THE FUNCTIONAL ARCHITECTURE OF MEMORY REPRESENTATIONS IN THE PARAHIPPOCAMPAL – HIPPOCAMPAL SYSTEM

THESIS

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ABSTRACT

Episodic memories are inherent to our lives. We naturally remember past experiences and become unsettled when their recollection falls short. Recollection is a fascinating and complex process. A memory is not a single piece of information. A memory reflects our rich experiences and comprises many aspects of information, some item-related (e.g. objects and their features) and others contextual (e.g. the scenery). Our brain must be configured to represent and process all these aspects so that we can later access and recollect the entire experienced episode. In the brain's medial temporal lobe lies a key assembly of regions for episodic memory, the parahippocampal-hippocampal system. The aim of this dissertation is to provide evidence and discuss characteristics of this system's functional architecture that serve episodic memory.

First, I focus on the representation and processing of experienced episodes in the parahippocampal-hippocampal system. Item and context information reach the system from largely segregated cortical processing streams. To what extent the information continues to be communicated in a segregated manner is unclear. With ultra-high field functional imaging, I provide novel empirical evidence, notably on a subregional level in humans, for two functional routes throughout the system. One route specifically processes scene information, in functionally connected parahippocampal, posterior-medial entorhinal cortices, and the distal subiculum. Another route, that connects perirhinal Area 35 and the retrosplenial cortex to anterior entorhinal subregions and the subiculum/CA1 border, shows no selectivity between scene and object processing. Additionally, I review evidence across species and conclude that the perirhinal cortex processes and integrates item-related features, irrespective of their nature, into unitized multidimensional item representations. Together, these insights suggest topographically specific routes through the human parahippocampal-hippocampal system, characterized by organized item-context convergence and unique context processing, respectively.

Subsequently, I examine which part of the system is particularly involved when we recollect episodes. Computational and animal models suggest hippocampal subfield CA3 plays a crucial role in completing a cue towards a whole memory representation. With ultra-high field functional imaging, I provide the first empirical evidence in humans for the involvement of subregion CA3 in the cortical reactivation of the information that makes up an episode. This insight bridges the gap between model-based observations and human brain function. It shows the specific functionality of subregion CA3 in accessing memory representations and reinstating them in the cortex for holistic recollection.

Finally, I discuss what happens to our memories when disease distorts their functional architecture. I provide a novel conceptual link between the information-specific architecture of the parahippocampal-hippocampal system, memorability, and altered memories with progressing Alzheimer's pathology. I propose that memory representations reflect the pathological distortion of the system along information-specific routes. Certain aspects may thus withstand decline in early pathology stages, causing a profile of fragmented representations with potentially diagnostic value.

My thesis advances insight into the functional architecture of memory representations in the human parahippocampal-hippocampal system at a rare level of subregional detail. I leverage ultra-high field functional imaging, translate long-held hypotheses from computational and rodent research to the human brain and incorporate insights across clinical and basic cognitive neuroscience. The findings sketch a specific representational architecture with subregional dynamics set up to keep information together that belongs together. This organizational scaffold has implications for the nature of memories and their recollection. My work contributes to insights on how cognitive functions like episodic memory emerge from the design of the human brain, and hence how we remember our past experiences.

CONTRIBUTIONS

Parts of this thesis have been published in the following peer-reviewed articles or book chapters for which I made the subsequently outlined contributions:

A. Theves, S.*, **Grande, X.* (shared first authorship),** Düzel, E., & Doeller, C. F. (accepted due for publication in 2023). Pattern completion and the medial temporal lobe memory system. In Kahana, M. & Wagner, A. (Eds.), *Handbook of human memory.* Oxford: Oxford University Press.

   As a shared first author I contributed substantially to conceptualizing, original writing and editing of the entire draft of the accepted chapter for the forthcoming book.

B. **Grande, X.**, Sauvage, M., Becke, A., Düzel, E. & Berron, D. (2022). Transversal functional connectivity and scene-specific processing in the human entorhinal-hippocampal circuitry. *eLife.*

   As a first author, I contributed substantially to the conceptualization, data analysis as well as writing and editing of the publication.

C. Fiorilli, J. P. N.*, Bos, J.J.*, **Grande, X.**, Lim, J., Düzel, E., & Pennartz, C.M.A. (2021). Reconciling the object and spatial processing views of the Perirhinal Cortex through task-relevant unitization. *Hippocampus.* *shared first authorship

   As a second author, I contributed substantially to the conceptualization and original writing of the parts of the publication that refer to human research as well as to the entire synthesis and discussion. I contributed to the editing of the full paper.

D. **Grande, X**., Berron, D., Horner, A. J., Bisby, J. A., Düzel, E.*, & Burgess, N.* (2019). Holistic recollection via pattern completion involves hippocampal subfield CA3. *Journal of Neuroscience*. *shared authorship

   As a first author, I contributed substantially to the conceptualization, data acquisition, data analysis of the study as well as original writing and editing of the publication.

E. **Grande, X.**, Berron, D. Maass, A., Bainbridge, W., & Düzel, E. (2021). Content-specific vulnerability of recent episodic memories in Alzheimer's Disease. *Neuropsychologia.*

   As a first author, I contributed substantially to the conceptualization, original writing and editing of the publication.

Throughout the thesis, I indicate the parts that belong to the respective publications.

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CHAPTER I

GENERAL INTRODUCTION

I. General Introduction

Our identity is formed by our experiences. The ability to recollect these past episodes is a fascinating capacity of the human brain that will be central to my thesis. Despite being one of the most studied subjects in cognitive neuroscience, many aspects of how the brain achieves episodic recollection are still a mystery. Conditions of impaired memory like Alzheimer's dementia remain frightening and challenging for humankind.

How a cognitive function like episodic memory emerges, is embedded in the brain's design. Comparable to the architecture of a building, that allows, for example, for a theatre to put on productions inside and thus fulfill its function, anatomical and neural scaffolding in our brain allows us to reflect and process episodic information such that we can recollect them later.

This thesis contributes by bridging our understanding of brain structure and memory function. To achieve this, I translate insights on the emergence of memory function from animal research and computational models to the human brain. I merge branches of cognitive and clinical neuroscience and psychology to relate the experience of recall to functional states of the brain. My focus is on the parahippocampal-hippocampal system which has been identified as critical for episodic memory function and recollection (Eichenbaum et al., 2007; Squire et al., 2004).

In six chapters, I discuss how the functional architecture of the human parahippocampal-hippocampal system gives rise to episodic memory representations. My thesis focusses on three general open questions. (1) How does the system reflect and process our experienced episodes? (2) Which part of the system is particularly involved when we remember past episodes? (3) What happens to our memories when parts of the parahippocampal-hippocampal architecture are distorted?

After a general introduction (Chapter I) into the structure and function of the system, I reveal and extend upon essential aspects of the functional organization and information processing within the parahippocampal–hippocampal system. I present and discuss novel empirical evidence for dedicated information processing routes within the system (Chapter II). In accordance with these findings, I propose a functional role of the PrC within the parahippocampal gyrus beyond the traditional understanding of information processing (Chapter III). I thereafter present and discuss novel empirical evidence for how the system accesses stored information and contributes to episodic recollection (Chapter IV). Subsequently, I evaluate how the recent insights on the functional architecture of the parahippocampal-hippocampal system influence our understanding of episodic memory decline in Alzheimer's dementia (Chapter V). The general discussion (Chapter VI) describes implications of my work for the functional architecture of representations, for how they serve memory and for their distortion following pathology spread in the parahippocampal-hippocampal system.

1.1 Representations to recollect the past

In the 1970's, Endel Tulving[1] coined the term "episodic memory" to describe the recollection of our past (Tulving, 1972, 1983a). Our episodic memory can retain a record of personal experiences in rich detail. Experiences incorporate multifaceted aspects of information from different senses, content

[1] Note that during this thesis, I was inspired by many accounts of memory, not only Tulving's. Even though his almost philosophical speculations largely influenced research and the idea of how we remember the past, he himself refined his concept of an "episodic memory" (see Tulving, 1983b; Tulving, 2002). Others questioned what exactly an episodic memory constitutes, and even more importantly, how it differs from other types of memory (e.g. semantic memory as I touch upon in Chapter V; see e.g. Renoult et al., 2019; Squire & Zola, 1998). Likewise, there is a debate about the extent to which episodic memory is specific to humans (Aggleton & Pearce, 2001; Clayton et al., 2001; Morris, 2001). By no means, the work of my thesis is exclusively related to one versus another type of memory. However, our ability to recollect a memory, that is, to reinstate an event, its story, its essential elements and our own position in it, is the type of remembrance that may emerge directly from the functional architecture I studied.

types and at various levels of specificity. To describe the elements that constitute memory content, I will refer to "information" throughout this thesis. To form what we call a "memory", all these pieces of information are integrated to be later recollected, a process for which a cue matching only a single detail of the original experience can be sufficient (Marr, 1971; Schacter et al., 1978; Tulving, 1983b, 2002).

The brain can exploit its impressive memory function as it is set up to reflect information from the outer world in certain states within its own structure and reactivate these states later on. Any externally or internally generated experience produces changes in the brain. If preserved and consolidated, access to these brain states and their reinstatement may be achieved later on. This process enables recall of the episode, accompanied by a sense of reliving the original experience (Eichenbaum, 2016; Goode et al., 2020; Josselyn et al., 2015; Josselyn & Tonegawa, 2020; Tulving, 1983b).

Here, I refer to the brain states that hold mnemonic information as 'memory representations' and I refer to them at the level of subregions within the brain. Note that throughout the literature multiple terms appear, often interchangeably, including 'memory traces' (Buzsáki, 1989; Sutherland, 2000), 'engrams' (Hebb, 1950; Josselyn & Tonegawa, 2020; Schacter et al., 1978; Tonegawa et al., 2015) or 'representations' (e.g. Tulving, 1974 ; see Josselyn et al., 2015 and Dudai & Morris, 2013 for reviews). Memory representations can be found on different neural levels, from synapses (Asok et al., 2019), to single cells (Quiroga et al., 2005), to cell populations (e.g. Ghandour et al., 2019; Roy et al., 2016; Tanaka et al., 2014) and at the level of thousands of cells across brain regions (as in e.g. Cooper & Ritchey, 2019; Horner et al., 2015; Staresina et al., 2012 but many others). They may emphasize different aspects of the outer world, depending on the hierarchy-level of the processing stream and the type of content that is funneled into the respective region. Some types of representations serve as indices or pointers and merge many different types of information into a small population of cells (Tanaka & McHugh, 2018; Teyler & Rudy, 2007). These pointers interact with representations that are distributed across several, mostly cortical, regions that contain rich and detailed aspects of information (O'Reilly & Rudy, 2000).

Where and how an episode is being represented in the brain and accessed later on is still subject to extensive discussion. In the following, I will review, explore and discuss how the parahippocampal-hippocampal system is set up to process and represent information in a way that allows recollection and episodic memory.

1.2 THE STRUCTURE OF THE PARAHIPPOCAMPAL-HIPPOCAMPAL SYSTEM

1.2.1. Regions of the parahippocampal-hippocampal system

The parahippocampal-hippocampal system[2] is a complex assembly of interconnected regions in the medial temporal lobe (Van Strien et al., 2009). The system consists of the parahippocampal gyrus and the hippocampal formation (see Figure 1 [A]). The parahippocampal gyrus gives rise to three main structures: posteriorly the parahippocampal cortex and anteriorly the perirhinal and entorhinal cortices (Ding & Van Hoesen, 2010; Insausti & Amaral, 2004; Witter, Wouterlood, et al., 2000). Both, the parahippocampal and perirhinal cortices are located inferiorly to the hippocampal formation. The

[2] For the anatomical subregions and their wiring pattern, I focus on the key elements for the current thesis. Throughout this thesis, I largely adhere to terminology that refers to the human brain, however much insight comes from rodent and monkey data (Lavenex & Amaral, 2000; Van Strien et al., 2009). As, however, the knowledge on anatomical projections mostly stems from rodents due to the infeasibility of conducting invasive and ex vivo methods like histological staining and tract-tracing in humans, I will present the wiring scheme of the *rodent* parahippocampal-hippocampal system in the second half of this section.

PrC is cytoarchitectonically divided into Brodmann Area 35 and Brodmann Area 36 (Ding & Van Hoesen, 2010). Some anatomists also refer to Area 35 as the transentorhinal cortex as it evolves medially into the EC (e.g. Braak & Braak, 1991; see Berron et al., 2017 for a brief discussion). The EC itself embraces the most anterior part of the hippocampal formation medially (see Figure 1 [B]).

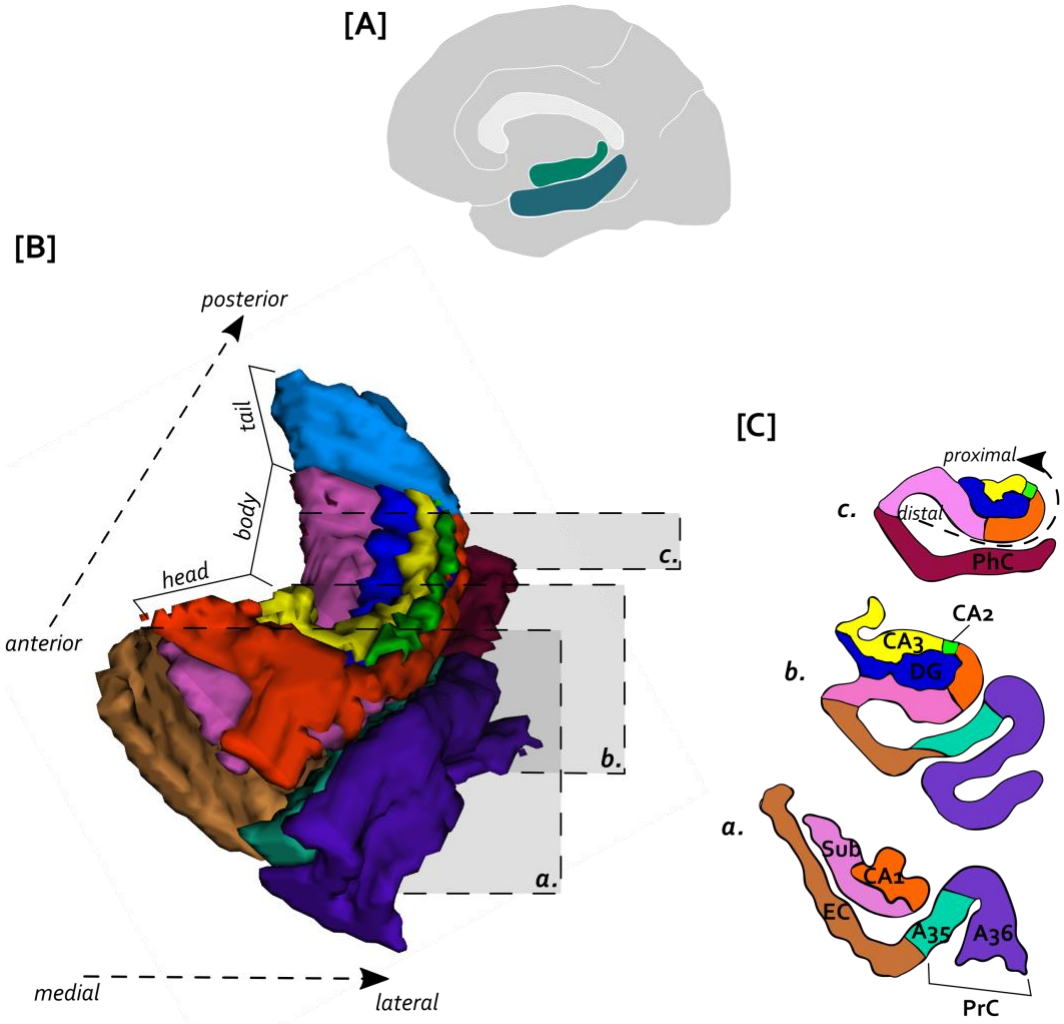

Figure 1. Subregions within the parahippocampal-hippocampal system. *Displayed is the location of the parahippocampal-hippocampal system on a sagittal cut through a schematized human brain [A], the parahippocampal-hippocampal system of a right hemisphere in a 3 D rendering [B] and in coronal slices, drawn by hand [C], reflecting coronal cuts along the planes [B] a. b. and c. Subregions are coloured and names assigned in part [C]. Three axes help to describe the anatomy of the structure in the human brain: the anterior-posterior, medial-lateral (visible in [B]) and the proximal-distal axis (visible in [C]). The anterior-posterior axis is also termed "longitudinal axis" and the proximal-distal axis "transversal axis". The parahippocampal-hippocampal system is located in the medial temporal lobe and constitutes several subregions. The parahippocampal part (blue in [A]) consists posteriorly of the PhC (in rodents "postrhinal cortex", visible in [B] and [C] c.) and anteriorly of the PrC with A36 and A35. A35 is also called transentorhinal cortex as it transitions towards the medially evolving EC. The hippocampus proper (green in [A]) is embedded in the parahippocampal system and divided into an anterior "head", middle "body" and posterior "tail" part (see [B]). The hippocampus consists of the subregions Sub, CA1, CA2, CA3 and the DG. While the topography of hippocampal subregions changes considerably along the longitudinal axis of the head (see for example the differences between [C] a. and [C] b.), the structure is rather consistent along the longitudinal axis of the body and resembles [C] c. The depicted subregions are based on an exemplar segmentation that followed the protocol of Berron et al. (2017). PrC – perirhinal cortex; A35 – Area 35; A36 – Area 36; PhC – parahippocampal cortex; Sub – subiculum; DG – dentate gyrus; CA – cornu ammonis.*

The hippocampal formation is folded within the parahippocampal gyrus (see Figure 1 [B]). It has several subregions, including the subiculum, the DG and CA1, CA2 and CA3 (Insausti & Amaral, 2004; Van Strien et al., 2009). Two main axes are used to describe the human hippocampus[3]: the transversal and the longitudinal axis. The former refers to the distance of a position to the dentate gyrus, attributed as either distal or proximal and the latter refers to the anterior to posterior position within the brain. Along the longitudinal axis, the hippocampal formation is divided into the head, the body and the tail (see Figure 1 [B]). The hippocampal subregions extend along the full longitudinal axis while neighboring each other along the transversal axis in a scroll-like shape (see Figure 1 [C]). Note however, that in the hippocampal head, the organization of hippocampal subregions follows a more complex pattern, distinct from the organization in the hippocampal body (see Figure 1 [C] a.-c. for a schematic depiction; Ding & Van Hoesen, 2015; Insausti & Amaral, 2004).

1.2.2. Anatomical connections within the parahippocampal-hippocampal system

The anatomical wiring of the parahippocampal-hippocampal system follows an overall hierarchical pattern. The system mainly receives and sends out projections to other brain regions via the parahippocampal gyrus, while in turn the parahippocampal gyrus and hippocampal formation are densely interconnected, with the hippocampus on top of the hierarchy (Lavenex & Amaral, 2000).

Along the parahippocampal gyrus, the topography of neocortical connections generally follows two streams. Main reciprocal connections to the neocortical and also subcortical areas go to the basal ganglia, amygdala, unimodal sensory areas, the visual and temporal association cortices and the posterior parietal cortex (see Figure 2) (Burwell, 2006; Tomás Pereira et al., 2016). While posterior parietal projections are stronger towards the postrhinal cortex in rodents (the homologue to the human parahippocampal cortex), ventral temporal association cortices project more strongly onto the PrC (for an overview see Burke et al., 2018). Moreover, the postrhinal cortex exhibits connections to the anterior cingulate and retrosplenial cortices while the PrC connects to the insular, medial-, orbitofrontal and piriform cortices (Burwell, 2006; Burwell & Amaral, 1998b). Similar to the PrC, the EC projects reciprocally to insular, medial-, orbitofrontal and piriform cortices in its lateral part (Doan et al., 2019; Witter, Doan, et al., 2017).

Within the parahippocampal gyrus, a recent finding emphasizes cross-projections between two main pathways that continue the differential neocortical connections instead of the former parallel anatomical wiring scheme. The PrC is directly connected with the lateral part of the EC whereas the postrhinal cortex exhibits bidirectional projections with the medial entorhinal subregion (Burwell & Amaral, 1998a, 1998b; Koganezawa et al., 2015). Cross-projections have been pointed out between post- and perirhinal cortices, medial and lateral EC (Burwell & Amaral, 1998b; Dolorfo & Amaral, 1998; for the monkey see Lavenex et al., 2004; for an overview see Kerr et al., 2007) and also between the postrhinal and the lateral EC (Doan et al., 2019; Nilssen et al., 2019; see Figure 2). Traditionally the wiring scheme in the parahippocampal gyrus was considered fully parallel (Witter, Naber, et al., 2000). Particularly strong postrhinal to PrC and postrhinal to lateral EC projections now emphasize cross-talk (Nilssen et al., 2019).

The hippocampal formation receives main projections from the EC via the perforant path that innervates the hippocampal subregions CA1, DG and CA3. The EC projections are input and output of two main pathways within the hippocampus, the temporo-ammonic path and the trisynaptic circuitry (Amaral & Witter, 1989; Witter, Kleven, et al., 2017). The main incoming pathways to the hippocampus stem from superficial entorhinal layers. Deep entorhinal layers receive the main

[3] Note that I refer to the subiculum, DG and CA subregions as 'hippocampus' throughout my thesis while some anatomists point out that the hippocampus proper is only defined by the CA fields (Insausti & Amaral, 2004).

outcoming projections of the hippocampal formation via CA1 and subiculum (Amaral & Witter, 1989). The superficial entorhinal input layers are interconnected with the deep entorhinal output layers (Dolorfo & Amaral, 1998; Van Strien et al., 2009; see Figure 2).

