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Hippocampal dentation: Structural variation and its association with episodic memory in healthy adults

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ABSTRACT

While the hippocampus has long been identified as a structure integral to memory, the relationship between morphology and function has yet to be fully explained. We present an analysis of *hippocampal dentation*, a morphological feature previously unexplored in regard to its relationship with episodic memory. "Hippocampal dentation" in this case refers to surface convolutions, primarily present in the CA1/subiculum on the inferior aspect of the hippocampus. Hippocampal dentation was visualized using ultra-high resolution structural MRI and evaluated using a novel visual rating scale. The degree of hippocampal dentation was found to vary considerably across individuals, and was positively associated with verbal memory recall and visual memory recognition in a sample of 22 healthy adults. This study is the first to characterize the variation in hippocampal dentation in a healthy cohort and to demonstrate its association with aspects of episodic memory.

1. Introduction

The role of the hippocampus in declarative memory has been implicated and extensively investigated since the surgical removal of the medial temporal lobe of Patient H. M. (Scoville and Milner, 1957). Although he suffered from severe declarative memory deficits, H.M.'s motor memory and working memory remained functionally intact, leading to the theory that these types of memory are processed separately (Corkin, 1984). Declarative memory is defined by the ability to recall everyday facts (semantic memory) and personal experience (episodic memory) (Eichenbaum, 2004; Squire, 1992), with consolidation occurring principally in the hippocampus (Duvernoy et al., 2013; Eichenbaum, 2000, 2004; Squire et al., 2004).

Regarding hippocampal structure, the dentate gyrus of the human hippocampus derives its name from its ridged, "tooth-like" appearance on its intraventricular aspect (also known as the margo denticulatus) that is unique to humans and higher primates (Duvernoy et al., 2013). Similarly, the CA1/subicular region of the hippocampus proper also may show an undulating contour that takes on a "dentated" appearance on MRI, though to a highly variable degree. In some individuals the undulations become quite prominent and form folds in the inferior aspect of the hippocampus (Duvernoy et al., 2013) as can be seen clearly in high resolution images in the sagittal plane through the body and tail of the hippocampus (Fig. 1). We have coined the term "hippocampal dentation" to refer to this morphologic feature of the inferior aspect of the hippocampus proper, most notably CA1, which has been observed previously (Simic et al., 1997; Van Groen et al., 2008) but not quantified or described empirically in regard to its dramatic variation in prominence between individuals. Given that there is considerable variability in how the border between CA1 and the subiculum is defined (Ding and Van Hoesen, 2015; Insausti and Amaral, 2012), we are using the more general term of CA1/subiculum. Of note, the contour of CA1 and CA4 seem to be somewhat correlated, though not perfectly so; however, dentation seems to be independent of the complex fine-scale folding of the granule cell layer (see cell stain sagittal sections at http://neurosciencelibrary.org/Specimens/primates/human/sections/sagittal-cell/husa0782.jpg or Fig. 7.18B in Duvernoy's atlas of the human hippocampus (Duvernoy et al., 2013)).

Given that the CA1 cell layer is known to play a role in episodic memory (Bartsch et al., 2011; Farovik et al., 2010; Zola-Morgan et al., 1986), our observation of significant variability in hippocampal dentation led us to theorize a functional role of hippocampal dentation.

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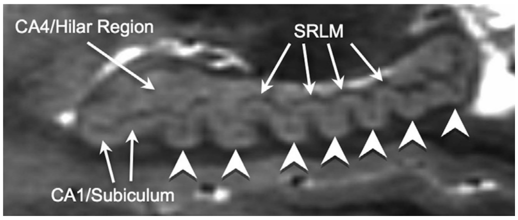

Fig. 1. This image depicts an ultra-high resolution sagittal view of the hippocampus, which is necessary to clearly differentiate the gray matter of CA1/subiculum and CA4/hilar region from the dark band of white matter constituted by the strata radiatum, lacunosum, and moleculare (SRLM). Arrows indicate the dark SRLM layer and the CA1/subiculum and CA4 areas; arrowheads indicate the dentes on the hippocampal body and tail, of interest in this study.

Based on previous research indicating a positive association between cortical gyrification and cognitive functioning (Luders et al., 2008), we hypothesized that a greater degree of total hippocampal dentation would be associated with better episodic memory performance in healthy adults. Specifically, hippocampal dentation was hypothesized to reflect larger CA1/subiculum surface area and increased capacity for episodic memory functioning. We also predicted hemispheric specialization of this relationship – that is, that greater left hippocampal dentation would be associated with better verbal memory, while greater right hippocampal dentation would be associated with better visual memory. Furthermore, some research suggests that the anterior (body) and posterior (tail) regions of the hippocampus may have different functional roles (Bast et al., 2009; Maguire et al., 2000), and may be differentially impacted in pathologic states (Maller et al., 2007). However, debate remains over the specific functional roles along the long axis of the hippocampus (Strange et al., 2014), indicating a need for further investigation of this topic (Poppenk et al., 2013). Therefore, as an exploratory hypothesis, we predicted that the dentation of the body and tail of the hippocampus may be differentially involved in episodic memory, reflected by variation in the degree of hippocampal dentation along its long axis.

