



Hippocampal subfield volumes at 7T in early Alzheimer's disease and normal aging



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ABSTRACT

We compared hippocampal subfield and entorhinal cortex (ERC) volumes between patients with mild cognitive impairment (MCI), Alzheimer's disease (AD), and controls without cognitive impairment. Additionally, we investigated the relation between age and hippocampal subfields and ERC in controls. We performed ultra-high field 0.7 mm³ 7Tesla magnetic resonance imaging in 16 patients with amnesic MCI, 9 with AD, and 29 controls. ERC, subiculum, cornu ammonis (CA)1, CA2, CA3, and dentate gyrus (DG) & CA4 were traced on T2-weighted images. Analyses of covariance, adjusted for age, sex, and intracranial volume showed that compared with controls and patients with MCI, patients with AD had significantly smaller ERC, subiculum, CA1, CA3, and DG&CA4 volumes. Trend analyses revealed similar associations between ERC and hippocampal subfields and diagnostic group. Older age was significantly associated with smaller CA1 and DG&CA4 volumes. In conclusion, almost all hippocampal subfields and ERC show volume reductions in patients with AD compared with controls and patients with MCI. Future, larger studies should determine which subfields are affected earliest in the disease process and what mechanisms underlie the volume loss.

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1. Introduction

The hippocampal formation and entorhinal cortex (ERC) structures, which are both crucial for declarative memory (Milner, 2005) are early sites for the pathologic processes of Alzheimer's disease (AD) (Duyckaerts et al., 2009). This is reflected in volume loss as visible on magnetic resonance imaging (MRI) scans (Jagust et al., 2006), which is already detectable in an early stage of AD and in prodromal stages of dementia, such as mild cognitive impairment (MCI) (Pihlajamaki et al., 2009). Importantly, this volume loss of the hippocampal formation and ERC is strongly associated with memory impairment in patients with MCI and AD (Apostolova et al., 2006; Kerchner et al., 2012).

The hippocampal formation consists of several subfields (Duvernoy et al., 2005): cornu ammonis (CA) 1–4, subiculum (SUB),

and the dentate gyrus (DG). The ERC, adjacent to the hippocampal formation, provides a large part of the input into the hippocampal formation (Duvernoy et al., 2005) and will therefore also be investigated in this study. It should be noted that this subdivision into subfields and vocabulary is not universally accepted. For example, the area we refer to as CA4 (also called hilus) (Duvernoy et al., 2005) is by other authors considered part of CA3 (Mai and Paxinos, 2012). The ERC and hippocampal subfields have different cellular and molecular characteristics (Duvernoy et al., 2005; Mai and Paxinos, 2012; Thompson et al., 2008). Therefore, they are thought to be differentially vulnerable to processes associated with aging and to conditions such as AD (Small et al., 2011).

In the last 2 decades, much progress has been made in the in vivo assessment of the ERC and hippocampal subfields using MRI. Several sophisticated methods have been developed. At 1.5Tesla (T) mostly surface mapping is used (Apostolova et al., 2006; Frisoni et al., 2006; Qiu et al., 2009). At higher field strengths subfields are mostly segmented on coronal images (La Joie et al., 2013; Mueller et al., 2010; Yassa et al., 2010). Nevertheless, many methodological challenges remain. Limits of extant methods include

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relatively low in- and out-of-plane resolution and contrast-to-noise ratio. This prohibits, for example, the assessment of the DG in most surface based studies. Moreover, the relatively low in- and out-of-plane resolution and contrast-to-noise ratio leads to the lumping together of subfields or to loss of detail on the longitudinal axis (e.g., excluding head and tail). Recently, 7T MRI has become available with ultra-high resolution and improved contrast-to-noise ratio enabling a detailed 3-dimensional visualization of the inner structure of the hippocampal formation. Using high resolution isotropic 7T MRI, we developed a protocol for delineating ERC, SUB, CA1, CA2, CA3, and DG&CA4 covering most of the head, body, and tail of the hippocampal formation and showed that this protocol has good intra-rater reliability (Wisse et al., 2012).