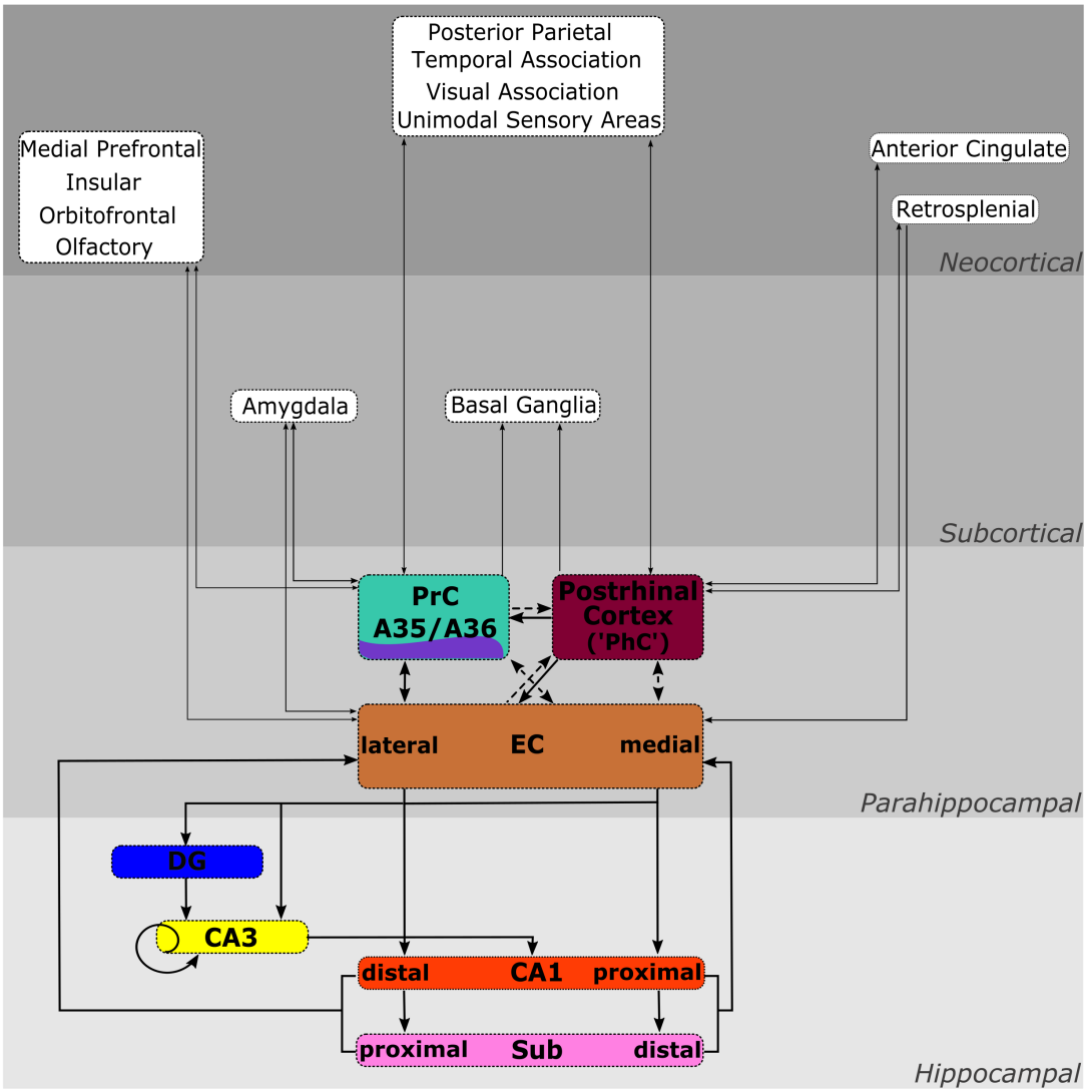

Figure 2. Anatomical wiring of the parahippocampal-hippocampal system. *Crucial projections for this thesis are the two pathways connecting the parahippocampal gyrus with the hippocampal formation: One pathway from perirhinal to lateral EC to distal CA1 to proximal subiculum and the other pathway from postrhinal (in humans parahippocampal) cortex to the medial EC, proximal CA1 and distal subiculum. Note that these two pathways do not run in parallel within the parahippocampal gyrus. Critical cross-projections exist from postrhinal to perirhinal and postrhinal to lateral EC. The two pathways largely continue differential bidirectional neocortical projections that the perirhinal and postrhinal cortices yield. The retrosplenial cortex, for example projects to the postrhinal – medial EC pathway only. In addition, it is relevant for this thesis to point towards the recurrent projections within hippocampal subfield CA3. Note that the colouring of subregions corresponds to the colouring in Figure 1. For clarity, not all known projections are presented. Projections between hippocampal subregions and subcortical or neocortical structures are omitted. Stippled arrows refer to projections of lesser strength, the neocortical projections are, however, not weighted here. The full scheme is based on rodent data as most anatomical connectivity data stems from these species. High correspondence, however, exist with the human brain for the parahippocampal-hippocampal projections. The parahippocampal cortex is the human homologue for the rodent postrhinal cortex. EC – entorhinal cortex; PrC – perirhinal cortex; A35 – Area 35; A36 – Area 36; PhC – parahippocampal cortex; Sub – subiculum. This figure is adapted and edited from Fiorilli et al., 2021, published under Creative Commons Attribution 4.0 International License (CC-BY 4.0, https://creativecommons.org/licenses/by/4.0/).*

Within the temporo-ammonic pathway the parallel organization of projections extends from the EC towards CA1 and is also evident in projections to the subiculum (Kerr et al., 2007; Witter & Amaral, 1991, 2020). The lateral EC mainly connects to distal CA1 and proximal subiculum in contrast to the medial EC that projects to the proximal CA1 and distal subiculum (Naber et al., 2001). Reciprocal

wiring exists between the EC and the respective CA1 and subiculum subregions (for overviews see (Amaral & Witter, 1989; Nilssen et al., 2019; for evidence in monkeys see Witter & Amaral, 1991, 2020).

Within the trisynaptic circuitry, projections follow a more unidirectional pattern (but see Scharfman, 2007) and the EC perforant path projections are continued by mossy fiber projections from the DG to CA3 (Andersen et al., 1971; Lorente De Nó, 1934). In subregion CA3, dense recurrent collateral connections exist that build a network entailing connections with itself (Lorente De Nó, 1934). Schaffer collaterals continue the circuitry further from CA3 to CA1 and projections exit the hippocampus from CA1 to the subiculum and then to the deep EC layers (Amaral & Witter, 1989; Andersen et al., 1971).

Importantly, there is generally consistency across species in the anatomy and wiring of the parahippocampal-hippocampal system, irrespective of differential brain orientations, shape, location or size of subregions (Manns & Eichenbaum, 2006). The main differences between rodent and primate anatomical wiring seem to exist in the neocortical connections, presumably reflecting species-specific sensory processing (Burwell et al., 1995; Duvernoy et al., 2013; Manns & Eichenbaum, 2006; for a functional connectivity study in humans see Libby et al., 2012; for comparisons between the rodent and the monkey brain see Suzuki, 2009). Overall, the anatomy described can serve as a schema for the structural architecture of the human parahippocampal-hippocampal system, while keeping in mind that the exact anatomical wiring of the subregions has not yet been revealed in humans.

1.3 THE FUNCTIONAL ARCHITECTURE OF THE PARAHIPPOCAMPAL-HIPPOCAMPAL SYSTEM

1.3.1 Information-specific processing streams enter the parahippocampal-hippocampal system

The anatomical wiring of the parahippocampal-hippocampal system has implications for the organization of memory function and suggests partially segregated processing of item-related and contextual episodic information (Eichenbaum et al., 2007; Ranganath & Ritchey, 2012; Witter et al., 2000). The differential neocortical inputs into the parahippocampal region originate from previously identified 'what' and 'where' information processing streams of the visual system (Haxby et al., 1991; Ungerleider & Haxby, 1994; in rodents see Manns & Eichenbaum, 2006; Connor & Knierim, 2017). Despite connections between both streams, contextual aspects of episodes are mainly processed along the 'where' stream that incorporates posterior-medial cortical regions, including the retrosplenial, parahippocampal and medial EC. Item-related aspects seem, however, largely processed along the 'what' stream that incorporates anterior-temporal cortical regions, including the perirhinal and anterior-lateral EC (Berron et al., 2018; Eichenbaum et al., 2007; Ranganath & Ritchey, 2012; Ritchey et al., 2014). It is important to note that no clear definitions of the informational content in both streams yet exist. To capture the rather broad nature of the attributed information, I adhere generally to an 'item versus context' nomenclature throughout this thesis (while others also used, e.g. 'what versus where', 'non-spatial versus spatial', 'object versus scene', 'local versus global' – see Chapter VI for a discussion).

Evidence in rodent data

Early rodent electrophysiological and lesion evidence relate the perirhinal and postrhinal cortices to 'what' and 'where' visual streams, respectively, with similar functions in navigation and memory, despite recent anatomical evidence for cross-talk (Nilssen et al., 2019). The PrC is involved in object processing and recognition (Albasser et al., 2009; Bartko et al., 2007a; Ennaceur et al., 1996; Ennaceur & Aggleton, 1997; G. Norman & Eacott, 2004, 2005; Otto & Eichenbaum, 1992). The postrhinal cortex

codes for the position of an animal in space (LaChance et al., 2019) and the context of a memory (Furtak et al., 2012; Murray et al., 2007; G. Norman & Eacott, 2005; see for an overview Aminoff et al., 2013).

Further rodent findings supported a bias for contextual versus item-related information processing within entorhinal subregions, respectively (however, lately found to be less strict). The medial and lateral ECs contain different cell types. The medial EC contains a high percentage of cells whose firing patterns are modulated by spatial aspects of the environment. Specific grid cells have been identified with a regular hexagonal firing pattern that provides a global spatial metric of the environment (Hafting et al., 2005; for evidence in monkeys see Killian et al., 2012 and bats see Yartsev et al., 2011). Other cells have been found to code for the head direction or the borders of an environment (Sargolini et al., 2006; Solstad et al., 2008). The lateral EC contains cells that represent information about objects and sequences of events (Tsao et al., 2013, 2018) but these may also include contextual information (Deshmukh & Knierim, 2011; Wilson, Langston, et al., 2013; Wilson, Watanabe, et al., 2013). Neunuebel and colleagues (2013) simultaneously recorded cell firing patterns in the rodent medial and lateral EC. While recording, the arrangement of local and global cues in the environment was varied to parametrically alter the mismatch between the animals' local and global reference frames. Medial entorhinal cells responded mainly to the global cue and were thus coherent between initial and altered environments whereas the lateral entorhinal cells lacked strong spatial responses.

Rodent studies, moreover, suggest that context and item-related processing streams continue between the EC and the transversal axis of the hippocampus, notably subiculum, CA1 and presumably CA3 (Beer et al., 2018; Flasbeck et al., 2018; Ku et al., 2017; Nakamura et al., 2013; Y. Nakazawa et al., 2016).

Evidence in human data

Evidence in humans supports context and item-related processing in parahippocampal and PrC, respectively, despite the recent anatomical findings that acknowledge cross-talk. Converging functional imaging data supports two functionally connected networks that are formed by the proposed anterior-temporal and posterior-medial stream and biased to process item-related and contextual aspects of memories, respectively (Berron et al., 2018; Libby et al., 2014; Reagh & Yassa, 2014; Ritchey et al., 2015; S.-F. Wang et al., 2016). Within the parahippocampal-hippocampal system, lesion and functional studies have shown a critical involvement of the PrC in object and parahippocampal cortex in scene information processing (for an overview see Ranganath & Ritchey, 2012). Scene recognition and processing as well as spatial cue representations for navigation are attributed to the parahippocampal cortex (Aguirre & D'Esposito, 1999; Epstein et al., 2001; Köhler et al., 2002; Takahashi & Kawamura, 2002). Retrieval that lacks rich contextual detail (i.e. based on familiarity instead of recollection) and complex object perception are attributed to the PrC (Barense, 2005; Buffalo et al., 1998; Haskins et al., 2008; A. C. H. Lee, Bussey, et al., 2005; Martin et al., 2015; see for overviews Brown & Aggleton, 2001; Eichenbaum et al., 2007; Squire et al., 2007). Given the recently emphasized projections from the parahippocampal towards the PrC, the PrC, however, may be sensitive for contextual aspects as well (Nilssen et al., 2019; see Figure 3). This is a relevant observation for the first question of my thesis on how the system reflects our experienced episodes.

Human homologues to the rodent functional entorhinal subregions have been identified but functional differences within hippocampal subregions have not been systematically examined. The functional connectivity between the perirhinal and parahippocampal cortex and the human EC leads to a functional segregation in anterior-lateral and posterior-medial subregions (Maass et al., 2015; Navarro Schröder et al., 2015). These have been indicated to continue the biased representational

cortical streams for item-related and context information, respectively (Maass et al., 2015; Navarro Schröder et al., 2015; Reagh & Yassa, 2014; Schultz et al., 2012; see Figure 3). The functional connectivity pattern also implies further continuation of representational streams in the proximal versus distal subiculum (Dalton et al., 2018; Maass et al., 2015). However, it is not yet known whether the segregated organization continues within the human hippocampus, a question that I will address in this thesis.

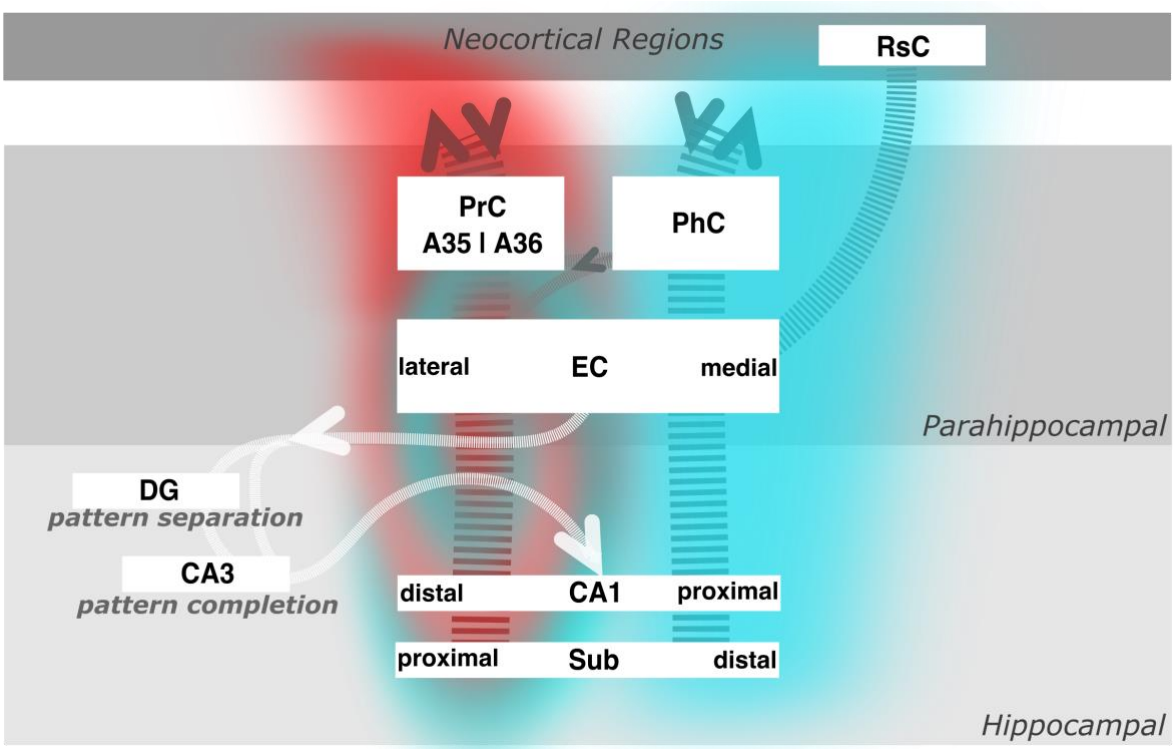

Figure 3. Proposed information flow and functional architecture in the human parahippocampal-hippocampal system. *'What' and 'where' information processing pathways from the visual streams project towards the parahippocampal gyrus. Based on the rodent anatomical wiring and on rodent and initial human functional data, a bias for processing item-related ('what', red) information versus context ('where', cyan) information is proposed along the RsC, PrC – lateral EC – distal CA1 – proximal Sub (Sub) and PhC– medial EC – proximal CA1 – distal Sub route, respectively. However, recent rodent research suggests considerable overlap between both routes, particularly from the context towards the item-related processing route (cyan – red convergence). Information enters the hippocampus via the EC and is projected towards DG, CA3 and CA1. Novel information is thought to be stored in separated patterns in an interplay between DG and CA3. In CA3, incoming information may be completed towards already stored patterns. If successfully completed, the representation is reinstated in the cortex via CA1 and subiculum (that also feeds back to the EC). The depicted functional architecture follows from recent literature but warrants evidence, particularly in the human brain. The proposed information flow and functional architecture thus set the basis for the current thesis' questions: (1) How is information communicated and processed throughout the subregions of the human parahippocampal-hippocampal system? (2) How are human hippocampal subregions involved in reinstating distributed cortical representations for memory retrieval? and (3) Which effects may a disruption of the parahippocampal-hippocampal system by Alzheimer's pathology have on memory representations and their recollection? PrC – perirhinal cortex; EC – entorhinal cortex; Sub – subiculum; PhC – parahippocampal cortex; CA – cornu ammonis; DG – dentate gyrus; RsC – retrosplenial cortex*

1.3.2 Distinct hippocampal subregions compute pattern separation and pattern completion

Distinct features of the hippocampal subregions DG and CA3, moreover, motivated ideas about an implementation of pattern separation and completion computations that orchestrate memory representations and enable their access for recollection. These computations are essential for memory function because they organize memory representations by making them distinct from each other (pattern separation) and they complete parts of memories to previously stored representations (pattern completion). First formulated by David Marr (Marr, 1971; and earlier by Richard Semon in 1904, see Schacter et al., 1978), these ideas inspired subsequent physiologically grounded theoretical

and computational models on the emergence of episodic memory from the hippocampal formation (Kesner & Rolls, 2015; Kumaran & McClelland, 2012; McNaughton & Morris, 1987; O'Reilly & McClelland, 1994; O'Reilly & Norman, 2002; Treves & Rolls, 1994). Both computations work on hippocampal representations that are thought to not reflect the original experience in detail. Instead, they may enable access and reinstatement of the detailed distributed cortical representation (i.e. brain state) during the original experience.

[4] ⌈Given the information flow within the hippocampus, the following mechanisms have been suggested to underlie memory formation and recollection: incoming information via entorhinal projections is dispersed onto a significantly larger cell population in the DG, minimizing potential overlap and creating sparse and independent neural representation patterns ('pattern separation') in DG before being passed to subfield CA3 (O'Reilly & McClelland, 1994; Rolls, 1996; see Figure 3).
CA3 is, given its dense recurrent collateral connections, thought to operate as an autoassociative system[5] (Amaral et al., 1990; Ishizuka et al., 1990; Rolls & Treves, 1994; Treves & Rolls, 1994). Importantly for this thesis, such a system allows the recall of complete memories cued by sensory input from the EC (McNaughton & Morris, 1987; O'Reilly & McClelland, 1994; Rolls & Treves, 1994; Rudy & O'Reilly, 1999; Treves, 2004; Treves & Rolls, 1994). During encoding, plasticity at CA3-CA1 synapses is regulated to couple sparse CA3 patterns with information-rich CA1 representations. This process is elicited when incoming information cannot be completed towards a previously stored pattern (Kaifosh & Losonczy, 2016; McClelland & Goddard, 1996). During recall, CA1 activity is then proposed to monitor CA3 activity and, upon pattern completion in CA3, converge to the pattern that was coactive with the previously complete CA3 pattern during encoding. The enriched pattern in CA1 can then activate respective cortical representations to elicit a recollective experience during retrieval (Kaifosh & Losonczy, 2016; McClelland & Goddard, 1996; Treves & Rolls, 1994).

Evidence in rodent data

One essential branch of experimental support for pattern separation and completion computations in hippocampal DG and CA3, respectively, stems from electrophysiological recordings during navigation in rodents. Recordings in hippocampal place cells provide valuable empirical data on the general information processing mechanisms in the hippocampus (e.g. I. Lee et al., 2004; I. Lee & Kesner, 2004; J. K. Leutgeb et al., 2007; Neunuebel et al., 2013; Neunuebel & Knierim, 2014; Vazdarjanova & Guzowski, 2004; Wills et al., 2005). Place cells discharge only at a cell-specific region in the environment, the so-called 'place field' (O'Keefe & Dostrovsky, 1971). Place fields are temporally stable in constant environments but alter their firing patterns in response to significant changes of the environmental context (J. K. Leutgeb et al., 2007; S. Leutgeb et al., 2005; Wills et al., 2005). This change in representation between environments, called remapping, may provide a window into studying the information representation within the hippocampus.

In the DG, cells show substantial remapping, even if changes between environments are minimal, thus providing support for pattern separation in DG (J. K. Leutgeb et al., 2007). Notably, however, pattern separation is defined based on the processing of incoming information from the EC. Following the methods outlined in Neunuebel et al. (2013), the findings of a second study supported pattern separation in DG (Neunuebel & Knierim, 2014). DG's differential responses for input that only partially

[4] paragraphs between ⌈⌋ symbols are included with minor edits from the draft of a chapter that has been accepted for publication by Oxford University Press in the forthcoming book "Handbook of Human Memory" by Theves[+], Grande[+] et al. ([+] shared first authorship) edited by Michael Kahana and Anthony Wagner due for publication in 2023.
[5] Autoassociative systems are able to embed different memories as distinct, stable patterns, so called "attractor states" (Steemers et al., 2016; Wills et al., 2005), which have the quality to attract neighboring activity patterns to move towards them. Attractor networks are thought to incorporate several preferred positions in a state space and activity induced by external inputs would ultimately approach the attractor to which the input is most closely correlated.

varies (in the local cues but not the global cues) provides evidence for DG's role in separating overlapping input patterns (Neunuebel & Knierim, 2014).

