Neurobiology of Aging 38 (2016) 188–196

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Cortical thinning of parahippocampal subregions in very early Alzheimer's disease

Sabine Krumm [a,b,*], Sasa L. Kivisaari [c], Alphonse Probst [a,d], Andreas U. Monsch [a,b], Julia Reinhardt [e], Stephan Ulmer [f,g], Christoph Stippich [b,e], Reto W. Kressig [a,h], Kirsten I. Taylor [a,b,i,1]

[a] Memory Clinic, University Center for Medicine of Aging Basel, Felix-Platter Hospital, Basel, Switzerland
[b] Faculty of Psychology, University of Basel, Basel, Switzerland
[c] Department of Neuroscience and Biomedical Engineering, Aalto University School of Science, Aalto, Finland
[d] Department of Neuropathology, Institute of Pathology, University Hospital Basel, Basel, Switzerland
[e] Department of Radiology, Division of Diagnostic and Interventional Neuroradiology University Hospital Basel, Basel, Switzerland
[f] Institute of Neuroradiology, University Hospital Schleswig-Holstein, Kiel, Germany
[g] Medical Radiological Institute (MRI), Zurich, Switzerland
[h] Faculty of Medicine, University of Basel, Basel, Switzerland
[i] Centre for Speech, Language and the Brain, Department of Experimental Psychology, University of Cambridge, Cambridge, UK

ARTICLE INFO

Article history:
Received 9 February 2015
Received in revised form 2 November 2015
Accepted 3 November 2015
Available online 10 November 2015

Keywords:
Perirhinal cortex
Entorhinal cortex
Parahippocampal cortex
Amnestic mild cognitive impairment
Atrophy
Structural MRI

ABSTRACT

The stereotypical pattern of neurofibrillary tangle spreading in the earliest stages of typical Alzheimer's dementia (AD) predicts that medial perirhinal cortex (mPRC) atrophy precedes entorhinal cortex (ERC) atrophy, whereas the status of the parahippocampal cortex (PHC) remains unclear. Atrophy studies have focused on more advanced rather than early AD patients, and usually segment the entire PRC as opposed to the mPRC versus lateral PRC (lPRC). The present study therefore determined the extent of ERC, mPRC, lPRC, and PHC atrophy in very early AD (mean Mini-Mental State Examination score = 26) patients and its presumed prodrome amnestic mild cognitive impairment (mean Mini-Mental State Examination score = 28) compared to demographically matched controls. PHG structures were manually segmented (blinded rater) and cortical thicknesses extracted. ERC and mPRC were similarly atrophied in both patient groups. The lPRC was atrophied in the AD group only. Thus, atrophic changes in very early AD broadly map onto the pattern of neurofibrillary tangle spreading and suggest that mPRC, ERC, and lPRC, but not PHC-associated functional impairments, characterize very early-stage AD.

1. Introduction

The early stages of Alzheimer's dementia (AD) are associated with atrophy of the parahippocampal gyrus (PHG, i.e., entorhinal cortex [ERC], perirhinal cortex [PRC] and parahippocampal cortex [PHC]) of the medial temporal lobe (MTL). In typical AD, neurofibrillary tau pathology begins in the transentorhinal cortex (i.e., medial PRC [mPRC]), from where it spreads to the ERC (transentorhinal stages) and to the hippocampal subfields (limbic stages) before spreading into the lateral PRC (lPRC) and isocortical structures (Braak and Braak, 1991; Braak and Del Tredici, 2006; Kordower et al., 2001; Taylor and Probst, 2008). Most investigations of atrophy in AD or its putative prodrome amnestic mild cognitive impairment (aMCI) focus on ERC and hippocampal atrophy, but rarely on that of the PRC, in particular its medial versus lateral aspects (e.g., Du et al., 2001). Also, it is unclear to what extent the PHC is affected in the earliest stages of AD. Finally, it remains unclear whether the brunt of PHG thinning is concentrated in specific anterior-to-posterior levels and, thus, which corresponding coronal levels are optimally clinically informative for distinguishing between healthy normal controls (NCs) and very early AD patients. The present study addresses these questions by manually segmenting the key PHG structures on high-resolution magnetic resonance imaging (MRI) scans according to a

