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Making Head or Tail of the Hippocampus

A Long-Axis Account of Episodic and Spatial Memory

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Abstract
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While episodic and spatial memory both depend on the hippocampus, opposite gender differences in these functions suggest they are partly separate, with different neural underpinnings. The anterior and posterior hippocampus differ in structure and whole-brain connectivity, and studies point to the posterior hippocampus being more involved in spatial memory while the anterior hippocampus' role in episodic memory is less clear. This thesis aims to explore the role of the anterior and posterior hippocampus, and associated brain regions, in episodic and spatial memory. Paper I studied gender differences in hippocampal activation underlying differences in spatial memory performance. Better performance in men was accompanied by greater right-lateralization of hippocampal activation compared to women. Paper II investigated regions of gray matter that covaried in volume with the anterior and posterior hippocampus, and whether these covariance patterns depended on gender and were related to behavior. The anterior and posterior hippocampus showed different patterns of covariance, with the anterior hippocampus covariance pattern observed in women and the posterior hippocampus covariance pattern primarily in men. Paper III considered whether the location of hippocampal recruitment in episodic memory depends on memory content. Verbal stimuli were associated with more anterior, and left-lateralized, encoding activations than pictorial stimuli, which in turn were associated with more posterior and bilateral encoding activations. This was not observed during retrieval. Paper IV investigated whether resting-state connectivity associated with the anterior and posterior hippocampus predicts episodic and spatial memory performance, respectively. Resting-state connectivity associated with the anterior, not posterior, hippocampus predicted episodic memory performance, while resting-state connectivity associated with the posterior, not anterior, hippocampus predicted spatial memory performance. This thesis lends further support to differences in function and structure between the anterior and posterior hippocampus suggesting that these two sub–segments play different roles in episodic and spatial memory. Further, it suggests that gender differences in anterior and posterior hippocampus function underlies gender differences in episodic and spatial memory, respectively. Considering the anterior and posterior hippocampus, as well as men and women, separately, is hence important when studying the effect of age and pathology on the hippocampus and associated memory functions.

Keywords: hippocampus, fMRI, episodic memory, spatial memory, gender differences

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I   Persson, J., Herlitz, A., Engman, J., Morell, A., Sjölie, D., Wikström, J., & Söderlund, H. (2013) Remembering our origin: gender differences in spatial memory are reflected in gender differences in hippocampal lateralization. *Behavioural Brain Research*, 256: 219–228

II   Persson, J., Spreng, R. N., Turner, G., Herlitz, A., Morell, A., Stening, E., Wahlund, L-O., Wikström, J., & Söderlund, H. (2014) Sex differences in volume and structural covariance of the anterior and posterior hippocampus. *NeuroImage*, 99:215–225

III   Persson, J., & Söderlund., H. (in press) Hippocampal hemispheric and long-axis differentiation of stimulus content during episodic memory encoding and retrieval: an activation likelihood estimation meta-analysis. *Hippocampus*

IV   Persson, J., Stening, E., Nordin, K., & Söderlund., H. (2015) Predicting episodic and spatial memory performance from hippocampal resting-state functional connectivity: evidence for an anterior-posterior division of function. (Unpublished manuscript)

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Contents

Abbreviations

ALE	Activation Likelihood Estimation
BOLD	Blood Oxygen Level Dependent
CA	Cornu Ammonis
DG	Dentate Gyrus
fMRI	functional Magnetic Resonance Imaging
ITI	Inter-Trial Interval
LTP	Long-Term Potentiation
LV	Latent Variable
MTL	Medial Temporal Lobe
MRI	Magnetic Resonance Imaging
MTT	Multiple Trace Theory
PET	Positron Emission Tomography
PLS	Partial Least Squares
RVR	Relevance Vector Regression
TIV	Total Intracranial Volume
VBM	Voxel-Based Morphometry

Introduction

The human brain has a remarkable capacity for storing and retrieving knowledge of the world, our surroundings, as well as unique events from our own lives. While we do constantly forget things, the amount of information that we can store seems virtually limitless and some memories last up to a lifetime. We have all experienced how a smell or a photograph can suddenly bring back memories dating back several years, triggering a vivid re-experience of an event from our distant past that we may not have pondered on for a long time. Or, imagine the relative ease with which we can conjure up an image of a familiar environment and use this mental map to find our way back from the grocery store, and even plan a novel route in case of a traffic jam.

While mentally reliving events from our personal past, termed episodic memory, and using map-like representations to flexibly navigate in our environment, here referred to as spatial memory, may seem like rather different phenomena, decades of research have shown that they do in fact depend on the same brain structure, the hippocampus. Indeed, in patients with Alzheimer's disease, where the hippocampus and adjacent structures are among the first to be affected, early symptoms include episodic memory loss and spatial disorientation.

Different theories have emerged to define a general role for the hippocampus underlying both of these functions. Some theories emphasize the spatial nature of the hippocampus, with episodic memories being dependent on its integrity due to them taking place in a spatial context (unlike, for example, memories of facts, which are free from context). Others focus on the mnemonic role of the hippocampus, pointing to its importance for associating items or events with their encoding context, whether this context is spatial in nature or not.

In contrast to these integrative views of hippocampal function, there is evidence to suggest that episodic and spatial memory may be partly separate functions, depending on different subregions of the hippocampus. First, lesion studies on rodents and imaging studies in humans suggest a special role for the posterior part of the hippocampus in spatial memory, with the function of the anterior aspect being less clear. Second, gender differences on the behavioral level in humans have been found, with a tendency for women to perform better on episodic memory and for men to excel on spatial memory. Whatever the reason for these differences, they suggest that episodic and

spatial memory functions are at least partly separate processes. In this thesis, I consider the neurological basis of episodic and spatial memory, and of the above mentioned gender differences, to pursue the idea that the hippocampus is better understood as a heterogeneous structure with at least an anterior and posterior part, sub-serving episodic and spatial memory, respectively, than as a homogeneous region with no functional differences along its longitudinal extension.
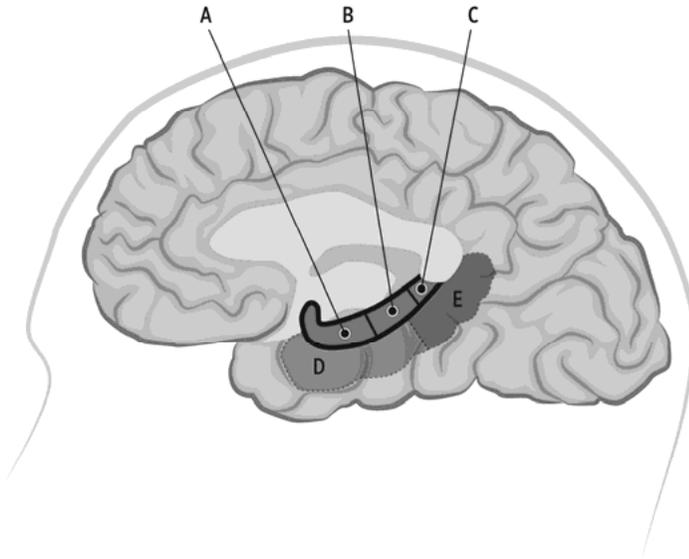
The Hippocampus

Deep within the temporal lobe of the human brain, resting on the floor of the temporal horn of the lateral ventricle, lies an elongated structure called the hippocampus (see Figure 1). This brain region was first described by the 16th century anatomist Julius Caesar Arantius in 1579, who likened its appearance to that of a sea horse, a hippocampus. Viewing this structure in a plane perpendicular to its longitudinal axis reveals its internal anatomy, consisting of two c-shaped laminae that wrap around each other (see Figure 2). The first of these c-shaped structures, the cornu ammonis (CA; meaning Ammon's horn), extends from the parahippocampal gyrus, which is found on the medial surface of the temporal lobe. It is commonly further divided into sub-regions termed CA1 through CA4 (though usually only CA1 and CA3 are considered). Wrapping around the cornu ammonis is the dentate gyrus (DG), termed after its teeth-shaped appearance from a medial view (Duvernoy, 2005; Kandel, 2013). Throughout this thesis, the term hippocampus refers to the CA, DG and subiculum, excluding the entorhinal cortex, and with no clear distinctions being made between the parasubiculum, presubiculum, and subiculum.

Anatomy, internal circuitry, and connectivity

Considering the longitudinal axis of the hippocampus, it can be divided into three sub-regions, head, body, and tail, going from the anterior to the posterior extreme (see Figure 1). While its gross anatomy appears drastically different between the head and tail, both the CA/DG configuration and the internal circuitry of the hippocampus are largely preserved throughout its longitudinal extent. The hippocampal circuitry is best considered from a cross-sectional view (see Figure 2). The hippocampus receives the bulk of its cortical afferents from the entorhinal cortex in the parahippocampal gyrus. In the trisynaptic pathway, pyramidal cells send projections via the perforant path to granular cells in the DG. The mossy fiber axons of these cells in turn terminate in CA3, whose pyramidal neurons make synaptic contact with those of CA1, via the Schaffer collaterals. CA1, finally, projects back to the entorhinal cortex. A direct pathway also exists, consisting of projections from the entorhinal cortex directly to the CA1. Thus, information flows through the hippocampus in a largely serial and unidirectional fashion (Du-

vernoy, 2005). The hippocampus is well interconnected with the neocortex. The perirhinal and parahippocampal cortices, both part of the parahippo-campal gyrus, recieve input from uni- and polymodal association cortices, which they in turn project onto the hippocampus via the entorhinal cortex (Suzuki & Amaral, 1994a, 1994b). The hippocampus thus receives highly processed input from distributed brain regions.

Figure 1. Medial view of the right hemisphere with a schematic representation of the hippocampus (A–C) and parahippocampal gyrus (D–E). (A) hippocampal head, (B) hippocampal body, (C) hippocampal tail, (D) perirhinal cortex, and (E) parahippo-campal cortex.
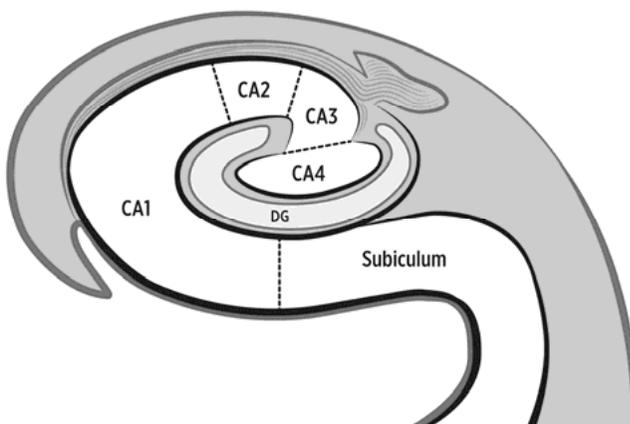
Figure 2. Cross-sectional view of the hippocampus showing its sub-regions. CA = Cornu Ammonis; DG = Dentate Gyrus.

Mechanisms for memory

Before the neural mechanisms of memory encoding were known, Hebb (1949) proposed synaptic plasticity as a possible mechanism for how the brain becomes altered by experience. The idea was simple; if a cell takes part in persistently firing another, the synaptic coupling between those cells is strengthened. A mechanism for synaptic plasticity in the hippocampus was first observed by Lømo in 1966 (Lømo, 2003). He found that after a high-frequency train of stimulation in the presynaptic part of the perforant path in the rabbit hippocampus, subsequent presynaptic stimulation led to a heightened response in the postsynaptic DG cells. This so called long term potentiation (LTP) could persist for several days. LTP has since been demonstrated in all synapses of the trisynaptic pathway, but the underlying mechanisms differ. LTP in the Schaffer collaterals is of particular interest for the hippocampus' role in memory, since it is associative.

Schaffer collateral LTP is mediated by postsynaptic N-Methyl-D-Aspartate (NMDA)-receptors that work as incidence detectors, that is, they activate only when postsynaptic depolarization and synaptic release of glutamate co-occur. Due to the properties of the NMDA-receptor, a weak stimulus that is not by itself sufficient to induce synaptic plasticity, can, in the presence of a strong input, become significant, allowing associations to be formed between, for example, a significant event and the context in which it took place. Blocking NMDA receptors in the CA1 area of mice, impairs the formation of new, but not the expression of already formed, spatial memories. Hence, NMDA-mediated LTP in the hippocampus is a strong candidate mechanism underlying its role in long term memory (Kandel, 2013).

Taken together, the hippocampus receives highly processed and distributed sensory input, as well as exhibiting synaptic plasticity mechanisms enabling the hippocampus to link together the cortically distributed representations that comprise the complex spatial environments that we encounter, as well as the events occurring within them, storing these associations for later reinstatement.

The hippocampus and episodic memory

In 1953, Henry Molaison (H.M.), then 27 years old, underwent a surgical procedure whereby a portion of his medial temporal lobe (MTL), bilaterally, was removed, including the amygdala and the anterior half of the hippocampus and parahippocampal gyrus. This was done in an attempt to treat his severe and medically intractable epilepsy, and while it did reduce the frequency of seizures, it also had the catastrophic consequence of introducing severe anterograde amnesia. That is, he lost the ability to form new long-term memories of post-surgical events. He also displayed retrograde amnesia with what appeared to be a temporal gradient, that is, memories formed during a few years prior to surgery were lost while older memories were retained. However, as reviewed below, his retrograde amnesia was later found to affect memories from the entire life-span. His case was one of pure amnesia, in that intellectual abilities, perception, attention, and language were intact (Augustinack et al., 2014; Scoville & Milner, 1957).

H.M. also showed evidence of preserved memory abilities. He had an intact working memory and could acquire new skills, despite having no memory of prior training episodes. Priming and classical conditioning were also intact (Augustinack et al., 2014; Corkin, 1968; Milner, Corkin, & Teuber, 1968). These findings, together with lesion studies in primates, led to the formulation of an MTL memory system model (Squire & Zola-Morgan, 1991), which states that the hippocampus and surrounding cortex plays an important, but time limited, role in the acquisition and retention of memories for both facts and events, referred to as declarative memory. According to this view, the MTL is initially necessary to retrieve a memory, by binding together the distributed neocortical sites that together represent the past event. However, over time this memory trace becomes independent of the MTL through a process termed systems consolidation. Although this view of hippocampal functioning has been very influential, it has subsequently been challenged.

Case studies on patients with more circumscribed lesions have shown that damage restricted to the hippocampus is sufficient to produce amnesic symptoms similar to those of H.M. (Rosenbaum et al., 2005; Zola-Morgan, Squire, & Amaral, 1986). Notably, in the case of one patient K.C., it became apparent that hippocampal damage selectively impairs episodic memory, while sparing semantic memory (Rosenbaum et al., 2005). Episodic memory refers to memory of personally experienced events, tied to a specific place

and time, or spatiotemporal context, and associated with a recollective experience that entails a subjective awareness of mentally re-experiencing the past event, so called autonoetic awareness. Semantic memory, on the other hand, refers to generalized, factual knowledge, associated with a sense of knowing, but without the recollective experience that is characteristic of episodic memories, and removed from its spatiotemporal encoding context (Tulving, 2002). Accordingly, K.C. had factual knowledge of his personal life, and while he could recognize and name family members from photographs, he could not recall the occasion on which the picture was taken or any episodic details associated with it (Rosenbaum et al., 2005).

