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Differential association of left and right hippocampal volumes with verbal episodic and spatial memory in older adults

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ABSTRACT

The hippocampus plays a critical role in verbal and spatial memory, thus any pathological damage to this formation may lead to cognitive impairment. It is suggested that right and left hippocampi are affected differentially in healthy or pathologic aging. The purpose of this study was to test the hypothesis that verbal episodic memory performance is associated with left hippocampal volume (HV) while spatial memory is associated with right HV. 115 non-demented adults over age 70 were drawn from the Einstein Aging Study. Verbal memory was measured using the free recall score from the Free and Cued Selective Reminding Test – immediate recall (FCSRT-IR), logical memory immediate and delayed subtests (LM-I and LM-II) from the Wechsler Memory Scale-Revised (WMS-R). Spatial Memory was measured using a computerized dot memory paradigm that has been validated for use in older adults. All participants underwent 3 T MRI with subsequent automatized measurement of the volume of each hippocampus. The sample had a mean age of 78.7 years (SD=5.0); 57% were women, and 52% were white. Participants had a mean of 14.3 years (SD=3.5) of education. In regression models, two tests of verbal memory (FCSRT-IR free recall and LM-II) were positively associated with left HV, but not with right HV. Performance on the spatial memory task was associated with right HV, but not left HV. Our findings support the hypothesis that the left hippocampus plays a critical role in episodic verbal memory, while right hippocampus might be more important for spatial memory processing among non-demented older adults.

1. Introduction

Hippocampus, a bilateral structure within the middle temporal lobe, is well known for being an essential part of neural network of learning and memory. Several studies have indicated that hippocampal volume (HV) can predict performance on a variety of memory tests in healthy controls (Convit et al., 2003; Hackert et al., 2002; Rosen et al., 2003; Van Petten, 2004) and pathological diseases including schizophrenia(Seidman et al., 2002), Alzheimer disease (AD) (Dubois et al., 2014), and hippocampal sclerosis observed in temporal lobe epilepsy (Adda et al., 2008; Griffith et al., 2004).

Prior studies indicate that pathological factors may lead to brain asymmetry (Toga and Thompson, 2003). It has been suggested that right and left hippocampi are affected differentially in progressive phases of memory loss (Shi et al., 2009). Though not always consistent, left HV's association with different episodic memory tests is stronger than right HV association with the same tests in normal cognition, MCI, and AD groups (Shi et al., 2009). Other studies have suggested specialized roles for structures in the right side of brain including dorsolateral prefrontal cortex, occipital cortex and hippocampus structures in spatial and navigational memory (Nemmi et al., 2013; Persson et al., 2013).

In healthy populations, reports of the correlation between HV and its corresponding behavioral expression have been inconsistent. While some studies (Hackert et al., 2002; Rosen et al., 2003) have shown larger total HV is associated with better performance on episodic memory, other studies have found no

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significant correlation between these measures in healthy older adults (MacLullich et al., 2002; Maguire et al., 2000; Marquis et al., 2002). A meta-analysis of studies in older adults have yielded a weak positive relationship between episodic memory and HV (Cyma Van Petten, 2004). Other studies have reported hippocampal atrophy in subjects with amnestic mild cognitive impairment (aMCI) (Jessen et al., 2006; Muller et al., 2005). In addition, HV has been suggested as a predictive measure of disease progression and worsening of memory function in a variety of neurodegenerative diseases including AD (den Heijer et al., 2006; Dubois et al., 2014) and Parkinson's disease (Brück et al., 2004). Overall, it seems that these relationships are most obvious in individuals with advanced stages of cognitive impairment or age-related neurodegeneration, which result in a reduction of HV.

Identifying specific function of right and left hippocampi and their effect on cognitive tests may facilitate efforts toward earlier detection of pathological changes that lead to cognitive decline and AD. The purpose of the current study was to characterize associations between left or right HV and performance on episodic verbal and spatial memory tests in a population of non-demented older adults. We hypothesized that performance on verbal memory tests would be associated with left HV and performance on a spatial memory task would be associated with right HV.

