



High field structural MRI reveals specific episodic memory correlates in the subfields of the hippocampus



S.G. Travis^a, Y. Huang^a, E. Fujiwara^{a,b}, A. Radomski^b, F. Olsen^c, R. Carter^b, P. Seres^c, N.V. Malykhin^{a,b,c,*}

^a Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada

^b Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

^c Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada T6G 2V2

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ABSTRACT

The involvement of the hippocampus (HC) in episodic memory is well accepted; however it is unclear how each subfield within the HC contributes to memory function. Recent magnetic resonance imaging (MRI) studies suggest differential involvement of hippocampal subfields and subregions in episodic memory. However, most structural MRI studies have examined the HC subfields within a single subregion of the HC and used specialised experimental memory paradigms. The purpose of the present study was to determine the association between volumes of HC subfields throughout the entire HC structure and performance on standard neuropsychological memory tests in a young, healthy population. We recruited 34 healthy participants under the age of 50. MRI data was acquired with a fast spin echo (FSE) sequence yielding a $0.52 \times 0.68 \times 1.0 \text{ mm}^3$ native resolution. The HC subfields – the cornu ammonis 1–3 (CA), dentate gyrus (DG), and subiculum (SUB) – were segmented manually within three hippocampal subregions using a previously defined protocol. Participants were administered the Wechsler Memory Scale, 4th edition (WMS-IV) to assess performance in episodic memory using verbal (Logical Memory, LM) and visual (Designs, DE; visual-spatial memory, DE-Spatial; visual-content memory, DE-Content) memory subtests. Working memory subtests (Spatial Addition, SA; and Symbol Span, SSP) were included as well. Working memory was not associated with any HC volumes. Volumes of the DG were correlated with verbal memory (LM) and visual-spatial memory (DE-Spatial). Posterior CA volumes correlated with both visual-spatial and visual-object memory (DE-Spatial, DE-Content). In general, anterior subregion volumes (HC head) correlated with verbal memory, while some anterior and many posterior HC subregion volumes (body and tail) correlated with visual memory scores (DE-Spatial, DE-Content). In addition, while verbal memory showed left-lateralized associations with HC volumes, visual memory was associated with HC volumes bilaterally. This is the first study to examine the associations between hippocampal subfield volumes across the entire hippocampal formation with performance in a set of standard memory tasks.

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1. Introduction

It has been over half a century since the famous case of patient H.M. and his bilateral medial temporal lobe (MTL) resections gave psychologists strong evidence that the MTL is required for learning and memory (Scoville & Milner, 1957). Subsequent studies of the hippocampus (HC) – a bilateral structure within the MTL – have found that volumetric measurements taken via Magnetic Resonance Imaging (MRI) can predict performance on a number of

common neuropsychological tests and episodic memory paradigms. This is true for healthy controls with intact HC tissue (Foster, Meikle, & Goodson, 1999; Hackert et al., 2002; Convit, Wolf, Tarshish, & de Leon, 2003; and Rosen et al., 2003) and in patients with temporal lobectomies (Scoville & Milner, 1957; Loring et al., 1993). This relationship can also be seen in pathological instances where reduced HC volume is highly correlated with poorer memory performance, such as in Alzheimer's disease; (Köhler et al., 1998), schizophrenia (Seidman et al., 2002; and O'Driscoll et al., 2001), and hippocampal sclerosis observed in temporal lobe epilepsy (Lencz et al., 1992; Baxendale, Thompson, & Van Paesschen, 1998; Pegna et al., 2002; Griffith et al., 2003; Griffith, Pyzalski, Seidenberg, & Hermann, 2004). In healthy populations with intact HC tissue, however, the correlation

* Correspondence to: Department of Biomedical Engineering, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada T6G 2V2.

Tel.: +1 780 248 1120; fax: +1 780 492 8259.

E-mail address: nikolai@ualberta.ca (N.V. Malykhin).

between the volume of the hippocampus and its corresponding function are usually less consistent (Rodrigue & Raz, 2004; Van Petten, 2004). It seems that these relationships are most obvious in individuals with significant cognitive impairments from neurological disorders or age-related neurodegeneration which result in a reduction of HC volume. It is less clear whether HC volume–memory associations are detectable in a young, healthy population.

We know from selective lesion studies in rats that the HC is functionally subdivided along the septotemporal axis into dorsal and ventral regions, with each region being associated with a distinct set of behaviors (Bannerman et al., 2004). It has been suggested that the dorsal HC – referred to as the posterior HC in primates – has a preferential role in spatial learning. The ventral HC – equivalent to the primate anterior HC – may have a preferential role in anxiety-related behaviors (Bannerman et al., 2004). In humans, the HC is subdivided along the anteroposterior axis into subregions. These subregions as we will refer to them are the HC head, body, and tail (Duvernoy, 2005), listed from most anterior to most posterior. In studies which examine the HC in just two anteroposterior subdivisions, it has been suggested that the anterior HC may have a preferential role in anxiety-related behaviors and verbal memory, while the posterior HC has a preferential role in spatial learning. Specifically, in a structural MRI study, Szeszko et al. (2006) found that in healthy individuals stress correlated most strongly with anterior HC volume. HC head size is positively correlated with word learning (Hackert et al., 2002), and similarly Chen, Chuah, Sim, & Chee (2010) found that greater anterior HC volumes were associated with delayed verbal memory. Posterior HC volumes correlate with spatial memory, both in Chen et al. (2010), and Woollett and Maguire (2011), who demonstrated in a longitudinal study that successfully certified taxi drivers had an increase in posterior HC grey matter volumes, compared to controls and apprentices who did not pass their qualifying exam.