This, and other observations, led to the formulation of the Multiple Trace Theory (MTT; Nadel & Moscovitch, 1997), according to which the hippocampus plays a permanent role in episodic memory, but a time limited one in semantic memory. This theory agrees that memories can become independent of the hippocampus over time, through repeated retrieval and re-encoding into multiple memory traces, strengthening associations between neocortical representations within the overlap of these traces. However, in the process these memories become decoupled from their original encoding context and lack the phenomenological qualities, such as vividness and sense of re-experiencing the past, that accompany hippocampus-dependent episodic memories; they become semantic memories. Thus, MMT predicts life-long retrograde amnesia for episodic memories following hippocampal damage. By carefully reexamining H.M. and other amnesic cases, using a standardized interviewing procedure that teases apart episodic and semantic components of autobiographical memory (The Autobiographical Interview; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002), this prediction was supported. A lifelong deficit in the retrieval of autobiographical episodic memories was found, while remote semantic memory retrieval was comparable to controls, much like in the case of K.C (Rosenbaum et al., 2008; Steinvorth, Levine, & Corkin, 2005).

In conclusion, years of research on amnestic cases point to a crucial and permanent role for the hippocampus in episodic memory, by binding together representations of the discrete components and their context, which together comprise a unique event, into a memory trace for later reinstatement.

The hippocampus and spatial memory

The hippocampus is thought to hold cognitive map-like representations of our environments, enabling flexible navigation within them, an idea that was first proposed by Tolman, based on observations in rodents (Tolman, 1948). Then, the prevailing view was that spatial learning was the result of reinforced stimulus-response associations. Tolman observed that rodents that had been trained to traverse a maze for a food reward would, when finding that this route had been blocked, choose a novel route leading to the reward. This was a strong indication that the rodents had developed an internal representation of the environment and could use this "map" to plan a novel, untrained route. It was not until 1971, however, that a neural mechanism for this cognitive map was revealed (O'Keefe & Dostrovsky, 1971). At that time, while the case of H.M. had spurred interest in studying hippocampal function in rodents, the tasks used were not appropriate for tapping hippocampal functioning and a failure to observe memory impairment following hippocampal lesions led to the conclusion that the rodent hippocampus served a different function, being instead involved in behavioral inhibition (e.g. Kimble, 1968).

When O'Keefe and Dostrovsky (1971) recorded cellular activity in the hippocampus of freely moving rats, they observed cells that fired only in specific spatial locations. Further testing has shown that these place cells respond regardless of head orientation or specific sensory cues (O'Keefe, 1976), and that several place cells firing at different locations together make up a complete map of the environment. The firing locations of cells are reinstated when revisiting a familiar environment, but are rearranged between place cells if the environment is sufficiently altered, through a process termed remapping (Moser & Moser, 1998). Taken together, place cells exhibit properties that implicate a role for them in spatial memory. Based on these findings, O'Keefe and Nadel (1978) formulated the cognitive map theory of hippocampal function, linking Tolman's idea of a cognitive map to hippocampal place cells, and proposing that we have an innate spatial framework through which we internally represent and experience the world.

That these spatial representations held within the hippocampus play a causal role in navigation and spatial memory has since been demonstrated with lesion studies, most famously with the Morris Water Maze (Morris, Garrud, Rawlins, & O'Keefe, 1982; Morris, 1981). In this task, a platform is hidden below the surface of opaque water in a tank. Normal rats quickly

learn to swim directly toward this platform even from novel starting points, as long as the platform remains stationary over trials. However, after hippocampal lesioning, performance is profoundly impaired, but on par with controls when navigating to a visible platform. Hence, the hippocampus is crucial for solving spatial tasks that rely on allocentric (world-centered), viewpoint-independent spatial representations of the environment, or cognitive maps.

While much research on the hippocampus role in spatial memory has focused on rodents, spatial deficits in humans following hippocampal damage are well documented. H.M. had profound difficulties navigating in his own neighborhood, and with formal testing, he was impaired on maze learning tasks (Corkin, 2002). Further, patients with unilateral lesions of the hippocampus are impaired on tasks designed to emulate the Morris Water Maze and other spatial memory tasks (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004). However, similarly to the selective deficits in episodic memory following hippocampal damage, schematic knowledge of familiar environments is preserved in amnesic patients. A London taxi driver with bilateral hippocampal lesions was able to navigate a virtual version of London using main routes, but showed impaired performance in situations that required retrieving detailed spatial representations (Maguire, Nannery, & Spiers, 2006). Similar findings have been made with patient K.C. as well (Rosenbaum et al., 2000). Importantly, single-cell recordings in humans during virtual navigation have identified hippocampal units that exhibit place cell properties (Ekstrom et al., 2003).

It is worth noting that navigation is enabled by different memory systems, associated with different cognitive strategies. What is commonly referred to as an allocentric, or spatial, strategy is dependent on the hippocampus and relies on the spatial relationships between landmarks, independent of viewpoint, allowing for flexible navigation in the sense that any goal can be reached directly from any starting point. In contrast, an egocentric (self-centered), or route-based, strategy relies more on the striatum, uses stimulus-response associations (for example turn left at the school building) and thus is less flexible (Bohbot, Del Balso, Conrad, Konishi, & Leyton, 2013; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). This thesis focuses on the spatial navigation and memory functions sub-served by the hippocampus.

Integrative views of hippocampal function

As reviewed above, two lines of research have demonstrated the central role of the hippocampus in episodic memory on the one hand, and in spatial memory and navigation, on the other. These observations lead to the question of how to best characterize hippocampal function in a way that takes both of these observations into account. In other words, is there a common underlying function that the hippocampus serves in both episodic and spatial memory? Here, two prominent viewpoints are briefly reviewed.

The hippocampus is fundamentally spatial

According to this view, the hippocampus is specialized for processing spatial information and episodic memories are reliant on this brain region to the extent that they involve spatial representations. O'Keefe and Nadel (1978) proposed a link between Tulving's concept of episodic memory and their cognitive map theory of hippocampal function, arguing that the hippocampus plays a permanent role in the memory for events that are tied to a spatio-temporal context, by virtue of cognitive maps, with an emphasis on the spatial component of context. In support of this, hippocampal damage leads to impairment in an object-location task only when recognition is assessed from a novel viewpoint, a task that requires an allocentric representation (King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004). Similarly, the hippocampus is thought to be important for scene construction, or recollecting the spatial context of an episodic memory in service of mental imagery that is core to the recollective experience (Burgess, 2008; Hassabis & Maguire, 2007).

The hippocampus is fundamentally relational

According to the relational memory viewpoint, the hippocampus is important for storing associations among elements that comprise an event, where spatial relationships are but one example. In other words, there is nothing special about spatial (Cohen & Eichenbaum, 1991). Other associations that rely on the hippocampus include item-item and sequential, or temporal, associations, and non-spatial associative networks (Eichenbaum, 2000,

2004). In support of this, it has been observed that many hippocampal cells do not display pure place cell properties, but respond to conjunctions between, for example, an odor and its location (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999). Further, the spatially selective firing of hippocampal cells is sensitive to task demands and the strategy used to solve the task (Smith & Mizumori, 2006). One study that directly compared the spatial and relational viewpoints of hippocampal functioning found that the hippocampus was only activated during spatial navigation but not non-spatial relational processing on closely matched tasks, supporting the former viewpoint (Kumaran & Maguire, 2005).

Both these views point to similarities and overlapping processes between episodic and spatial memory. At the same time, the two memory types are theoretically separable, with spatial representations within the hippocampus not necessarily being confined to declarative long-term memory, but reflecting online processing or gradually acquired spatial knowledge as well, while some episodic memories can be rich in temporal and linguistic associations with less emphasis on spatial associations (see e.g. Burgess, Maguire, & O'Keefe, 2002). I will now turn to evidence at the behavioral level suggesting that episodic and spatial memory are partly separate functions.

Gender differences in hippocampal functions

Overall, men and women are similar on many cognitive measures, as well as within other psychological domains (Hyde, 2005). However, some gender differences consistently emerge. While women tend to outperform men in verbal and episodic memory tasks, a male advantage is usually seen in certain spatial abilities. I will now consider these two instances of cognitive gender differences in turn.

Gender differences in spatial tasks

A large-scale review of gender differences within several domains by Maccoby and Jacklin (1974) established the presence of a male advantage on a range of spatial tasks. However, this review did not differentiate between subtypes of spatial abilities. In a meta-analysis by Linn and Petersen (1985), studies were grouped into categories of spatial tests with homogeneous effect sizes, and gender differences were observed within spatial perception tasks and mental rotation, with the largest effect sizes in the latter category. This finding was confirmed in a later meta-analysis (Voyer, Voyer, & Bryden, 1995). Notably, in a spatial task where memory for the location of objects presented in a spatial array was assessed, this gender difference was reversed, instead showing a female advantage (Voyer, Postma, Brake, & Imperato-McGinley, 2007). This task depended on egocentric representations of the objects in relation to oneself. Using a virtual version of the Morris Water Maze, a task tapping allocentric spatial representations as noted earlier, Astur, Ortiz and Sutherland (1998) found a large gender difference favoring males after taking differences in video gaming experience into account. Where cognitive processes are concerned, men and women tend to employ different strategies for solving spatial navigation tasks, where women rely more on landmarks, verbal strategies and egocentric representations and men on geometry, spatial strategies and allocentric representations for navigation (Dabbs Jr., Chang, Strong, & Milun, 1998; Frings et al., 2006; Sandstrom, Kaufman, & Huettel, 1998). The spatial tasks showing gender differences range from traditional paper and pencil tasks, to large-scale navigation. While likely tapping somewhat different functions, one study did find that traditional small scale tasks, such as mental rotation, predicted performance in estimating directions and distance in a real-life environment,

with both tasks showing gender differences (Hegarty, Montello, Richardson, Ishikawa, & Lovelace, 2006).

Gender differences in episodic memory tasks

Although receiving less attention, gender differences favoring females in episodic memory (Herlitz, Nilsson, & Bäckman, 1997; Herlitz & Rehnman, 2008) have also been identified. These differences have been observed with a range of study materials, including words and narratives, face-name pairings, pictures, and odors, using both recall and recognition assessments. Included here are also the object-location tasks mentioned under the preceding heading. This female advantage in episodic memory remained when controlling for the female advantage in general verbal abilities, and no gender differences were observed on verbal semantic memory tasks (Herlitz et al., 1997). A few studies have focused on gender differences in face recognition and found that women's greater performance on this type of task is greater for female than male faces (Lewin & Herlitz, 2002; Lovén, Herlitz, & Rehnman, 2011).

In summary, the few cognitive domains where gender differences are reliably found are visuospatial and verbal abilities, extending into performance on spatial and episodic memory tasks. Curiously, these two memory types are those mainly associated with hippocampal function. Thus the observation of opposite gender differences in episodic and spatial memory suggests that they may be partly separate functions, in which case they may have different neural underpinnings as well. I will now turn to evidence of structural and functional differentiation within the hippocampus, and consider the possibility that episodic and spatial memory depend on different parts of the hippocampus.

Long-axis differentiation of the hippocampus

In contrast to viewing the hippocampus as a homogeneous structure, there is evidence of differences in structure and function along its longitudinal axis. The hippocampal anatomy along this dimension is sometimes divided into three sub-segments, head, body, and tail, distinguished by differences in gross anatomy (Malykhin et al., 2007). However, accounts of functional heterogeneity within the hippocampus usually only make a distinction between an anterior and posterior part, a division which is often poorly defined anatomically. Here, as well as in papers II and IV a distinction is made between the anterior and posterior hippocampus, where the anterior hippocampus corresponds to the hippocampal head, and the posterior hippocampus to the body and tail, with the delineation between them just posterior of the uncal apex (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). In paper I the posterior hippocampus is instead defined as corresponding to the hippocampal tail, excluding the hippocampal body. Note that due to being differently oriented in the rodent brain, the anterior and posterior hippocampus are instead referred to as ventral and dorsal, respectively, when considering these species. I will be using the terms anterior/ventral and posterior/dorsal interchangeably, depending on context.

Differences in structure and cell properties

Anatomically, there is a difference in the proportions between sub-regions, with a smaller DG to CA ratio in the anterior compared to the posterior hippocampus, as measured by manually tracing the volumes on structural magnetic resonance imaging (MRI) scans (Malykhin, Lebel, Coupland, Wilman, & Carter, 2010). On a molecular level, marker genes have been used to parcellate the hippocampus into dorsal and ventral sub-segments that differ in the expression of a number of genes within CA1 (Dong, Swanson, Chen, Fanselow, & Toga, 2009), CA3 (Thompson et al., 2008), and DG (Fanselow & Dong, 2010). Further, field potentials in CA1 following stimulation differs, with more complex spiking patterns in the ventral than dorsal hippocampus (Gilbert, Racine, & Smith, 1985), and the concentration of metabolites is higher in the posterior than anterior hippocampus, as revealed with magnetic resonance spectroscopy (King et al., 2008). Finally, the density of axon terminals for norepinephrine, dopamine, and serotonin is greater in the

ventral than dorsal hippocampus (Gage & Thompson, 1980; Verney et al., 1985); while greater cholinergic innervation is observed in the dorsal than ventral hippocampus (Amaral & Kurz, 1985).

Differences in connectivity

A combination of tracer studies in animals and imaging studies in humans has revealed important differences between the anterior and posterior hippocampus in terms of connectivity as well. Internally, the hippocampus is organized in a lamellar fashion in the perforant and mossy fiber paths, and while longitudinal connectivity is present within the CA3, there is overall little direct connectivity between the anterior and posterior parts (Sloviter & Lømo, 2012). The anterior and posterior hippocampus receive projections from two sparsely interconnected parts of the entorhinal cortex, the medial and lateral bands, respectively, as tracer studies in rodents and monkeys have shown. The entorhinal cortex, in turn, receives the bulk of its input from two regions in the MTL, the perirhinal and parahippocampal cortex (Fanselow & Dong, 2010). Distinct cortical afferent projections to the perirhinal and parahippocampal cortices have been observed in the macaque brain. The perirhinal cortex receives the bulk of its input from unimodal visual areas TE and TEO. Weaker input is also observed from the dorsal bank of the superior temporal sulcus, as well as orbitofrontal and insular cortices. Notably, the perirhinal cortex receives virtually no input from the parietal lobes. The parahippocampal cortex, in contrast, receives projections from the cingulate and retrosplenial cortices, as well as visual area V4 and the posterior parietal cortex (area 7a). Importantly, the perirhinal and parahippocampal cortices are also interconnected with each other (Suzuki & Amaral, 1994a). While the perirhinal and parahippocampal cortices project to both the medial and lateral bands of the entorhinal cortex in rodents (Fanselow & Dong, 2010), connectivity as measured in the resting state in humans show that the anterior hippocampus is preferentially connected to the perirhinal, and the posterior hippocampus to the parahippocampal, cortex (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Libby, Ekstrom, Ragland, & Ranganath, 2012).