Similarly, supporting evidence for pattern completion computations in CA3 has been obtained. Neunuebel and Knierim (2014) also recorded in CA3, revealing that in CA3 the initial and the altered environment were represented more similarly to each other than any of its inputs (Neunuebel & Knierim, 2014). Likewise, remapping studies show that CA3 follows an attractor-like pattern: Previously acquired firing rates of circle and square-shaped environments shift abruptly upon encountering intermediate shapes of the environments (Wills et al., 2005). In another study, evidence was also provided for pattern completion but the changes in firing rates were rather, suggesting support for a higher complexity in the working of attractor systems (S. Leutgeb et al., 2005). Further critical evidence for pattern completion signatures in the rodent CA3 has been obtained by manipulating the presence or quantity of cues during spatial memory retrieval. When disrupting N-methyl-D-aspartate receptors (important for the creation of long-term-potentials and memory formation) in CA3, memory is intact when cues are presented but impaired when external cues in a water maze are largely removed (Fellini et al., 2009; K. Nakazawa et al., 2002). Others (Gold & Kesner, 2005; Kesner & Warthen, 2009) investigated pattern completion in a delayed match-to-sample task by varying the number of cues available to influence the recall of spatial location. Lesioning the CA3 region (Gold & Kesner, 2005) or the input of the perforant path from EC to CA3 (Kesner & Warthen, 2009) impaired retrieval in dependance on the amount of provided cues. In rodents, different experimental approaches could thus provide empirical support for the proposed role of CA3 in completing incoming cue information to stored patterns. ⌋

Evidence in human data

[6] ⌈To investigate processes like hippocampal pattern separation or pattern completion non-invasively in humans is a challenging endeavor because hippocampal CA3 and DG are considerably small regions (Adler et al., 2014). Given the relatively low resolution of non-invasive brain imaging in humans, inferences on neural mechanisms remain indirect and largely rest on a convergence between cognitive task demands and compound brain activity patterns of medial temporal lobe structures.

Supporting evidence for pattern separation processes in the human DG comes from several studies employing high-resolution fMRI at 3 Tesla but they were not able to functionally dissociate DG from CA3 (Bakker et al., 2008; Kirwan & Stark, 2007; Lacy & Stark, 2012). Importantly, Berron and colleagues leveraged high-field functional imaging at 7 Tesla to show that the DG (but not other subregions) specifically differentiates between very similar stimuli (Berron et al., 2016). A rare lesion case, constrained to the DG additionally supported that the DG is critical to separate similar items in memory (Baker et al., 2016).

A specific link between pattern completion and CA3 is so far not empirically supported in humans. Various studies provide general evidence for hippocampal involvement in retrieval tasks that require pattern completion (amongst many others Bosch et al., 2014; Cooper & Ritchey, 2019; Gordon et al., 2014; Horner et al., 2012, 2015; Pacheco Estefan et al., 2019; Staresina et al., 2012, 2016; Trelle et al., 2020). A functional differentiation between subregions during cued recall is challenging with 3 Tesla imaging (J. Chen et al., 2011; Dudukovic et al., 2011). An initial effort to delineate CA3 functionally from other hippocampal subregions (particularly here DG) in a neuroimaging study used an approach that resembled rodent remapping studies (Bonnici et al., 2012). During the judgment of morphed,

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ambiguous scenes in relation to two original scenes, the classification accuracy was higher in CA3 and CA1 than in other hippocampal subregions. Thus, while the stimulus was perceptually ambiguous, the representations in CA3 and CA1 reflected the participant's decision on whether the ambiguous scene resembled original scene A or B. This functional activity pattern is interpreted as reflecting pattern completion as the decision requires the retrieval of a previously stored pattern based on a differential input. Note that many studies were unable to differentiate pattern completion signatures in CA3 from CA1. In addition to early observations (Bakker et al., 2008), Hindy and colleagues (2016) demonstrated that after initially learning sequences of cue, action, and outcome within the temporal sequence task, CA3 and CA1 reinstated the outcome when only cue and action were presented. Likewise CA1 activity at retrieval relates to cortical reinstatement of previously learned associations (Tompary et al., 2016). Dimsdale-Zucker and colleagues (2018) similarly reported a pattern completion signature in CA1 as higher representational similarity was demonstrated between items that share the same context (Dimsdale-Zucker et al., 2018). The challenges in isolating functional activity in CA3 may have complicated a dissociation between the specific contributions of different hippocampal subregions to pattern completion. ⌋ I will address that issue within this thesis.

1.4 The susceptibility of the parahippocampal-hippocampal system to decline

The parahippocampal-hippocampal system is vulnerable to acute lesions and neurodegeneration. Early cases of acute, focal lesions have revealed the importance of the system for cognitive functions like episodic memory, and also have revealed the information-specific processing biases of certain regions. Two prominent individuals with amnesia, H.M. and K.C., who developed lesions due to surgical brain damage and traumatic brain injury, provided the first insight into a key role of the parahippocampal-hippocampal system in explicit (H.M.) and episodic (K.C.) memory (Milner et al., 1968; Rosenbaum et al., 2005, 2012). The specific association between the hippocampal circuitry and episodic recollection has then been strengthend in groundbreaking studies with cases of developmental amnesia. They showed a profound impairment in the recollection of episodes, despite intact semantic knowledge acquisition and average intellectual capacities (Düzel et al., 1997, 2001; Vargha-Khadem et al., 1997). In contrast, lesions restricted to the parahippocampal gyrus and a spared hippocampus allowed successful recollection (e.g. Bowles et al., 2007). Different lesions along the hippocampal-parahippocampal system also entailed specific profiles of information dependent impairments. Perirhinal lesions lead to deficits in processing object stimuli, while hippocampal lesions and more posterior lesions on the parahippocampal gyrus impaired aspects of scene processing (e.g. Epstein et al., 2001; A. C. H. Lee, Bussey, et al., 2005; Milner et al., 1968; Mishkin et al., 1998). These insights fuelled the perspective on information-specific processing in the parahippocampal-hippocampal system (Graham et al., 2010; Ranganath, 2010). Acute conditions like encephalitis, ischemia or herpes simplex lead to structural impairment that is discrete, heterogeneous and appears abruptly.

A progressive and more consistent decline across individuals is associated with neurodegeneration in aging and the highly prevalent condition of neurodegeneration in Alzheimer's disease. A major risk factor of Alzheimer's disease is age. Aging processes lead to widespread physiological changes that affect the structure and function of particularly frontal and temporal cortices (Buckner, 2004; Fjell & Walhovd, 2010; Grady, 2008; Hedden & Gabrieli, 2004; Raz et al., 2005; Raz & Rodrigue, 2006; Salat et al., 2004; Tromp et al., 2015). As a result aged individuals face behavioral difficulties with episodic memory, but also with executive functions (Daselaar & Cabeza, 2008; Grady & Craik, 2000; Shing et al., 2008). Remembered information is less rich and the ability to bind multiple elements in memory

is impaired (Levine et al., 2009; Old & Naveh-Benjamin, 2008; Piolino et al., 2003; St Jacques et al., 2012; Yonelinas et al., 2007).

In some individuals, the neurodegeneration becomes pathological and cognitive alterations exceed into a manifestation of Alzheimer's dementia, a clinical syndrome that is characterized by fundamental impairment of various cognitive functions (e.g. memory, language, reasoning, orientation, see McKhann et al., 2011 for diagnostic criteria). One of the earliest symptoms is episodic memory decline and a distortion of the experiential nature of memories (Morris & Kopelman, 1986; Piolino et al., 2003).

The two hallmark pathologies of Alzheimer's disease are neurofibrillary tau tangles and beta-amyloid plaques that both progress on different, predetermined trajectories (Braak & Del Trecidi, 2015; Hyman et al., 1989; McKhann et al., 2011). Amyloid pathology begins in medial cortical structures, including retrosplenial cortex, posterior cingulate, precuneus and medial frontal areas (Grothe et al., 2017; Mattsson et al., 2019; Palmqvist et al., 2017; Villeneuve et al., 2015). In contrast, cortical tau pathology begins in the transentorhinal area before spreading to the EC, parts of the hippocampus, then the PrC, the lateral temporal lobe and finally cortical frontal and parietal regions (Braak et al., 2006; Braak & Braak, 1995).[7] ⌈The pathology, ultimately concomitant of cell loss in the respective brain regions, thus affects brain regions that are crucial for successful episodic memory (Jagust, 2018; Jagust et al., 2006). Accumulating evidence shows that tau pathology in the parahippocampal-hippocampal system best predicts episodic memory decline while amyloid-burden alone shows only weak associations to episodic memory performance (Hanseeuw et al., 2019; Lowe et al., 2018; Maass et al., 2017; Sperling et al., 2019). However, more rapid progressive memory decline is likely when both types of pathology converge (Betthauser et al., 2019; Düzel et al., 2022).

Critically, the pathology is evident more than a decade before the first clinical symptoms develop ('preclinical stage'; Braak & Braak, 1991; Ossenkoppele et al., 2019). Before clinical symptoms of Alzheimer's dementia manifest, the entorhinal and perirhinal cortices show atrophy (Das et al., 2019; de Flores, Das, et al., 2020; deToledo-Morrell et al., 2004; Hirni et al., 2016; Krumm et al., 2016; Olsen et al., 2017; Wolk et al., 2017; L. Xie et al., 2018; Yushkevich et al., 2015). Within the hippocampus, main atrophy in early disease stages has specifically been reported in hippocampal subregion CA1 (Adler et al., 2018; Delli Pizzi et al., 2016; Yushkevich et al., 2015; for an overview see de Flores et al., 2015). In addition to these structural changes, tau pathology is related to a disrupted anterior-temporal network function with decreased entorhinal function and entorhinal-hippocampal disconnection (Adams et al., 2019; Berron et al., 2020, 2021; Harrison et al., 2019; Maass et al., 2019). Moreover, the EC has been found less activated in mild cognitive impaired individuals during a mnemonic discrimination task, while DG/CA3 show increased functional activity in comparison to age-matched controls (Yassa et al., 2010). Hyperactivity in the hippocampus has been shown in individuals at early disease stages in comparison to functional activity within age-matched controls (Bakker et al., 2012, 2015; Dickerson et al., 2005; Yassa, Mattfeld, et al., 2011). The hippocampal hyperactivity is likely caused by the decrease in entorhinal input (Leal et al., 2017; Ward et al., 2015). The progression of Alzheimer's disease thus disturbes the balance within the hippocampal formation, before the pathology spreads further throughout the brain and causes more profound damage.

At which point age-related and pathological Alzheimer's processes lead to differential profiles in episodic memory decline, e.g. due to the heterogeneous way that hippocampal subregions are affected, has yet to be determined and requires assessments that tax cognitive alterations

[7] paragraphs between ⌈⌋ symbols are published in *Neuropsychologia* in Grande et al. (2021) and integrated into the thesis with minor edits (see Chapter V).

appropriately (Jack et al., 2010). About 30% of seemingly healthy individuals over 65 years of age bear "hidden" amyloid pathology, whereas more than 60% of elderly people show tau pathology in the medial temporal lobe (Braak & Braak, 1997), with cognitive alterations that are not necessarily detectable. Early traces of tau and amyloid only recently became detectable with amyloid and novel tau PET methods which may allow presymptomatic detection. However, due to its invasive nature, PET is not always employed in aging studies. This may lead to the classification of participants into "healthy agers" based on broad cognitive assessments, despite early stages of tau and amyloid. This has complicated a clear differentiation between Alzheimer's-specific and healthy aging-related profiles when assessing neurodegeneration, alterations in hippocampal structure and related cognitive alterations (de Flores et al., 2015). While healthy aging leads to stronger atrophy in the DG and presumably CA3 subregions (Adler et al., 2018; Nadal et al., 2020; B. J. Small et al., 2004; West, 1993) Alzheimer's pathology first affects the (lateral) EC, the subiculum and CA1 subregions (de Flores et al., 2015; S. A. Small et al., 2011). It seems that healthy aging exerts a different topology of neurodegeneration within the parahippocampal-hippocampal system than Alzheimer's disease, particularly within subregions of the parahippocampal-hippocampal system. In this thesis, I will address what these observations imply for memory decline and assessment in Alzheimer's disease.

1.5 AIM AND OUTLINE OF THE THESIS

The aim of this thesis is to advance our knowledge of how the human parahippocampal-hippocampal system is functionally organized to bring about episodic memory. I investigate how human experiences are represented and processed throughout the system to be remembered later on. Given the above reviewed literature, I approach this aim from the following three different questions:

1. *How is information communicated and processed throughout the subregions of the human parahippocampal-hippocampal system?* Despite previous achievements in linking the anatomical wiring of the parahippocampal-hippocampal system to information-specific processing routes, fundamental knowledge gaps remain. Given the recently emphasized cross-talk between information-specific pathways in the parahippocampal gyrus, it is unclear how cortical sources of information uniquely map onto the human EC. Whether and where the processed information within the EC is segregated into item-related and contextual information needs to be explored. In addition, it is unclear, how the information is further communicated along the hippocampal transversal Subiculum/CA1 axis. I will address these questions empirically in Chapter II. Moreover, it is conceptually unclear, how parahippocampal ('contextual') cross-projections towards the PrC can be reconciled with the traditional view of item-related processing in PrC. Chapter III combines animal and human literature and proposes how both types of information converge in the PrC. Overall, the acquired knowledge will allow me to outline how the parahippocampal-hippocampal system represents and processes experience-related distributed cortical representations to form retrievable memories.
2. *How are human hippocampal subregions involved in reinstating distributed cortical representations for memory retrieval?* A holistic recollective experience requires the cortical reinstatement of the episodic representation from encoding. Access to these distributed cortical representations in turn requires pattern completion, a mechanism that has been related to hippocampal subregion CA3. However, evidence in humans is lacking. In Chapter IV, I therefore empirically assess whether subregion CA3 is specifically involved in the holistic reinstatement of cortical representations. The acquired evidence allows me to draw the link between the functionality of the hippocampal circuitry and accessing distributed memory representations for a sense of recollection.
3. *Which effects may a disruption of the parahippocampal-hippocampal system by Alzheimer's pathology have on memory representations and their recollection?* The current insights into the functional architecture of memory representations have not yet been linked to information-specific memorability nor to the disruption of the system under Alzheimer's pathology. In Chapter V I conceptually elaborate on how stages of neurodegeneration may be reflected in information-specific loss and how this may influence clinical assessment. This work will show how memory representations can reflect vulnerabilities within the parahippocampal-hippocampal system, with diagnostic potential.

In the General Discussion I will discuss these empirical findings and proposals in the light of our current understanding of the functional architecture of representations within the parahippocampal-hippocampal system. I focus on implied characteristics of these representations, their interaction within the system and how they can be accessed to gives rise to episodic memory. I finally discuss the implications of my findings for memory representations under a distorted system as in Alzheimer's disease, and conclude by highlighting future avenues for research.

1.6 ULTRA-HIGH FIELD FUNCTIONAL IMAGING: THE EMPIRICAL METHOD FOR THIS THESIS

Studying the functional architecture of the human parahippocampal-hippocampal system in meaningful detail (Questions 1 and 2) requires a method that can reveal functional heterogeneities within subregions. A suitable, non-invasive method is ultra-high field fMRI. I used this method to acquire empirical data in Chapter II and Chapter IV of this thesis. Here, I briefly outline the benefits and challenges that come with employing ultra-high field imaging in the parahippocampal-hippocampal system.

The principle of fMRI relies on correlations between behavior and oxygenated blood level changes (BOLD signal) in the brain. The changes in oxygenated blood level can be assessed spatially over time, and give information about the metabolic demand that brain regions require. The obtained BOLD signal is thus an approximation of the actual neural signal, correlating with local field potentials and thus peri-synaptic activity (Logothetis, 2002; Logothetis et al., 2001; but see Angenstein et al., 2009; Ekstrom, 2010 as well). Functional MRI is thus an indirect method that allows inference into metabolic demands. While the spatial resolution is considerably high, especially in ultra-high field fMRI, the temporal resolution is at the scale of seconds due to latencies in the hemodynamic response. Functional MRI is excellent to study the functionality of multiple regions at once, in contrast to electrophysiological recordings and tract-tracing in animals or intracranial electrophysiology in humans. In addition, functional effects during complex tasks can be studied with considerable anatomical precision.

Important advances allow functional imaging with an increasingly fine-grained spatial resolution, making the method suitable to study the subregion-specific questions in my thesis. To detect subregion-specific neural activity with fMRI, contamination of the signal by activity from neighboring areas needs to be reduced. This requires high spatial resolution and accurate anatomical localization of functional activity in the respective subregions. Initial studies using 3 Tesla fMRI (e.g. Eldridge et al., 2005; Kirwan & Stark, 2007; Zeineh et al., 2001) achieved a resolution of around 3.375mm³ (around 1.5 mm isotropic; Carr et al., 2010). However, higher functional resolution is required for this thesis, given that the coronal thickness of single subregions can be below 1.5mm (Adler et al., 2018; de Flores, Berron, et al., 2020; Yushkevich et al., 2009). More recent ultra-high field fMRI of the medial temporal lobe at 7 Tesla achieved submillimeter resolution of isotropic voxel size (Berron et al., 2016; Koster et al., 2018; Maass et al., 2014; Navarro Schröder et al., 2015). Recently, the anatomical delineation of hippocampal subregions with in vivo MRI data has considerably improved by combining 7 Tesla imaging with new segmentation protocols (Berron et al., 2017; Wisse et al., 2017). Ultra-high field imaging also increases the signal-to-noise ratio in the parahippocampal-hippocampal system that is generally low due to high susceptibility artefacts caused by the nearby ear canals (Olman et al., 2009).

In Chapter II and Chapter IV structural and functional data were acquired for each participant. The structural data served to relate functional differences over time to specific anatomical regions as the functional data is acquired with less spatial precision. The main sequences and contrasts are T2* EPIs with millimeter and submillimeter resolution, as well as T2 and T1 structural images. While the T1 data was obtained for the whole brain, the T2 and T2* images were acquired for a restricted FOV to allow increased spatial precision and higher resolution. As my aim was to gaiin insight into the architecture of the parahippocampal-hippocampal system, the FOVs covered that area specifically. The structural T2 image was acquired perpendicular to the longitudinal axis of the hippocampus and the functional T2* data was acquired in orientation with the longitudinal axis of the individual's hippocampus (see Figure 4[B])

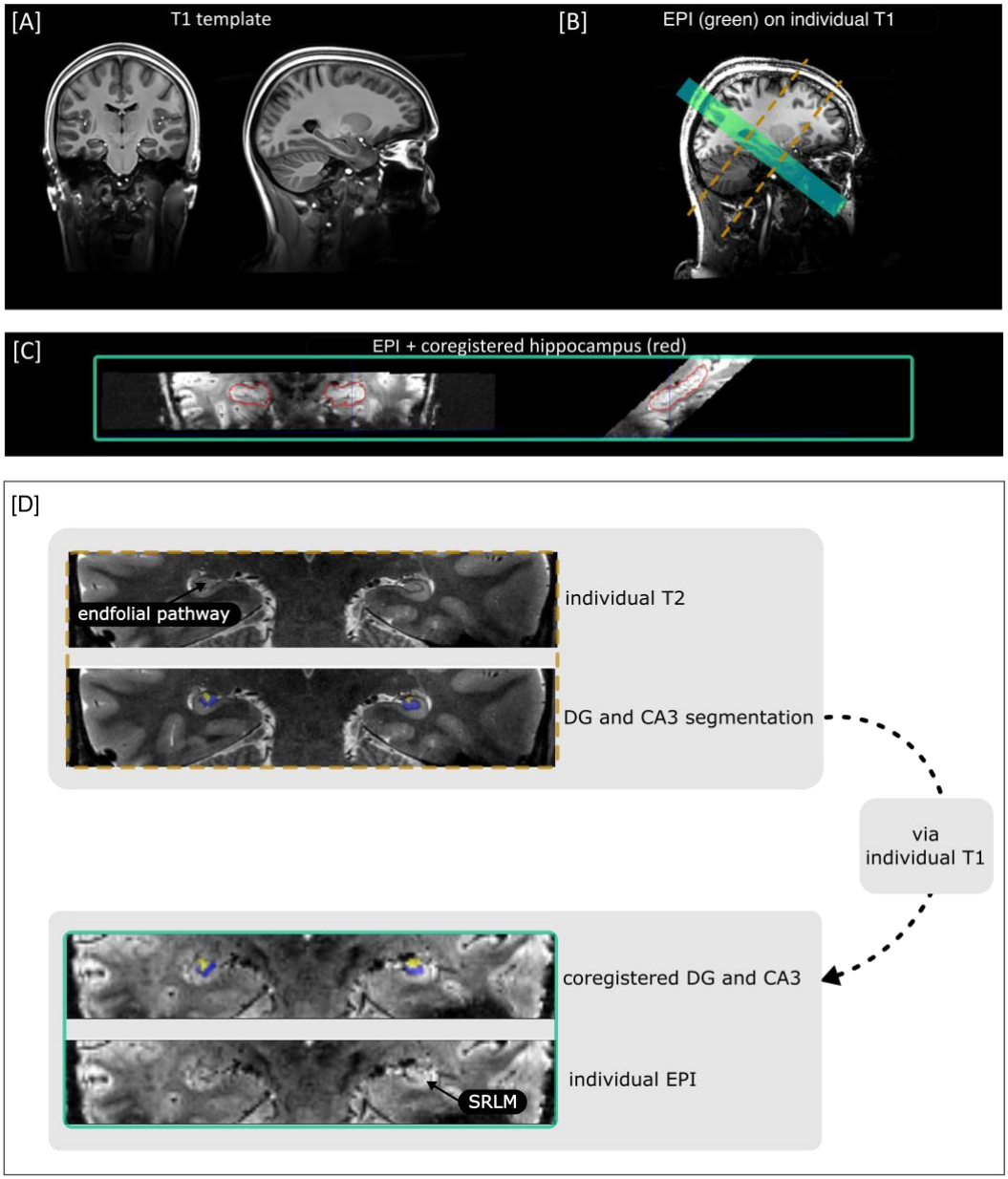

Figure 4. Examples of acquired images with 7 Tesla MRI, their coregistration and the segmentation of hippocampal subregions DG and CA3. *Per participant, structural T1 ([B]) and T2 images (brown stippled line in [B] and [D]) are acquired as well as functional echo-planar images (EPI, green overlap in [B], green line in [C] and [D]). The T1 images cover the whole brain while T2 and EPIs are acquired only from a part of the brain, covering the parahippocampal – hippocampal system ([B]). To display functional results, the T1 images across all participants are transformed into a study-specific T1 group template, an example of which is displayed in [A] with coronal (left) and sagittal (right) views. All images in [B], [C] and [D] refer to different representative example participants. An individual T1 image and the correspondingly acquired structural T2 (between brown stippled lines) and functional EPI (overlay in green) are schematized in [B]. The T2 image is oriented orthogonal to the longitudinal axis of the hippocampus. The brown stippled lines indicate the orientation and schematize the area of the brain that is covered by ultra-high resolution structural T2 imaging. The EPI is oriented along the longitudinal axis of the hippocampus and the green rectangle shows the area of the brain that is covered by functional imaging. The segmentation of subregions was performed on individual T2 images (Berron et al., 2017, [D], brown outline). Segmented masks were then coregistered to the individual EPI space via the whole-brain individual T1 images. A coronal (left) and sagittal (right) view on the coregistration between an individual EPI and the segmented hippocampal mask in T2 space (red outline) is presented in [C]. Coregistered DG (blue) and CA3 (yellow) subregion masks are displayed on the participant's mean EPI image in [D] (green outline), with the lowest panel corresponding to the respective mean EPI. Crucial hippocampal features for the segmentation (SRLM and the endfolial pathway on T2 images) are indicated. Corresponding slices in T2 and EPI space are shown. Figure parts [C] and [D] are reproduced and adapted from Grande et al., 2019, published under Creative Commons Attribution 4.0 International License (CC-BY 4.0, https://creativecommons.org/licenses/by/4.0/)*

