris et al., 2008; Xie et al., 2009).

The purpose of this study is to evaluate whether anatomically constrained subregional HP shape measurements may add additional information beyond total HP volume to identify aspects of hippocampal structure that are associated with AD pathology and late-life cognitive performance. To accomplish this, we used data from the Alzheimer's Disease Neuroimaging Initiative (www.loni.ucla.edu/ADNI) to relate MRI-based HP measures to cerebrospinal fluid (CSF)-based AD pathology measures, clinical neuropsychological instruments, and clinical diagnosis of mild cognitive impairment (MCI) and AD. According to the recently described temporal sequence of biomarker changes in AD (Jack et al., 2010), changes in CSF amyloid precede changes in total HP volume among cognitively normal individuals possibly by years, and yet pathologic studies have shown that HP injury is already occurring among those with abnormal CSF amyloid concentration (Braak and Braak, 1991; Gómez-Isla et al., 1996). Because a marker of such mild and early HP damage could play an important role in early detection and quantification of AD pathological effects, we focused on cognitively normal participants, while additionally extending the analyses to mildly impaired and demented groups.

2. Methods

2.1. Subjects

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (www.loni.ucla.edu/ADNI). The ADNI was a 5-year study with a primary goal of testing whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Subjects were recruited from over 50 sites across the USA and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, including approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years.

This study includes data from 390 Caucasian ADNI subjects who completed cognitive and clinical evaluations, along with MRI scans, at their baseline visit; 219 of them completed a lumbar puncture for measurement of CSF levels of amyloid and tau. Summary data are shown in Table 1.

2.2. Clinical diagnosis and cognitive evaluation

The clinical assessment and cognitive testing of ADNI subjects followed a standardized protocol that was described previously (Petersen et al., 2010). At each evaluation, all participants underwent a standardized clinical evaluation and cognitive tests. Inclusion criteria for the normal group included Mini Mental State Examination (MMSE) scores between 24 and 30, a Clinical Dementia Rating Scale (CDR) sum of boxes score of 0, and no evidence of major depression, MCI, or dementia. Participants were included in