Taken together, evidence from monkeys and rodents of hippocampal-cortical interconnections places the hippocampus on top of a hierarchy, receiving highly processed input from diverse uni- and polymodal association areas (Lavenex & Amaral, 2000). This structural organization is characterized by two parallel pathways, corresponding to the dorsal and ventral visual streams (Goodale & Milner, 1992). While interconnectivity between these two pathways is present at different levels of the hierarchy, imaging studies in humans suggest that they are partly kept separate even within the hippocampus.

Apart from the entorhinal cortex, the anterior and posterior hippocampus show distinct patterns of connectivity with other brain regions as well. The anterior hippocampus is interconnected with the amygdala, temporal pole and ventromedial prefrontal cortex, via the uncinate fasciculus, while the posterior hippocampus shows connectivity with the retrosplenial and anterior cingulate cortices and mammillary bodies, via the fornix. This has been demonstrated in rodents, and confirmed in humans using tractography and resting-state connectivity (Fanselow & Dong, 2010; Kahn et al., 2008; Kier, Staib, Davis, & Bronen, 2004; Libby et al., 2012; Poppenk & Moscovitch, 2011).

In sum, the anatomy, cellular and electrophysiological properties, and internal organization of the hippocampus, as well as its structural and functional whole-brain patterns of connectivity, all show important differences along this brain regions' longitudinal extent. This enables the anterior and posterior hippocampus to receive different information, as well as to process the information differently, ultimately optimizing the two sub-segments for different functions.

Differences in function

The idea of the anterior and posterior hippocampus as functionally distinct sub-segments is not a new one. In 1968, Nadel reported on the effect of ventral versus dorsal lesions in the rat hippocampus, though this was before its role in memory was demonstrated (Nadel, 1968). This issue has been revisited in more recent years from different viewpoints, based to different degrees on lesion and imaging studies.

Encoding versus retrieval

Based on hippocampal activations from several positron emission tomography (PET) studies during episodic encoding or retrieval, it was proposed that the anterior hippocampus was important for encoding episodic memories, while the posterior part was mainly involved in episodic retrieval (Lepage, Habib, & Tulving, 1998). This model was termed the hippocampal encoding/retrieval (HIPER) model. The validity of the model was soon brought into question when a later study failed to replicate the findings (Schacter & Wagner, 1999). Due to this, and the lack of a theoretical framework, the model has remained outside the focus of attention. However, more recent meta-analyses based on functional MRI (fMRI) studies have provided new support for HIPER (Kim, 2014; Spaniol et al., 2009) when using more advanced meta-analytical approaches.

Vestibular versus visual memory

Another view on functional differences between the anterior and posterior hippocampus focuses on the hippocampus' role in spatial navigation (Hüfner, Strupp, Smith, Brandt, & Jahn, 2011). Vestibular stimulation frequently activates the anterior hippocampus, while visual stimulation activates the posterior part. Based on this finding, the anterior hippocampus is proposed as important for aspects of navigation building on vestibular input, such as path integration, while the posterior part is involved in visually based navigation, such as landmark recognition and processing of visual flow. Note, however, that the anterior hippocampus does receive visual input from the temporal cortex, as reviewed above.

Cognitive versus emotional functions

It has been proposed that the anterior hippocampus is primarily involved in emotional and motivational functions while the posterior hippocampus is more important for cognitive functions (Fanselow & Dong, 2010; Murty, Ritchey, Adcock, & LaBar, 2010). This is consistent with the connectivity between the anterior hippocampus and the amygdala, insula and ventromedial prefrontal cortex, as well as its interactions with the hypothalamic-pituitary-adrenal (HPA) axis through which it exerts control over stress responses. Lesion studies showing differential effects in spatial cognition on the one hand and anxiety related behaviors and fear conditioning on the other are taken to support this. At the same time, dorsal hippocampal lesions have been shown to impair contextual fear conditioning as well (Kim & Fanselow, 1992; Quinn, Loya, Ma, & Fanselow, 2005) suggesting that the anterior and posterior hippocampus may both contribute to emotional functions.

Memory remoteness and novelty

Comparisons of hippocampal activations evoked by retrieving recent and remote autobiographical memories showed that activations associated with recent memories were confined to the anterior hippocampus, while remote memory activations were distributed along the hippocampal axis (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004). In a similar study, both the anterior and posterior hippocampus were recruited during autobiographical memory retrieval, though anterior hippocampus activation increased with the remoteness of the retrieved memories up to one year and then decreased (Söderlund, Moscovitch, Kumar, Mandic, & Levine, 2012). The seemingly contradictory findings of these studies may be due to them assessing memories of different age ranges. Still, they both indicate that the distribution of activation along the hippocampal axis is modulated by the remoteness of autobiographical memories. A machine learning approach to classifying

between memories of different ages based on fMRI data showed that the posterior hippocampus contained more information than the anterior hippocampus about remote memories (Bonnici et al., 2012). The more distributed activation to remote memories has been interpreted in light of MTT, which proposes that older memories, which have been repeatedly retrieved and re-encoded into multiple memory traces, are more likely to be distributed along the hippocampal axis (Gilboa et al., 2004), or alternatively, that reconstruction of the encoded events at retrieval take place in the posterior hippocampus, and that remote memories rely more on this process than more recent ones (Bonnici et al., 2012).

Occuring on a much shorter time-scale, the anterior and posterior hippocampus have been found to play different roles depending on the novelty of stimuli as well. While the anterior hippocampus activity decreased in response to repeated presentations of stimuli, the opposite pattern was observed in the posterior hippocampus (Strange & Dolan, 1999).

An episodic-spatial account of long-axis specialization

Complementary to the above viewpoints, the functional distinction between the anterior and posterior hippocampus may be viewed in terms of episodic and spatial memory. This is congruent with their differences in connectivity, as reviewed above. The dorsal visual stream, showing connectivity mainly with the posterior hippocampus, is associated with spatial representations, while the ventral visual stream, showing preferential connectivity with the anterior part, is associated with non-spatial object representations (Goodale & Milner, 1992; Suzuki & Amaral, 1994a). The regions showing connectivity with the posterior hippocampus, including the posterior parietal cortex, the retrosplenial cortex, and the parahippocampal cortex, are all involved in spatial functions (Ciaramelli, Rosenbaum, Solcz, Levine, & Moscovitch, 2010; Epstein, 2008), suggesting a role for the posterior hippocampus in spatial memory. In contrast, the regions associated with the anterior hippocampus, including the perirhinal and anterior temporal cortex and the amygdala, suggests that this sub-segment may be involved in episodic memory. The perirhinal cortex is involved in item encoding and recognition (Brown & Aggleton, 2001; Staresina & Davachi, 2008) and lateral and anterior parts of the temporal cortex are areas associated with semantic memory (Peelen & Caramazza, 2012; Rogers et al., 2006). Semantic retrieval is tightly linked to episodic encoding (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). The connectivity between the anterior hippocampus and amygdala can also be linked to episodic memory, with emotionality of retrieved autobiographical memories modulating hippocampal activity (Addis, Moscovitch, Crawley, & McAndrews, 2004) and emotionally salient stimuli being associated with enhanced episodic memory (Kensinger & Schacter, 2005).

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Several lines of evidence point to a special role for the posterior part of the hippocampus in spatial functions. First, cell recordings in rats have shown that the density of place cells is greater in the dorsal than ventral part and that dorsal place cells respond with higher spatial specificity to locations than ventral cells (Jung, Wiener, & McNaughton, 1994). In line with this, selective lesions of the dorsal, but not ventral, hippocampus lead to impaired performance on the water maze task (Moser, Moser, Forrest, Andersen, & Morris, 1995). In a seminal study, it was shown that the posterior hippocampus was larger in London taxi drivers than in controls, while the anterior part was smaller. Further, posterior hippocampal volume showed a positive correlation with the time spent as a taxi driver with a corresponding negative correlation in the anterior hippocampus (Maguire et al., 2000). Later, a longitudinal study took advantage of the fact that becoming a London taxi driver involves years of studying the complex street layout of the city. Those that qualified showed a significant increase in posterior hippocampus gray matter, with no change in trainees that failed, strengthening the conclusion that spatial learning and memory causes structural changes in the posterior hippocampus (Woollett & Maguire, 2011).

While the role of the anterior hippocampus is more uncertain, there are findings to suggest that it is preferentially involved in episodic memory. One study investigated hippocampal activation during episodic and spatial retrieval in Toronto residents by showing them pairs of well-known landmarks from the city. In the spatial condition, they judged, for example, which landmark was furthest to the north, while in the episodic condition they had to determine which landmark they had most recently visited. Spatial retrieval uniquely recruited the right posterior hippocampus, while the episodic condition was associated with right anterior and more distributed left hippocampal activation (Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012). Further, successful encoding of associations between stimuli, a task commonly used to assess episodic memory, involves anterior hippocampal activation (e.g. Chua, Schacter, Rand-Giovannetti, & Sperling, 2007). A recent meta-analysis on PET and fMRI studies found that spatial memory encoding recruits the posterior hippocampus and adjacent MTL, while episodic memory encoding recruits more anterior segments (Kühn & Gallinat, 2014). However, these episodic encoding related activations were distributed along a large part of the hippocampal axis and parahippocampal gyrus. Given that this reflected clustered activation across many individual studies, with diverse ways of assessing memory, different aspects of episodic memories may influence the long-axis location of activations. For example, as mentioned above, while retrieval of recent autobiographical memories recruits the anterior hippocampus, remote autobiographical memory activations are more spread out along the hippocampus' axis (Gilboa et al., 2004). Also, while the initial retrieval of autobiographical memories activates the anterior hippocampus, elaborating on the retrieved episode is associated with

posterior hippocampus activations (McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2013). More research is needed to determine what aspects influence the recruitment of different sub-segments along the hippocampus during episodic encoding and retrieval.

Lateralization of hippocampal function

In addition to functional differences between the anterior and posterior hippocampus, there is evidence supporting lateralization of hippocampal functioning, that is, the left and right hippocampus being functionally different, and findings from patients with unilateral hippocampal lesions and resections are particularly informative in this case. Studies on patients undergoing unilateral MTL resection to treat epilepsy show that resection of the left, but not right, hippocampus impairs memory on verbal tasks, including learning and retention of prose passages (Frisk & Milner, 1990), word recognition and recall (Baxendale, 1997; Bohbot et al., 1998) as well as verbal associative memory (Meyer & Yates, 1955). In contrast, right hippocampal and parahippocampal resections, but not left, lead to impaired performance on visuo-spatial tasks (Bohbot et al., 1998). After navigating through a virtual town, patients with left hippocampal resections were impaired on episodic memory for events occurring within the environment, while those with right sided resections were impaired on scene recognition and map drawing from memory of the same environment (Spiers et al., 2001). This is consistent with lateralized hippocampal activations on the same task (Burgess et al., 2002).

Hippocampal lateralization within spatial memory, reflecting cognitive strategy, has also been observed. In a virtual water maze task with verbalizable cues, both left- and right-sided hippocampal resections resulted in impaired performance compared to controls, whereas using abstract, non-verbalizable, cues led to impaired performance for right-resected patients only (Barkas, Henderson, Hamilton, Redhead, & Gray, 2010). In healthy participants, left-lateralized hippocampal activation predicted spontaneous employment of an egocentric, sequential strategy, while right-lateralized activation predicted use of an allocentric spatial strategy (Iglói, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010). Gender differences in hippocampal lateralization during a spatial task have also been reported, with more left-lateralized activation in women and right-lateralized activation in men, related to women's greater reliance on a verbal strategy and men's preferential use of a non-verbal spatial strategy (Frings et al., 2006).

Taken together, there are functional differences between the left and right hippocampus, with spatial memory being associated mainly with the right hippocampus and episodic memory with the left hippocampus, though this

lateralization may depend on the degree to which the task enables a verbal strategy.

To summarize this introduction, the human hippocampus is known to be crucial for intact episodic memory, as well as spatial memory. While theoretical views on hippocampal functioning have attempted to place these two memory functions within a common framework, opposite gender differences in episodic and spatial memory performance suggest that they may be partly separate functions, depending on different brain regions.

Earlier findings indicate that the anterior and posterior hippocampus show important differences in structure and function, with the posterior hippocampus being important for spatial memory and the anterior hippocampus possibly being preferentially involved in episodic memory. Still, more research is needed in this regard.

Given this functional division along the hippocampal axis, gender differences in the function and structure of the anterior and posterior hippocampus, reflecting behavioral differences, would be expected. However, the neural underpinnings of these gender differences are largely unknown. Understanding the gender differences in these memory functions on a neural level would be helpful in developing our theoretical understanding of hippocampal function, and has potential clinical relevance, with many pathologies being associated with hippocampal atrophy, which may affect men and women differently. Indeed, gender differences in hippocampal volume reduction in schizophrenia and mild cognitive impairment have been observed (Bryant, Buchanan, Vladar, Breier, & Rothman, 2014; Fleisher, Grundman, Jack Jr, & et al, 2005), and the effect of unilateral hippocampal resection as a treatment for epilepsy was different for men and women (Trenerry, Jack Jr., Cascino, Sharbrough, & Ivnik, 1995).

While the importance of the posterior hippocampus for spatial memory abilities is fairly well established, the role of the anterior hippocampus in episodic memory is more unclear. More research is needed to establish if, and under what circumstances, the anterior hippocampus sub-serves episodic memory function. Finally, the anterior and posterior hippocampus are part of partly separate networks, as evident from their differing whole-brain connectivity. Whether the proposed functional division between these two hippocampal sub-segments extends to their respective networks as well remains to be established.

Magnetic resonance imaging

MRI is a widely used neuroimaging method within cognitive neuroscience research, to assess regional morphology and activation across the entire brain. It provides a good tradeoff between spatial and temporal resolution, meaning that it is well suited for studying regional fluctuations in brain activity over time. In MRI, the subject is placed in a strong static magnetic field along which the protons in the brain align themselves, and a radiofrequency pulse is then emitted that excites the protons. When the radiofrequency pulse is switched off, the protons will once again realign with the magnetic field during which they emit a signal that is used to reconstruct an image of the brain. By changing the timing of different parameters in this basic imaging sequence, images of different modalities can be acquired. This thesis takes advantage of two such imaging modalities.

The anatomical images that are the basis for volumetric assessment of brain structures are three-dimensional images, with the advantage of having high spatial resolution and good contrast between gray and white matter. For this reason, they are also used to overlay functional activation maps on, to provide better localization of where changes in brain activity occur.

fMRI takes advantage of regional increases in oxygenated blood that follow increases in neural activity in response to a task. The signal measured in fMRI, being sensitive to these changes in blood oxygenation, is referred to as the blood-oxygenation-level dependent (BOLD) signal. Due to the nature of this signal, absolute levels of neural activity cannot be inferred from it, but have to be assessed relative to a control, or baseline, task. Therefore, tasks used with fMRI often alternate between two conditions, chosen such that contrasting them against each other will isolate the brain regions that are involved in, for example, the cognitive process of interest (Huettel, Song, & McCarthy, 2009).The term activation in this thesis refers to such relative differences in BOLD response.