Aiming for high resolution images requires exceptional caution. Even small individual movements in the range of 1-2mm risk data misattribution, as the hippocampal subregions are very small. To help resolve this issue, online motion correction was applied to all high-field functional data using a point-spread-function (In & Speck, 2012; Zaitsev et al., 2004). The subsequent data analysis also required special attention, not only due to the high spatial precision but also due to the lack of optimized tools for high-resolution analyses at 7 Tesla in conventional neuroimaging analysis. A tailored combination of tools was used, as described in the methods section of Chapter II and IV, including SPM (Penny et al., 2011), FSL (Greve & Fischl, 2009) and ANTS (Avants et al., 2009).

The anatomical assignment of functional activity to certain subregions is challenged by the fact that the obtained images do not depict cytoarchitectonic information in sufficient detail (Adler et al., 2014, 2018; de Flores, Berron, et al., 2020), as well as by the continuous histological transitions between the subregions (Adler et al., 2014; Amaral & Witter, 1989). Despite a recently implemented atlas-based segmentation following the established segmentation protocol for 7 Tesla MRI images (Berron et al., 2017), data for this thesis was acquired before an automatized segmentation. All subregion analyses required time-consuming, careful, and anatomically skilled manual segmentation (see Figure 4 [D]).

After the segmentation of subregions, the coregistration is a challenge. The segmentations were performed on ultra-high resolution T2 images that are able to depict structures like the endfolial pathway and the SRLM. Information on functional activity is, however, derived from the EPIs. Both types of images are acquired with different image parameters as indicated above (i.e., different resolutions, different brain coverage, and a different acquisition angle). These aspects challenge the coregistration process, i.e. the mapping of functional and structural images into the same space. As no default analysis pipeline exist, a tailored set of algorithms from various packages (SPM, FSL, ANTS) were applied to first register the T2 to T1 images within each individual, then the EPI to T1 images. Finally, the segmented masks were warped from the T2 space to the EPI space with the obtained warping and inverse warping matrices (see Figure 4 [C] and [D]). Careful and rigorous manual checking of each coregistration step within every individual was essential to detect mismatches in warping and assure spatial precision of the obtained results.

To visualize and infer results on group level, a study-specific template needed to be calculated (see Figure 4 [A]). This assures the maintenance of high anatomical precision, as the currently available normalization references come in different resolution and contrasts from 7 Tesla. Study-specific templates were built with ANTS (Avants et al., 2010).

CHAPTER II

SEGREGATION AND CONVERGENCE OF REPRESENTATIONS IN THE PARAHIPPOCAMPAL-HIPPOCAMPAL SYSTEM

II. PARAHIPPOCAMPAL-HIPPOCAMPAL ROUTES FOR SEGREGATION AND CONVERGENCE OF ITEM – CONTEXT INFORMATION

The striking organization of anatomical wiring in the parahippocampal-hippocampal system may reflect two segregated functional routes for item-related and context information. Given recent rodent findings of cross-talk instead of a strictly parallel wiring scheme, it however, remains open how segregated item-related and contextual information from cortical streams is communicated throughout the system in humans. In this chapter, I examine first, how the EC communicates with cortical sources of the item-related and contextual streams. To probe item and context information, I assess object and scene processing, respectively. Second, I explore how information continues between the EC and the transversal Sub/CA1 axis. This chapter has been published in *eLIFE* (Grande et al., 2022). With minor edits the manuscript is integrated into the thesis.

2.1 INTRODUCTION

In the General Introduction, I described entorhinal and hippocampal subregions as a critical functional circuitry within the parahippocampal-hippocampal system that binds cortical information into cohesive representations (Eichenbaum et al., 2007; Ritchey et al., 2015). The interaction of the entorhinal-hippocampal circuitry with cortical information streams and the circuitry's inner communication are key to the formation of these cohesive representations. In this chapter, I advance insight into how the human entorhinal cortex receives information from cortical streams via parahippocampal regions and the retrosplenial cortex. I advance knowledge on how information proceeds between the EC and the transversal Sub/CA1 axis in the human brain. These insights are relevant to our understanding of the parahippocampal-hippocampal system's fundamental role in cognitive functions such as episodic memory. They will allow me to sketch how the system represents and processes experience-related distributed cortical representations to form retrievable memories.

To briefly summarize from the General Introduction, large-scale cortical information streams, that originate in the visual 'where' and 'what' pathways and process context and item information (Berron et al., 2018; Haxby et al., 1991; Ranganath & Ritchey, 2012; Ritchey et al., 2015; Ungerleider & Haxby, 1994), map onto the EC in a complex manner and define functional EC subregions. Recent rodent research updates the former conception of a parallel mapping of contextual and item information via parahippocampal and perirhinal cortices onto medial versus lateral EC subregions (*cf*. posterior-medial versus anterior-lateral EC subregions as the human homologues; Maass, Berron et al., 2015; Navarro Schröder et al., 2015). Instead of a strict parallel mapping, profound cross-projections exist from the parahippocampal cortex towards the PrC and the lateral EC (Nilssen et al., 2019). In accordance, information seems to converge in the rodent lateral EC (Doan et al., 2019). The update, thus, implies a more complex functional organization than parallel and segregated context and item information routes. Moreover, this advance highlights the retrosplenial cortex as an additional source to convey information directly from the cortical context processing stream onto the EC. The retrosplenial cortex projects to the medial EC and, like the parahippocampal cortex, is part of the scene processing stream (e.g. involved in scene translation; Vann et al., 2009; Nilssen et al., 2019; Witter, Doan, et al., 2017). The update, furthermore evokes the question how cortical sources of information uniquely map onto the EC and which kind of information is processed in the resulting functional EC subregions.

As I outlined previously, within the entorhinal-hippocampal circuitry, an important direct way of communication exists between the EC and hippocampal subiculum and CA1 (the temporo-ammonic pathway). How functional EC subregions communicate towards the transversal Sub/CA1 axis in

humans is, however, unclear. Similarly, the extent to which specific contextual and item information processing routes might emerge, despite information convergence in the EC, is unknown. As mentioned in the General Introduction, on one hand, rodent research indicates a transversal organization where contextual and item information is processed along two anatomically wired routes, the medial EC – distal subiculum – proximal CA1 route and the lateral EC – proximal subiculum – distal CA1 route, respectively (Witter, Doan et al., 2017; note sparse functional evidence in the subiculum: Ku et al., 2017; Cembrowski et al., 2018; but frequent reports in the rodent CA1 region: Beer et al., 2018; Henriksen et al., 2010; Igarashi et al., 2014; Nakamura et al., 2013; Y. Nakazawa et al., 2016). Initial functional and structural connectivity data also indicate such a transversal connectivity profile in humans (Maass et al., 2015; Syversen et al., 2021). In accordance, scene information, in line with spatial context, seems preferentially processed in the distal subiculum (Dalton et al., 2018; Dalton & Maguire, 2017; Zeidman et al., 2015) and hints exist for preferential object processing, in line with item-related information, at the subiculum/CA1 border (Dalton et al., 2018). On the other hand, anatomical projections in the monkey show a longitudinal profile on top of the transversal profile with mainly the anterior-lateral and posterior-lateral entorhinal portions projecting to the distal subiculum – proximal CA1 and proximal subiculum – distal CA1, respectively (Witter & Amaral, 2020). According to information convergence in the EC, a recent report finds convergence along the rodent transversal CA1 axis (Vandrey et al., 2021). In humans, visual stream projections towards the entorhinal-hippocampal circuitry, similarly suggest convergence of context and item information in the subiculum/CA1 border region but preserved scene (i.e. spatial context) processing in the distal subiculum (Dalton & Maguire, 2017). A detailed examination of the latter hypothesis is, however, lacking while the diversity of findings emerging from the literature calls for a thorough investigation to elucidate whether multiple transversal processing routes exist within the human entorhinal-hippocampal circuitry.

To summarize, our conception of how information travels towards the entorhinal-hippocampal circuitry underwent key changes which warrant an extensive exploration of the circuitry's functional organization. First, rodent research shows that there is no strict parallel mapping of cortical information from the perirhinal and parahippocampal cortex towards the EC. Second, information seems to converge already before the hippocampal cortex. These changes add to several knowledge gaps. First, it is unclear in which subregions of the entorhinal-hippocampal circuitry contextual and item information are processed. The general connectivity patterns in the human entorhinal-hippocampal circuitry have not yet been directly related to information processing. Moreover, it is unclear how context information from the retrosplenial cortex maps onto the human EC as a critical source of the cortical context processing stream. Hence, it is also unclear how retrosplenial information is communicated between the EC and the hippocampus. Finally, it remains elusive whether a transversal functional segregation can be extended towards the human CA1 region in analogy to the rodent literature.

Here, I leverage ultra-high field 7 Tesla fMRI data and advance the earlier findings on human entorhinal subregions and the transversal intrinsic functional connectivity pattern in the subiculum (Maass et al., 2015). With a combination of functional connectivity and information processing analyses, I seek to answer two sets of questions. Regarding functional connectivity, I ask where the parahippocampal, perirhinal and retrosplenial cortical sources uniquely map onto the human EC and how these functionally connected routes continue between EC subregions and the transversal Sub/CA1 axis. Note that early cortical tau pathology in Alzheimer's disease accumulates specifically in perirhinal Area 35 from where it spreads towards the lateral EC (Braak & Del Tredici, 2020). As one aim of the thesis is to assess clinical implications from the parahippocampal-hippocampal architecture, I distinguish between perirhinal Area 35 and Area 36. Regarding information processing,

I ask whether and where contextual and item information remain specifically processed in the EC and along the transversal Sub/CA1 axis. Note that I operationalize both aspects of information as scene versus object processing, respectively. I test the hypotheses of (1) a transversal functional connectivity pattern and (2) multiple information processing routes within the entorhinal-hippocampal circuitry. Thus, following the updated conception of a non-parallel cortical context and item information mapping onto the EC in rodents, I will show how cortical information streams map via parahippocampal regions and the retrosplenial onto the EC in humans. This mapping will then be the detailed starting point to investigate the functional connectivity and information processing within the entorhinal-hippocampal circuitry.

The following hypothesis are examined:

(1) I predict that while some EC subregions have a preference to functionally connect with the subiculum/CA1 border, others preferentially connect with the distal subiculum and proximal CA1. I will identify EC subregions based on unique cortical source contributions. Therefore, my predictions remain in accordance with Maass et al. (2015): I expect that the EC subregion preferentially connected with the parahippocampal cortex ($EC_{PHC\text{-}based}$ seed) maps towards the distal subiculum and EC subregions connected with the perirhinal cortex ($EC_{Area35\text{-}based}$ seed, $EC_{Area36\text{-}based}$ seed) map towards the proximal subiculum, a mapping that I predict to be extended towards the distal CA1.

(2) I predict a route of segregated context processing and another route of convergent information processing. Following the proposal by Dalton and Maguire (2017) and the updated cross-projections from the context to the item information processing stream (Nilssen et al., 2019), I expect scene processing in the distal subiculum. The updated parahippocampal cross-projections imply convergence wherever specific item processing had been expected previously. Thus, I explore whether any entorhinal-hippocampal subregions still process item information specifically. However, I largely expect to find evidence consistent with convergence of item and context information within the entorhinal-hippocampal circuitry.

2.2 METHODS

The current data is part of a larger study that examines exercise effects on cognition. The data, subject to the current study, is acquired during the baseline measurement before any intervention took place. In the following, I focus on the study set up and methodological aspects of direct relevance for the current questions and data analyses.

2.2.1 Participants

In total, 32 healthy participants (15 female) with a mean age of 25.5 years (range 19 to 35 years, standard deviation 4.3 years) were included in the current data analyses. All participants were right-handed, finished education on A-level (German Abitur or comparable) and reported absence of any neurological or psychiatric diseases. General exclusion criteria determined by the 7 Tesla MR scanning procedure were applied (e.g. metallic implants, tinnitus, known metabolic disorders). All participants gave informed consent prior to participation and received a monetary compensation. The study received approval by the ethics committee of Otto-von-Guericke University, Magdeburg (Germany).

2.2.2 Task

While functional images were acquired, participants engaged in a mnemonic discrimination task (see Berron et al., 2018). The item-context task consisted of 64 objects and 64 scenes. In two runs,

participants encoded always two stimuli, two 3D rendered objects in the object condition and two 3D rendered rooms in the scene condition and subsequently identified the following two same or similar stimuli as novel or old. Ten scrambled images were presented in blocks at the beginning and end of each run and served as baseline condition. All stimuli were presented for three seconds. In the recognition phase, participants had to respond during that time. Each stimulus was followed by a noise stimulus to prevent after-image and pop-out effects. The short alternating encoding/recognition sequences were embedded in an event-related design.

2.2.3 Data acquisition

All MRI data was acquired with a 7 Tesla Siemens MR machine (Erlangen, Germany) using a 32-channel head coil. First structural images were obtained. A whole-brain MPRAGE volume was acquired with isotropic voxel size 0.6mm, TR 2500ms; TE 2.8 ms, 288 slices in an interleaved manner (FOV 384 x 384 x 288). Thereafter, a partial structural T2*- weighted volume (TR 8000ms; TE 76 ms, interleaved, 55 slices, FOV 512 x 512 x 55), orientated orthogonal to the main longitudinal hippocampal axis was obtained with a resolution of 0.4 x 0.4mm in-plane and a slice thickness of 1 mm.

The subsequent acquisition of functional data took place in two runs à 14 min (332 volumes each) employing EPI. The volumes had a resolution of 1 mm isotropic and were partial (40 slices, TR 2400 ms, TE 22 ms, FOV 216 x 216 x 40, interleaved slice acquisition), oriented along the longitudinal axis of the hippocampus.

All EPIs were distortion corrected with a point-spread function method and motion corrected during online reconstruction (Zaitsev et al., 2004).

2.2.4 Data analyses

Preprocessing

Preprocessing and statistical modeling of fMRI data was performed with SPM12 (Penny et al., 2011). The individual functional images were slice time corrected and smoothed with a full-width half-maximum Gaussian kernel of 1.5 mm. To preserve a high level of anatomical specificity, smoothing was performed with a kernel smaller than two times the voxel size. The artifact detection toolbox ARTrepair (Mozes & Whitfield-Gabrieli, 2011) was subsequently used to identify outliers regarding mean image intensity and motion between scans (threshold in global intensity: 1.3 %; movement threshold: 0.3 mm). Identified outliers are included as spike regressors in subsequent statistical modeling.

Task effects in the functional data were removed by fitting general linear models (with regressors for all task conditions, outliers and movement parameters) to the data. The obtained residual images were saved for the intrinsic functional connectivity analyses later. Note that task-related parameter estimates were extracted for the final information processing analysis, as described later.

Structural data processing and segmentation

Structural template calculation (T1-weighted) and segmentation. To examine and illustrate group-level results later on, a group specific T1-weighted template was calculated using ANTS buildtemplateparallel.sh (Avants et al., 2010). For illustration purposes and to aid group analyses, in addition, the T1 template was manually segmented into hippocampal subregions subiculum and CA1 with ITK-SNAP (Yushkevich et al., 2006) based on the segmentation rules described in Berron et al. (2017). The first slice in each hemisphere that did not contain the uncus anymore, served as start of the hippocampal body in all hippocampal subregions. Moreover, to evaluate results across the transversal axis, the subiculum masks in each hemisphere were sagitally cut in five equally wide

segments within each coronal image. As the CA1 region gets more and more tilted towards the hippocampal tail, the three transversal CA1 segments were determined based on manual segmentation. Therefore, the two outer CA1 borders in transversal axis were connected with a line. From the middle point of that line, two straight lines were drawn in a 60° angle to determine equally sized transversal CA1 segments within each coronal slice and hemisphere. Related to the overall size of the subregions, we opted to build five subiculum and three CA1 segments along the transversal axis from proximal to distal ends (see supplementary V for more information).

Segmentation of individual regions of interest. Regions of interest in the parahippocampal-hippocampal system were manually segmented according to the segmentation protocol by Berron et al. (2017). Based on individual T1-weighted and T2-weighted images, the parahippocampal cortex, Area 35, Area 36 and the EC were delineated (see supplementary IV for quality assurance measures). Moreover, I ran a Freesurfer 6.0 segmentation on the group T1 template to segment the isthmus cingulate cortex as retrosplenial mask (Desikan et al., 2006; Fischl, 2012). Note here that Syversen et al. (2021) used a similar region, however excluded the most superior part. For individual retrosplenial masks, the obtained mask was co-registered from the group T1 template space to the individual T1 space by making use of the alignment matrices obtained during above described T1 group template calculation. For this alignment process I used ANTS WarpImageMultiTransform.sh (Avants et al., 2011). The retrosplenial, parahippocampal and perirhinal Area 36 and Area 35 regions served as source regions for an initial functional connectivity analysis that I conducted to obtain functional subregions within the EC.

Co-registration of individual structural data to functional data space. For later functional data extraction, the individual T1-weighted and T2-weighted structural images were co-registered and resliced to the EPIs. Therefore, ANTS was used to transfer the T2-weighted structural image to the participant's T1 space (Avants et al., 2011). For the co-registration between individual T1-weighted and echo-planar images, FSL epi_reg was applied (Jenkinson & Smith, 2001). All subsequently segmented individual masks were co-registered to the participant's functional EPIs using the obtained warping matrices. ANTS WarpImageMultiTransform.sh was applied for T2 to T1 co-registration and FSL flirt was used for T1 to EPI co-registration (Avants et al., 2011; Jenkinson & Smith, 2001).

ROI preparation for seed regions in functional connectivity analyses. All masks that served as source and seed regions throughout the functional connectivity analyses (retrosplenial, parahippocampal, perirhinal Area 36 and Area 35 and the later defined entorhinal subregions) were thresholded according to mean intensity to prevent signal dropout and thus a distortion of the average functional signal extracted from seed regions for the connectivity analysis. Therefore, I followed Libby et al. (2012) and Maass, Berron et al. (2015), to remove all voxels from each ROI that showed a mean intensity over time of less than two standard deviations from the mean intensity across all voxels. The thresholding was performed before each seed-to-voxel functional connectivity analysis.

Functional connectivity analyses at the participant level

Two different functional connectivity analyses were performed that build upon the approach by Maass et al. (2015). The first analysis served to identify functional subregions ("seeds") within the EC that uniquely connect to functionally and clinically relevant cortical sources. The second, core analysis, then evaluated the intrinsic functional connectivity pattern between these entorhinal seeds and hippocampal subiculum and CA1. Both functional connectivity analyses were performed on residuals of task-related functional data, creating a dataset that resembles resting-state data

(Gavrilescu et al., 2008; Maass et al., 2015). In the following, I describe the analysis procedure in detail. Note, that all analyses were conducted independently in both hemispheres.

