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Research report

Roles of hippocampal subfields in verbal and visual episodic memory

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HIGHLIGHTS

- Neurocognitive tests tapping specific HC subfields can help target at-risk individuals.
- Subiculum was associated with verbal and visual episodic memory.
- CA1 was associated with verbal and visual episodic memory.
- No other subfields were associated with verbal or visual episodic memory.
- Our results suggest that CA1 and subiculum are responsible for retrieval.

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ABSTRACT

Introduction: Selective hippocampal (HC) subfield atrophy has been reported in older adults with mild cognitive impairment and Alzheimer's disease. The goal of this study was to investigate the associations between the volume of hippocampal subfields and visual and verbal episodic memory in cognitively normal older adults.
Methods: This study was conducted on a subset of 133 participants from the Einstein Aging Study (EAS), a community-based study of non-demented older adults systematically recruited from the Bronx, N.Y. All participants completed comprehensive EAS neuropsychological assessment. Visual episodic memory was assessed using the Complex Figure Delayed Recall subtest from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Verbal episodic memory was assessed using Delayed Recall from the Free and Cued Selective Reminding Test (FCSRT). All participants underwent 3T MRI brain scanning with subsequent automatic measurement of the hemispheric hippocampal subfield volumes (CA1, CA2-CA3, CA4-dente gyrus, presubiculum, and subiculum). We used linear regressions to model the association between hippocampal subfield volumes and visual and verbal episodic memory tests while adjusting for age, sex, education, and total intracranial volume.
Results: Participants had a mean age of 78.9 (SD = 5.1) and 60.2% were female. Total hippocampal volume was associated with Complex Figure Delayed Recall ($\beta = 0.31$, $p = 0.001$) and FCSRT Delayed Recall ($\beta = 0.27$, $p = 0.007$); subiculum volume was associated with Complex Figure Delayed Recall ($\beta = 0.27$, $p = 0.002$) and FCSRT Delayed Recall ($\beta = 0.24$, $p = 0.010$); CA1 was associated with Complex Figure Delayed Recall ($\beta = 0.26$, $p < 0.002$) and FCSRT Delayed Recall ($\beta = 0.20$, $p = 0.025$).
Conclusions: Our findings confirm previous research on the specific roles of CA1 and subiculum in episodic memory. Our results suggest that hippocampal subfields have sensitive roles in the process of visual and verbal episodic memory.

1. Introduction

The association between the hippocampus and episodic memory is well established [1–4]; however, within the hippocampus,

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the roles of task-specific structures are still emerging, and only a few studies have investigated the association between hippocampal subfields and psychometric tests of memory in healthy older adults.

Hippocampal (HC) subfields include the cornu ammonis (CA1, CA2-3), CA4-dente gyrus (DG), the presubiculum and the subiculum. Previous research suggests that CA2, CA3, and DG are input structures, responsible for encoding, while the CA1 and subiculum are output structures, responsible for retrieval [5–9]. fMRI studies have further suggested specialized function for each subfield in hippocampal formation. Zeineh et al. [8] used a face-name associated task to study mnemonic processing in 10 healthy young adults; results showed that the CA2, CA3 and DG were involved in encoding whereas the subiculum showed more activation during recall, thus suggesting a double dissociation of activation patterns and tasks. In a similar experiment, Nauer et al. [9] assessed 34 healthy young adults on their working memory abilities for visuospatial information using complex visual outdoor scenes in delayed match-to-sample (DMS) tasks; results in this study showed that the hippocampal subfields CA1, CA3, DG and subiculum remained activated well into the delayed period, suggesting an ongoing mechanism of long-term information processing. Nauer et al. [9] refer to this as "ongoing encoding", in which the immediate and delayed tasks are explained as one continuous process of activity reflecting ongoing encoding of stimuli.

Structural MRI studies have also shown these associations in case-control studies [10–12]. Muller et al. [12] explored verbal episodic memory using the California Verbal Learning Test II (CVLT-II) in individuals with temporal lobe deficits and healthy controls; they found that immediate verbal recall was associated with larger CA3 and DG volumes, while delayed verbal recall was associated with larger CA1 volumes. They also found similar results in another study using the same test on cognitively impaired older adults [11]. Research has also shown that CA1 volume declines with increasing age [13], and that compared to age-matched controls, Alzheimer's disease (AD) subjects show more atrophy in the CA1 and subiculum [14,15]. CA1 has also been associated with delayed verbal recall in AD [10], further suggesting CA1′s role in retrieval that is associated with AD [15]. These findings have been extended to younger healthy adults in a study [16] that applied structural MRI to the study of hippocampal formation in younger adults; results showed that CA1, CA2/CA3 and DG played significant roles in verbal and visual memory retrieval.