In addition, this thesis takes advantage of the whole-brain spatial information in the MR-images to look at the covariation between the hippocampus and other brain regions in terms of gray matter volume, as well as fluctuations in activation at rest. Functional connectivity in the resting state is reflective of the underlying structural connectivity while also being sensitive to indirect connectivity between brain regions (Greicius, Supekar, Menon, & Dougherty, 2009; Honey et al., 2009). Covariance in gray matter volume between brain regions, while less studied, has been shown to correspond to

both structural and functional connectivity, and is observed for sets of brain regions that are involved in similar functions (Alexander-Bloch, Giedd, & Bullmore, 2013). Consequently, the study of structural covariance and resting-state functional connectivity in relation to the hippocampus has the potential to increase our understanding of its functional-anatomic organization and whether this differs between its anterior and posterior aspects.

Aims

The overarching aim of this thesis is to investigate the role of the anterior and posterior hippocampus in episodic and spatial memory. First, gender differences in function (paper I) and structure (paper II) of the hippocampus will be studied, focusing on differences in the anterior and posterior hippocampus, which may underlie differences in episodic and spatial memory performance. Further, due to the heterogeneity of episodic memories, and the distributed hippocampal activations associated with them, factors that may determine the long-axis location of hippocampal activation during episodic memory encoding and retrieval will be considered (paper III). Finally, the role of the anterior and posterior hippocampal whole-brain networks, as reflected in resting-state connectivity, in episodic and spatial memory will be considered (paper IV). In all papers, hippocampal lateralization will be taken into account.

More specifically, this thesis will address whether

- gender differences in spatial memory performance are related to gender differences in anterior and posterior hippocampal activation during a spatial memory task (paper I)
- men and women differ in volume of the anterior and posterior hippocampus, and their associated regions, and whether this is related to episodic and spatial memory performance (paper II)
- the content of episodic memories, i.e. stimulus type, determines the long-axis location of hippocampal encoding and retrieval activations (paper III)
- patterns of resting-state connectivity associated with the anterior and posterior hippocampus are predictive of episodic and spatial memory, respectively (paper IV)

Methods

Project overview

Papers I, II and IV are all based on two data collections made at the Akademiska Hospital and the Department of Psychology, Uppsala University. During the first data collection, memory tasks were performed inside the scanner using fMRI, while during the second data collection, all memory tasks were performed outside the scanner. These two data sets are here referred to as the functional and structural data sets, though functional resting-state data were indeed collected in the later structural data set.

Functional data set

Participants

24 participants (12 women, 12 men) were recruited from the Uppsala University campus area via flyers. Those who were between 18 and 35 years of age, right-handed with no contraindications for MRI, and without any history of substance abuse, brain injury or neurological disease, were eligible for inclusion. Women and men were comparable in terms of age and years of education (see Table 1). All participants gave informed consent as approved by the regional ethics review board in Uppsala and received either monetary compensation or cinema vouchers.

Procedure

All data collection took place at the Akademiska Hospital. After training on practice versions, participants were put in the scanner where they performed fMRI versions of the memory tasks. These tasks were presented via goggles connected to a laptop computer, and participants used MRI-compatible buttons to perform them. In addition, a structural image and diffusion tensor imaging (DTI) data were collected (the latter used to assess white matter integrity and not considered further in this thesis). Order of presentation of the fMRI tasks was word-list encoding, pointing, object-location encoding, water maze, and word-list retrieval. Object-location retrieval was performed outside the scanner due to time constraints. After scanning, participants also rated their cognitive strategy used to solve the spatial tasks and their video gaming habits, as well as performing a neuropsychological test battery con-

sisting of cognitive pencil-and-paper tasks and giving a saliva sample for gene analysis. Gene data were not considered in this thesis.

Materials

For the purpose of this project, four different tasks were developed by means of careful piloting to assess episodic and spatial memory.

Episodic memory tasks

A word-list and an object-location task were used to measure episodic memory ability. The word-list task (see Figure 3A) consisted of 80 target words to be remembered during the encoding phase and 80 additional words used as distractors in the recognition phase where words were classified as either old or new. Targets and distractors consisted of equal parts abstract and concrete nouns and were matched on frequency (Molander, 1984). During encoding, words were presented one at a time and participants were instructed to memorize the words and make a concrete/abstract decision on each. During a subsequent recognition test, targets and distractors were presented one at a time, randomly intermingled, and participants had to make an old/new decision on each item. Each word was presented for 2 s in randomized order with a cross hair presented for .5 s after each word. Additional null-events were included where a cross hair was presented instead of a word, effectively creating a varying inter-trial interval (ITI) with a minimum duration of .5 s. This was done to optimize the data for fMRI-analysis.

The object-location task (see Figure 3B) consisted of 88 line drawings of concrete objects (Snodgrass & Vanderwart, 1980) presented centered within one of either quadrant of the screen with equal probability in randomized order during encoding. As in the word-list task, additional null-events were included. Each object was presented for 1.5 s with a minimum ITI of .5 s. Participants were instructed to remember the objects including their location while performing a semantic decision task, categorizing the items as either naturally occurring or man-made. During retrieval, which was self-paced, target objects were presented centered on the screen intermingled with 44 distractors, and participants made an old/new decision on each item. When classifying an item as old they were asked to indicate which quadrant of the screen the item was originally presented within. Apart from introducing a spatial component, this also serves as a form of source memory assessment.

While these two episodic memory tasks showed the expected gender differences during piloting, no gender difference was observed in either the functional or structural data set (see Table 1).

Spatial memory tasks

Two tasks of navigation and spatial memory within a virtual environment were employed, a pointing task and a water maze task. The pointing task

(see Figure 3C), based on the published description of a similar task (Lawton & Morrin, 1999), consisted of mazes with 2, 4 or 6 right-angle turns with two layouts of each length including their mirrored counterparts, resulting in a total of 12 unique mazes. Distance between each consecutive turn was held constant and no alternative paths were present. Participants were instructed to travel, using buttons that allowed forward movement and left and right turns, from the start of the maze to the end while keeping track of the direction from their current position towards the starting point. When the end point was reached, an arrow appeared, which the participants were instructed to turn so that it pointed towards the starting point. As a control condition, "mazes" without any turns, again of three different lengths, were included, where participants walked straight forward and rotated the arrow 180° clockwise and back. This condition was designed to control for brain activity associated with visual stimulation and motor demands of the task. Mazes occurred in a randomized order, alternating with straight mazes. Total task duration was 8 min 30 s. This task can be conceptualized as a path integration task (Wolbers, Wiener, Mallot, & Büchel, 2007).

The water maze task (see Figure 3D) was based on the paradigm frequently used to study spatial learning in rodents (Morris, 1981). The environment consisted of a square room with a circular pool of water centered within it. There was nothing to distinguish locations within the environment, except for four visual cues, two windows and two paintings, with one cue placed on each wall, off-center and at varying distances from the nearest corner. The task used a block design, alternating between blocks of trials with hidden and visible platforms. During the experimental condition, a non-visible platform was placed within the pool under the surface, and its location remained constant over trials. At each trial onset, participants were placed in one of three starting positions within the pool, facing the walls at an angle where no cue was visible. No starting point occurred in the quadrant where the platform was placed. Participants were instructed to "swim" around the pool, using response buttons, and search for the platform. When the platform was reached, the position was locked, the platform was raised to the surface with a message indicating that it was found, and participants had 1 s (5 s for the first trial) to rotate left and right in order to orient themselves within the environment, after which a new trial began. Participants were instructed to remember the position of the platform and to navigate back to it as quickly as possible on succeeding trials. During the control condition, participants navigated to a visible platform placed at one of six randomly chosen locations within view from the participants' starting position. Each block of hidden trials had a 50 s duration, while blocks of visible trials lasted 30 s, with 5 blocks of each condition. Maximum trial time was 35 s and new trials were sampled until the current block expired, upon which the ongoing trial was interrupted and a message displayed for 3 s indicated onset of the next block. The entire task lasted for 8 min 15 s.

For each of the four memory tasks, a brief practice version was administered outside the scanner, using different stimuli, to ensure that participants had understood the instructions and to give them time to get acquainted with the task.

Neuropsychological measures

Verbal knowledge. A synonyms test was used to assess general verbal knowledge, consisting of 30 multiple-choice items with five alternatives for each item (Dureman, 1960).

Trail-Making Test (TMT) A and B. The TMT is a well-used test to assess visual search, processing speed, flexibility and executive functioning (Reitan, 1958; Tombaugh, 2004). It consists of two forms with a connect-the-dot task. In the A version, 25 dots with numbers should be connected in increasing order, while in the B version, alternating between numbers and letters is required. The outcome measure is the time to complete the task, and the participant is prompted whenever a mistake is made.

Letter-digit substitution. This task requires substituting digits for letters according to a key that pairs the numbers 1 to 9 with different letters. After 10 practice items, participants are instructed to complete as many consecutive items as they can in 60 s. This task taps many different processes, such as visual scanning, psychomotor speed, sustained attention and flexibility (Elst, Boxtel, Breukelen, & Jolles, 2006; Lezak, 2004).

A

| vetenskap | + | forskning |
| 2 s | .5 s | 2 s |

B

| | | |
| 1.5 s | .5 s | 1.5 s |

C

D
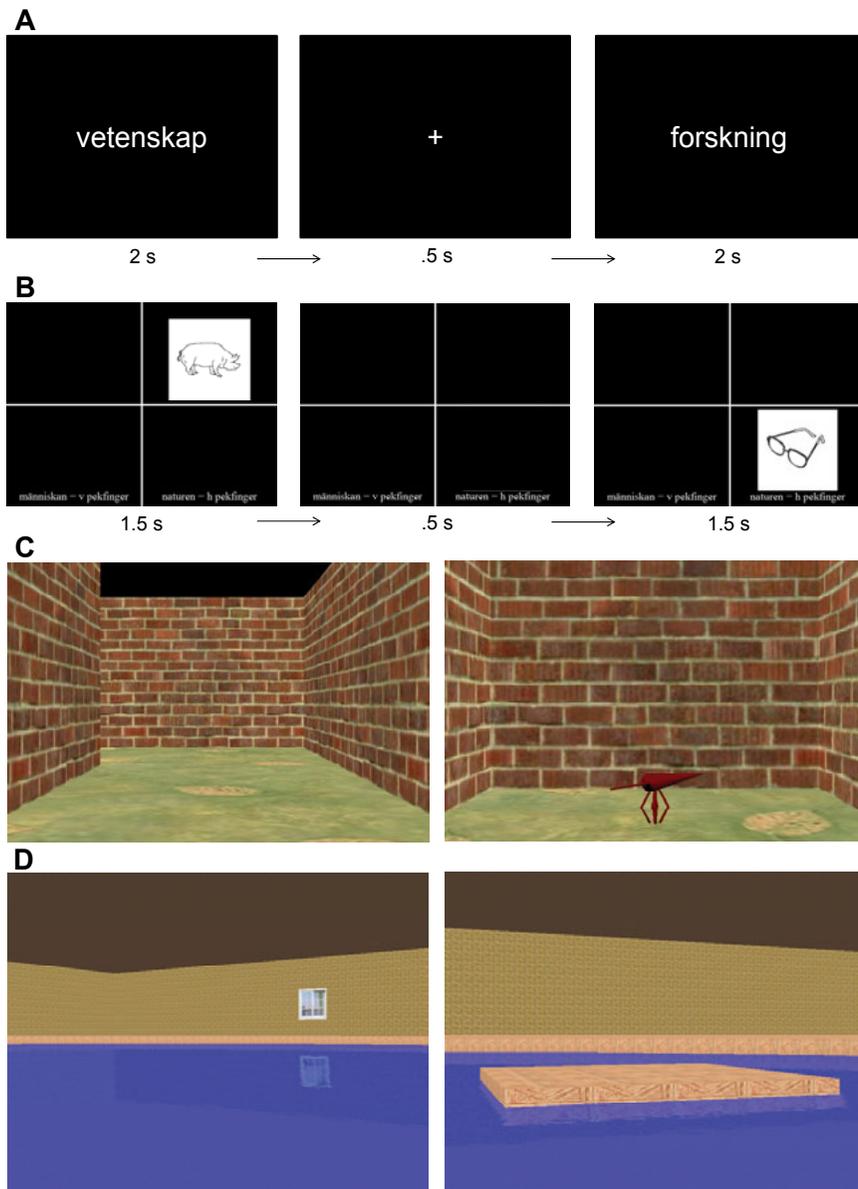
Figure 3. Illustration of the episodic and spatial memory tasks employed. (A) The encoding phase of the word list task. Words were presented for 2 s each separated by a cross-hair for .5 s. (B) The encoding phase of the object-location task. Line drawings were presented in one of four quadrants of the screen for 1.5 s each, separated by an inter-trial interval of .5 s. (C) The pointing task consisted of mazes with right-angle turns (left). An arrow at the end of each maze was used to indicated the direction towards the starting point (right). (D) The water maze consisted of a circular pool centered in a quadratic room with cues placed on the surrounding walls (left). A platform was hidden in the pool in a fixed location, surfacing when found by the participant (right).

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Structural data set

Since there are many similarities between this and the previous functional data collection, only the differences in procedure and tasks are highlighted here.

Participants

The recruitment followed the same procedure as that of the previous sample. Here, 76 participants (38 women, 38 men) were recruited with women and men being of similar age and education length (see Table 1).

Procedure

Data collection took place on three different occasions. First, cognitive testing was done at the Department of Psychology, Uppsala University, with the episodic and spatial memory tasks being performed on a desktop computer. Second, MRI scanning was performed at the Akademiska Hospital, using the same scanning sequences for structural and DTI images as in the previous study. In addition, resting-state scans were collected, with participants fixating their gaze on a cross hair centered in their visual field during fMRI acquisition for 6 minutes. Third, participants gave a blood sample for analyzing biological markers, not included in this thesis. These three occasions could take place in any order but close in time. However, 21 participants had previously taken part in a pilot study where the same cognitive measures were used. Therefore, the MRI scanning of this sub-sample was more than a year removed from the cognitive testing.

Materials

Episodic memory tasks

The word-list and object-location tasks were similar to their fMRI counterparts, with the same targets and distractors, but without the additional null-events. The retrieval part of both tasks was self-paced while the timing of the encoding part was preserved from the fMRI versions.

Spatial memory tasks

The pointing task was essentially the same as the fMRI version, except that the control condition, with straight "mazes", was removed.

The water-maze task underwent a few changes compared to the fMRI version. First, the control condition, with visible platforms, was removed. Second, the block design was abandoned in favor of a self-paced task with 18 trials with a hidden platform, six for each starting point. After 60 s of trial duration, the platform was raised to the surface and a displayed message indicated that it was visible. Otherwise, there were no time limits in this

version of the task. For each trial, after reaching the platform, 10 s were allotted to orientation by rotating left and right before the next trial onset.

Neuropsychological measures

In addition to the verbal knowledge, TMT and letter-digit substitution tests, two more cognitive measures were included.

Verbal fluency. In this task, participants orally produce words beginning with a given letter for the duration of one minute, for each of the letters F, A, and S. Each produced word is given a score, excluding names and different forms of the same word. This task indexes cognitive flexibility as well as semantic memory functioning (Lezak, 2004).

Mental Rotation. A redrawn version of the Vandenberg and Kuse (1978) Mental Rotations Test was used (Peters et al., 1995). Each of 20 items consisted of five perspective drawings of three-dimensional objects; a target stimulus to the left and four stimuli to the right, of which two were rotated versions of the target and two were distractors of a different shape. For each item, one point was awarded for each correct answer and one point was subtracted for each incorrect answer. Ten minutes were allowed for completing the task.