To determine functional entorhinal seed regions I first performed a seed-to-voxel semipartial correlation analysis with the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) between the individually extracted residuals from retrosplenial, parahippocampal and perirhinal Area 36 and Area 35 sources as well as the voxels within the segmented EC mask of each individual. The regions I call cortical sources served as seeds in that analysis. Note that the semipartial correlations calculate the variance in a voxel that is uniquely explained by the source, excluding contributions from other sources. Entorhinal seeds for the core functional connectivity analysis, after alignment between participants and group-level analysis (see the following paragraphs). This procedure yielded four entorhinal subregions, one containing the entorhinal voxels that preferentially functionally connect to the retrosplenial (1530 voxels), one containing the entorhinal voxels that preferentially functionally connect to the parahippocampal cortex (145 voxels) and one each that contained the preferentially functionally connected voxels to perirhinal Area 35 (298 voxels) and Area 35 (751 voxels), respectively (see supplementary II for further information). All four entorhinal seed masks were determined on group level and co-registered back to each participant, then serving as seed regions for the core functional connectivity analysis between EC seeds and hippocampal subregions.

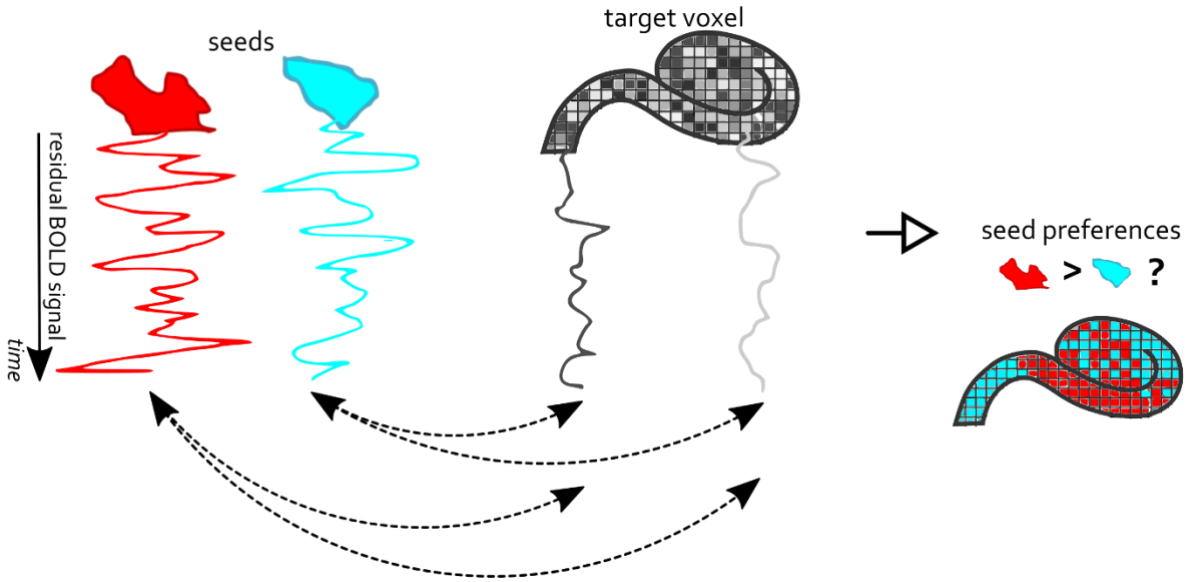

Figure 5. Schematic procedure for seed-to-voxel functional connectivity analysis, illustrated here with two seeds. *Residual BOLD signal ("task-free") over time is extracted from segmented seed regions, as well as individual voxels of the target area. Signals from either seed are correlated with signals from voxels, respectively. Subsequently, the seed preferences are determined by the highest correlation value for either seed in every voxel of the target area, yielding connectivity maps of the target area.*

For the core functional connectivity analysis (entorhinal seeds-to-hippocampal subregion voxels), an analogous seed-to-voxel semipartial correlation analysis was performed on the individual residual functional imaging data using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). Note again that the semipartial correlations calculate the variance in a voxel that is uniquely explained by the seed, excluding contributions from other seeds. Now the four entorhinal subregions served as seeds and functional connectivity was examined with the whole brain (later masked by the hippocampal subregion masks). For each functional connectivity analysis mean time series were extracted from the respective seed region and entered as regressor of interest. White matter and CSF time series, realignment parameters and outliers served as regressor of no interest. The functional data from the residuals was band-pass filtered (0.01 - 0.1 Hz) and semipartial correlations were obtained between the seed timeseries and all other brain voxel's timeseries. The obtained beta maps contained Fisher-transformed correlation coefficients and were used for subsequent group analyses.

Alignment between participants

To be able to perform group statistics on the resulting topography beta maps, the individual data was aligned to group space. Here, the T1 template image served as reference space. Using the inverse of the previously obtained individual warping matrices from EPI to individual T1, first the standardized beta maps were co-registered from epi to individual T1 space. In a further step, the statistical maps were then aligned between individual T1 space to the group T1 template space, by making use of the alignment matrices obtained during above described T1 group template calculation. For this alignment process I used ANTS WarpImageMultiTransform.sh (Avants et al., 2011).

Functional connectivity analyses at group level

For both functional connectivity analyses, I performed steps at group level. First, before performing the core functional connectivity analysis between entorhinal seeds and hippocampal voxels, I had to determine the entorhinal seeds, that is, the functional subregions of the EC. Again, I largely followed Maass, Berron et al. (2015) approach to ensure comparability of results. The seeds were determined based on their functional connectivity with functionally relevant sources from the cortical item and context information processing streams, that are the perirhinal Area 35 and Area 36, the parahippocampal cortex and the retrosplenial cortex (see Nilssen et al., 2019). The resulting z-transformed correlation maps were aligned for each participant to the group template T1 space and subjected to four one-sample T-tests (one for each source preference map) to reveal significant clusters of entorhinal connectivity preferences per source across all other entorhinal seeds, respectively. Then, the four resulting statistical maps (one for each source) have been thresholded at $T > 3.1$. Each entorhinal voxel now was attributed to be preferentially connected to one of the four source regions, based on the voxel's maximum T value across the thresholded one-sample t-test maps. Those voxels that did not reach the threshold of $T > 3.1$ in any of the four statistical maps have not been attributed to be preferentially connected to any of the four cortical sources. Finally, across hemispheres I selected for each source preference an equal number of these highest preference voxels across all t-tests (the number is determined by the hemisphere with the lowest relevant number of voxels). This yielded above stated four entorhinal subregions and seed masks. Note, the functional subregions in the EC that I identified on group level generally overlap for the preferences towards the PrC (Area 35 and Area 36) and towards the parahippocampal cortex with the findings by Maass et al. (2015).

Second, to investigate the functional connectivity profile between the four entorhinal seeds and the subiculum and CA1 subregion across individuals, I evaluated connectivity preferences to either seed within all transversal segments of the subiculum and CA1 target regions. Therefore, mean values for connectivity estimates to either EC seed are extracted from the group aligned but participant-specific beta maps out of each transversal segment, averaged along all coronal slices. Note, that segment-based extraction is necessary due to the varying number of sagittal slices that cover the respective regions along the longitudinal axis of the hippocampal body. Based on these participant-level connectivity results, connectivity preference plots for all four entorhinal seeds have been created to depict tendencies along the transversal Sub/CA1 axis.

A hierarchical repeated-measures ANOVA testing procedure was employed to reveal significant differences in the transversal hippocampal connectivity patterns between entorhinal seed regions. Therefore, in a first step, an overall repeated measures ANOVA (4 seed X transversal segments) was performed per target region (subiculum or CA1) to reveal whether significant differences in seed connectivity estimates exist across the transversal axis of the respective target region. If the overall seed X transversal segment interaction effect was significant (FDR corrected according to Benjamini

and Hochberg, 1995), in a second step, one-way repeated measures ANOVAs have been performed for each seed to identify those entorhinal seeds that indeed show a differential connectivity pattern across the transversal axis of the target region (all FDR corrected according to Benjamini and Hochberg, 1995). If more than one seed main effect was significant, finally we determined whether these seeds exhibit an opposing connectivity pattern across the transversal axis of the respective hippocampal subregion by evaluating the pair-wise seed X transversal segment interaction effects on the extracted connectivity estimates.

For a more detailed topographical display of the entorhinal-hippocampal connectivity results, I calculated one-sample t-test on the aligned, standardized beta maps that we obtained in the first-level analyses for each seed respectively. Crucially, the resulting group-level one-sample t-test statistical maps were only used to display results but not for any further statistical inference. To depict the topography of the respective voxel-wise seed preferences, the resulting group-level t-maps were thresholded with T> |0.001| and masked with the respective subregion of interest. To depict general tendencies in the connectivity profile, for each voxel in the region of interest the preferred seed connectivity was determined by attributing it to the seed with the highest T value across the one-sample t-test maps. The resulting maps were depicted in 3D plots, generated with ITK-SNAP (Yushkevich et al., 2006) that provide an overview of each voxel's preference for the respective seed functional connectivity at a glance.

Functional analysis of information-specificd activity at participant level

To asses whether different types of information are processed in cortical source regions that the entorhinal-hippocampal circuitry communicates with, I evaluated object and scene processing in the four cortical source regions. Therefore, results from the initially fitted general linear models (used to remove task effects) were examined. Contrast estimates were calculated between the beta estimates obtained from task conditions in which individuals saw objects versus scenes (rooms) on the screen and conditions in which individuals saw the scrambled stimuli (baseline). I extracted parameter estimates for the object versus baseline and the scene versus baseline contrast from the retrosplenial and parahippocampal cortex and from perirhinal Area 36 and Area 35. All parameter estimates were extracted from the previously segmented regions of interests, coregistered to the individual EPI space. With repeated measures ANOVAs (information condition X source region) I investigated whether contrast estimates differed under scene and object conditions in the respective regions. Effect of interest was the interaction between the information condition and the source regions. Post-hoc paired-samples t-test were performed if the interaction effect was significant, to reveal in which source region functional activity between scene and object processing conditions differed significantly from each other (all FDR corrected according to Benjamini and Hochberg, 1995).

Similarly, I investigated whether object and scene information is differentially processed within entorhinal seed regions and along the transversal Sub/CA1 axis. Here, the resulting contrast value maps for object > baseline and scene > baseline were then co-registered to the T1 group template space. Subsequently, individual mean contrast estimates have been extracted from the four entorhinal seed regions and from those transversal segments that had previously been used for the evaluation of the intrinsic functional connectivity results (three or five segments in CA1 and subiculum, respectively). With repeated measures ANOVAs (information condition X entorhinal region or information condition X transversal segment) I investigated whether contrast estimates differed under scene and object conditions in the respective regions. Effect of interest thus, was again the interaction between the information condition and the subregion or segment, respectively. Post-hoc paired-samples t-tests were performed if the respective interaction effect was significant, to reveal in which subregion or segment functional activity between scene and object processing

conditions differed significantly from each other (all FDR corrected according to Benjamini and Hochberg, 1995).

2.3 RESULTS

Aim of Chapter II is to comprehensively investigate functional connectivity and information processing within the entorhinal-hippocampal circuitry and the contribution of cortical item-related and contextual processing streams. The information processing was operationalized by object (item) and scene (context) conditions. In the following, I first report the information processing characteristics of the cortical source regions. I continue to describe the four obtained entorhinal seeds and display the intrinsic functional connectivity pattern with the entorhinal seed regions along the transversal Sub/CA1 axis. Thereafter, I report the information processing characteristics of the entorhinal and hippocampal subregions.

Specifc scene processing in retrosplenial and parahippocampal cortices and specific object processing in perirhinal regions

In a first step I examined information processing in cortical source regions. This is to verify whether retrosplenial, parahippocampal and perirhinal regions process scene and object information in a specific segregated manner. Repeated-measures ANOVAs in both hemispheres showed a significant interaction effect between condition and region (right: $F(3,93) = 60.4229$; $p < .001$; left: $F(3,93) = 47.3421$; $p < .001$). Subsequent paired-samples t-tests show significantly more functional activity in the object than scene condition in Area 36 (bilateral: $p_{FDR} < .001$) and the left Area 35 ($p_{FDR} = .0011$). No significant difference between object and scene conditions is observed in the right Area 35 (right: $p_{FDR} = 0.9821$). There is a significant effect of more functional activity in the scene than object condition in the parahippocampal (bilateral: $p_{FDR} < .001$) and retrosplenial cortex (bilateral: $p_{FDR} < .001$, see Figure 6). Thus, in cortical source regions, scene information is specifically processed in the retrosplenial and parahippocampal cortices while the perirhinal Area 36 and Area 35 (left hemisphere) show specific object processing.

Four cortical sources divide the entorhinal in retrosplenial-, parahippocampal, Area 35- and Area 36-based seeds

The four entorhinal subregions, that I later used as seeds to determine the topography of entorhinal-hippocampal connectivity, are based on intrinsic functional connectivity preferences with either the parahippocampal cortex, the retrosplenial cortex, perirhinal Area 36 or Area 35. These cortical regions are in general concordance with Maass et al. (2015) but consider recent advances that put forward the retrosplenial cortex as a critical source from the cortical context processing stream (Nilssen et al., 2019) and evaluate perirhinal Area 35 and 36 separately.

Based on functional connectivity preferences with the four sources - parahippocampal cortex, retrosplenial cortex, Area 36 and Area 35 - I obtained four entorhinal seeds. The seeds refer to different parts of the EC whose voxels expressed preferential functional connectivity to either cortical source. For the $EC_{PhC\text{-}based}$ seed, the majority of voxels can roughly be described as clustering in the posterior-medial entorhinal portion, for the $EC_{RsC\text{-}based}$ seed in the anterior-medial portion, for the $EC_{Area35\text{-}based}$ seed in the anterior-lateral portion and for the $EC_{Area36\text{-}based}$ seed in the posterior-lateral entorhinal portion (see supplementary II for exact voxel counts and supplementary III for gradients in functional connectivity). Note that both perirhinal-based entorhinal seeds extended along the anterior to

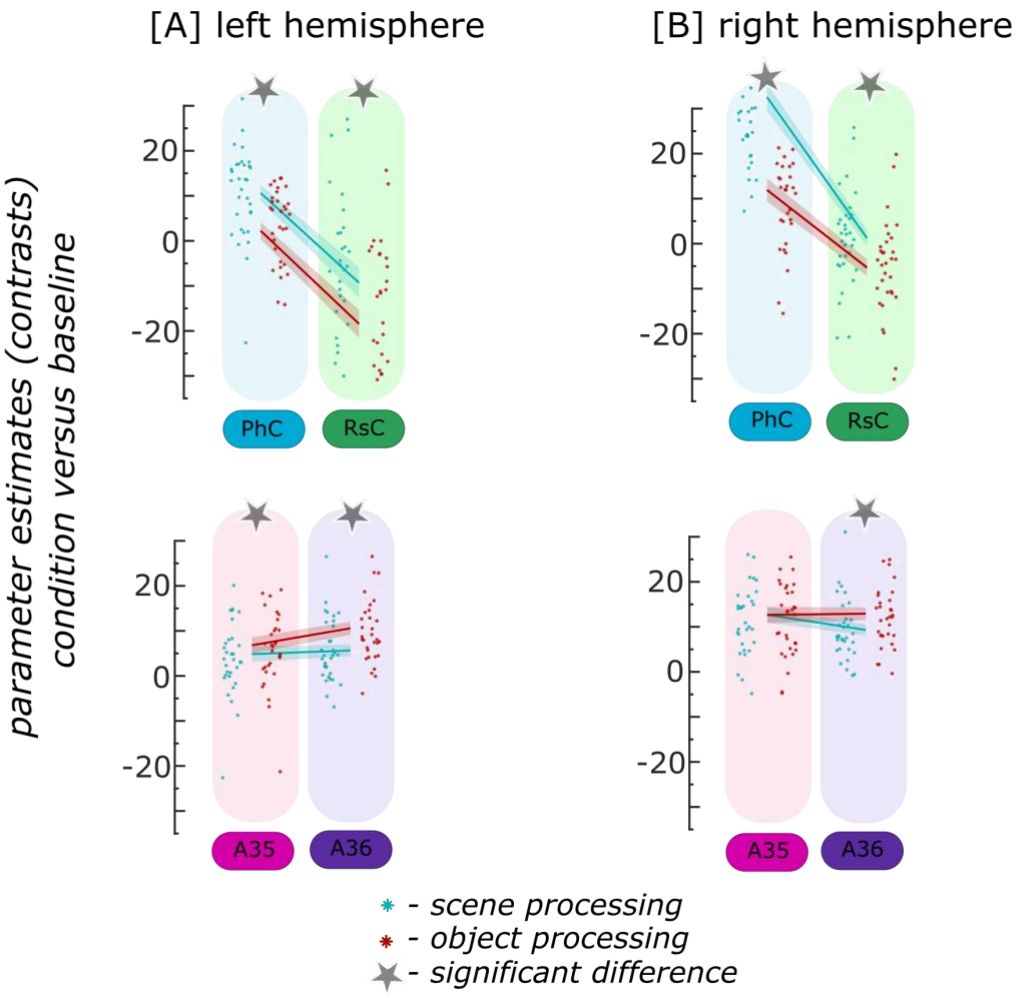

Figure 6. Functional activity during scene and object conditions in cortical source regions. *Displayed are the extracted parameter estimates for the object versus baseline contrast (red) and the scene versus baseline contrast (cyan) from four cortical source regions in the [A] left and [B] right hemisphere, per individual (dots) and summarized across individuals (lines). Repeated measures ANOVAs revealed a significant interaction between condition and cortical source region in both hemispheres. The displayed significant differences (asterisks) are obtained with FDR-corrected post-hoc tests and refer to p < .05. During the object condition, participants were presented with 3D rendered objects on screen, during the scene condition with 3D rendered rooms and during the baseline condition they saw scrambled pictures. The shaded area around the lines refer to standard errors of the mean. PhC – parahippocampal cortex (blue), RsC – retrosplenial cortex (green), A35 – perirhinal Area 35 (pink), A36 – perirhinal Area 36 (purple).*

posterior axis such that the $EC_{Area35\text{-}based}$ progressed more along deep entorhinal portions (with a main focus anteriorly) and the $EC_{Area36\text{-}based}$ along superficial entorhinal portions (with a main focus posteriorly, see Figure 7 and the medial reflection of the EC seeds). It is important that these are rough qualitative descriptions of the main clusters, without quantification or an established relationship to coherent cytoarchitectonic regions. I will therefore continue to refer to them as $EC_{RsC\text{-}based}$, $EC_{PhC\text{-}based}$, $EC_{Area35\text{-}based}$ and $EC_{Area36\text{-}based}$ seeds throughout the chapter. In the General Discussion, I will refer to these entorhinal seeds using the approximate longitudinal and transversal axis descriptions to place the results into the broader context of the existing literature.

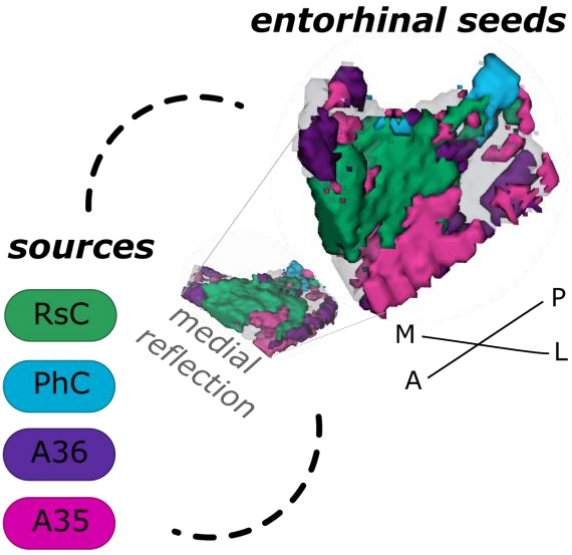

Figure 7. Entorhinal seed regions based on connectivity preferences to cortical regions. *Displayed is the right entorhinal cortex (EC) as a 3D image with colored seed regions. The seed regions have been identified based on a source-to-voxel functional connectivity analysis and resulting connectivity preference to either the right retrosplenial cortex (RsC, green), parahippocampal cortex (PhC, blue), Area 36 (A36, purple) or Area 35 (A35, pink) sources. Note that preferences to Area 36 are best visible from a medial perspective on the EC as depicted in the medial reflection. Seed regions have been determined based on the thresholded (T > 3.1) maximum voxels across four one-sample t-tests at group level, one per source. M – medial; L – lateral; A – anterior; P – posterior.*

Distal subiculum is functionally connected with the $EC_{PhC\text{-}based}$ seed while the subiculum/CA1 border is connected with $EC_{RsC\text{-}based}$ and $EC_{Area35\text{-}based}$ seeds

Following the characterization of entorhinal seeds, I focused on the functional connectivity between these entorhinal subregions and hippocampal subiculum and CA1 to test the hypothesis of a transversal functional connectivity pattern. When extracting estimates of connectivity preferences across individuals from proximal and distal hippocampal subregion segments for either entorhinal seed, repeated measures ANOVAs revealed significant seed X segments interaction effects along the transversal Sub/CA1 axis (see Figure 8; subiculum: $F(12,372) = 19.561$; $p < .001$; CA1: $F(6,186) = 3.212$; $p = .024$; please refer to supplementary III for gradient depictions).