* Corresponding author at: Felix-Platter Hospital, University Center for Medicine of Aging Basel, Memory Clinic, Schanzenstrasse 55, CH-4031 Basel, Switzerland. Tel.: +41 (0)61 265 94 25; fax: +41 (0)61 265 37 88.
E-mail address: sabine.krumm@fps-basel.ch (S. Krumm).
[1] Present address: Biomarkers and Clinical Imaging, Neuroscience, Ophthalmology, and Rare Diseases (NORD), Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland.

http://dx.doi.org/10.1016/j.neurobiolaging.2015.11.001

cytoarchitectonic-, chemoarchitectonic-, and connectivity-based protocol (Insausti et al., 1998; Kivisaari et al., 2013b; Taylor and Probst, 2008) in a large group of healthy control subjects and very early AD patients.

The progressive accumulation of neurofibrillary tangles (NFTs) is assumed to be causally related to cortical atrophy in AD (Ball, 1978; Gómez-Isla et al., 1997). Pyramidal cells in the mPRC are the first cortical neurons to be affected by NFTs (stage I; Braak and Braak, 1991, 1995; Kordower et al., 2001). We note that the mPRC corresponds to Braak and Braak (1991) "transentorhinal cortex" (Taylor and Probst, 2008). Next, cells in layer II of the ERC are affected before pathology spreads to the hippocampal formation (stage II) and into layer IV of the ERC (stage III) (Braak and Del Tredici, 2006). The lPRC is affected in stage III (Braak and Braak, 1991; Braak and Del Tredici, 2006; Van Hoesen et al., 2000). If atrophy mainly results from tau pathology, this progression of pathology predicts that cortical thinning of the mPRC precedes that of the lateral ERC. However, this pattern may not be apparent on structural MRI, since the involvement of a single cortical layer (e.g., mPRC stages I, II) may not cause sufficient cortical thinning for its detection on structural MRI scans. That is, ERC atrophy may be visible on MRI before mPRC atrophy, because 2 independent cortical layers of the ERC (i.e., layers II and IV) are affected early in the disease process compared to a single mPRC layer. Moreover, it is unclear whether the PHC is affected by the pathological tau accumulation in the earliest stages of AD. This is a critical point, since early PHC atrophy could explain some of the cognitive (e.g., visuospatial: Epstein and Kanwisher, 1998) impairments associated with early AD.

MRI-based studies of regional PHG integrity in mild-to-moderate AD patients consistently report atrophy of these structures. Juottonen et al. (1998) compared the ERC, entire PRC, and temporopolar cortex volumes of 30 AD patients (Mini-Mental State Examination [MMSE; Folstein et al., 1975] range 14–28) with 32 NC participants. They found that each region was significantly atrophied in AD patients, with the ERC significantly more severely affected than the entire PRC. Similarly, Teipel et al. (2006) reported comparable extents of atrophy when analyzing the volumes of the entire PRC, PHC, and ERC of AD patients ($n = 34$; MMSE scores ≥ 10) to NCs ($n = 22$). Measures of cortical thickness may provide a more accurate measure of atrophy than 3-dimensional volumes, especially in anatomically highly variable regions such as the PRC, where volumetric measurements are confounded by the size of this structure which varies widely between individuals according to the depth and number of collateral sulci (CS; Insausti et al., 1998). Using mean cortical thickness measurements, Lerch et al. (2005) demonstrated severe cortical thinning of the entire PHG in 19 AD patients (MMSE range, 10–29) compared to 17 NCs, with a significant group difference in the anterior portion of the left ERC, which was the only cytoarchitectonic field that was individually segmented. Dickerson et al. (2009) segmented each PHG subfield in 29 AD patients (MMSE range, 16–28) and found significant cortical thinning of the ERC, mPRC (estimated by the medial bank of the collateral sulcus), and PHC compared to 47 NC participants. Taken together, these studies demonstrate significant and comparable extents of atrophy in the ERC, PRC, and PHC in the mild-to-moderate stages of AD.