Table 1. *Demographical information and task performance, as a function of data set and gender.*

	Functional data set		Structural data set	
	Women (N=12)	Men (N=12)	Women (N=38)	Men (N=38)
Demographics				
Age	25.0 (3.4)	25.1 (2.7)	23.5 (3.6)	24.4 (3.4)
Years of education	15.4 (1.9)	16.0 (1.4)	14.7 (2.0)	15.0 (1.6)
Episodic memory tasks				
Word-list, item recognition (d')	2.0 (.5)	1.6 (.5)	2.0 (.4)[a]	2.1 (.6)
Object-location, item recognition (d')	2.0 (.5)	2.0 (.5)	2.2 (.4)	2.2 (.5)
Object-location, location memory (proportion correct)	.48 (.1)	.44 (.2)	.45 (.1)	.48 (.2)
Spatial tasks				
Pointing, pointing error (degrees)	40.1 (18.8)*	22.4 (11.2)*	43.6 (14.6)***	21.7 (10.8)***
Water maze, latency (s)	19.8 (5.0)	17.4 (7.9)	30.8 (10.0)***	20.2 (7.4)***
Mental rotation (correct minus incorrect items)	N/A	N/A	12.9 (8.5)***	26.5 (7.8)***
Neuropsychological measures				
Verbal knowledge (correct items)	22.5 (4.4)	22.7 (3.5)	22.5 (4.5)	23.0 (4.1)
Trail-making test A (s)	24.3 (7.4)	23.7 (5.1)	30.8 (10.1)	26.6 (9.8)
Trail-making test B (s)	53.4 (13.6)	53.2 (12.1)	57.8 (18.1)	54.5 (17.4)
Letter-digit substitution (correct items)	42.8 (7.5)	39.8 (6.2)	37.8 (6.0)	37.9 (5.0)
Verbal fluency (number of words, F+A+S)	N/A	N/A	50.5 (10.9)	50.5 (11.2)

[a] One female participant excluded due to missing data.

* Gender difference significant at *p*<.05

*** Gender difference significant at *p*<.001

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Paper I

Background

While gender differences in spatial tasks that rely on the hippocampus are frequently observed, little is known about the potential underlying gender differences in hippocampal function. Earlier findings, though somewhat equivocal, point to functional differences along the hippocampal axis, and between hemispheres, placing the right posterior hippocampus as a central node in spatial memory functions. Earlier studies that considered gender differences in brain activation to a spatial navigation task found a greater left posterior hippocampus activation in men than women (Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000), and no gender differences in activation when controlling for performance (Ohnishi, Matsuda, Hirakata, & Ugawa, 2006). However, none of these studies did explicitly assess hippocampal laterality and long-axis effects of activation in relation to gender differences.

Here, the aim was to investigate potential gender differences in hippocampal activation during a spatial task that could underlie the frequently observed gender differences in performance. Using a pointing task, previously shown to produce gender differences (Castelli, Latini Corazzini, & Geminiani, 2008; Lawton & Morrin, 1999) we predicted a male advantage in performance, and recruitment of the posterior hippocampus in all participants. Further, we investigated gender differences in the pattern of hippocampal activation in terms of hippocampal long-axis (anterior/posterior) and laterality, and its relationship to performance.

Methods

This paper is based on the functional data set (N=24) and the fMRI version of the pointing task (see Figure 3C). Men and women did not differ on the general cognitive measures (see Table 1). For fMRI analysis, each maze was divided into two phases, a navigation phase, consisting of traversing the maze, and a pointing phase, where participants used the arrow at the end of the maze to indicate the direction towards their starting point. Activation was assessed by contrasting mazes with turns against straight "mazes", separately for each maze length and task phase. Contrast estimates for each participant were extracted from regions of interest corresponding to the left and right

hippocampal head and tail, to assess potential gender differences in hippo-campal activation patterns. Finally, based on activation differences between men and women, a laterality index (a measure of the relative distribution of activations between hemispheres) of hippocampal activation was calculated to assess the relationship between hippocampal lateralization of activation and task performance. Given the use of virtual environments, reported video gaming habits were included as a covariate when assessing gender differences in performance and hippocampal activation.

Results

Men made more accurate estimations of the direction to their starting point than did women (see Table 1). As regards task related activations, both men and women recruited the bilateral posterior hippocampus during both the navigation and pointing phases compared to the control condition. When patterns of hippocampal activation were considered, men showed a right-lateralization of activation during the navigation phase not present in women (see Figure 4A), while both men and women showed a greater posterior compared to anterior activation during the pointing phase, though this poste-rior to anterior difference was greater in women (see Figure 4B). Both the laterality × gender interaction during navigation and the axis × gender inter-action during pointing disappeared when controlled for performance. Indi-vidual laterality indices during the navigation phase correlated with perfor-mance, with greater right-lateralization being associated with better perfor-mance (see Figure 5).

When controlled for current video gaming habits, gender differences in performance, as well as in hippocampal lateralization during navigation, disappeared. While the effect of gender on performance dropped from a me-dium (η^2=.121) to a small effect size (η^2=.035) when controlling for video gaming habits, the effect of video gaming was of a medium effect size (η^2=.096), suggesting that video gaming habits explains a large part of gen-der differences in performance on the pointing task.

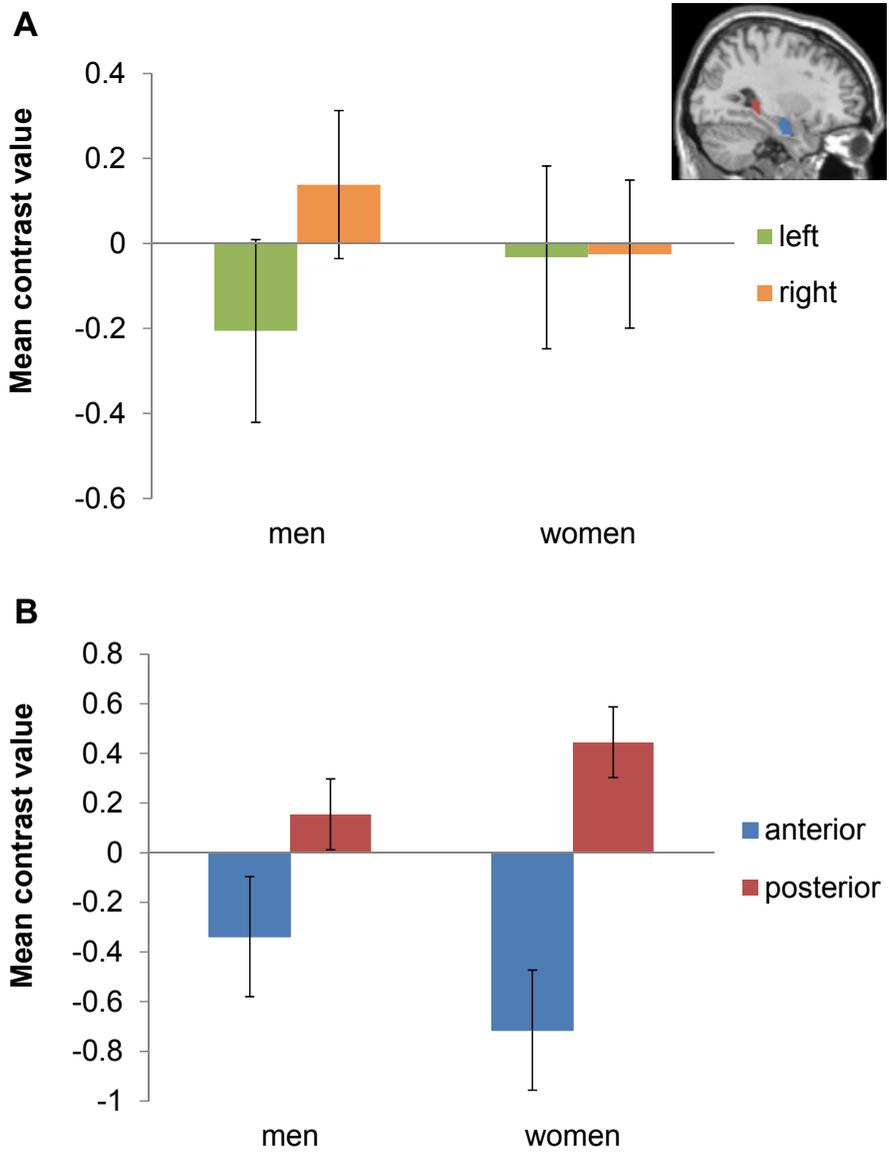*Figure 4.* (A) Hippocampal activation as a function of gender and laterality, illustrating the gender × laterality interaction during the navigation phase. (B) Hippocampal activation as a function of gender and the hippocampal long-axis, illustrating the axis × gender interaction during the pointing phase.

Discussion

Confirming earlier findings, it was found that men performed better than women on the pointing task (Castelli et al., 2008; Lawton & Morrin, 1999). Throughout the task, both men and women recruited the posterior hippocampus, consistent with its importance in spatial memory functions.

During the navigation phase, men showed greater right-lateralization of hippocampal activation than women, and right-lateralization was associated with better performance across all participants. This is in line with a right-lateralization of spatial functions, and suggests that gender differences in lateralization of hippocampal activation may underlie the gender differences in spatial performance. In a previous study, gender differences in hippocampal lateralization were related to differences in the cognitive strategy employed, with a greater left-lateralization in women being associated with a verbal strategy, and right-lateralization in men with a non-verbal, spatial strategy (Frings et al., 2006). Thus, the relationship between gender differences in lateralization and in performance in the present study may be mediated by gender differences in strategy to solve the task.

In the pointing phase, women showed a greater recruitment of the posterior versus anterior hippocampus compared to men. This may reflect a compensatory mechanism, with a greater effort during the estimation of the direction to the starting point due to less spatial processing during the navigation phase. When video gaming habits were taken into account, the observed gender differences in both performance and hippocampal lateralization disappeared, suggesting that video gaming experience is a contributing factor to these differences.
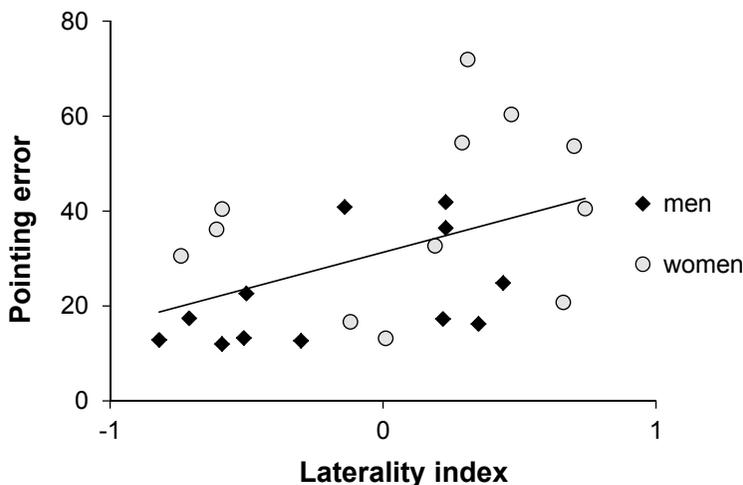
Figure 5. The relationship between lateralization of hippocampal activation during the navigation phase and spatial memory performance. The greater the right-lateralization (more negative laterality index) the smaller the pointing error.

Paper II

Background

Given gender differences in episodic and spatial memory on the one hand, and findings suggesting different roles for the anterior and posterior, as well as right and left, hippocampus in these memory functions on the other, regionally varying gender differences in hippocampal morphology may be expected. Most studies to date that have looked at volumetric gender differences only considered overall hippocampus volume, and while some found a greater hippocampus in women than men, relative to total intracranial volume (Filipek, Richelme, Kennedy, & Caviness, 1994; Giedd et al., 1996; Murphy et al., 1996), many studies did not find any difference (Bueller et al., 2006; Jack et al., 1989; Lange, Giedd, Xavier Castellanos, Vaituzis, & Rapoport, 1997; Mu, Xie, Wen, Weng, & Shuyun, 1999; Pruessner, Collins, Pruessner, & Evans, 2001; Tisserand, Visser, van Boxtel, & Jolles, 2000). Further, comparison of the left and right hippocampus found no gender difference in volumetric laterality of the hippocampus (Giedd et al., 1996; Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Maller et al., 2007). However, if gender differences in hippocampal volume vary along its anterior-posterior axis, such differences may be masked when overall volume is considered.

Earlier studies have found covariation in gray matter volume between brain regions that also show functional connectivity and that are associated with the same cognitive functions (Alexander-Bloch et al., 2013). In one study, individuals with a greater anterior hippocampus also had greater volume in regions known to be connected with it (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007). Given that the anterior and posterior hippocampus show structural, and resting-state, connectivity with distinct sets of brain regions, they can be expected to covary in volume with different parts of the brain. Hence, it is possible that gender differences in anterior and posterior hippocampus volume is accompanied by differences in how these hippocampal segments covary in volume with other brain regions as well, here referred to as structural covariance.

Here the aim was to assess gender differences in the volume and structural covariance of the anterior and posterior hippocampus. An additional aim was to investigate any potential relationship between the volume and struc-

tural covariance of these two subsegments on the one hand, and performance in episodic and spatial memory tasks on the other.

Methods

This paper was based on the structural data set (N=76). Men and women did not differ in general cognitive ability, except that men performed better in mental rotation, a spatial task (see Table 1). First, voxel-wise brain volume was assessed using a method called Voxel-Based Morphometry (VBM; Ashburner, 2007; Ashburner & Friston, 2000, 2005) which was applied to the morphological T1-weighted scans. From this, anterior and posterior hippocampal volumes, as well as total intracranial volume (TIV), were calculated.

Then, to assess the structural covariance of the anterior and posterior hippocampus in men and women, partial least squares (PLS; McIntosh & Lobaugh, 2004; McIntosh, Bookstein, Haxby, & Grady, 1996; Spreng & Turner, 2013) were used on the VBM-preprocessed volumetric images. PLS is a multivariate method akin to principal component analysis, but suitable for finding patterns of covariance between neuroimaging data and some exogenous measure (such as behavioral measures or seeds). In the current application, PLS identifies a set of latent variables (LV) that maximizes the covariance between volumetric brain patterns on the one hand, and anterior and posterior hippocampus volume on the other. Both seeds and whole-brain volumetric data were weighted against TIV to remove its influence on regional volume estimates.

Finally, the relationship between hippocampal volume, as well as structural covariance, and episodic and spatial memory performance, was explored.

Results

There was no gender difference in overall hippocampal volume. However, there was a gender × axis interaction, such that the posterior hippocampus was larger in women than in men, with no difference in the anterior hippocampus.