Several in vivo and ex vivo studies have investigated ERC and hippocampal subfield atrophy patterns in AD and aging, thus far with variable results. Human autopsy studies have shown that subfields are differentially affected by AD, with volume or neuron loss particularly in the ERC, SUB, and CA1 (Gomez-Isla et al., 1996; Price et al., 2001; West et al., 1994) but also in the DG (West et al., 1994). Several in vivo MRI studies confirm these results (Frisoni et al., 2006; Kerchner et al., 2010; Killiany et al., 2002; La Joie et al., 2013; Mueller et al., 2010). Others, however, observed volume decrements mainly in the CA2&3 area or the combined CA2, 3, 4&DG area (Lim et al., 2012; Qiu et al., 2009). Compared with AD, autopsy or MRI studies of patients with MCI report a more restricted profile of subfield atrophy, mostly pointing toward atrophy in the ERC and CA1 (Killiany et al., 2002; Kordower et al., 2001; Mueller et al., 2010; Price et al., 2001), although atrophy in CA2, CA3, and the DG has also been reported (Hanseeuw et al., 2011; Yassa et al., 2010). With regard to aging, there is a marked variation in subfields that are found to be affected (Apostolova et al., 2012; La Joie et al., 2010; Mueller and Weiner, 2009; Simic et al., 1997). A recent paper commented that “earlier studies report that aging affects only selected hippocampal subfields but no 2 studies have agreed on the exact regions involved” (Apostolova et al., 2012). The variation between these previous MRI studies probably result from different approaches in subfield segmentation and limited resolution and contrast-to-noise ratio. In this respect, a previous high-resolution 7T MRI study in patients with AD is of particular interest. In that study, the investigators used a dedicated protocol, with high in plain resolution, albeit with lower resolution along the hippocampal axis (anisotropic voxels $0.22 \times 0.22 \times 1.50 \text{ mm}^3$), to measure the thickness of hippocampal subfields and layers of CA1 in the body of the hippocampal formation (Kerchner et al., 2010). They found that a specific layer of CA1, the apical neuropil layer is very sensitive to AD (Kerchner et al., 2010) and related to delayed recall in patients with AD (Kerchner et al., 2012). We used 7T MRI to develop a protocol with isotropic voxels tuned at visualizing the hippocampal formation along the complete longitudinal axis in as much detail as possible because of the suggested anterior to posterior gradient of vulnerability along the longitudinal axis of the hippocampal formation to AD (Martin et al., 2010).

The aim of this study was therefore to compare subfield volumes of the hippocampal formation and ERC between patients with MCI, patients with AD, and older subjects without cognitive impairment using our new protocol at isotropic high resolution 7T MRI. Additionally, we investigated the effect of aging on ERC and hippocampal subfields volumes in the older persons without cognitive impairment.

2. Methods

2.1. Study population

Participants without cognitive impairment (controls) were selected from 2 sources: (1) participants from the Utrecht Diabetic

Encephalopathy Study 2 (UDES2) (Reijmer et al., 2013); and (2) participants of the PREDICT-MR study (Wisse et al., 2012). Both UDES2 and PREDICT-MR recruited their subjects from general practices in Utrecht and surrounding areas. Participants were eligible for the present 7T study if they met the following criteria: (1) age between 65 and 80 years; (2) Mini Mental Status Examination (MMSE) score ≥ 27 ; (3) no psychiatric or neurologic disorder that could affect cognitive functioning; (4) no recent non-disabling stroke (< 2 years) or any disabling stroke, major depression, or a history of alcohol or substance abuse; (5) no contraindications for the 7T MRI scanner; (6) the 7T MRI included a T2 image, needed for hippocampal subfield segmentation.

Thirteen participants of the PREDICT-MR met the inclusion criteria for this 7T study. One participant was excluded from the analysis because the T2 image contained movement artefacts. A second participant developed memory complaints, visited the memory clinic, received the diagnosis MCI and was at that time included in the memory clinic cohort described in the following. This participant was excluded from the control group, leaving 11 PREDICT participants for this 7T study (1 with diabetes mellitus [DM]). Fourteen participants of the UDES2 without DM met the inclusion criteria for this 7T study and were included. In addition, we selected a random sample of the participants with DM from the UDES2 study ($n = 4$), to ensure that the prevalence of DM in the control group of this 7T study was in accordance with the prevalence of DM in the Dutch population (14%–21%) (National Compass of Public Health, 2011). Thus, the total study sample comprised 29 controls (UDES2: $n = 18$; PREDICT-MR: $n = 11$), (Supplementary Fig. 1). The 2 groups did not differ significantly with respect to mean age (UDES2: 70 ± 3 years; PREDICT-MR: 71 ± 4 years; $p = 0.16$) and sex distribution (UDES2: 61% women; PREDICT-MR: 46% women; $p = 0.41$), and differed marginally on MMSE score (UDES2: mean MMSE = 29.2; PREDICT-MR: mean MMSE = 28.4; $p = 0.053$).

Patients with amnesic MCI or early-stage AD were recruited between February 2011 and November 2012 through the memory clinic of the University Medical Center Utrecht (Brundel et al., 2012). Diagnoses were established by a multidisciplinary team. Diagnoses of possible and probable AD were made according to the clinical criteria of the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). A diagnosis of MCI was based on Petersen criteria (Petersen et al., 1999). Patients were eligible for this 7T study if the following criteria were met: (1) MMSE score ≥ 20 (Tombaugh and McIntyre, 1992); (2) no other psychiatric or neurologic disorder that could affect cognitive functioning; (3) no recent nondisabling stroke (< 2 years) or any disabling stroke, major depression, or a history of alcohol or substance abuse; (4) no contraindications for the 7T MRI scanner; (5) the 7T MRI included a T2 image, needed for hippocampal subfield segmentation. Twenty-seven patients met the criteria. However, the T2 images of 2 patients contained movement artefacts and could not be used, leaving 25 patients with amnesic MCI ($n = 16$) or AD ($n = 9$) for the present analysis. DM was present in 13% of the patients with amnesic MCI and 22% of patients with AD.

The studies were carried out in accordance with the principals of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participants.

2.2. Imaging protocol: 7T

Imaging was performed on a 7T MRI whole body scanner (Philips Healthcare, Cleveland, OH, USA) with volume transmit and 16 or 32 channel receive coil (Nova Medical, Cleveland, OH, USA). The following sequence, covering the entire brain as part of a larger

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