The comparable degree of PHG atrophy reported in the aforementioned studies does not at first blush map onto the progression of NFT pathology as described by Braak and Braak (1995). However, the AD patients investigated were either in mild-to-moderate stages of the disease, or the samples were highly variable with respect to disease stage (MMSE scores range from 10 to 29). Thus, neurofibrillary pathology was presumably more dense and widespread compared to patients in the early stages of the disease. Therefore, very early AD patients who are expected to be in early stages of NFT pathology should be examined (Geddes et al., 1997; Nelson et al., 2012). Second, it is essential to segment the mPRC from the lPRC, as cortical NFT begins in the mPRC (stage I), whereas the lPRC is only affected by NFT in stage IV. The anatomic borders of the mPRC corresponding to Braak and Braak's "transentorhinal region" were described by Taylor and Probst (2008) and subsequently integrated into an MTL segmentation protocol (Kivisaari et al., 2013b) incorporating aspects of the Insausti et al. (1998) criteria. Given the high anatomic variability of the CS, which defines mPRC and lPRC boundaries, it is necessary to segment these structures manually to achieve anatomic precision (Hanke, 1997; Pruessner et al., 2002).

The purpose of the present study was to adopt the approach described previously to determine the location and extent of cortical thinning in the ERC, mPRC, lPRC, and PHC in 2 groups of patients with very early AD, that is, a group of aMCI patients presumed to be in the prodromal phases of AD (Petersen et al., 2006), and a group of mildly affected AD patients. All regions of interest (ROIs) were manually segmented by an investigator blinded to diagnosis (Sabine Krumm) using an anatomical protocol recapitulated here (Kivisaari et al., 2013b). Specifically, we aimed to determine whether, in the very early stages of AD, (1) the mPRC and/or ERC is significantly atrophied (1 vs. 2 layers) and (2) PHC thinning is apparent. The first question tests the hypothesis that cortical thinning maps onto the pattern of neurofibrillary pathology, and the second question addresses the unknown status of the PHC in the earliest stages of AD. Both issues are highly clinically relevant as they advise clinicians of the anatomic structures to focus on during the diagnostic process and indicate which corresponding cognitive impairments are expected in the early stages of AD (see e.g., Kivisaari et al., 2012). Finally, we asked whether (3) cortical thinning is maximized in specific anterior-to-posterior coronal levels which would reflect the optimal slices on which to clinically detect very early AD.

2. Methods

2.1. Participants

Data from 121 native Swiss-German or German-speaking adults were included in the present study: 64 healthy control participants (NC) and 57 individuals with very early AD (see the following paragraph). The healthy control participants had undergone a thorough medical screening and neuropsychological testing to ensure that they were cognitively (i.e., neurologically and psychiatrically) healthy. Specifically, exclusion criteria included severe auditory, visual or speech deficits; severe sensory or motor deficits; severe systemic disease; continuous mild-to-intense pain; diseases with severe or probable impact on the central nervous system (e.g., neurologic disorders including cerebral-vascular disease, generalized atherosclerosis, and psychiatric problems); and intake of potent psychoactive substances except mild tranquilizers. In addition, all NCs received normal scores on the MMSE (Folstein et al., 1975), California Verbal Learning Task (Delis et al., 1987), Clock Drawing Test (Critchley, 1953), and short version of the Boston Naming Test (Kaplan et al., 1983).

Thirty-four participants (16 male, 18 female) were diagnosed with AD according to NINCDS-ADRDA and DSM-IV criteria (American Psychichiatric Association, 1994) and 23 patients (11 male, 12 female) with mild neurocognitive disorder because of AD according to DSM-IV and Winblad et al. (2004) criteria (aMCI; single-, or multi-domain). All patients had been recruited from the Memory Clinic, University Center for Medicine of Aging in Basel, Switzerland, where they had received neuropsychological testing, MRI scanning, and medical and neurological examinations including blood analyses.