In the subiculum, additional repeated measures ANOVAs showed that the $EC_{Area35\text{-}based}$ ($F(4,124) = 8.913$; $p_{FDR} < .001$), $EC_{RsC\text{-}based}$ ($F(4,124) = 10.538$; $p_{FDR} < .001$) and $EC_{PhC\text{-}based}$ ($F(4,124) = 42.201$; $p_{FDR} < .001$) seeds displayed a significant main effect across the transversal subiculum segments. These differential functional connectivity preferences across the transversal axis of the subiculum interacted significantly in a subsequent repeated measures ANOVA ($EC_{PhC\text{-}based}$ versus $EC_{RsC\text{-}based}$ seed preference interaction: $F(4,124) = 46.452$; $p_{FDR} < .001$; $EC_{PhC\text{-}based}$ versus $EC_{Area35\text{-}based}$ seed preference interaction: $F(4,124) = 35.208$; $p_{FDR} < .001$). This pattern provides statistical evidence for an increase in preferential functional connectivity with the $EC_{PhC\text{-}based}$ seed towards the distal portion of the subiculum while the preferential functional connectivity with the $EC_{Area35\text{-}based}$ as well as the $EC_{RsC\text{-}based}$ seeds rather increased towards the proximal portion of the subiculum.

In hippocampal CA1, additional repeated measures ANOVAs showed that the connectivity preference towards the $EC_{RsC\text{-}based}$ seed displays a significant main effect across the transversal axis of CA1 ($F(2,62) = 10.489$; $p_{FDR} < .001$). In distal CA1, the preferential functional connectivity with the $EC_{RsC\text{-}based}$ seed was higher than in the proximal portion of CA1. In right CA1, a similar but weaker transversal pattern was observed for connectivity preferences with the $EC_{Area35\text{-}based}$ ($F(2,62) = 4.146$; $p_{FDR} = .041$;

note in the left hemisphere a comparable transversal pattern was observed for the $EC_{PhC\text{-}based}$ and $EC_{RsC\text{-}based}$ portions, see supplementary I).

Thus, in the entorhinal-hippocampal circuitry, voxels in the distal subiculum were preferentially functionally connected with the $EC_{PhC\text{-}based}$ portion whereas voxels in the subiculum/CA1 border were preferentially connected with more anterior EC portions ($EC_{RsC\text{-}based}$ and $EC_{Area35\text{-}based}$).

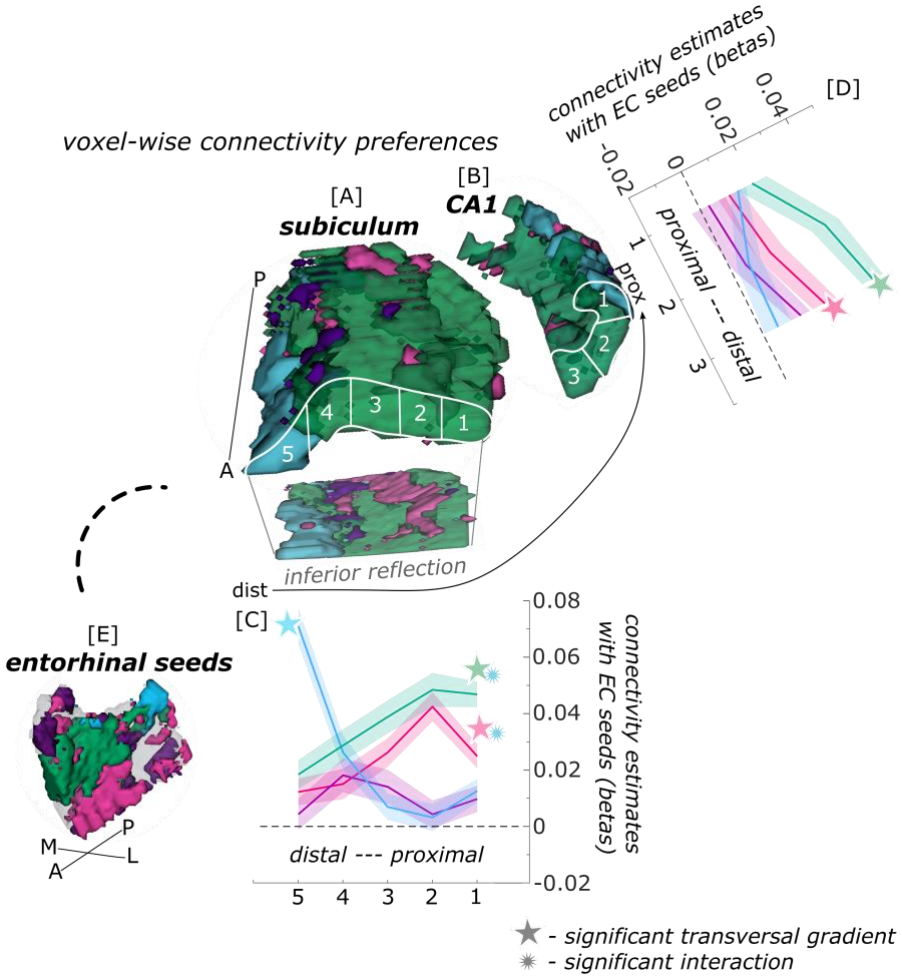

Figure 8. Functional connectivity preferences to entorhinal seeds along the transversal axis of subiculum and CA1. *Displayed are the results of a seed-to-voxel functional connectivity analysis between the displayed right entorhinal seeds and the right subiculum and CA1 subregion. The 3D figure displays voxel-wise connectivity preferences to the entorhinal seeds (color coded to refer to the respective entorhinal seed [E]) on group level ([A] - subiculum; [B] - CA1). Note that preferences to the $EC_{Area35\text{-}based}$ seed (pink) are located mainly in the inferior subiculum and CA1 and are therefore best visible in the inferior reflection. To display mean connectivity preferences across participants along the transversal Sub/CA1 axis, beta estimates were extracted and averaged from equally sized segments from proximal to distal ends (five segments in subiculum [A], three segments in CA1 [B]; schematized in white on the 3D figures) on each coronal slice and averaged along the longitudinal axis. Repeated measures ANOVAs revealed significant differences in connectivity estimates along the transversal axis of CA1 [D] and subiculum [C] with interaction effects in the subiculum. Displayed significances obtained by FDR-corrected post-hoc tests and refer to $p < .05$. Shaded areas in the graphs refer to standard errors of the mean. EC – entorhinal; M – medial; L – lateral; A – anterior; P – posterior; prox – proximal; dist – distal.*

Distal subiculum and $EC_{PhC\text{-}based}$ exhibit higher functional activity in the scene condition while other subregions show no significant difference between conditions

Besides the intrinsic functional connectivity patterns within the entorhinal-hippocampal circuitry, I also examined the characteristics of scene and object information processing to test the hypothesis of multiple information processing routes within the entorhinal-hippocampal circuitry.

First, I focused on the entorhinal seed regions. When extracting task-related parameter estimates from object and scene conditions, a repeated measures ANOVA showed a significant interaction between region and information type (object versus scene, $F(3,93) = 20.927$; $p < .001$). Post-hoc t-tests revealed that only in the $EC_{PhC\text{-}based}$ seed region functional activity in the scene condition was significantly higher than in the object condition ($p_{FDR} < .001$), while in the remaining three entorhinal seed regions no significant difference between scene and object conditions existed (see Figure 9).

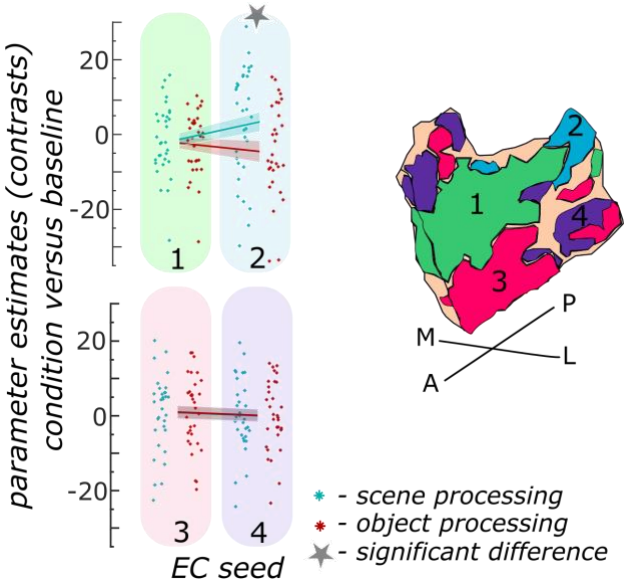

Figure 9. Functional activity during scene and object conditions in entorhinal seed regions. *Displayed are the extracted parameter estimates for the object condition versus baseline contrast ("object information processing", red) and the scene condition versus baseline contrast ("scene information processing", cyan) from each entorhinal seed region (EC seed) per individual (dots) and summarized across individuals (lines). A schematic depiction of the respective entorhinal seed regions is displayed by a 3D drawing of the right EC. A repeated measures ANOVA revealed a significant interaction between condition and seed region. The displayed significant difference is obtained with FDR-corrected post-hoc tests and refers to p < .05. During the object condition, participants were presented with 3D rendered objects on screen, during the scene condition with 3D rendered indoor rooms and during the baseline condition they saw scrambled pictures. The shaded area around the lines refers to standard errors of the mean. EC – entorhinal; M – medial; L – lateral; A – anterior; P – posterior.*

When extracting task-related parameter estimates for scene and object conditions from proximal and distal segments of hippocampal subregions within each participant, I found a significant interaction between transversal segments and information type only in the subiculum ($F(4,124) = 15.994$; $p < .001$) and not in CA1 as revealed by a repeated measures ANOVA. Post-hoc t-tests showed significantly higher functional activity in the scene than object condition (both $p_{FDR} < .001$) only in the distal subiculum segments. In all other segments along the subiculum transversal axis, there was no significant difference in functional activity related to scene and object conditions (see Figure 10).

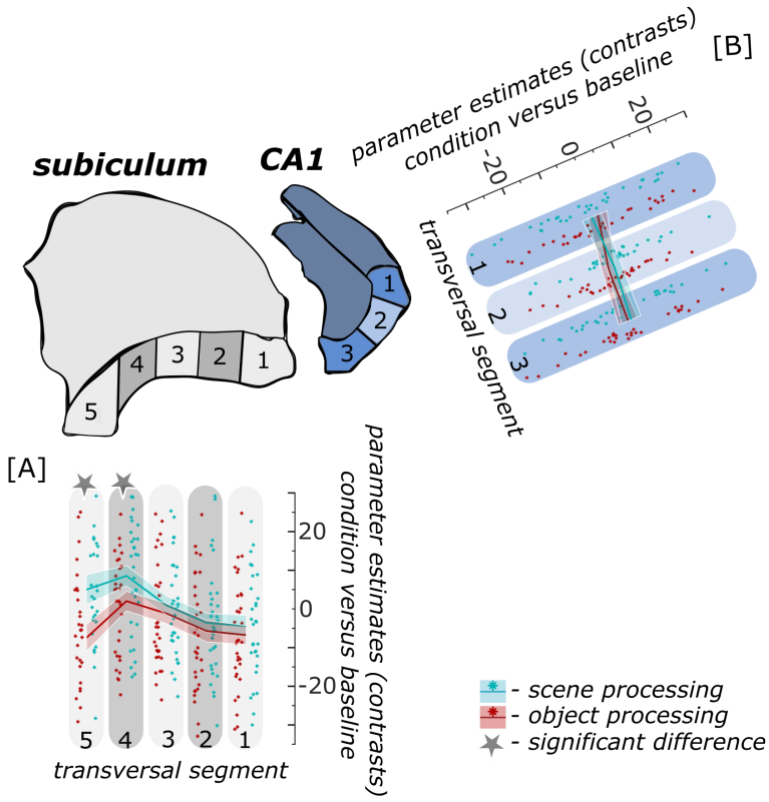

Figure 10. Functional activity during scene and object conditions along the transversal axis of subiculum and CA1. *Displayed are the extracted parameter estimates for the object condition versus baseline contrast ("object information processing", red) and the scene condition versus baseline contrast ("scene information processing", cyan) from the respective transversal segments in the subiculum ([A] grey) and CA1 ([B] blue) per individual (dots) and summarized across individuals (lines). A schematic depiction of the respective transversal segment is displayed by a 3D drawing of the right subiculum and CA1 subregion. Repeated measures ANOVAs revealed a significant interaction between condition and seed region in the subiculum only. The displayed significant difference is obtained with FDR-corrected post-hoc tests and refers to p < .05. During the object condition, participants were presented with 3D rendered objects on screen, during the scene condition with 3D rendered indoor rooms and during the baseline condition they saw scrambled pictures. The shaded area around the lines refers to standard errors of the mean.*

2.4 DISCUSSION

In this chapter, I aim to advance insight into the organizational principles of information processing within the entorhinal-hippocampal circuitry and the circuitry's embedding in large-scale cortical processing. I thereby approach the question how information is communicated and processed throughout the subregions of the human parahippocampal-hippocampal system. Leveraging ultra-high field 7 Tesla fMRI, I find a resemblance between the intrinsic functional connectivity pattern and subregional biases in context information processing (operationalized by the scene condition) in the entorhinal-hippocampal circuitry. In the EC, I observe a topographical mapping of regions from the cortical context and item information processing streams, including the retrosplenial, parahippocampal and perirhinal Area 35 and 36 cortices. This mapping continues to determine a transversal organization of information routes between the EC and the human hippocampal circuitry. These results unify previous evidence and exhibit novel features in the human brain that can be a window into the parahippocampal-hippocampal system's critical role in memory function.

Context information is processed within an $EC_{PhC\text{-}based}$ – distal subiculum route

I identified regions in the entorhinal-hippocampal circuitry that are dedicated to process context information (operationalized by scene stimuli). These regions consisted of two functionally connected portions: the $EC_{PhC\text{-}based}$ and the distal subiculum. The subiculum showed a transversal difference in intrinsic functional connectivity with a preference to the $EC_{PhC\text{-}based}$ in its distal portions (of note: the

$EC_{PhC\text{-}based}$ was defined by entorhinal voxels with preferential functional connectivity to the parahippocampal cortex which shows context-specific processing). Importantly, the distal subiculum and the $EC_{PhC\text{-}based}$ were the only studied entorhinal-hippocampal subregions that exhibited specific functional activity for context information.

These findings provide clear evidence for a hypothesized transversal difference in context information processing within the human subiculum. The data also replicate the earlier functional and structural connectivity reports in humans as well as anatomical findings of a route between posterior-medial EC (based on parahippocampal connectivity) and distal subiculum (Maass et al., 2015; Syversen et al., 2021; Witter, Naber, et al., 2000). The scene or spatial context information processing bias has previously mainly been reported for the EC (in rodents, operationalized by spatial processing conditions: Neunuebel et al., 2013; Keene et al., 2016; in humans, operationalized by scene stimulus conditions: (Berron et al., 2018; Navarro Schröder et al., 2015; Reagh & Yassa, 2014; Schultz et al., 2012). Long overlooked in animal studies, the importance of the subiculum as a translator of hippocampal information towards the entorhinal and other cortical structures gets more and more acknowledged (O'Mara, 2006; Roy et al., 2017). Here, I contribute to the sparse investigations regarding the nature of information processed along the transversal axis of the subiculum (see Ku et al., 2017). The observation is in line with the hypothesis that the distal subiculum is more involved in processing context than items based on previous findings in the human brain. While the subiculum in general was associated with scene discrimination (Hodgetts et al., 2017), a growing body of evidence relates particularly the medial hippocampus to context processing. This entails two medial areas, the pre- and parasubiculum, that we attribute to the distal subiculum in our current segmentation. Especially the area that resembles the pre- (or here: distal) subiculum has been shown to be involved in scene construction (Dalton et al., 2018). Recently, a gradient with coarser voxel-wise autocorrelation signals in the medial hippocampus has been reported, a finding that implies larger representations in the distal subiculum (Bouffard et al., 2022). In the latter two studies, however, the authors did not specifically extract data from the transversal axis of hippocampal subregions. Here, the joint investigation of functional entorhinal-subiculum connectivity and type of information processing along the full transversal axis of the subiculum, is the first to show a clear preference of context information towards the distal portion, in comparison to more proximal portions.

Information processing is consistent with convergence within the anterior entorhinal portions – subiculum/CA1 border route

The data revealed another route that did not show differences in context and item information processing (operationalized by scenes and objects, respectively). Both, the $EC_{Area35\text{-}based}$ and the $EC_{RsC\text{-}based}$ portion exhibited preferential functional connectivity with the subiculum/CA1 border. Comparable levels of functional activity in scene and object conditions along these entorhinal-hippocampal pathways are consistent with information convergence.

While I again confirm earlier findings and previously stated hypotheses, several features in the data are fundamentally novel. First, I provide initial human evidence for a functional connection between the $EC_{Area35\text{-}based}$ and the subiculum/CA1 border. Non-primate and primate anatomical data as well as ex-vivo and in vivo structural connectivity data in humans show the possibility of information flow along that route (Syversen et al., 2021; Witter, Doan, et al., 2017; Witter & Amaral, 1991, 2020). The results now underpin a functional relevance of that connection beyond the subiculum (for the subiculum see Maass et al., 2015). The findings are derived based on a voxel-wise analysis, unconstrained by a priori selection of ROIs. Thereby, I confirm the long-held proposal of a transversal functional organization in human hippocampal subregions subiculum and CA1.

Convergence of scene and object information is compatible with recent rodent work that shows joined coding of context and item information along CA1 and within the lateral EC (Deshmukh & Knierim, 2011; Doan et al., 2019; Vandrey et al., 2021; Wilson, Langston, et al., 2013; Wilson, Watanabe, et al., 2013; Yeung et al., 2019). Indeed, the information processing in the cortical source regions showed specific item processing in perirhinal source regions. The lack of increased item processing in the anterior EC subregions and subiculum/CA1 border is thus unlikely to be a result of increased noise in the object condition. Instead, increased item processing in perirhinal cortical source regions indicates subsequent convergence in entorhinal-hippocampal subregions, as hypothesized based on the updated cortical mapping scheme onto the EC.

The results cannot confirm previous reports about higher functional activity for item than context processing within these areas in the human brain (Reagh and Yassa, 2014; Navarro Schröder et al., 2015; Berron et al., 2018; also indicated in Dalton et al., 2018 and Schultz et al., 2012). Neither did we observe proximodistal differences in CA1 for item versus context (also operationalized as nonspatial versus spatial) information processing as suggested by several rodent studies (Beer et al., 2018; Henriksen et al., 2010; Nakamura et al., 2013; Nakazawa et al., 2016). Differences in experimental design and contrasts could have contributed to these discrepancies (i.e. specific object information processing versus convergence). Previous studies used a variety of different conditions to tackle context and item information processing (e.g. temporal versus spatial context in Beer et al., 2018 or imagined objects on a 2D or 3D grid in Dalton et al., 2018). In contrast to the current data, previous human studies moreover did not derive functional data from specific, functionally defined entorhinal portions in the same dataset. As most previous studies were conducted in the light of the "parallel mapping hypothesis", the related assumptions influenced the examined subregions, which may have altered the extracted measures.

Regarding the human proximal CA1, a firm conclusion is limited with the current data. First, the functional connectivity results vary between hemispheres. In both hemispheres, proximal CA1 shows a different connectivity profile compared to distal CA1. However, even though statistically not significant, the preferences on group level indicate increased functional connectivity with the $EC_{PhC\text{-}based}$ portion in the right but with the $EC_{Area35\text{-}based}$ portion in the left hemisphere. Second, the absence of a difference in information processing along the transversal axis is no evidence for similar information processing across CA1. As mentioned in the previous paragraph, experimental differences in operationalization of what we consider to be "item" versus "context" processing play a role here. Thus, future research will have to identify defining characteristics of information processing along the transversal CA1 axis in a less constraint manner to allow conclusions on distinct information processing in proximal CA1.

In addition, I observed a previously unreported resemblance in functional connectivity profiles of $EC_{RsC\text{-}based}$ and $EC_{Area35\text{-}based}$ portions in the anterior EC. The sources of these entorhinal portions are part of cortical context and item processing streams, respectively. This is also evident following increased context processing in the retrosplenial and increased item processing in perirhinal cortical source regions (Figure 6). To my knowledge, the $EC_{RsC\text{-}based}$ portion has not yet been identified in earlier investigations. While anatomical projections from the retrosplenial to deep medial EC layers have been confirmed in rodents, they appear in the posterior EC (Czajkowski et al., 2013; Sugar et al., 2011). Recently, Syversen et al. (2021) found structural connectivity between the human retrosplenial cortex and the medial EC, but again not in the anterior part of the EC. Their EC segmentation, however, followed different rules which may have contributed to differences in the topographical evaluation of the region. Also, structural and functional connectivity methods may yield different results, in particular as I identified EC subregions with a different set of cortical source regions. Under

the assumption that retrosplenial connectivity defines the medial EC (Witter, Doan, et al., 2017), the mapping of the $EC_{RsC\text{-}based}$ to the subiculum/CA1 border opposes conventional views that the medial EC communicates with the distal subiculum and proximal CA1 (based on rodent anatomy – see e.g. Nilssen et al., 2019). Whether species differences exist in the retrosplenial cortex – EC – hippocampus connectivity pattern or whether functional and structural connectivity diverge needs further investigation in the future.

Relevance of the current findings on the functional organization of the parahippocampal-hippocampal system

The current findings advance insight into the organization of the parahippocampal-hippocampal system on multiple levels. Recent efforts to understand how the human entorhinal-hippocampal circuitry accomplishes conjunction and segregation of information largely focused on the longitudinal hippocampal axis (Brunec et al., 2018, 2020; Robin & Moscovitch, 2017). The transversal axis of the hippocampus has been approached by studies in humans that did not directly relate connectivity findings to information processing and did not assess subregion-specific organization (Bouffard et al., 2022; Kharabian Masouleh et al., 2020; Paquola et al., 2020; Plachti et al., 2019; Vos de Wael et al., 2018; for an overview see Genon et al., 2021). Dalton & Maguire (2017), however, made a relevant proposal based on visual processing pathways and information processing. In correspondence to our results, they proposed the subiculum/CA1 border as a point of convergence between context and item information processing streams. While their conclusion was based on direct parahippocampal, retrosplenial and perirhinal connections to the hippocampus, we found that both, the $EC_{Area35\text{-}based}$ (that is connected with the cortical item processing stream) and the $EC_{RsC\text{-}based}$ (that is connected with the cortical scene processing stream) show connectivity with the subiculum/CA1 border (see also Figure 6 for information processing in cortical source regions). Convergence is potentially also achieved via recurrency within the entorhinal-hippocampal system and cortical regions (cf. Koster et al., 2018 for evidence on recurrency). These considerations are an exciting future research avenue and remain speculative based on the current data due to insufficient temporal resolution.

