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## The Parahippocampal-Hippocampal Region: Differentiation in Structure and Function

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# chapter

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# 1

## Introduction, scope and aims

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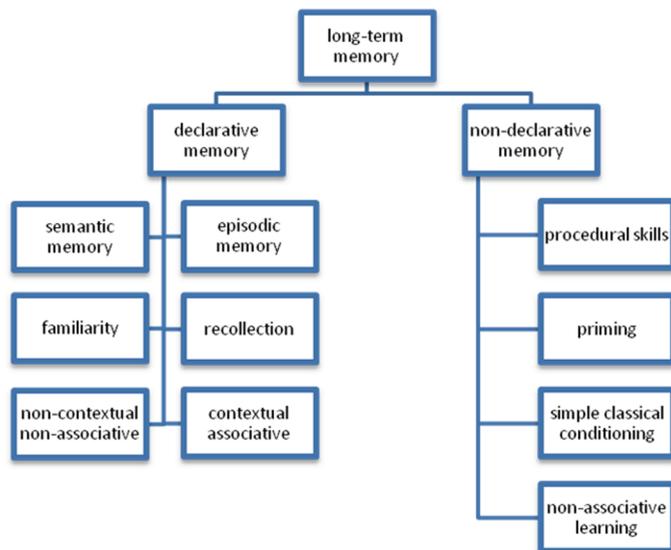
### Preface

The hippocampal formation (HF) and adjacent parahippocampal region (PHR) are brain regions under intensive investigation. This research is important because it may help find a cure for diseases that are closely linked to pathology in these regions. Perhaps the most (in)famous example is Alzheimer's disease, which has a high human cost due to its characteristic cognitive decline, but is also an economic burden in an ageing population in which a significant percentage of the total healthcare budget is used for treatment of the disease (Hollander de et al., 2006). Research already uncovered many aspects of HF - PHR structure and function. For example, many details of the HF – PHR anatomy are already known and functionally it is evident that the HF and PHR are involved in a rich variety of cognitive processes such as recognition of objects, navigation through spaces, association of unrelated stimuli, visual perception and above all, in memory. Yet, our understanding is not enough to cure disease and explain how these regions perform their functions. Therefore, fundamental scientific advancement of our understanding of the HF and PHR is needed. The basic scholastic quest for knowledge about the structure and function of the HF and PHR forms the heart of this thesis. Here, several experimental studies are described that delve deep into the anatomical structure and the functions that may depend on that structure (Crick and Koch, 2003). The results of these studies provide valuable additions to the current knowledgebase, but are only a few examples out of the many possible interesting experiments that could have been conducted in order to help answer those questions that currently remain unanswered.



The aim of this thesis is to increase our fundamental knowledge of the anatomical structure and unique functional contributions of the HF - PHR sub-regions (Box 1). Functionally, the HF and PHR are best known for their role in memory (e.g. (Eichenbaum et al., 2007)). Here, we therefore do not entail tackling questions about if the HF - PHR system is involved in memory, but rather about how it is involved. In order to understand the involvement of HF and PHR in memory, we first need to look at the memory concept itself. Memory is not a unitary concept (Milner et al., 1998), but can be divided into multiple types of memory (Figure 1). However, not all memory forms are dependent on the integrity of the HF and PHR. The type of memory that the HF and PHR are involved in, is grouped under the term declarative memory (Cohen and Squire, 1980), which is defined as the conscious recollection of facts and events. Damage to the HF and PHR can cause serious memory disorders, which was first discovered in the famous patient H.M (Scoville and Milner, 1957).