The PLS analysis revealed two significant LVs. The first LV reflected structural covariance common to the anterior and posterior hippocampus in both men and women, while the posterior hippocampal volume in women was less related to this pattern. Here, a larger hippocampus overall was accompanied by larger volume in the bilateral MTL, thalamus, insula and posterior cingulate cortex. Conversely, a larger hippocampus was associated

with smaller volume in the middle frontal gyrus, supramarginal gyrus, superior parietal lobule, and middle occipital gyrus (see Figure 6).
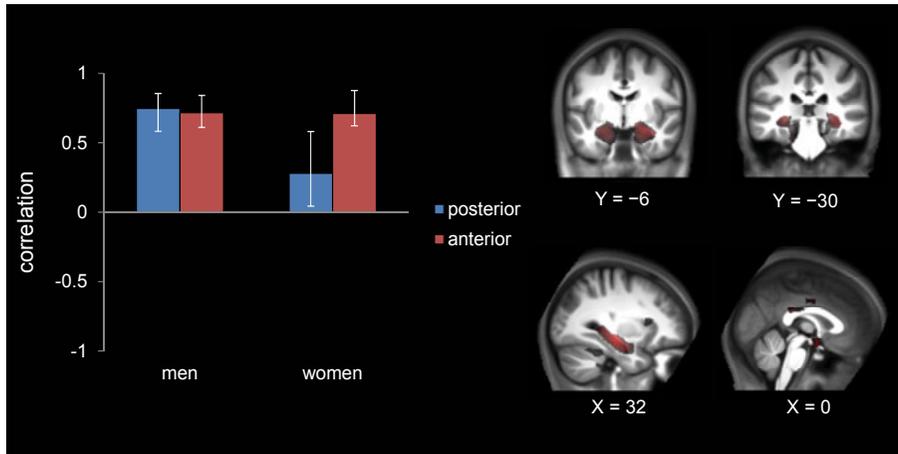
Figure 6. The first latent variable (LV). The bars on the left show the relationship between the seed regions and the covariance pattern; the images on the right show the brain regions related to this pattern. This LV captures common structural covariance for the anterior and posterior hippocampus in both men and women, though the posterior hippocampus in women is less related to this covariance pattern.

The second LV reflected a gender × axis interaction, with one covariance pattern found for the anterior hippocampus in women only, such that women with a larger anterior hippocampus tended to have a larger anterior temporal lobe bilaterally. A dissociated covariance pattern for the posterior hippocampus was observed, with a larger posterior hippocampus being associated with greater volume in the lingual gyrus, medial and lateral parietal lobe, orbitofrontal cortex and cerebellum, bilaterally, among other regions. This posterior hippocampus covariance was more evident in men than women (see Figure 7).
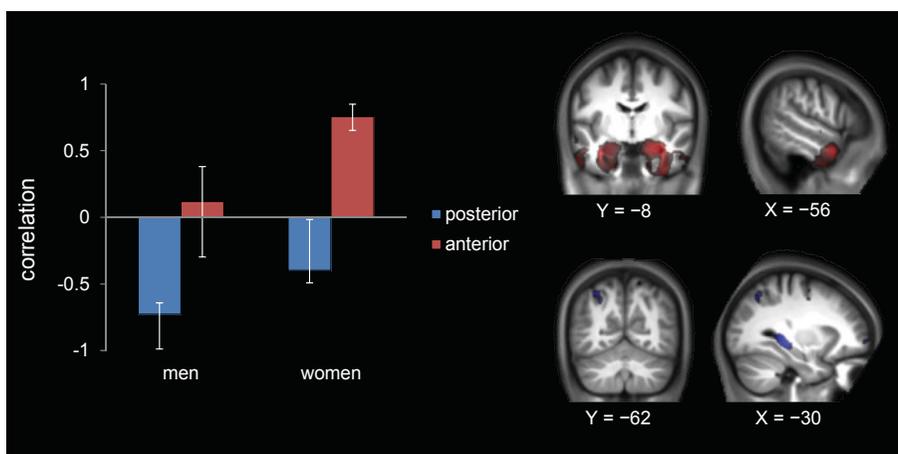
Figure 7. The second latent variable (LV). The bars on the left show the relationship between the seed regions and the covariance pattern; the images on the right show the brain regions related to this pattern. This LV reflects different patterns of structural covariance for the anterior hippocampus, in women only, and the posterior hippocampus, to a greater extent in men. Red colored brain regions are part of the anterior hippocampus structural covariance pattern, while blue regions are associated with the posterior hippocampus.

Men performed significantly better on the spatial pointing and water maze tasks. No difference was found in the episodic object-location or word-list tasks (see Table 1). The only relationship between memory performance and volumetric measures was found with the word-list task in men. A negative correlation between word-list performance and posterior hippocampal volume was observed in men, and a corresponding negative correlation between word-list performance and the gray matter volume associated with the first LV in men. No significant correlations were found in women between memory and hippocampal volume or structural covariance.

Discussion

Consistent with several earlier findings, there was no overall gender difference in hippocampal volume. However, women had a larger posterior hippocampus compared to men, suggesting that there are regional gender differences in volume, which may be masked when considering overall size. Similarly, women and men showed different patterns of structural covariance, with a covariance pattern associated with the anterior hippocampus in women and another pattern associated with the posterior hippocampus in men. These covariance patterns correspond well with the resting-state networks

that have been associated with the anterior and posterior hippocampus, respectively, and may be reflective of structural and functional interactions between these regions (Alexander-Bloch, et al., 2013).

Given the hypothesized connection between the anterior hippocampus and episodic memory, and the posterior hippocampus and spatial memory, a greater covariance in the anterior hippocampus with its associated regions in women, and a corresponding finding in the posterior hippocampus in men, is congruent with observed gender differences in these memory functions. However, no such correlations with memory performance in the included measures were observed. Overall, the relationship between structure and memory was weak to non-existent, with only negative relationships for word-list performance in men. This finding needs to be interpreted in light of the many correlations calculated in this exploratory analysis. It is however worth noting that earlier studies have found negative relationships between hippocampal volume and memory performance in young adults (DeMaster, Pathman, Lee, & Ghetti, 2013; Van Petten, 2004).

While there are studies showing a relationship between structural covariance and functional and structural connectivity, as well as synchronized maturation between brain regions, more research is needed to better understand the biological mechanisms underlying structural covariance and to what extent it is reflective of individual differences in behavior (Alexander-Bloch, et al., 2013; Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013).

This study provides evidence of structural differences between the anterior and posterior hippocampus in relation to other brain regions that are congruent with differences in resting-state connectivity. It further suggests that gender is an important factor to take into account when considering brain morphology.

Paper III

Background

The findings of paper I pointed to a central role for the right posterior hippocampus in spatial memory, in line with functional differences within the hippocampus, both in terms of laterality and its long-axis. Indeed, a recent meta-analysis of functional neuroimaging studies found that the location of hippocampal activations during encoding depended on memory type, with spatial memory encoding activations being localized to the posterior-most segment of the hippocampus, while episodic memory encoding recruited a more anterior and extended part of the hippocampus longitudinal axis (Kühn & Gallinat, 2014). These more distributed activations may reflect the heterogeneous nature of episodic memories, for example in terms of memory content. If autobiographical memory is not considered, visual stimuli employed in studies of episodic memory can be divided into verbal (words, sentences) and pictorial (objects, faces, scenes), and range from highly spatial (scenes) to essentially non-spatial (words, objects). Taking this heterogeneity into account may further our understanding of functional differences between hippocampal sub-segments.

In terms of laterality, functional differentiation within episodic memories is fairly well established, with the left hippocampus being more involved in verbal, and the right hippocampus in non-verbal, encoding (Golby et al., 2001). Differentiation within episodic memories along the hippocampal axis is less clear. As regards differences in connectivity, the anterior hippocampus interacts with the perirhinal and anterior temporal cortices, areas involved in semantic memory (Friederici, 2011; Rogers et al., 2006), making it well situated to process verbal stimuli, which requires retrieval from semantic memory. The posterior hippocampus, in contrast, interacts with regions involved in spatial processing (Kahn et al., 2008). Further, a recent proposal defines functional differences along the hippocampal axis in terms of spatial granularity, ranging from fine-grained spatial representations in the posterior hippocampus to coarse spatial representations in the anterior segment (Evensmoen et al., 2013; Nadel, Hoscheidt, & Ryan, 2012; Poppenk et al., 2013). Taken together, this is congruent with a role for the posterior hippocampus in spatial tasks, and predicts that the location of hippocampal episodic memory related activations along the hippocampal axis is dependent

on the verbalizability and spatial granularity of the memory content to be encoded or retrieved.

Here, activation likelihood estimation (ALE), a meta-analytic approach, was employed to explore the effect of stimulus type, comparing pictorial and verbal stimuli, on the location of episodic encoding and retrieval activations within the hippocampus in terms of laterality and long-axis location. Verbal stimuli were expected to activate the left hippocampus to a greater degree than pictorial stimuli. Further, verbal stimuli were expected to activate a more anterior part of the hippocampus than pictorial stimuli. Finally, within pictorial stimuli, highly spatial stimuli, such as scenes, were expected to activate more posterior regions of the hippocampus compared to essentially non-spatial stimuli, such as objects.

Methods

A database search, together with a search of the references in the included studies, yielded a total of 94 studies containing 173 activation foci that fulfilled the inclusion criteria. Briefly, studies were considered whose participants were young healthy adults, and that reported peak coordinates for hippocampal activation during encoding or retrieval of visual stimuli (words/sentences, faces, scenes/buildings, and objects), either as single items or item-item associations, and that modelled their data using a general linear model (GLM).

ALE is a method for making meta-analytical inferences from neuroimaging data (Eickhoff et al., 2009; Turkeltaub et al., 2012; Turkeltaub, Eden, Jones, & Zeffiro, 2002). In essence, it takes coordinates of activation foci and models probability distributions of activations based on sample size. Probability maps are then combined across studies for a given effect of interest and are used to assess regions of above chance clustering of the individual foci. It also allows for directly contrasting between groups of studies to assess regions of significant differences in activation between two effects of interest. Here, the analysis space was restricted to the hippocampus to answer the question of, given episodic memory related activation of the hippocampus, whether the location of this activation depends on the stimulus type employed. Since the number of studies from each category of pictorial stimuli was limited, the main analyses focused on the comparison between pictorial and verbal stimuli. In addition, a descriptive analysis was run for the subcategories of pictorial stimuli, since they were expected to activate different hippocampal regions. However, their limited number precluded any direct contrasting between them.
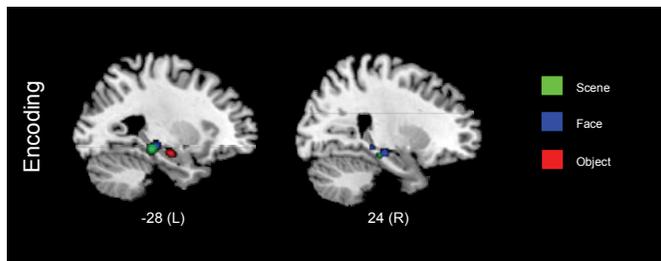
Results

When the overall effect of stimulus type is considered, the clustering of hippocampal activations for pictorial and verbal stimuli was found to overlap in the left hippocampus. Contrasting the two stimulus types showed greater clustering in the left anterior hippocampus to verbal stimuli and greater clustering to pictorial stimuli in the right posterior hippocampus (see Figure 8). The same was true when only encoding activations were considered, with the addition of a left posterior clustering to pictorial stimuli. However, during retrieval, there was overall less clustering, and more overlap between pictorial and verbal stimuli. The remaining analyses focus on encoding.
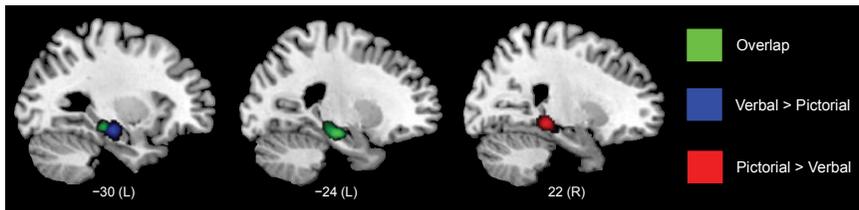
Figure 8. Overlap between, and differences in, clustering of activations to verbal and pictorial stimuli overall (both encoding and retrieval). Verbal stimuli recruit the left anterior hippocampus to a greater extent than pictorial stimuli, which instead recruit the left posterior hippocampus.

With respect to item encoding, the same pattern appeared as in the overall analysis. For within stimulus type associations (pictorial–pictorial versus verbal–verbal), the same pattern of clustering remained, but activation to pictorial stimuli did not differ significantly from verbal activations, perhaps due to a limited number of available studies. Across-stimulus type associations (pictorial–verbal) were more distributed along the hippocampal axis compared to within-stimulus type associations.

Finally, a descriptive analysis of sub-categories of pictorial stimuli showed that objects were associated with a left anterior clustering of activations, while scenes and faces showed bilateral and more posterior clustering (see Figure 9).

Figure 9. Above-chance clustering of activations during encoding of scenes, faces and objects, respectively.

Discussion

Overall, the results supported the expectation that verbal stimuli engage more anterior regions of the hippocampus than pictorial stimuli, and that, within pictorial stimuli, object activations were more anteriorly located than scene activations. The results were also consistent with a left-lateralization of verbal representations (e.g. Golby et al., 2001), with verbal stimuli being left-lateralized, and pictorial stimuli right-lateralized or bilateral. These findings held for encoding, but not retrieval, of episodic memories.

The results can be interpreted in terms of differences along the hippocampal axis in its internal representations, and its connectivity with other brain regions. Where differences in connectivity are concerned, the anterior hippocampus is preferentially connected to the perirhinal cortex, which is implicated in object perception and recognition, while the posterior hippocampus shows connectivity with the parahippocampal cortex which has been associated with spatial stimuli, such as scenes (e.g. Davachi, 2006). Further, the posterior hippocampus is connected to regions involved in spatial processing, while the anterior hippocampus interacts with brain regions involved in semantic memory (Epstein, 2008; Kahn et al., 2008; Rogers et al., 2006). This pattern of connectivity fits well with current findings, where activations to verbal and non-verbal stimuli, as well as to scenes and objects, are spatially separated. Internally, the hippocampus has been proposed as holding spatial representations at an increasingly detailed level moving from its anterior to posterior extreme (Evensmoen et al., 2013). This provides another framework for interpreting the findings, with scenes needing to be encoded at a spatially fine-grained level since they are complex and often highly similar, while objects and words (perhaps depending on the imagery they evoke) are arguably non-spatial in nature, and coarse, global representations of the objects or the concepts entailed by words are sufficient to distinguish between them.

The meta-analytical approach used here allows for summarizing findings within the field and drawing general conclusions across studies that are heterogeneous in many aspects. At the same time, the lack of control inherent in meta-analyses leaves open the possibility that there are other aspects of the memory tasks that vary systematically with stimulus type and that may have influenced the results. Hence, studies that systematically vary the memory content to assess its effect on location of hippocampal recruitment are needed.