Regarding the question how information is communicated and processed throughout the subregions of the human parahippocampal-hippocampal system, I nevertheless hypothesize the existence of two processing routes: one that processes converged item and context information and one that processes context information specifically. Thus, context and item information processing converge before the hippocampus. This seems to occur already in the anterior EC, given item-specific and context-specific processing in the cortical source regions of the $EC_{Area35\text{-}based}$ and $EC_{RsC\text{-}based}$ subregions, respectively. Here, items may be bound together with ´defining scene-like or contextual features (akin to the "item-in-location" idea in Connor & Knierim, 2017; Knierim et al., 2014). In addition, the dedicated scene processing that we observe along the $EC_{PhC\text{-}based}$ – distal subiculum route, may functionally underpin ideas about a slowly changing contextual scaffold that the hippocampus utilizes to incorporate detailed information from the item-in-context converged route into meaningful chunks of cohesive memory representations ("events"; Behrens et al., 2018; Clewett et al., 2019; Robin, 2018; Robin & Olsen, 2019). Altogether, the functional organization indicates that when a memory is to be formed, some degree of convergence happens already before the hippocampus, nevertheless keeping specific aspects of scene or context information separated. This conclusion is in accordance with the updated cortical mapping scheme onto the EC (Nilssen et al., 2019). The topographical specificity of the results support the necessity of functionally assessing the entorhinal-hippocampal circuitry with high spatial resolution and investigate memory function at a subregional level (H. Lee et al., 2020). The features I identified can inform future hypotheses on how the hippocampus achieves the formation of cohesive representations that serve memory function.

For completeness, I noted differences in functional connectivity along the longitudinal axis of the subiculum. For instance, I observe more widespread functional connectivity of the $EC_{Area35\text{-}based}$ in the posterior subiculum whereas functional connectivity with the $EC_{PhC\text{-}based}$ portion seems more prominent in the anterior subiculum. The latter is consistent with previous reports (Dalton et al., 2019). The former, however, needs to be explored further by taking different segmentation protocols and seed regions into account. Note, that Maass et al. (2015) did not report longitudinal differences in connectivity strength between the EC and the subiculum. Future work needs to investigate in how far these observations relate to the reported gradient in functional connectivity and information resolution along the hippocampal longitudinal axis (e.g. Brunec et al., 2018 but many more).

From a clinical perspective, it is remarkable that the current functional connectivity pattern resembles the topology of cortical tau pathology (Lace et al., 2009). In the literature, it is suggested that tau propagates along functional routes within the brain (Franzmeier, Neitzel, et al., 2020; Vogel et al., 2020). As mentioned beforehand, earliest cortical tau pathology accumulates in the perirhinal Area 35 and the anterior-lateral EC from where it spreads to the subiculum/CA1 border (Berron et al., 2021; Braak & Braak, 1995; Kaufman et al., 2018). The topology of early tau pathology in Alzheimer's disease thus mirrors the regions that we find biased towards $EC_{Area35\text{-}based}$ connectivity (Braak & Braak, 1991; Lace et al., 2009; Roussarie et al., 2020). Tau pathology in Alzheimer's disease is associated with memory impairment (Bejanin et al., 2017; Berron et al., 2021; Nelson et al., 2012). As I will lay out in more detail in Chapter V and in the General Discussion, information processing might be affected accordingly as reports have shown an association between Alzheimer's related tau pathology and item memory in early disease stages (Berron et al., 2019; Maass et al., 2019). However, given the finding of activity patterns consistent with item – context convergence in those subregions of the hippocampal-entorhinal circuitry that are affected by early tau pathology, item-in-context memory tasks might have increased sensitivity to memory impairment. Moreover, both, the entorhinal portion based on retrosplenial connectivity ($EC_{RSC\text{-}based}$) and the entorhinal portion based on Area 35 connectivity ($EC_{Area35\text{-}based}$), are functionally connected to the subiculum/CA1 border. This overlapping functional connectivity pattern in the hippocampus might be a way along which tau and amyloid pathologies in Alzheimer's disease could interact. This is consistent with early hypometabolism and cortical tau progression in the retrosplenial cortex and early amyloid in posterior parietal regions (Grothe et al., 2017; Palmqvist et al., 2017; Ziontz et al., 2021). This is relevant for the third aim of my thesis and in Chapter V and in the General Discussion I will elaborate on how the revealed functional connectivity and information processing profile may guide future hypotheses on the propagation of Alzheimer's pathology and related functional and cognitive impairment.

Limitations

First, the biases in seed connectivity in the left hemisphere were generally weaker and proximal CA1 results were less consistent across hemispheres. I conducted all analyses independently for both hemispheres to allow internal replication of our findings, however, whether partially different effects indeed signal a lateralization of the entorhinal-hippocampal organization in humans or whether the task or another parameter influenced these observations, is subject for further research.

Second, while it is unlikely that our functional connectivity pattern is the result of spatial proximity, increased correlation between spatially adjacent regions is an inherent problem of functional connectivity analyses. Distances between seed and target regions differ and may cause patterns in the functional connectivity data. To diminish the influence of neighboring regions in target regions the smoothing kernel was smaller than two times the voxel size. It is important to stress moreover, that the pattern of our results is not easily explainable by spatial distance between seed and target regions. The $EC_{Area35\text{-}based}$ or $EC_{RsC\text{-}based}$, for instance, are not adjacent to the subiculum/CA1 border.

Further evidence is the observation of roughly comparable results for neighboring seeds and targets (e.g. $EC_{PhC\text{-}based}$ and distal subiculum) when I perform the functional connectivity analyses with seed and source regions in the contralateral hemisphere.

Third, the perspective here was entirely functional. To what extent there is a correspondence to structural connectivity (Syversen et al., 2021) remains to be determined, considering different experimental task constraints and contrasts. Note also that as a first step towards an understanding of the system's functional organization and to increase comparability with earlier studies, I assessed functional connectivity and information processing within the parahippocampal-hippocampal system with univariate methods. These allow relative comparisons between functional activity levels in different conditions. Consequently, I am neither able to assess what the EC is processing during the baseline condition, meaning the absolute level of functional activity, nor am I able to verify that information processing is similar across conditions in for example the $EC_{Area35\text{-}based}$ seed. Univariate methods, moreover, average the signal over regions of interest. To capture hidden voxel-wise patterns of activity that scale with the processing of certain representations, future studies could examine information pathways with multivariate methods that evaluate informational content in the activity pattern of voxels instead of in an averaged manner (Kragel et al., 2018; Kriegeskorte et al., 2008). Moreover, recent methodological advances can be employed in the future that study functional connectivity based on the underlying content representations between regions (Basti et al., 2020) .

Fourth, the study in this chapter is originally conducted within the assumption that (functional) connectivity profiles reveal functional subregions. Based on that idea, the medial EC should be identified based on i.a. retrosplenial connectivity. Thus, I reason a surprisingly anterior yet medial EC mapping of the retrosplenial cortex. This approach has been followed by Maass et al. (2015) but also in numerous anatomical connectivity studies in animals (see Witter et al., 2017). It is possible that species differences lead to our $EC_{RsC\text{-}based}$ that is more anterior than one would expect based on animals. However, given that the medial subregion in the primate EC remains posterior, another possibility is that the retrosplenial functional connectivity cluster maps onto the lateral EC. The data does not allow me to verify this latter option. It is unclear, however, why functional subregions in line with predictions from animal research can be identified for some cortical source-to-EC mappings (like the parahippocampal cortex) but not for others. In combination with closely matched histological or structural magnetic resonance imaging data, future work can reveal more about the nature of retrosplenial mapping on the human EC.

In general, the quantification of the transversal connectivity pattern should be considered with some caution from the anatomist's perspective. The segmentation of subregions on functional data is an approximation because the anatomical ground truth cannot be captured by any segmentation protocol (even histological data leads to divergent opinions). This shortcoming is amplified by group comparisons that do not account for participant-specific anatomy. Future research is needed to evaluate how the functionally derived entorhinal seeds relate to histologically derived entorhinal subregions (Oltmer et al., 2022) or entorhinal subregions based on structural connectivity (Syversen et al., 2021). For a dedicated comparison of subregions, it is essential to pay close attention to the segmentation of the EC itself. Note moreover, that I excluded the head and the tail of the hippocampus in the current investigation. The head is highly complex in its subregion topography (Ding and Van Hoesen, 2015; Berron et al., 2017) and prevents clear hypotheses regarding a transversal pattern. For the tail we lack an established segmentation protocol (de Flores, Berron, et al., 2020; DeKraker et al., 2018). In future, advanced segmentation methods and evaluations in the participant-space will improve this issue and reveal the organization in more detail.

In sum, leveraging ultra-high field functional imaging, I provide a comprehensive in vivo exploration of the functional organization within the human entorhinal and hippocampal subregions and the circuitry`s embedding within cortical information processing streams. Within the entorhinal and hippocampal subiculum, the data partially support a continuation of cortical item and contextual information processing with convergence in anterior and lateral entorhinal portions ($EC_{Area35\text{-}based}$, $EC_{RsC\text{-}based}$, $EC_{Area36\text{-}based}$), proximal subiculum and CA1, while the posterior-medial entorhinal portion ($EC_{PhC\text{-}based}$) and distal subiculum process scene or context information specifically. Topographically, this organization of information processing overlaps with our identified pattern of functional connectivity. The data yield spatially organized information processing along functionally connected subregions in the human EC and transversal Sub/CA1 axis. This chapter advances insight into how information is communicated and processed throught the parahippocampal-hippocampal system.

CHAPTER III

UNITIZED ITEM REPRESENTATIONS IN THE PERIRHINAL CORTEX

III. UNITIZED ITEM INFORMATION IN THE PERIRHINAL CORTEX CAN CONTAIN CONTEXT INFORMATION

Abundant evidence shows segregation of item and context information in the parahippocampal gyrus (also in the previous chapter) but the recently updated anatomical wiring emphasizes also cross-projections from the contextual stream towards the PrC. To reconcile these, I here explore literature on the PrC as a region that, while traditionally being associated specifically with item processing, may also be responsive to contextual aspects under certain circumstances. Chapter III has been published as a review in *Hippocampus* (Fiorilli et al., 2021) with me as the formal second author. I edited the parts of the publication that were not originally drafted by me, and with minor edits in the remaining parts, I integrated the manuscript into the current thesis.

3.1 INTRODUCTION

Given the anatomical connections reviewed in the General Introduction, the PrC is a polymodal association area that receives inputs from many uni- and polysensory areas (Burwell, 2001; Burwell et al., 1995; Burwell & Amaral, 1998a; Furtak et al., 2007; Suzuki & Amaral, 1994). The PrC is also input and output of the medial temporal lobe, with connections to the entorhinal-hippocampal circuitry (Burwell et al., 1995; Burwell & Amaral, 1998a; Insausti et al., 1997; Witter, Naber, et al., 2000), some of which I functionally investigated in the previous Chapter II. As introduced already in this thesis, the PrC is traditionally considered part of the cortical item processing stream. Contextual information, however is cortically processed in another stream that comprises the parahippocampal cortex and retrosplenial cortex. As I comprehensively investigated in the previous chapter, both streams communicate with different portions of the entorhinal-hippocampal circuitry (Grande et al., 2022; Burwell, 2000; Furtak et al., 2007; Goodale & Milner, 1992; Knierim et al., 2014; Otto & Eichenbaum, 1992; Witter et al., 2000). Chapter II was motivated by rodent findings of no strict anatomical dissociation between both pathways in their mapping onto the EC. Here, I explore what this means for the PrC and why, despite cross-talk, the PrC might still be fundamental for processing item information (as also indicated in Chapter II; Agster & Burwell, 2009; Doan et al., 2019; Nilssen et al., 2019).

To recapitulate from the General Introduction, the classical distinction between 'item and context' streams has been supported by evidence for different cell types, specific cognitive impairments after lesions, single unit recordings during cognitive tasks and non-invasive functional imaging (Hafting et al., 2005; Knierim et al., 2014; McNaughton et al., 2006). Regarding the PrC, the evidence across species and methods supports a perirhinal function in item processing (Albasser et al., 2015; Bartko et al., 2007a; Brown & Banks, 2015; Ennaceur et al., 1996; Ennaceur & Aggleton, 1997; G. Norman & Eacott, 2005; Otto & Eichenbaum, 1992; von Linstow Roloff et al., 2016; Young et al., 1997; Zhu & Brown, 1995).

Besides its role in item recognition, the PrC has been related to solving feature ambiguity (Buckley & Gaffan, 1998; Buffalo et al., 1999; Bussey et al., 2002; Bussey & Saksida, 2005, 2007; Meunier et al., 1993; Saksida et al., 2006, 2007) and the processing of complex stimuli, both within and across different sensory modalities (Bartko et al., 2007b; Feinberg et al., 2012; Jacklin et al., 2016; Kent & Brown, 2012; Ramos, 2016). Critically, recent work in rodents and monkeys suggested that the PrC processes information on task-related context that can be spatial or temporal (Bos et al., 2017; Eradath et al., 2015; Keene et al., 2016). This is in line with the previously mentioned update showing coorss-projections from the cortical context stream onto the PrC (that is in turn part of the cortical item processing stream; Agster & Burwell, 2013; Doan et al., 2019; Kerr et al., 2007; Nilssen et al.,

2019; Van Strien et al., 2009). The current Chapter III brings animal and human literature together to examine how seemingly contradictory finings on item-related versus contextual processing in the PrC can be unified when acknowledging unitized representations in the PrC that merge task-relevant information.

3.2 THE PERIRHINAL CORTEX IN SENSORY ITEM PROCESSING AND RECOGNITION

3.2.1 Evidence from lesion studies

In this part, I summarize reported deficits in sensory processing and memory caused by PrC lesions in the rodent, monkey and human brain. Animal and human lesion studies give important insight into the neural basis of behavior. Their strength lies in the possibility to infer causality between brain regions and cognitive functions. In humans, two principal approaches have been taken as I also mentioned in the General Introduction. First, focal lesions have been investigated that overlap anatomically with the PrC. Here, drawing specific conclusions on PrC functionality is difficult as these lesions are mostly unilateral (and therefore cause limited impairment) or cover more areas than only the PrC. Second, widespread neural injury is studied that can be acute in nature (e.g. due to an encephalitis) or caused by progressive neurodegeneration as in the context of Alzheimer's, semantic or frontotemporal dementia. The relationship between PrC damage and cognitive impairment then has to be established through quantification of PrC integrity (i.e. volume or cortical thickness). Accurate identification of anatomical PrC borders is, however, challenging (Berron et al., 2017; Ding & Van Hoesen, 2010). In animals, lesions can be induced. This gives more control over the lesioned area and reversible lesions even allow within-subject comparisons.

For decades, research on PrC was heavily influenced by the tradition of region – function mapping. Much studies investigated whether perceptual or mnemonic processes drive the PrC. Moreover, much insight into perirhinal function comes from research that focused on the debated dissociation between hippocampus and parahippocampal gyrus regions serving recollection versus familiarity-based recognition, respectively (see e.g. Brown and Aggleton, 2001; Buckley & Gaffan 2006; Eichenbaum et al., 2007; Naya 2016; Squire et al., 2004; Wais, 2008).

Lesions in rodents

Rodents with a PrC lesion perform often normal on familiarity-based item recognition[8] when the delay between item sampling and recognition is short (< 10-40 min), longer delays, however, lead to impairment (Ennaceur et al., 1996; Ennaceur & Aggleton, 1997; G. Norman & Eacott, 2005; Otto & Eichenbaum, 1992). The stimulus complexity influences how long a delay can be without leading to impairments (Albasser et al., 2015; Bartko et al., 2007a; G. Norman & Eacott, 2005). When objects are perceptually similar, even immediate recognition can be impaired in PrC-lesioned rodents (Bartko et al., 2007a). The perirhinal role in item recognition thus depends on item complexity and perceptual ambiguity.

The mechanisms that underlie the described impairments were studied by McTighe et al. (2010). They presented either two novel or two familiar objects during the recognition phase of a spontaneous item recognition task. PrC-lesioned rats explored the novel objects less, but did not increase exploration of familiar objects. The impairment was thus related to a problem in novelty detection of new objects. Critically, when the rodents spent the retention period in the dark, familiarity-based recognition was

[8] In rodents, item recognition is commonly assessed using a spontaneous object recognition paradigm (Albasser et al., 2010; Ennaceur & Delacour, 1988). in which the innate preference of rodents to explore novel items over familiar ones is used to assess whether rats recognize items as familiar or not. Impairments in recognizing items as familiar are characterized by a failure to preferentially explore a new object over an old one that has been explored before (Albasser et al., 2010; Ennaceur & Delacour, 1988). Critically, differences in exploration times reflect item familiarity. This might occur without recollection of item identity from episodic memory.

intact. McTighe et al. (2010) hypothesized that the visual input during the retention period may lead to memory interference. PrC lesions thus may induce an increased susceptibility to the visual input (but see Albasser et al., 2015; Olarte-Sánchez et al., 2015 who did not find evidence for interference). Differences between studies may have arisen due to various experimental set ups (e.g. curiosity-driven item exploration as in McTighe et al., 2010, or baited objects as in Albasser et al., 2015) or the extend of lesions (Olarte-Sánchez et al. 2015).

More insight into the role of the PrC in recognition comes from stimulus discrimination in operant conditioning paradigms. Here, impairments in PrC-lesioned rodents only arose when complex visual stimuli with shared features were used (Eacott et al., 2001). This result indicates that the PrC is only necessary when different visual features need to be integrated, but not for solving feature ambiguity of a single visual feature. Comparable results were found in tactile, auditory and olfactory tasks (Feinberg et al., 2012; Kent & Brown, 2012; Kholodar-Smith et al., 2008; Lindquist et al., 2004; Ramos, 2014, 2016). For instance, PrC-lesioned rats only showed deficits when the combination of individual tactile features was crucial to solve the task, whereas hippocampal lesions left performance intact (Ramos, 2014, 2016). Moreover, PrC lesions impaired fear conditioning to discontinuous or complex (natural) sounds, but not to pure tones (Kent & Brown, 2012; Kholodar-Smith et al., 2008; Lindquist et al., 2004). Together, these studies demonstrate a perirhinal role in sensory-independent processing of complex stimuli that require the integration of multiple features (note that Clark et al. (2011) show contradicting evidence, however, Murray & Wise, 2012 argue that their task could be solved by specific attention to parts of the visual stimulus).

Moreover, the PrC is involved in multisensory processing. Causal evidence therefore comes from PrC-lesioned rodents (with intact hippocampus) which show deficits in cross-modal item familiarity-based recognition (Albasser et al., 2010; Reid et al., 2012). PrC-lesioned rodents were, however, not impaired in olfactory- and/or tactile-only versions of a similar cross-modal task. Strikingly, multisensory pre-exposure caused later familiarity-based recognition to become completely PrC-dependent, even under unisensory conditions that were initially PrC-independent (Winters & Reid, 2010). Reversible PrC inactivation with lidocaine impaired familiarity-based recognition in all task variants (cross-modal, visual, and tactile, Jacklin et al., 2016). Presumably, neural mechanisms, mediated by the PrC, form a multisensory item representation after the exploration via multiple sensory modalities.

Lesions in primates

Extensive empirical evidence exists for a perirhinal role in resolving feature ambiguity in monkeys (Buckley & Gaffan, 1998; Buffalo et al., 1999; Bussey et al., 2002; Bussey & Saksida, 2005, 2007; Meunier et al., 1993; Saksida et al., 2006, 2007). For instance, PrC-lesioned monkeys (in contrast to monkeys without lesion) were impaired in a reward paired associate task under high levels of stimulus ambiguity, not however when rewarded associated pairs were entirely distinct from images in unrewarded pairs. Critically, successful performance in the highly ambiguous stimulus condition depended on combined information of both paired images because every single image could also be part of an unrewarded pair. Together, lesion studies in rodents and monkeys suggest the requirement of an intact PrC for item recognition, complex stimulus processing and feature ambiguity solving.

Likewise, perirhinal function has been investigated in human lesion studies. Impairment in memory tasks for humans has been particularly noted with familiarity judgments about item stimuli or item-related information (Buffalo et al., 1998; Stark and Squire, 2000; Bowles et al., 2007; Brown and Aggleton, 2001). The reinstatement of episodic memories (recollection) is still intact despite perirhinal damage (but intact hippocampus), whereas item recognition is impaired (Bowles et al., 2007, 2010; Martin et al., 2011). Likewise, item processing is impaired with PrC lesions in perceptual discrimination

tasks, notably when the complexity and feature ambiguity of the stimuli is high and when multisensory integration of information is necessary (Barense, 2005; Barense et al., 2007; A. C. H. Lee et al., 2006; A. C. H. Lee, Buckley, et al., 2005; A. C. H. Lee, Bussey, et al., 2005; Mundy et al., 2013; Newsome et al., 2012). A recent study with rare cases of focal perirhinal lesions confirmed impaired visual discrimination when feature ambiguity is high (Inhoff et al., 2019). As mentioned before, much investigations of the human PrC used to be driven by the debate on whether perirhinal function is critical for perception and memory, given its involvement in familiarity-based recognition (Brown and Aggleton, 2001; Graham et al., 2010; Squire et al., 2007; Brown and Banks, 2015). In many task settings, however, perception is at least partly driven by memory and current views on brain function are more representationally driven (Graham et al., 2010; Kent et al., 2016; Pennartz, 2015; Peterson & Enns, 2005).