Multiple theories exist about the relation between the MTL sub-regions and their functions in aspects of declarative memory. Here, a concise introduction is given to those theories that are relevant to this thesis. Perhaps most renowned is the declarative theory of memory, which states that the HF has a time limited, but crucial role in all memories that can be consciously retrieved. According to this theory, memories ultimately become stored in the neocortex and can be retrieved without the HF (Squire et al., 2004; Tulving, 1972). One striking feature of conscious recall that will be addressed in this thesis is that input arising from a single sensory domain, for example a visual input, may trigger multimodal conscious recollection. Another theory of declarative memory named Multiple Trace Theory (MTT; Nadel and Moscovitch, 1997) states that the HF and PHR are required for all conscious memories and that each time a memory trace is recalled, a new HF-encoded memory trace is added for it, thus making these memories less susceptible to disruption. Similar to the declarative memory theory, multiple trace theory differentiates the role of the HF for two memory types. The first is episodic memory, which refers to the recollection of events and personal experiences. This type of memory is thought to be mediated by the HF at all times. However, due to a process termed semantization, elements of episodic memory become stored as factual information without a specific context. This type of memory is referred to as semantic memory, and according to MTT this memory type can be retrieved independently of the HF. Another distinction of memory type that received substantial attention in the literature is between recollection and familiarity based recognition. Recollection refers to memory retrieval in the absence of the stimulus and recognition to memory retrieval in the presence of the to-be-remembered item. The dual process theory of memory (Eichenbaum et al., 2007) states that the HF is of crucial importance for recollection but not for recognition. Familiarity based recognition is most strongly linked to PHR function and in particular to the



**Figure 1: Multiple systems of long-term memory**

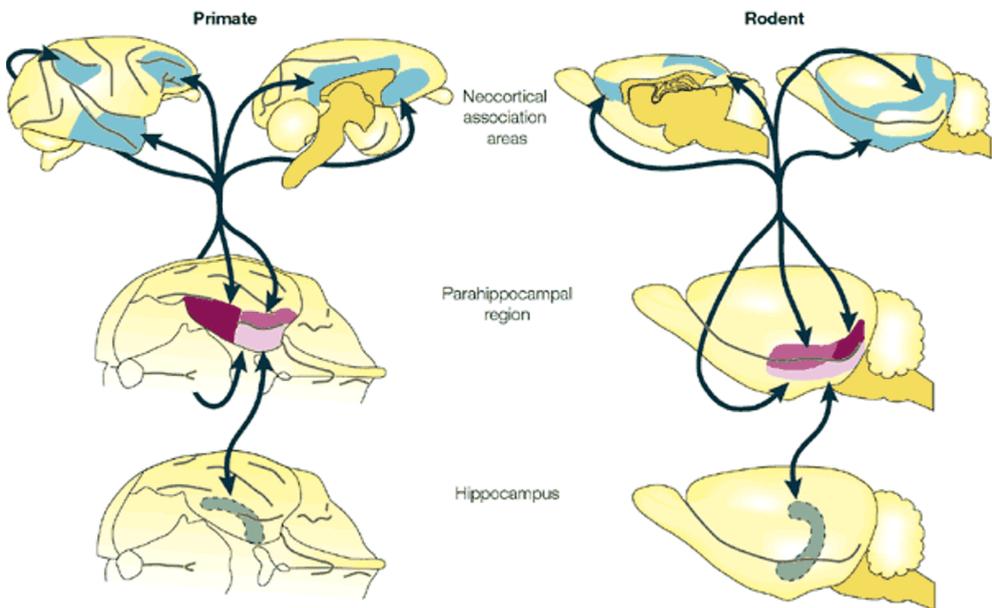
The hippocampal formation and parahippocampal region are critically involved in declarative memory.

perirhinal cortex (Haskins et al., 2008). However, others strongly oppose this dualistic view and have argued for recollection and familiarity based recognition both by the HF and the PHR (Squire et al., 2007).

Other theories of memory are less concerned with the time-limited role of the HF and PHR in declarative memory. Instead they focus on the question whether the HF and PHR are solely involved in mnemonic processing or if they are also involved in other types of information processing. For example, the PHR receives visual information largely through two separate hierarchical information processing streams. A ventral visual stream is defined which is involved in visual processing of object information, and a dorsal visual route that processes spatial visual information (Ungerleider and Mishkin, 1982). This has led some authors to investigate the PHR role in visual processing (Bartko et al., 2007a). Especially the mnemonic and visual properties of PER received attention, which resulted in the perceptual-mnemonic/feature conjunction model (Bartko et al., 2007b; Bussey et al., 2005). According to this model, conjunctions of visual features with different levels of complexity exist throughout the ventral visual-perirhinal-hippocampal stream. The model implies that the perirhinal cortex is engaged in visual object perception, depending upon the complexity of the visual input. When a simple visual stimulus is perceived, PER is not likely to be involved in storing the item in memory since higher order feature conjunction is not needed to generate a complete representation of the object. In contrast, when a complex visual image is perceived, one would expect PER