In this manuscript, we assess the relationships of HC subfield volume with standardized neuropsychological tests of visual and verbal memory. Identifying neurocognitive measures that tap onto hippocampal subfields may provide a more efficient method of targeting individuals at risk of AD. Psychometric tests that are associated with specific hippocampal subfields may suggest atrophy and consequently ensure a more proactive approach of referring at-risk individuals for imaging procedures and early diagnosis. Thus, the aim of our study was to explore the role of hippocampal subfields in delayed verbal and delayed visual recall in a sample of community-dwelling older adults without dementia. We hypothesized that CA1 and subiculum would be associated with performance on tests of visual and verbal memory recall.

2. Methods

2.1. Sample

This cross-sectional study was conducted on a subset of 133 older adults from the Einstein Aging Study (EAS). The EAS study design and methods have been described previously [17]. Briefly, the EAS is an ongoing community-based volunteer sample of individuals over the age of 70 living in the Bronx, New York. Participants are systematically recruited from Medicare and from voter registration lists from Bronx County, New York City Board of Elections. Participants with visual and/or auditory impairment that interfere with neuropsychological testing, psychiatric symptomatology that interferes with test completion, non-English speakers, a nonambulatory status, and a dementia diagnosis were excluded from the study. In addition, participants did not participate in the study if they were ineligible for an MRI (e.g. due to metallic implants, claustrophobia, etc.). Written informed consent was obtained on their first clinical visit. The study protocol was approved by the local institutional review board. In this study, we only selected participants who have participated in MRI studies between July 2011 and October 2014.

2.2. Visual and verbal episodic memory assessment

We used two tests that contained three measures of visual episodic memory:

i) Complex Figure subtest from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) – copy and delayed recall [18]: This test assesses immediate and delayed visual and spatial ability and visual episodic memory and is relatively language free. The first part of this test involves the immediate free-hand copying of a very detailed line drawing. In the second part, which is the delayed part, the participant is required to recall and reproduce the figure from memory after a 20 min delay. Scores are based on accuracy of drawing and placement. Possible scores range from 0 to 20 for each test condition. This test is frequently used to test for dementia or neuropsychological impairment. In this study we only assessed the delayed condition since our interest is in visual episodic memory.
ii) The Free and Cued Selective Reminding Test (FCSRT) [19] is an episodic memory test, which includes learning of 16 pictures by identifying and naming each picture. It also consists of three trials of immediate free recall, each of which is followed by cued recall in which a category cue is given to the subject to facilitate recall of the items not freely recalled. It also consists of a delayed free recall trail given after a 20 min delay. Delayed free recall (range 0–16) was used in these analyses.

2.3. MRI image processing

Imaging was performed using a 3.0 T MRI scanner (Achieva Quasar TX; Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil (Sense Head Coil; Philips Medical Systems, Best, the Netherlands). T1-weighted whole-head structural imaging was performed using sagittal three-dimensional magnetization-prepared rapid acquisition gradient echo (MP-RAGE) with TR/TE 9.9/4.6 ms; 240 mm^2 FOV; 240 × 240 matrix; partition thickness, 1 mm; and parallel acceleration factor 2.0. Furthermore, a 3D T2-weighted fluid-attenuated inversion recovery (T2W-FLAIR) acquisition was obtained with the following pulse sequence parameters: TR/TE/TI 11000/120/2800 ms; 240 × 240 mm FOV; 240 × 240 matrix; 1 mm partition thickness and parallel acceleration factor 2.0.

MRI data was processed using the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/). Image processing methods in the EAS have been previously described in detail [20]. Briefly, the processing stream starts with a hybrid watershed algorithm, which removes non-brain tissue, automated transformation to the Talairach reference space and segmentation of the subcortical white matter and deep gray matter. All volumes including cortical GM volume, total cerebral WM volume, ventricular volume, and total hippocampal volume (HV) were segmented using FreeSurfer's