Paper IV

Background

The findings of paper I and III suggest functional differences within the hippocampus in terms of memory type (episodic or spatial) and memory content of episodic memories (verbal or pictorial stimuli). At the same time, paper II, together with earlier resting-state connectivity findings (e.g. Kahn et al., 2008) provides evidence that the anterior and posterior hippocampus are associated with different sets of brain regions. These functional connectivity and structural covariance patterns are consistent with different roles in episodic and spatial memory, suggesting that the strength of the anterior and posterior hippocampus connectivity patterns at rest would be predictive of episodic and spatial memory performance, respectively. Earlier studies have shown overall resting-state activity, or connectivity, of the hippocampus to be predictive of cognitive function, either when measuring changes in resting-state invoked by an encoding task or when measuring resting-state data and cognitive measures on separate occasions (Wang et al., 2010; Wong et al., 2014; Woolley et al., 2015). Still, only one study has considered anterior and posterior hippocampus resting-state connectivity separately in relation to performance, and found that posterior hippocampus connectivity following encoding predicted recollection of proverbs (Poppenk & Moscovitch, 2011). Thus, the functional implication of the anterior and posterior hippocampus resting-state networks, when not measured following an encoding task, is largely unknown.

Here, a machine learning approach was employed to test whether patterns of the anterior, but not posterior, hippocampus resting-state connectivity is predictive of non-spatial episodic memory performance, while patterns of the posterior, but not anterior, hippocampus resting-state connectivity predicts spatial memory performance.

Methods

This paper was based on the structural data set (N=76) and the object-location (location memory and item recognition) and water-maze tasks were used as measures of episodic and spatial memory, respectively.

After preprocessing, resting-state connectivity was calculated for the anterior and posterior hippocampus, by correlating the mean time series of each seed region with all other voxels in the brain. Since right and left hippocampus connectivity was similar, only overall anterior and posterior connectivity was considered for illustrating the connectivity patterns. However, for predicting performance, left and right, anterior and posterior hippocampus were all considered. To illustrate the connectivity, regions of both overlapping and differing connectivity between the anterior and posterior hippocampus were assessed.

To assess whether hippocampal resting-state connectivity is predictive of memory performance, a machine learning approach, Relevance Vector Regression (RVR), was employed. In brief, RVR takes the resting-state data as input with the goal of finding patterns of resting-state connectivity that maximize the prediction of the memory performance measure. By repeating this procedure, each time leaving out one subject, and then using the resulting model on this subject's data to predict performance, the accuracy of the model can be assessed by comparing the predictions against actual performance (Chu, Ni, Tan, Saunders, & Ashburner, 2011; Tipping, 2001). Four separate models were trained for each memory measure, one for each seed region: the left and right, anterior and posterior hippocampus. Predictive accuracies of the models were compared in repeated-measures ANOVAs, with memory task (episodic, spatial), hippocampal axis (anterior, posterior), and hemisphere as factors.

Results

Regions of connectivity common to both the anterior and posterior hippocampus were found, as well as regions that showed greater connectivity with the anterior, compared to posterior, hippocampus, and conversely greater connectivity with the posterior, compared to anterior, hippocampus.

Using location memory performance in the object-location task as targets, above-chance predictions were achieved from RVR models trained on right anterior hippocampus connectivity, but not from models trained on left anterior, nor left or right posterior, hippocampus connectivity (see Figure 10). With item memory from the same task as targets, above-chance predictions were achieved from RVR models trained on both left and right anterior hippocampus connectivity, but not from models trained on left or right posterior hippocampus connectivity (see Figure 11) Conversely, when water-maze performance was used as targets, above-chance predictions were achieved based on left and right posterior, but not left or right anterior hippocampus connectivity (see Figure 12). The ANOVAs gave significant axis × memory interactions, regardless of which episodic memory measure was used (see Figure 13).
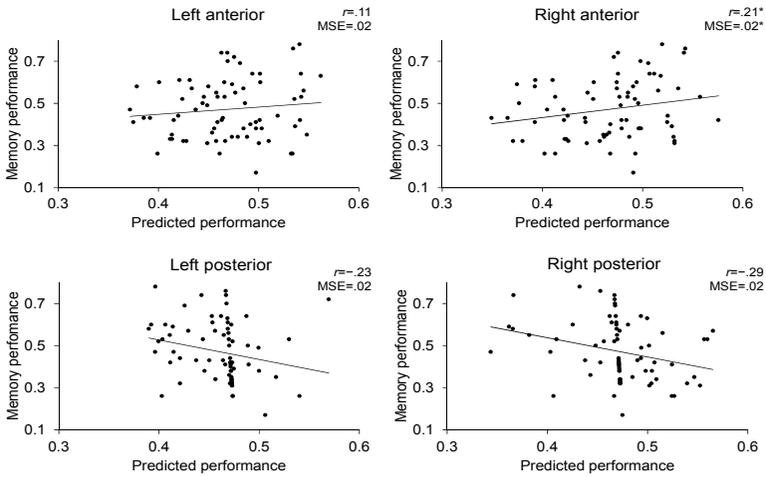
Object location (location)

Figure 10. Predictive accuracy of models trained to predict location memory performance in the object-location task from resting-state functional connectivity, for each seed region considered. Predicted values are plotted against actual performance for each participant. Correlations (r) and mean squared error (MSE) are presented, with an asterisk (*) denoting a permuted p-value <.05.

Object location (items)
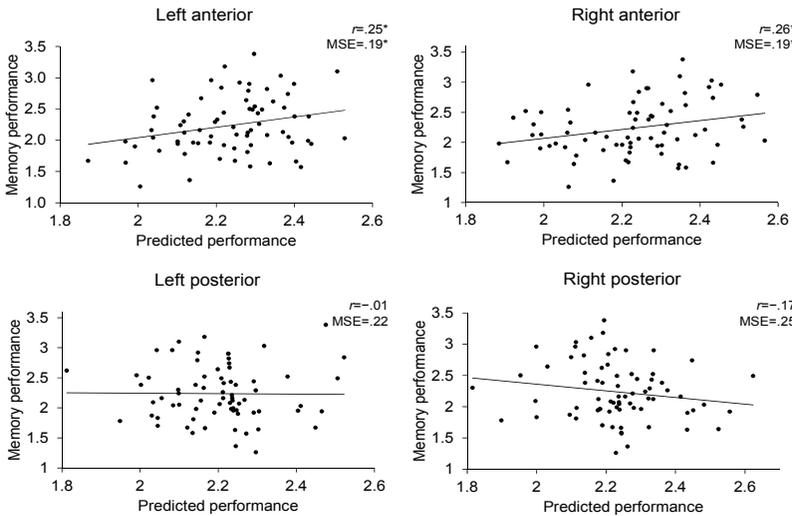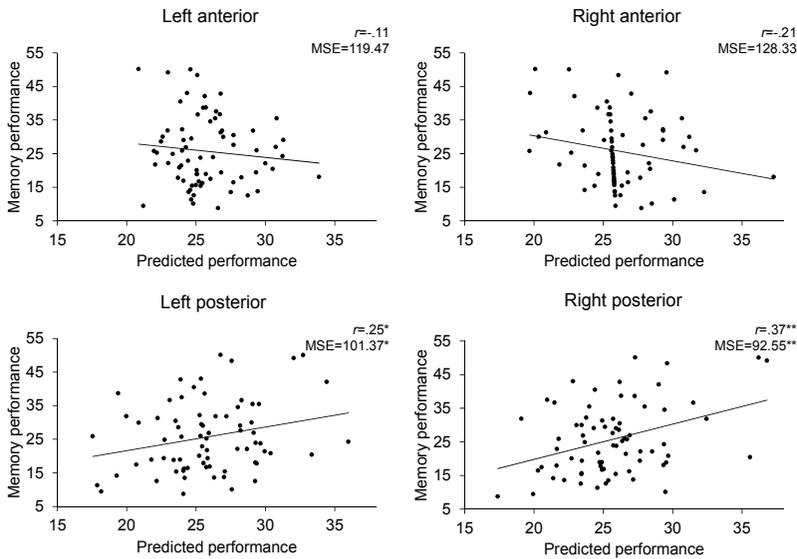

Figure 11. Predictive accuracy of models trained to predict item memory performance in the object-location task from resting-state functional connectivity, for each seed region considered. Predicted values are plotted against actual performance for each participant. Correlations (r) and mean squared error (MSE) are presented, with an asterisk (*) denoting a permuted p-value <.05.

Water maze

Figure 12. Predictive accuracy of models trained to predict water-maze perfor-
mance from resting-state functional connectivity, for each seed region considered.
Predicted values are plotted against actual performance for each participant. Correla-
tions (r) and mean squared error (MSE) are presented, with an asterisk (*) denoting a
permuted p-value <.05.

Discussion

The results lent support to the hypothesis that anterior, but not posterior,
hippocampal resting-state connectivity is predictive of episodic memory
performance, while posterior, but not anterior, hippocampal connectivity is
predictive of spatial memory performance. This was confirmed with axis-
memory interactions in model performance, suggesting a functional dissocia-
tion between the anterior and posterior hippocampus in terms of the types of
memory they support.

   The differences in resting-state connectivity between the anterior and pos-
terior hippocampus were overall congruent with earlier findings (Kahn et al.,
2008; Libby et al., 2012; Poppenk & Moscovitch, 2011). The anterior hippo-
campus showed preferential connection with the anterior temporal lobe, a
region associated with semantic memory in general (Rogers et al., 2006) and
specifically with conceptual representations of objects (Peelen & Caramazza,
2012). Interactions with semantic memory may be important for episodic
encoding (Tulving et al., 1994), especially given that the present object-
location measure employed a semantic decision task during encoding. In-
cluded in the anterior temporal lobe is also the perirhinal cortex, involved in

object perception and recognition and shown to interact with the hippocampus during episodic memory retrieval (Staresina, Cooper, & Henson, 2013). The posterior hippocampus showed preferential interaction with the parahippocampal cortex, retrosplenial cortex and part of the dorsal parietal lobes, all implicated in different aspects of spatial processing (Ciaramelli et al., 2010; Epstein, 2008; Snyder, Grieve, Brotchie, & Andersen, 1998). Taken together, the resting-state connectivity of the anterior and posterior hippocampus is consistent with their differing roles in episodic and spatial memory indicated by the present findings.

Resting-state connectivity can be seen both as reflecting structural connectivity (Greicius et al., 2009; Vincent et al., 2007), including indirect connections (Honey et al., 2009), and as reflective of the dynamics of ongoing cognition during unconstrained rest (Hutchison et al., 2013). Given that the resting-state and memory performance assessments in this study were temporally removed, in some cases more than a year, the more likely interpretation is that the regression models capture connectivity patterns that are reflective of the underlying architecture and relatively stable over time.
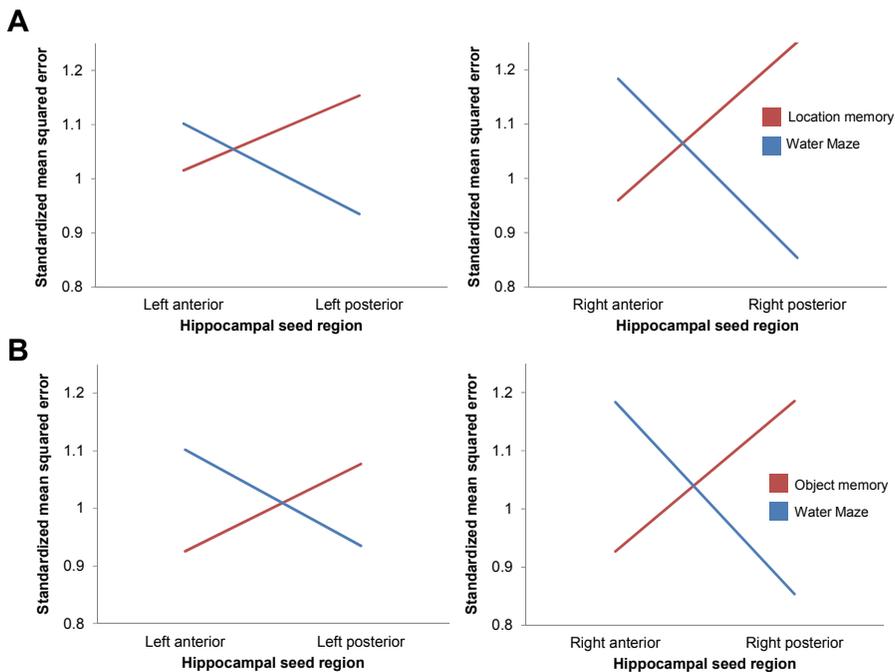
Figure 13. Model performance as measured with standardized prediction errors and as a function of memory task and hippocampal seed region, with (A) location memory and (B) object recognition memory as a measure of episodic memory. The plots illustrate cross-over interactions between hippocampal segment and memory task, such that resting-state connectivity with the anterior hippocampus was more predictive of object-location, than water maze, performance, while the opposite was true for posterior hippocampus resting-state connectivity.

General discussion

The main findings of this thesis are summarized below, followed by a general discussion based on these findings.

Main findings

- Gender differences in spatial memory performance are reflected in gender differences in hippocampal activation patterns, with
    - greater right-lateralization of the posterior hippocampal activation in men
    - a relationship between the degree of hippocampal right-lateralization and spatial memory performance
- The anterior and posterior hippocampus show distinct patterns of structural whole-brain covariance, largely consistent with earlier connectivity findings
- These structural covariance patterns differ as a function of gender, with the anterior hippocampus covariance being evident in women, and the posterior hippocampus covariance mainly in men
- The location of hippocampal activation during episodic memory encoding depends on the stimulus material used, both in terms of laterality and the hippocampus long-axis
- The resting-state connectivity of the anterior and posterior hippocampus reflects functionally distinct networks, with
    - patterns of anterior hippocampus connectivity predicting episodic memory performance
    - patterns of posterior hippocampus connectivity predicting spatial memory performance

Discussion

While there is general agreement that the hippocampus is important for both episodic and spatial memory, less is known about the specific contributions of the anterior and posterior hippocampus to these functions. The overarching aim of this thesis was to explore this issue, with the hypothesis that the anterior hippocampus is mainly involved in episodic memory and the poste-

rior hippocampus in spatial memory. The included papers have approached this question in different ways and, for the purpose of an overall discussion, these approaches can be summarized in three, partly overlapping, main points: first, given opposite gender differences in episodic and spatial memory performance, underlying gender differences in the structure (paper II) and function (paper I) of the anterior and posterior hippocampus were investigated. Second, the functional recruitment of the anterior and posterior hippocampus during episodic (paper III) and spatial (paper I) memory tasks was explored. Third, the interaction between the anterior and posterior hippocampus with other brain regions on the structural level, in terms of structural covariance (paper II), and the functional level, in terms of resting-state connectivity (paper IV), was investigated, as well as its potential relationship to memory performance. These three main points will here be discussed in turn.

The role of the anterior and posterior hippocampus in episodic and spatial memory

First, when gender differences are considered, on the functional level differences in right-lateralization of activation within the posterior hippocampus during a spatial memory task underlay gender differences in spatial memory performance (paper I), congruent with a special role for the right posterior hippocampus in spatial functions. At rest (paper IV), no gender differences in hippocampal function were present, as suggested by an inability to classify gender based on hippocampal resting-state connectivity (reported in the supplementary material). This suggests that the observed gender differences in paper I were triggered by the pointing task, rather than being reflective of an overall gender difference in intrinsic hippocampal activity. Further, in both papers I and IV, the same relationship between hippocampal function and memory performance was found in both men and women, which may be taken to imply that the neural underpinnings of episodic and spatial memory functions are similar for men and women, and gender differences in hippocampal activation are observed to the extent that performance differs.