## Box 1: The hippocampal parahippocampal system

In both monkeys and rats the origins of specific information for the hippocampus include virtually every neocortical association area. Each of these neocortical areas (blue) project to one or more subdivisions of the parahippocampal region, which includes the perirhinal cortex (purple), the parahippocampal cortex (or postrhinal cortex in rodents) (dark purple) and the entorhinal cortex (light purple). The subdivisions of the parahippocampal region are interconnected and send principal efferents to many subdivisions of the hippocampus itself (green), the dentate gyrus, the CA3 and CA1 areas, and the subiculum. So the parahippocampal region serves as a convergence site for cortical input and mediates the distribution of cortical afferents to the hippocampus. Within the hippocampus a large network is present that allows for conjunctions of information. The outcome of hippocampal processing is directed back to the parahippocampal region, and the output of that region is directed in turn back to the same areas of the cerebral cortex that were the source of input to this region. (Adopted from: Eichenbaum, 2000). Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience, Eichenbaum, 2000, copyright 2000. License number: 2032521267729.



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to be required to store the item in memory, since otherwise important aspects of the “whole object” would be left out from the representation. The similar line of reasoning would predict that the parahippocampal cortex, which receives a strong input from the dorsal visual stream, is involved in perception and memory for spatial visual information.

However, this has not yet been formalized in the perceptual-mnemonic/feature conjunction model but apparently is in line with several experimental findings (place area in the parahippocampal cortex (Epstein, 2008)). Finally, in addition to theories about a time-limited role of the HF and PHR in declarative memory and a role of the perirhinal cortex in the visual perception of objects, the HF and PHR have long been associated with spatial processing and navigation (O'Keefe and Dostrovsky, 1971). Different types of spatial information are represented in the PHR - HF circuitry. Three types of cells have been shown to contribute in a unique way to spatial processing. Place cells, which are typically found in CA3 and CA1 (Kjelstrup et al., 2008; O'Keefe, 1976), code for a location in a specific spatial environment, called a place field. In addition, the medial entorhinal cortex houses grid cells (Fyhn et al., 2004), which encode space as a set of activity peaks, organized in a hexagonal grid, covering the entire environment. Finally, the presubicular head direction cells (Taube et al., 1990a; Taube et al., 1990b) code for the orientation of the rat's head with respect to the environment, irrespective of the rat's location. Together, these cells and the unique constellation of connections within and between the HF and PHR, support a role in navigation.

Although most of these theories are not anatomically detailed, they provide researchers with key theoretical constructs. These constructs are necessary to express observations of neural activation into language, allowing the scientific debate about the structure and functions of the HF and PHR to take place. In this debate, information that was obtained using different methodologies is often combined. However, a difficulty that may arise is that different techniques provide explanations of HF and PHR function at different abstraction levels (Figure 2). For example, tract-tracing studies (see chapter 2 – Box 1) provide detailed information about the circuitry of the HF and PHR (e.g. chapters 2, 3), whereas functional magnetic resonance imaging (fMRI; Box 2) provides information about functional network activity (e.g. chapters 4, 5). These different approaches can complement each other, since a comprehensive knowledge of the HF – PHR connections lies at the basis of understanding its functions (Crick and Koch, 2003). A major challenge will be to integrate relevant models at different abstraction levels into one biologically comprehensive theory on the role of PHR–HF in learning and memory.

In this thesis, a combination of anatomical and functional methods is used with the aim to provide new network level explanations of the HF and PHR. To this end, experiments will be described addressing the PHR - HF connectivity at the level of anatomical connections in the rat (section 2), which provides important clues about regional functionality, but also at the level of a functional system, as was assessed using functional MRI in humans (section 3).