2. Methods

2.1. Participants

This cross-sectional study was conducted on 115 non-demented adults over the age of 70 enrolled in the Einstein Aging Study (EAS). The study design and methods of the EAS have been described in detail previously (Katz et al., 2012). Briefly, potential participants were recruited through systematic sampling from Medicare and voter registration lists for Bronx County, New York. Eligible participants were aged 70 and older, Bronx residents, non-institutionalized, and English-speaking. Exclusion criteria included severe visual or auditory impairments that precluded neuropsychological testing, active psychiatric symptomatology that interfered with the ability to complete assessments, and non-ambulatory status. Participants received annual in-person assessments including medical history, neuropsychological testing and general and neurologic examinations.

Participants who met diagnostic criteria for dementia or did not meet standard MRI eligibility criteria – safety contraindications or metallic implants that would create image artifacts – were excluded from this study. Dementia diagnosis was based on the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 2000) and was assigned at consensus case conferences attended by the study clinicians and licensed neuropsychologist, and included a comprehensive review of neuropsychological test results, relevant neurological signs and symptoms, and functional status (Katz et al., 2012).

All studies were approved by the Institutional Review Board of the Albert Einstein College of Medicine.

2.2. Verbal memory assessment

Details of the EAS neuropsychological test battery has been previously described (Katz et al., 2012). The Free and Cued Selective Reminding Test – Immediate Recall (FCSRT-IR) (Buschke, 1984; Grober et al., 1988) is an episodic memory test, which requires learning of 16 pictures by naming each picture and identifying the category to which it belongs. It also consists of three trials of immediate free recall (range 0–48), 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. Total recall is the sum of free and cued recall together. Since total recall demonstrates ceiling effects in our community-based sample (Zimmerman et al., 2015), in this analysis we only used the free recall score.

Logical Memory I (LM-I) from the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987) is an immediate declarative memory test (range 0–50), in which two different stories are read to the participant, and after each story the participant immediately recalls it from memory. Scores are given on the accuracy of the retelling of the story. In Logical Memory II (LM-II), recall is probed 20 min after the immediate condition.

2.3. Spatial memory assessment

Spatial memory was assessed using a computerized dot memory task. The dot memory task consisted of 3 phases: encoding, distraction, and retrieval. During the encoding phase, participants were shown and asked to remember the location of 3 red dots on a 5×5 grid. Participants were allowed to study the grid for a 3 s period. A distraction phase began after the grid was removed in which participants were presented with the letters F and E, and were required to locate and touch the Fs among the array of Es. This distraction phase lasted 8 s. In the retrieval phase, the 5×5 grid reappeared empty and the participants' task was to recall the locations of the 3 dots that had been presented in the encoding phase. Participants completed 11 trials (encoding, distractors, and retrieval). Scores were based on errors, with credit being based on the deviation from the correct positions. If all dots were recalled in their correct location participants were given a score of 0. If there were 1 or more retrieval errors, the Euclidean distance of the location of the incorrect dot to the correct grid location was calculated, with lower scores indicating more accurate placement and better performance (Siedlecki, 2007). In order to simplify interpretation of results, the reversed score (spatial error mean x -1) was used to report spatial memory function so that higher scores indicated better performance.

2.4. MRI acquisition and processing

Imaging was performed using a 3.0 T MRI scanner (Achieva Quasar TX; Philips Medical Systems, Best, the Netherlands) and 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. In addition, a 3D T2-weighted fluid-attenuated inversion recovery (T2W-FLAIR) acquisition was obtained with the following pulse sequence parameters: TR/TE/TI 11,000/120/2800 ms; 240×240 mm FOV; 240×240 matrix; 1 mm partition thickness and parallel acceleration factor 2.0.

2.5. Image processing

We processed all MRIs automatically using the FreeSurfer software package (version 5.2, available at http://surfer.nmr.mgh.harvard.edu/). Image processing methods in the EAS have been previously described in detail (Ezzati et al., 2015, 2014). T1 and T2-FLAIR images were used to segment the cortical and subcortical volumes including whole hippocampal formation by FreeSurfer's standard segmentation procedure using a probabilistic brain atlas (Fischl et al., 2002). Additionally, for each subject the estimated intracranial volume (TICV) was calculated by the procedure described by Buckner et al. (2004).