2. Materials and methods

2.1. Participants

Twenty-two right-handed, English-speaking healthy adults (10 males, 12 females), with a mean age of 29.3 years ($SD = 9.82$, range: 20–57 years), were included in the analysis. Sixty-eight percent of participants identified their race as Caucasian, 27% as African-American, and 5% as another race. On average, participants were highly educated, with a mean of 16.7 years of education ($SD = 2.55$, range: 12–22 years). Participants with MRI contraindications, known neurological conditions, or recent neuropsychological testing (i.e., past 5 years) were excluded from the study. The Institutional Review Board at our university approved the use of human subjects for this study. Written informed consent was obtained from each study participant prior to participating.

2.2. Neuropsychological assessment

Each participant completed a neuropsychological test battery to assess memory and general cognitive function lasting approximately 90 min. Participants completed one verbal episodic memory measure, the California Verbal Learning Test, Second Edition (CVLT-II) (Delis et al., 2000). This standardized measure involves five initial learning trials of a semantically-related 16-word list to measure learning (Acquisition score, based on total number of words recalled in five learning trials combined). An interference list is then presented, followed by a Short-Delay Free Recall and a Short-Delay Cued Recall. A 20-min delay precedes a Long-Delay Free Recall (LDFR), a Long-Delay Cued Recall, and a Recognition Trial. Acquisition (*t*-scores) and LDFR (z-scores) were considered outcome variables of interest. Scores were standardized based on participants' age and gender in accordance with standard scoring procedures (Delis et al., 2000).

Participants completed one non-verbal memory measure, the Rey Complex Figure Test (Meyers and Meyers, 1996). This standardized measure involves copying a complex geometric figure with 18 components onto a blank piece of paper. Participants are later asked to draw the figure from memory in an Immediate Recall trial (3 min following initial administration) and in a Delayed Recall trial (30 min after Immediate Recall trial). Following the Delayed Recall, participants complete a Recognition trial of individual components of the complex figure. This measure was scored based on standard clinical scoring procedures; specific scoring criteria for this measure are outlined in the technical manual (Meyers and Meyers, 1996). Outcome variables of interest included Delayed Recall (*t*-scores) and Rey Recognition (*t*-scores), corrected for participants' age in accordance with standard scoring procedures.

In order to obtain an intelligence quotient estimate, participants completed the Wechsler Abbreviated Scale of Intelligence (WASI), two-subtest version (Matrix Reasoning and Vocabulary subtests). This IQ score served as a brief estimate of overall intellectual functioning.

2.3. MRI acquisition

Participants underwent a structural MRI scanning protocol, conducted at our university on a 3T Philips Achieva scanner. The scanning protocol consisted of a standard clinical T1-weighted MPRAGE scan followed by a series of 12–16 ultra high-resolution (.5 × .5 × .75 mm) whole brain T2-weighted scans acquired using a variable flip-angle turbo spin-echo sequence (*BrainView* – Philips Healthcare, Einthoven, Netherlands). Each ultra high-resolution volume was acquired in only 6 min but had very low signal-to-noise ratio (SNR), therefore multiple scans were acquired, co-registered to the first scan, and averaged to produce final images with excellent SNR. The number of high-resolution scans acquired was determined by the participant's tolerance for a prolonged scanning session. Scans marred by head motion artifacts were excluded from post-processing. We refer to this method as *high-resolution multiple image co-registration and averaging* (HR-MICRA). Co-registration and averaging was performed using FMRIB's Linear Image Registration Tool (FSL-FLIRT; http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/flirt) (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The high resolution of HR-MICRA images in all 3 planes is necessary for precise and accurate visualization of hippocampal internal architecture and surface structure along the entire hippocampal length.

2.4. Dentation assessment

Through our experience reviewing high-resolution hippocampal images it became apparent that hippocampal dentation varies across individuals both in terms of the number of dentes and in the height of dentes (i.e., depth of folds). From this observation we developed a multi-point visual rating system that incorporates both the *quantity* and the *prominence* of dentes in the body and tail of the hippocampus separately. A visual rating scale was used in this case because the morphologic features being described were observed to be highly visually salient, and thus a visual rating was selected for simplicity and reliability. Regarding quantity, two points were assigned for four or more dentes, one point was assigned for one to three dentes, and zero points were assigned when no dentes were visible in a given area. Prominence was characterized as *arciform* (two points), *sinusoidal* (one point), or *absent* (zero points) (Table 1). Fig. 2 B and C demonstrate the qualitative differences between arciform and sinusoidal dentes. It should be noted that prominence was observed to be independent from quantity. That is, an individual may have many arciform or many sinusoidal dentes, or few arciform or few sinusoidal dentes, but each