## PART 2 STRUCTURAL DIFFERENTIATION

Chapter 2 provides a detailed overview of the rat HF - PHR connectivity in the rat, using a novel and interactive technique to display well known pathways as well as underexposed ones. The chapter addresses the tight relationship between anatomy and function and argues in favor of anatomically detailed models for explaining PHR – HF function. The chapter not only provides examples of how detailed knowledge of less known anatomical pathways can aid our understanding of the region, but also provides a unique, customizable tool for researchers to use in their own work (chapter 2, e-supplement 1). For those readers who are less familiar with the anatomical terminology of the region, the legend of chapter 2, e-supplement 1 provides an extensive description of the eight anatomical sub-regions of the rat PHR – HF, including their position in the brain, borders and lamination. The rat PHR – HF anatomy and connectivity is of course different from that of the human, but since many similarities are apparent, it provides a useful model.

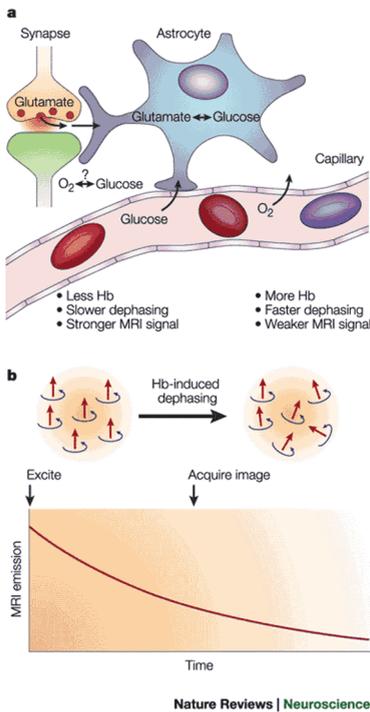
Chapter 3, the first experimental chapter, describes a relevant yet not well assessed aspect of the connectivity between the perirhinal, postrhinal and entorhinal cortex. Using anatomical tract-tracing methodology (see chapter 2, box 1), the existence of a neural substrate for association of information from PER and POR travelling to the HF via the EC was examined. PER is traditionally associated with “object” information and POR with “spatial” information. Convergence of PER and POR projections onto HF projecting neurons, would indicate that “object” and “spatial” information already becomes associated outside the HF.

## PART 3 FUNCTIONAL DIFFERENTIATION

Leaving rodent anatomy and connectivity behind, the third part of the thesis focuses on functional contributions of the PHR – HF sub-regions assessed with functional MRI in healthy human volunteers. Chapter 4 revolves around a basic question concerning PER functioning: is PER reactive to visual disparity. Using a state of the art three-dimensional display technique, we examined PER reactivity in response to the presence or absence of visual disparity in otherwise comparative visual objects. This experiment taps into the discussion concerning the visual and mnemonic role of PER. Based on the perceptual-mnemonic-feature-conjunction model, more extensive PER activation is expected in the most complex visual condition, in which stimuli are presented with visual disparity.

Chapter 5 examines the role of the MTL in retrieving stimuli from memory that were associated across multiple sensory modalities, i.e. crossmodal memory. A characteristic feature of conscious recall is that input arising from a single sensory domain, for example a visual input, may trigger the conscious recollection of an episode with all of