The functional specificity of these studies conceivably reflects an underlying structural differentiation along the anteroposterior axis. Specifically, the afferent and efferent external connectivity changes along this axis (Andersen, Bliss, & Skrede, 1971). The entorhinal cortex projects well-defined regions along the anteroposterior axis of the dentate gyrus (DG) (Dolorfo & Amaral, 1998), with input from the sensory cortex via entorhinal cortex entering mainly in the dorsal (posterior) two-thirds of the DG. This organization is similar for efferent connections back to cortical areas. Axons from cornu ammonis (CA) and subiculum (SUB) synapse onto the entorhinal cortex in a lateral-to-medial direction (Köhler, 1985; van Groen, van Haren, Witter, & Groenewegen, 1986; van Groen & Wyss, 1990). For a more detailed overview, see Moser and Moser (1998). If we consider this anteroposterior gradient of connective distinctiveness, we can infer that the HC head, body, and tail will have distinct roles in cognition. The HC head shows connections to amygdala, and uncinate fasciculus white matter which reciprocally projects to temporal pole, insula, and ventromedial prefrontal cortex (Kier, Staib, Davis, & Bronen, 2004). In contrast, resting-state fMRI has correlated posterior HC activity with both anterior and posterior cingulate, precuneus, and inferior parietal cortex (Poppenk & Moscovitch, 2011). Overall, the extant literature illustrates a specialization of hippocampal subregions, a finding which could be overlooked when examining the HC as a whole. For example Poppenk and Moscovitch (2011) reported that better performance on tasks of word pair, word-picture pairings and scene recognition was associated with positively with posterior and negatively with anterior HC volume, while overall HC volume was not sensitive to these measures. Therefore, separating a global volume of the HC into connectively-distinct subregions in studies of relationships between hippocampal volume and memory is vital.

Apart from anteroposterior subregion divisions, the HC has a heterogeneous inner structure that can be further delineated in

MR images into several histologically-defined subfields, including the cornu ammonis (CA1–3), dentate gyrus (DG), and subiculum (SUB) (for a full review, see Duvernoy, 2005). Each subfield houses a distinct population of neurons with distinct connectivity, suggesting a cytological basis for differential vulnerability of the subfields to different pathological processes. For example, severe stress can lead to a massive loss of CA3 pyramidal cells in the HC of rats and monkeys (Sapolsky, 2000), neuronal loss in CA1 is typical for Alzheimer's disease (West, Coleman, Flood, & Troncoso, 1994), and DG and CA subfields are affected in major depression (Stockmeier et al., 2004). In the trisynaptic circuit, afferent excitatory cortical inputs via entorhinal cortex pass through the perforant path to the granule cells of the DG. Mossy fibers arising from DG travel to CA3/4 before passing through remaining CA subfields via Shaffer collaterals then SUB, or passing directly from CA3/4 to the fimbria and on to the fornix. Alternatively, the direct intrahippocampal pathway receives input “directly” from entorhinal cortex to CA then SUB (Duvernoy, 2005). These pathways are largely conserved along the anteroposterior axis, in contrast to the afferent and efferent connections mentioned above (Andersen et al., 1971). This cytological distinctiveness between subfields could also be a basis for differential roles in memory. In rodents, studies examining immediate early gene activation in hippocampal subfields can reveal this functional heterogeneity. Increased c-fos activation in CA, but not DG or SUB corresponds to novel arrangements of familiar items (Wan, Aggleton, & Brown, 1999), and in dorsal hippocampus this corresponds with novel landmarks in a radial maze task (Vann, Brown, Erichsen, & Aggleton, 2000). In the DG, levels of another immediate early gene, Zif268, are correlated with spatial memory performance in the radial arm maze after only two training sessions, whereas CA expression of Zif268 is correlated with performance after five training sessions (Poirier, Amin, & Aggleton, 2008). Together this suggests a model of functional heterogeneity of subfields that is not only task-specific, but is also temporally-dependent.

Human studies of specialized roles of hippocampal subfields in memory are limited to a few recent high resolution (< 2 mm in-plane) fMRI studies (Bakker, Kirwan, Miller, & Stark, 2008; Das et al., 2011; Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Preston et al., 2010; Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2011; Yassa, Mattfeld, Stark, & Stark, 2011; Zeineh, Engel, Thompson, & Bookheimer, 2003) and ultra-high resolution (< 1 mm in-plane) high field structural MRI studies (Kerchner et al., 2012; Mueller, Chao, Berman, & Weiner, 2011; Mueller et al., 2012). In terms of encoding, input structures such as the DG, CA2, and CA3 are most active during this phase, while CA1, an output structure, is most active during successful retrieval (Eldridge et al., 2005; Zeineh et al., 2003). Bakker et al. (2008) found that a pattern completion task (the ability to recall a stored memory pattern in response to a degraded observation of elements of the stored pattern) elicited a blood-oxygen-level-dependent (BOLD) response in the CA1 and SUB, while pattern separation (the ability to keep distinct memory patterns separate) was associated with CA3/DG activity. More recently, this group reported an age-related reduction in pattern separation capacity in humans associated with both functional changes in CA3/DG activity and structural deterioration in the perforant path and CA3/DG area (Yassa et al., 2011). Preston et al. (2010) observed functional activation to both novel faces and scenes in all MTL regions. However, similar percentages of voxels were sensitive to novel faces and scenes in perirhinal cortex, entorhinal cortex and a combined region comprising the DG and CA2–3 subfields, whereas parahippocampal cortex, CA1 and SUB demonstrated greater sensitivity to novel scene than face stimuli. Suthana et al. (2011) reported increased activity within right CA2–3/DG sub-region during encoding compared to retrieval of spatial associations.

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