On the structural level, gender differences in structural covariance of the anterior and posterior hippocampus were observed (paper II). Assuming that this covariance partly reflects differences in connectivity strength and/or repeated co-recruitment of brain regions (see Alexander-Bloch, et al., 2013), it could be argued that the observed differences support the episodic–spatial division of labor between the anterior and posterior hippocampus, given that women usually perform better in episodic memory tasks and showed greater structural covariance associated with the anterior hippocampus, while men are usually superior in spatial tasks and showed greater structural covariance associated with the posterior hippocampus. However, the overall lack of

significant associations between the structural covariance patterns and memory performance does not support this interpretation. Relating back to paper I, the fact that gender differences in hippocampal activation in the pointing task remained after controlling for volume differences further suggests that it is the functional recruitment, not the underlying morphology, that explains differences in behavior. Still, hippocampal morphology may make a small contribution to cognitive performance that would require a larger sample size or more sensitive measures to detect, and the presence of gender differences in structural covariance suggest that gender may be an important factor to take into account when considering hippocampal morphology, for example in the context of atrophy related to aging or pathology, and its effect on cognition.

Second, turning to functional recruitment of the hippocampus in episodic and spatial memory, the posterior hippocampus was recruited during the pointing task, regardless of gender. In paper III the location of hippocampal recruitment along its long-axis during episodic memory encoding depended on the type of stimuli employed, with pictorial stimuli generally activating a more posterior region than verbal, especially highly spatial stimuli, such as scenes. Still, these activations were more anterior than the spatial memory activation in paper I. While no direct comparison is possible between papers I and III, the findings largely support the hypothesis of a functional division between the anterior and posterior hippocampus. They also suggest that a more fine-grained division between memory tasks, based on memory content, may be important to fully account for functional long-axis differences within the hippocampus, where the degree of spatial detail may be one dimension along which to classify memory tasks.

Third, the relationship between the hippocampus and other brain regions, and whether it is associated with memory performance, was considered at the structural (paper II) and functional (paper IV) levels in this thesis. The structural covariance and resting-state connectivity of the anterior and posterior hippocampus showed several areas of overlap. Areas associated with the anterior hippocampus, both in terms of volume and function, were the anterior temporal lobe, encompassing the perirhinal cortex, amygdala and temporal pole, as well as the anterior part of the fusiform, and inferior and middle, temporal gyri. Areas associated with the posterior hippocampus across both modalities were the parahippocampal cortex, lingual gyrus, precuneus, posterior parietal lobe and cerebellum. A correspondence between functional connectivity at rest and structural covariance has been demonstrated earlier (Alexander-Bloch, Giedd, et al., 2013) suggesting that the anterior and posterior hippocampus' structural covariance partly reflects co-recruitment with their respective connected brain regions. There were also differences between the structural covariance and resting-state connectivity findings, with more widespread and distal brain regions identified at the functional level,

which may reflect that resting-state connectivity is a more sensitive measure of whole-brain interactions than structural covariance.

When men and women were considered together, the structural covariance of the anterior and posterior hippocampus did not show any relationship with behavior. However, resting-state functional connectivity patterns were predictive of memory performance, with the anterior hippocampus connectivity predicting episodic memory, and the posterior hippocampus connectivity predicting spatial memory, but not vice versa. This suggests that the functional differences between the anterior and posterior hippocampus extend to their respective functional networks, and that it is reflected in intrinsic activity in addition to task-related recruitment of the hippocampus. Again, the findings indicate that hippocampal function, rather than morphology, is related to memory performance, even when function is considered at rest, rather than in relation to a task.

Taken together, the findings in this thesis lend further support to the anterior and posterior hippocampus being partly separate regions, both in terms of structure and function. At the functional level, the findings suggest that the anterior hippocampus is more involved in episodic memory functions, compared to the posterior hippocampus which is more involved in spatial memory, both when hippocampal activations and resting-state connectivity are considered. The findings also indicate that this functional division is not complete, and may depend on different aspects of the memories under consideration, with the memory content of episodic memories being an important one.

The hippocampus is affected in many neuropsychiatric and neurological disorders, which may be attributed to its vulnerability to oxidative and behavioral stress as well as its susceptibility to epileptogenic mechanisms (Bartsch, 2012). As such, understanding more about functional differences between hippocampal sub-segments, as well as related gender differences in structure and function, has potential clinical relevance if local effects of pathology on the hippocampus are reflected in certain memory functions more than others, or affect men and women differently. Still, many studies of pathological effects on the hippocampus do not consider sub-segments of it separately or use only one measure to assess hippocampal functioning. In studies that have taken these issues into account, it has been found that regionally specific hippocampal volume reductions in different pathologies are associated with specific effects on cognition, with anterior hippocampus atrophy being associated with verbal memory deficits in traumatic brain injury and schizophrenia (Ariza et al., 2006; O'Driscoll et al., 2001) and posterior hippocampus volume loss associated with spatial memory impairment in Alzheimer's disease and mild cognitive impairment (deIpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007). Further, regional hippocampal volume reduction associated with pathology and aging has been found to

differ between men and women (Bryant et al., 2014; Fleisher et al., 2005; Murphy et al., 1996). Hence, assessing both memory types with different study materials, as well as considering men and women separately, may be important to fully understand the effect that pathological and age-related hippocampal atrophy has on memory functions.

Revisiting other proposals of anterior and posterior hippocampus functioning

Given the many views of functional differences between the anterior and posterior hippocampus, the question is how the present proposal fits together with them. One of these views concerns a division between emotional and cognitive functions being associated with the anterior and posterior hippocampus, respectively (Fanselow & Dong, 2010). It can be argued that episodic memories are often more emotional than spatial ones, and emotion has been found to enhance both episodic memory and encoding related activation of the anterior hippocampus (Murty et al., 2010). As such, emotional and episodic memory roles for the anterior hippocampus are not necessarily incompatible.

Another view, the HIPER model, proposes different roles of the anterior and posterior hippocampus in encoding and retrieval, respectively (Kim, 2014; Lepage et al., 1998). Encoding and retrieval were only considered separately in paper III, where differences in location of activation between encoding and retrieval depended on stimulus type, and only verbal stimuli showing differences compatible with the HIPER model. This could indicate that this view of long-axis differentiation of hippocampal function holds for certain memory contents only.

As regards remoteness, this thesis only studies recently encoded memories. In practical terms, very remote memories can only be assessed as autobiographical memories. These are associated with activation of both the anterior and posterior hippocampus (Gilboa et al., 2004; Söderlund et al., 2012) which may reflect the fact that autobiographical memories generally are richer in content and contain spatial information to a greater degree. How the change over time in their distribution along the hippocampal axis relates to an episodic-spatial division of labor is more uncertain, but a greater distribution of very old memories may reflect that they have been retrieved and re-encoded together with the retrieval context, increasing contextual associations with the memory over time. Remote and well-rehearsed spatial memories seem to be preserved to some extent following hippocampal damage, although detailed spatial knowledge is affected (Maguire et al., 2006; Rosenbaum et al., 2000). Still, it remains to be seen whether a division of labor between episodic and spatial memory is evident for remote as well as recent memories.

In any case, the different proposals need not be mutually exclusive, and the function of the anterior and posterior hippocampus may depend on context. While the anterior and posterior hippocampus show different patterns of connectivity, hippocampal connectivity is also modulated by task (Robin et al., 2014), meaning that a given sub-segment of the hippocampus may receive input from different regions at different times. Thus, it is possible that, for example, a vestibular versus visual division of labor describes the function of the anterior and posterior hippocampus well when these two sub-segments receive inputs of the respective modalities that need to be integrated in the service of navigation (Hüfner et al., 2011), while in a different context, the anterior and posterior hippocampus may both receive predominantly visual input, but from the ventral and dorsal streams, respectively, placing them instead to process, for example, object versus spatial visual information. Nevertheless, episodic and spatial memory are both central to hippocampal functioning, and, supported by the overall findings in this thesis, viewing the anterior and posterior hippocampus as having different roles in episodic and spatial memory may prove useful in advancing our theoretical understanding of hippocampal function.

During the time in which the included works were prepared, another theory of functional differentiation along the hippocampal axis has emerged (Poppenk et al., 2013). This theory adheres to the view of the hippocampus being primarily spatial and proposes that spatial representations are held at an increasingly more detailed, or fine-grained, level, moving more posteriorly along the hippocampal axis, consistent with the observation that place cells code for increasingly smaller spatial fields within the environment, towards the posterior hippocampus (Jung et al., 1994). This is compatible with an episodic/spatial division of function, with episodic memories often involving a spatial context, though arguably at a coarse and global level, for example recollecting the general spatial setting of an episodic memory during retrieval. Spatial memory, on the other hand, often involves tapping spatial representations at a more fine-grained level, as in the pointing and water maze tasks where memory of specific locations is measured. This theory has been brought up in the discussion of the individual papers, most prominently in paper III, where it provided a framework for explaining different locations of hippocampal encoding related activations depending on the memory content. Still, a difference in spatial granularity may not provide a complete explanation for why verbal material is associated with more anterior hippocampal activations compared to pictorial material, and the fact that the anterior and posterior hippocampus show connectivity with different brain regions suggests that functional differences between them would be of a more qualitative, than merely quantitative, nature. It remains to be seen whether spatial representations or type of memory is the best way of conceptualizing long-axis differences of hippocampal function.

Lateralization of hippocampal function

While not the main focus of this thesis, functional differences between the left and right hippocampus have been previously observed, and the included papers further contribute to this issue. Performance on the pointing task was associated with right-lateralization of hippocampal activation, while verbal episodic memory encoding was accompanied by left hippocampus activation. These findings are in line with a role for the right hippocampus in spatial, and the left in verbal, functions. This is further corroborated by numerically more accurate predictions of spatial memory performance being made from the right than left hippocampus resting-state connectivity, though left hippocampus connectivity was predictive of spatial memory performance as well. However, the resting-state connectivity patterns of the left and right hippocampus were remarkably similar, and no overall lateralization of structural covariance was observed, even when testing explicitly for it. As such, differences in the association between the hippocampus and other brain regions are not as readily apparent when considering laterality as when comparing the anterior and posterior hippocampus.

Gender differences in lateralization in the pointing task were also observed, with more bilateral hippocampal activation in women than men, perhaps reflecting their greater employment of verbal strategies (Frings et al., 2006). Further, the structural covariance of the right hippocampus differed between women and men, possibly reflecting differences in its interaction with other brain regions, though its implication for memory functions is uncertain.

Limitations

Recognition memory depends on dual processes, recollection and familiarity, with only the former being hippocampus-dependent (Montaldi, Spencer, Roberts, & Mayes, 2006; Ranganath et al., 2004; but see Smith, Wixted, & Squire, 2011). Episodic memory tasks have been developed that attempt to isolate the recollective and associative qualities that set these memories apart from non-episodic declarative memories. Commonly, this is done either by assessing the subjective quality of memories, as in remember/know paradigms (Tulving, 1985), or by using an objective measure that distinguishes between familiarity and recollection, such as comparing item and source memory (Ranganath et al., 2004). In light of this, the word-list task, with its reliance on recognition memory, may not be ideal for tapping hippocampal functions. However, the object-location task did introduce a source memory component, in the form of location memory. Both recognition and source memory in this task could be predicted from anterior hippocampus resting-

state connectivity (paper IV), indicating that both item and location (source) memory in the task indeed captured hippocampal functioning.

While one aim of this thesis was to explore gender differences in hippo-campal functioning given performance differences, the commonly observed advantage for women in episodic memory was not replicated here. Although the reason for this is not clear, it could be due to these differences being of smaller effect size than gender differences in spatial memory, thus requiring larger sample sizes to observe (Herlitz & Rehnman, 2008; Voyer et al., 1995).

The spatial and episodic tasks differ in several aspects unrelated to the memory functions of interest, such as task difficulty, visual complexity, and the degree to which the subject is immersed in the task. Hence, it is possible that their reliance on different sub-segments of the hippocampus is due to other factors than the memory type that the tasks are designed to measure. Other studies have employed tasks that tap either non-spatial episodic, or spatial, memories from within the same environment, while keeping the pre-sented stimuli constant and only varying the instructions, which helps to rule out confounding variables (Burgess, 2002; Hirshhorn et al., 2012).

The fact that video gaming explained gender differences in performance on the pointing task leaves open the possibility that the task measures video gaming experience, rather than spatial abilities. While this cannot be exclud-ed, it is worth noting that, in the structural data set, pointing performance correlated with mental rotation performance ($r=.60$, $p<.001$), validating the task as a measure of spatial abilities. Unfortunately, mental rotation was not administered in the functional data set. Still, the versions of the task used in the two data collections are virtually identical.

Future Directions

The findings of this thesis lend further support to a functional differentiation between the anterior and posterior, as well as the left and right hippocampus, indicating that these hippocampal sub-segments have different roles in epi-sodic and spatial memory. Structural and functional differences between hippocampal sub-segments also interact with gender, something which may contribute to observed gender differences in these two types of memory. These findings, in turn, generate novel questions to be considered in future studies.

A general finding was that hippocampal function, not structure, was relat-ed to performance. However, this was tested with different methods in the different papers. It would be interesting to see whether an approach akin to that used in paper IV could be used to predict performance from multi-voxel patterns of volume within regions that show structural covariance with the

hippocampus, something that also could provide a link between gender differences in hippocampal structural covariance and memory performance.

Given that the functional differentiation between episodic and spatial memory could potentially be explained in terms of spatial representations at different levels of granularity, it would be worthwhile to directly compare these two viewpoints, for example by testing the episodic memory for the spatial configuration of actors within a social setting (fine-grained spatial), versus the temporal ordering of events in the same context (coarse spatial), to see whether the two types of memory are associated with different hippocampal sub-segments regardless of their level of spatial granularity.

While the low resolution of the data that this thesis is based on prevents the study of different hippocampal cross-sectional sub-regions, such as CA1, CA3 and the dentate gyrus, there is evidence that these regions make up different proportions of the hippocampal volume in the anterior and posterior segments. Being able to study their specific contributions to episodic and spatial memory within the anterior and posterior hippocampus, using high-resolution data, could provide further understanding of the functional differences between these two long-axis sub-segments.

Finally, dividing the hippocampus into two sub-segments, albeit a useful simplification in the context of this thesis, ignores the fact that there are differences between the hippocampal body and tail, as seen both in gene expression and connectivity (Fanselow & Dong, 2010). While the hippocampal body and tail were treated as the posterior hippocampus in paper II and IV, and the body was excluded in paper I, in paper III the episodic memory activations were seen in the hippocampal body as well as the head. More research is needed to clarify the different functional roles of these three sub-segments.

Concluding remarks

The findings in this thesis add to a growing body of literature which suggests that the hippocampus is indeed a heterogeneous structure, consisting of sub-regions with important functional differences. While a dichotomous division into an anterior and posterior part, and episodic and spatial memory, may be a simplification, considering the complexity of the hippocampal structure and shared features between the two memory types, it may prove to be a useful complement to our overall understanding of hippocampal functioning. An increased understanding of this functional heterogeneity, in turn, may have clinical implications, given the many pathologies that affect the hippocampus and its associated memory functions.

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