## Box 2: functional MRI.

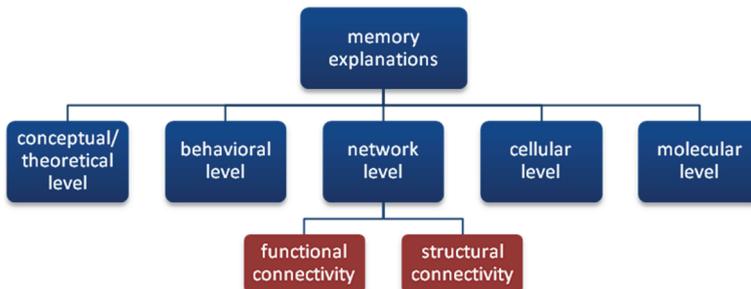


The fundamental signal for blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) comes from hydrogen atoms, which are abundant in the water molecules of the brain. In the presence of a magnetic field, these hydrogen atoms absorb energy that is applied at a characteristic radio frequency. After applying radio-frequency excitation, the hydrogen atoms emit energy at the same radio frequency until they gradually return to their equilibrium state. The MRI scanner measures the sum total of the emitted radio-frequency energy. The measured radio-frequency signal decays over time, owing to various factors, including the presence of inhomogeneities in the magnetic field. Greater inhomogeneities results in decreased image intensity, because each hydrogen atom experiences a slightly different magnetic field strength, and after a short time has passed (commonly called T2\*), their radio-frequency emissions cancel one another out. BOLD fMRI techniques are designed to measure primarily changes in the inhomogeneity of the magnetic field, within each small volume of tissue, that result from

its multimodal features. Based on rather restrictive data in non-human primates (Lee et al., 1988; Murray and Gaffan, 1994; Murray and Mishkin, 1985), it has been suggested that the perirhinal cortex, is crucially involved in such crossmodal binding. In chapter 5 we use functional MRI to assess differences in brain activity between sub-areas of the HF and PHR during crossmodal retrieval. Subjects learned unique associations between

**Figure 2: Memory explanations at different conceptual levels**

Explanations of memory can be given at different abstraction levels. The conceptual level, displayed on the left extreme, represents the highest abstraction level. The molecular level, on the right, represents the most concrete level. Network level explanations can be subdivided into structural (anatomical) and functional explanations of the circuitry.



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changes in blood oxygenation. Deoxy- and oxyhaemoglobin have different magnetic properties; deoxyhaemoglobin is paramagnetic and introduces an inhomogeneity into the nearby magnetic field, whereas oxyhaemoglobin is weakly diamagnetic and has little effect. Hence, an increase in the concentration of deoxyhaemoglobin would cause a decrease in image intensity, and a decrease in deoxyhaemoglobin would cause an increase in image intensity (see figure; Hb, haemoglobin).

The emerging model of the haemodynamic response posits that there are three phases of the BOLD fMRI response to a transient increase in neuronal activity: an initial, small decrease in image intensity below baseline (during the initial period of oxygen consumption), followed by a large increase above baseline (an oversupply of oxygenated blood, which is only partially compensated for by an increase in deoxygenated venous blood volume), and then by a decrease back to below baseline again (after the oversupply of oxygenated blood has diminished, it still takes some time for the blood volume to return to baseline). The BOLD fMRI signal also depends on the inflow of fresh blood that has not experienced the same history of radio-frequency excitation. This inflow effect, by itself (in the absence of any of the aforementioned changes in deoxyhaemoglobin concentration), would appear as an increase in image intensity, and it adds to the increase in image intensity during the second phase of the response. The figure shows the proposed relationship between synaptic activity, neurotransmitter recycling and metabolic demand (part a), and the effect of deoxyhaemoglobin on the MRI signal (part b). (Adapted from: Heeger and Ress, 2002). Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience, Heeger, 2002, copyright 2002. License number: 2032521511684

tactile, auditory, and spatial stimuli on the one hand, and a unique visual object on the other hand. To our knowledge, this is the only scientific account in which memory activation in these parts of the brain is compared across multiple (tactile – auditory – visual) sensory inputs in a single experimental paradigm. We further determined if activation in the MTL is modulated by inferential distance between the crossmodal stimuli. This allowed us to place crossmodal memory within the framework of recognition, recollection and perception (Davachi, 2006; Eichenbaum and Fortin, 2005; Mayes et al., 2007). We expected activation of the perirhinal cortex in relation to crossmodal retrieval. Furthermore, contemporary memory theory predicts increased hippocampal activation when stimuli are only indirectly associated, compared to when they are directly linked (Hannula and Ranganath, 2008).

Finally, in the last chapter, all results are summarized and evaluated in the light of the current understanding of HF – PHR structure and functioning: the general discussion. In this chapter, a new framework for HF – PHR functioning is introduced. The framework allows to relate the largely separated theories that were introduced above in a meaningful way, such that mnemonic, perceptual and spatial capabilities of the HF – PHR system are integrated into a common structure.

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