The overall picture arising from the lesion literature confirms the perirhinal role a in item-related recognition and perception, particularly refined to multisensory and complex feature integration of objects.

3.2.2 Evidence from functional studies

Permanent lesions may cause other brain regions to take over functions of a damaged region. Moreover, behavioral effects alone do not illuminate the neural mechanisms underlying a structure's function. Therefore, additional evidence for perirhinal involvement in item recognition and sensory processing comes from animal electrophysiology and human neuroimaging studies.

Functional evidence in rodents

When rodents are close to physical objects, recorded single units in PrC increase their firing rate (Burke et al., 2012; Deshmukh et al., 2012). Moreover, perirhinal neurons in rodents are sensitive to the prior presentation of items and show repetition suppression (i.e. decrease in firing rate; Ahn et al., 2019; Brown & Banks, 2015; von Linstow Roloff et al., 2016; Young et al., 1997; Zhu & Brown, 1995). This effect, however, is not present in open fields (Burke et al., 2012; von Linstow Roloff et al., 2016). One explanation could be prolonged stimulus exploration in these environments that decreases the initial novelty signal, another is differences in reward contingencies (von Linstow Roloff et al. 2016). In addition, immediate early gene studies show increased perirhinal c-fos expression upon exposure to novel items (Zhu et al., 1995) but not exposure to novel contexts or newly arranged objects (Aggleton & Brown, 2006; Zhu et al., 1995, 1997). Thus, the presence of novel items explicitely seems to elicit perirhinal involvement.

To gain insights in the mnemonic and perceptual roles of the PrC, Ahn and Lee, (2017) recorded PrC neurons while rats categorized morphed visual stimuli as being an egg or a toy figure. The presented stimuli were morphed to achieve various degrees of similarity. Thereby, it could be quantified whether activity of PrC neurons is correlated with continuous changes in sensory features of the stimulus, or rather with the rodent's perceptual categorization (egg or toy template). Nearly equal proportions of single units represented the perceptual stimulus feature and stimulus category.

Functional evidence in primates

In monkeys, studies investigated the representations of different visual stimuli in the PrC (Fujimichi et al., 2010; Naya, Yoshida, & Miyashita, 2003; Naya, Yoshida, Takeda, et al., 2003; Sakai & Miyashita, 1991). When, for example, being cued with a single image from a previously learned paired associate, some cell's firing pattern indicates anticipation and recall of the paired image. Hence, these cells fire selectively to the cue and increase their activity when waiting for the paired associate to be shown (Sakai & Miyashita, 1991). Other perirhinal cells code for paired associates such that activity to single

stimuli from a paired associate resembles each other (Fujimichi et al., 2010). Thus, PrC cells represent associates as unitized items. Note that firing patterns that code for stimulus associates emerge a few days after learning, which indicates a perirhinal role in long-term memory formation (Erickson & Desimone, 1999).

Regarding the human PrC, fMRI studies provide evidence that generally supports findings from animal and human lesion studies. Again, much literature was driven by the question on which cognitive function is supported by PrC. Recent accounts of human perirhinal function (and in general function of the parahippoampal-hippocampal system) tend to move away from a process-specific dissociation of function. Instead they attribute a specific representational role for the PrC in item-related information that may serve memory or perception, depending on task requirements (Bussey and Saksida, 2005; 2007; Murray et al., 2007; Graham et al., 2010; Bastin et al., 2019). Indeed, O'Neil and colleagues (2012) demonstrated differential functional connectivity profiles of the PrC, depending on whether a task required more perceptual or mnemonic judgments on stimulus material. In the memory task, the PrC was functionally connected to, a.o. ventrolateral prefrontal, anterior cingulate and posterior cingulate cortices, whereas in the perceptual task functional connectivity was stronger to, for instance, fusiform regions and dorsolateral prefrontal cortex (O'Neil et al., 2012). Throughout the literature, supporting evidence for a special bias of the human PrC to process item-related (object and often also face) information is reported (for reviews see e.g. Graham et al., 2010; Ranganath and Ritchey, 2012). Related to this type of information, perirhinal activity was functionally modulated when multiple types of information needed to be associated with an item, when new items were encountered, when items had to be (mostly visually) discriminated or when item-related information had to be retrieved (Awipi & Davachi, 2008; Barense et al., 2007, 2009, 2011; Bowles et al., 2010; Devlin & Price, 2007; Diana et al., 2010; Holdstock et al., 2005; A. C. H. Lee et al., 2006, 2008; Martin et al., 2015; Montaldi et al., 2006; Mundy et al., 2013; O'Neil et al., 2013; Staresina et al., 2011; Staresina & Davachi, 2008).

To briefly sum up, the PrC is engaged by complex, item-related stimulus material that entails multiple dimensions. Not only the association of attributes (e.g. an adjective associated with an item) and multisensory information (e.g. auditory, visual or tactile features of an item), but also information on the relationship to other items and item familiarity over the individual's lifetime can increase functional PrC activity in humans (Bowles et al., 2016; Duke et al., 2017; Holdstock et al., 2009; Staresina & Davachi, 2008; Taylor et al., 2006, 2009; Zeithamova et al., 2016). Again, this reflects the richness and multidimensionality of the item-related information assembled in the PrC, that can serve both, perceptual and mnemonic functions.

3.3 THE PERIRHINAL CORTEX PROCESSES SPATIAL CONTEXT AND TASK CONTINGENCIES

3.3.1 Evidence from lesion studies

Evidence for the involvement of PrC in contextual memory comes from lesion studies in rodents. Fear conditioning studies show impariments in the memorization of spatial contexts after perirhinal lesions. Bilateral perirhinal lesions reduce freezing behavior in pre-lesion conditioned spatial contexts, not however, in other types of fear conditioning (Bucci et al., 2000, 2002; Kent & Brown, 2012). Moreover, excitotoxic PrC lesions impaired item-in-location discrimination (Jo & Lee, 2010) (Jo & Lee 2010). Meanwhile, object discrimination, presumably based on simple features, remained intact (see also Bussey et al., 2001). When location discrimination was impaired following PrC lesion (as in Abe et al., 2009), these could, however, be relearned post-lesion (Abe et al., 2009). Mere location discrimination may thus not strictly depend on the PrC but rely on it under certain conditions.

The PrC only seems to represent certain spatial information. After PrC lesions, performance in allocentric tasks is largely intact (P. Liu & Bilkey, 2001; Ramos, 2013; Wiig & Bilkey, 1994), especially when delays between task acquisition and testing are relatively short (24 hours in Ramos & Vaquero, 2005). After long delays (e.g. 74 days in Ramos & Vaquero, 2005), however, retention and relearning are impaired. The PrC may thus holds representations for long-term allocentric memory. Moreover, a lesioned PrC may bias spatial processing towards egocentric navigation strategies in tasks that healthy control rats mainly used allocentric strategies to navigate to a goal (Ramos, 2017).

The PrC may facilitate allocentric strategies but to our knowledge no lesion evidence shows a necessity for the PrC in allocentric spatial navigation and memory (P. Liu & Bilkey, 2001; Ramos, 2013; Wiig & Bilkey, 1994). Lesion studies thus indicate that the PrC represents spatials contexts under certain circumstances and is recruited for some specific forms of spatial navigation.
To my knowledge, spatial processing under focal PrC lesions in humans and non-human primates has not been systematically studied to date. However, impaired scene discrimination is reported when the PrC is intact while the parahippocampal cortex, retrosplenial and hippocampus are affected by dementia-related pathology in humans (and vice versa for semantic dementia; see Graham et al., 2010 for an overview), potentially in line with the item-processing view of the PrC than the spatial processing view.

3.3.2 Evidence from functional studies

Functional evidence for spatial context coding in the rodent perirhinal cortex

A mixture of contextual and item coding was indicated in single unit recordings from the PrC in rodents. Generally, perirhinal neurons show elevated firing rates around one or multiple objects. When an item is added or moved to another location, PrC units update their activity patterns to now represent the changed item (Burke et al., 2012; Deshmukh et al., 2012). In these settings without elaborate task contingencies and in relatively simple environments, perirhinal cells display firing fields locked to objects in the environment but not to (allocentric) spatial locations. Two studies, however indicate a more complex interaction between the 'what' and 'where' streams within the PrC (Bos et al., 2017; Keene et al., 2016). Bos and colleagues showed that perirhinal neurons displayed activations and deactivations locked to the spatial segments of a maze. These neurons (72% of the PrC units) were neither affected by the performance in a visual discrimination task, nor affected by location or identity of a visual stimulus or tactile cues. Interestingly, firing field boundaries were locked to task-relevant spatial segments. Similarly, Keene et al. (2016) reported that a significant proportion of perirhinal cells differentiates between spatial contexts rather than mere objects in a context-guided olfactory association task. Different proportions of cells represented objects, spatial context or both. Thus, Keene et al. (2016) demonstrated that perirhinal neurons respond to multiple task components, whether they are item-related or contextual.

Note that spatial context modulations in the PrC have only been reported during tasks with clearly defined task contingencies where stimuli, actions and reward were spatially separated (Bos et al., 2017; Keene et al., 2016). In tasks with a simple context (e.g. foraging in an open field or spontaneous behavior), PrC neurons especially represent objects (Burke et al., 2012; Deshmukh et al., 2012). In a complex task, the perirhinal neurons are involved in segmenting the space in task-relevant chunks (Bos et al., 2017). Alternatively, PrC neurons code spatial aspects whenever the context itself is physically segmented (e.g. by doors as in Bos et al., 2017 and Keene et al., 2016 Bos et al., 2017 and Keene et al., 2016). In contrast, the most salient local features in the environments by Burke et al. (2012) and Deshmukh et al. (2012) were the objects. Thus, the degree of physical segmentation of the environment and task demands both may influence the spatial-contextual responses of PrC neurons.

Functional evidence for task contingency modulation in the animal PrC

Specific task contingencies modulate perirhinal involvement. This insight is supported by various studies using different reward schedules and task rules (Ahn & Lee, 2015; Bos et al., 2017; Kreher et al., 2019; Z. Liu & Richmond, 2000; von Linstow Roloff et al., 2016; Young et al., 1997). In the monkey, perirhinal cells represent contingent cue-outcome associations and their temporal contexts (Eradath et al., 2015). Perirhinal cell firing represented the outcome in the moment that the cue was predictive of an outcome, not however, in trials with random rewards (despite similarly previously established cue-outcome associations). Differentiation lasted from cue onset until the start of the next trial and thus resembles associative cue-outcome learning (Histed et al., 2009; Mulder et al., 2003). Even though a reversed trial sequence led to adaptation in the behavioral outcome expectation after 3 days, adaptation in the perirhinal cell representations occurred after 10 days. Presumably, perirhinal cells thus represent long-term cue-outcome associations and their temporal context (instead of mere outcome expectation; see (Kreher et al., 2019) for a similarly suggested perirhinal role in rodents).

Functional evidence for landmark and scene processing in the human perirhinal cortex

In humans, the PrC (together with other medial temporal lobe structures) appears to represent prospective goals in a spatial navigation task (T. I. Brown et al., 2016). This may also be interpreted as a type of item-related representation. Accordingly, functional evidence from a virtual reality study suggests a perirhinal role in wayfinding based on landmarks (Hartley et al., 2003). Posterior perirhinal and the human parahippocampal cortex are associated with landmark-related item processing (Martin et al., 2018). Another functional role of the PrC specifically in navigation or spatial context has, to my knowledge, not been investigated more extensively in humans at the time this manuscript was written. A clear association of the PrC with rich and complex item representations does not exclude a perirhinal involvement in any spatial processing. That said, in comparison to baseline measures, the PrC may sometimes show increased functional activity also to more spatial stimuli like scenes (Berron et al., 2018; Ross et al., 2018). If not explicitely tested for, the nature of functional imaging (especially univariate comparisons) may have masked subtle responses to PrC in specific situations. Studies with intracranial electrophysiological measures may allow to see fine-tuning of PrC neurons to spatial task components. Based on human imaging studies the PrC is biased towards item processing, while uts involvement in landmark-based wayfinding and scene processing cannot be excluded.

Nevertheless, the abovementioned results, mainly from animal studies, indicate that activity patterns from perirhinal neurons reflect more than item recognition signals or item percepts alone. Instead, the PrC supports a much broader variety of representations that seem to be dependent on the cognitive task at hand. This coheres with the attribution of a role in semantic meaning to the human PrC, as we outline in the following section.

3.4 UNITIZING ITEM-RELATED AND CONTEXTUAL PROCESSING IN THE PRC

Particularly animal literature shows that, indeed, segregated and specific item-related processing falls short for the functional behavior of the PrC. The PrC seems important in processing complex and ambiguous stimuli. Additionally, PrC neurons can represent diverse learned constructs, for instance spatial and temporal context as well as task contingencies (Ahn & Lee, 2015; Bos et al., 2017; Eradath et al., 2015; Keene et al., 2016; Z. Liu & Richmond, 2000; von Linstow Roloff et al., 2016; Young et al., 1997). Task contingencies may modulate the PrC via anatomical connectivity with motivational structures such as the ventral tegmental area, ventral striatum, amygdala and orbitofrontal cortex (see the General Introduction, Figure 2; Agster et al., 2016; McIntyre et al., 1996; Pikkarainen & Pitkänen, 2001; Witter & Groenewegen, 1986).The reciprocal functional and anatomical connections

between PrC, medial prefrontal and orbitofrontal cortex may convey information on task rules and predicted value of cues, action and context (Agster & Burwell, 2009; Burwell & Amaral, 1998a; Deacon et al., 1983; Delatour & Witter, 2002; McIntyre et al., 1996; Rusu & Pennartz, 2020; Sesack et al., 1989; Van Wingerden et al., 2010).

As I mentioned in the General Introduction and in Chapter II, there is ample cross-talk between the traditional 'item and context' routes. The PrC receives, for example, significant projections from the parahippocampal cortex, that is part of the cortical context stream (Burwell, 2000; Burwell & Amaral, 1998a, 1998b). The parahippocampal cortex projects to the medial and lateral EC, while the lateral EC also receives projections from the PrC (see Chapter II; Burwell, 2000; Burwell & Amaral, 1998a, 1998b; Doan et al., 2019; Kerr et al., 2007). Empirical evidence for the cross-talk are spatial firing patterns in the lateral EC (Connor & Knierim, 2017; Deshmukh & Knierim, 2011; Knierim et al., 2014; Neunuebel et al., 2013; Yoganarasimha et al., 2011; and see first hints in the human brain in Chpater II). In the PrC responses to spatial context (see above; Bos et al., 2017; Keene et al., 2016). Finally, ablating PrC reduces HPC place field stability across delays and reduces modulation of place cells by movement (Muir & Bilkey, 2001, 2003). Thus cross-talk within the item and context processing routes exist in the parahippocampal-hippocampal system, as also shown in the previous chapter (cf. Burwell, 2000; Nilssen et al., 2019; Van Strien et al., 2009).

In general, the PrC function is mainly related to complex, task-relevant information. Animal literature especially emphasizes a role for the PrC in the representation of complex stimuli that require an integration of various spatial-contextual features (in contrast to simple stimuli). Reconciliation of the clear findings on item-related processing but also findings of contextual processing is achieved when we built upon the proposed PrC recruitement in situations that require different features to be merged perceptually or conceptually into one entity (Bang & Brown, 2009; Bussey & Saksida, 2007; Ho & Burwell, 2014; Kent et al., 2016; Kent & Brown, 2012; Kholodar-Smith et al., 2008; Ranganath & Ritchey, 2012). This process is also called 'unitization' (Graf & Schacter, 1989). Unitization was initially attributed to the PrC in the context of fear conditioning (Kent & Brown, 2012). An emphasis on the PrC in unitization captures the conventional item-oriented nature of PrC as well as its occasionally reported responses to contextual aspects.

Conceptual considerations can explain why the PrC appears item-specific in many studies but may still integrate contextual aspects. For instance, is a house, street or neighborhood within a city considered to be contextual or do these entities constitute an 'object' in the item processing route? That means, the distinction between contextual descriptors and items is not conceptually unambiguous and rather depends on the current situation. When environments are simple, like an open field, no spatial attributes may be used to chunk the space (an unlikely scenario in the human world, though). Complex environments, however, allow to parse the space into chunks based on sensory discriminants. These spatial chunks then may be integrated and unitized into larger units, corresponding to large spatial fields (Bos et al., 2017). For instance, assemblies of buildings and landmarks can be integrated into larger units, e.g. residential blocks, or neighborhoods. When deciding in a complex task, such a process may help to reduce dimensions (Pezzulo et al., 2014). Critically, other types of information (e.g. time) can be unitized in a similar way when discrete entities share their behavioral relevance (Figure 11).

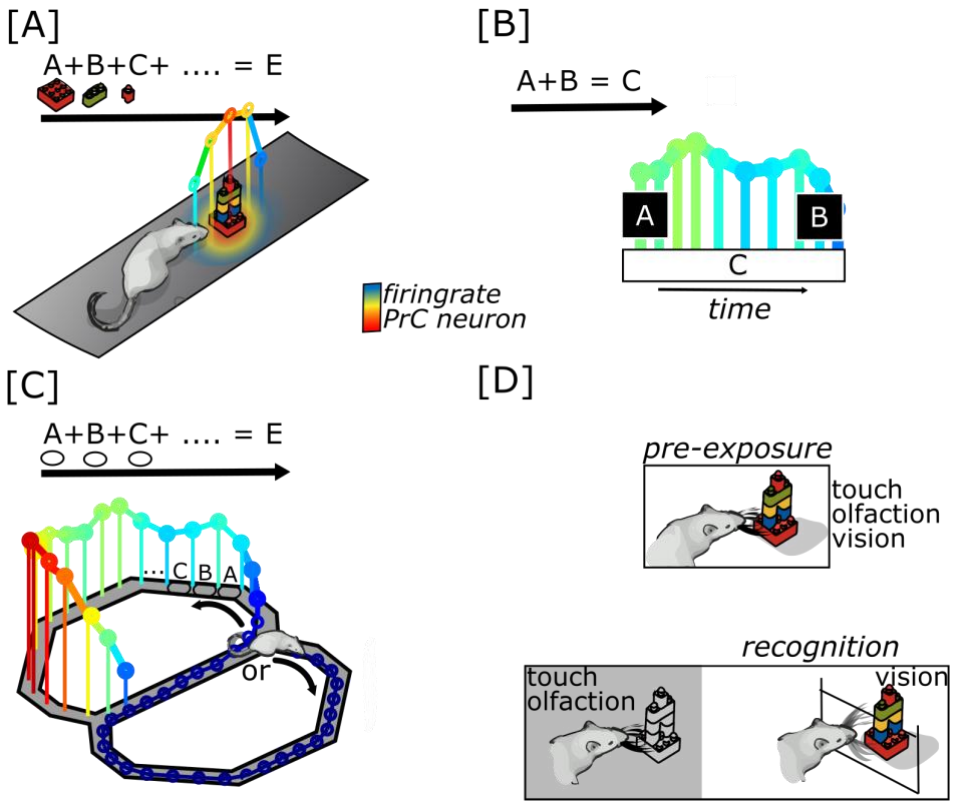

Figure 11. Different types of task-dependent unitization, proposed in the PrC. *[A] Illustration of unitized complex item-related features as reflected in rodent PrC single unit activity (Burke et al., 2012, Deshmukh et al., 2012). [B] Unitization of temporally paired associations, as reported in PrC neurons in the macaque (Fujimichi et al., 2010). [C] Illustration of spatial unitization in the rodent PrC neurons, as reflected by sustained responses for different spatial segments (Bos et al., 2017). [D] Unitization of multimodal item-related features in the rodent PrC, as indicated by a lesion study that showed how multimodal pre-exposure increases PrC requirement in later cross-modal item recognition (Jacklin et al., 2016).*

This emphasis on unitized representations in the PrC can serve to interpret results from human studies. Indeed, some fMRI and lesion studies in humans as well as the computational model by Bussey and Saksida (2007) point to the idea that feature ambiguity can be solved efficiently by unitization. Furthermore, functional activity changes in the PrC indicate unitized representations in that region (Bussey & Saksida, 2007; Cowell et al., 2006; D'Angelo et al., 2017; Delhaye et al., 2018; Fujimichi et al., 2010; Haskins et al., 2008; O'Neil et al., 2013; Rubin et al., 2013; Taylor et al., 2009). Still, directly supporting evidence is mixed. The PrC was more functionally active when unitization of words had to be carried out, e.g. in a condition where compound words had to be explicitly built versus a condition in which single words had to be entered into an associative sentence (Haskins et al., 2008). PrC damage affected performance in tasks that benefit from unitization of stimulus components (Delhaye, Bahri, et al., 2019). Furthermore, adopting a unitization strategy (i.e. encoding information by creating binding relations between elements) facilitated performance of amnesic patients with hippocampal damage in an associative memory paradigm (D'Angelo et al., 2015)). However, in another study, the unitization of visual stimuli was not directly associated with a BOLD increase in PrC activity (Staresina & Davachi, 2010). In this study, participants had to encode pictures of items. In some conditions these items were displayed as being cut into two or four pieces and arranged such that they did not appear as a coherent item because each piece was attached and tilted towards the sides of the screen. In this condition, the items needed to be visually integrated. While PrC activity parametrically increased when more item-related information was encoded, the demand of the unitization condition (e.g. whether the item was cut in multiple pieces) did not modulate perirhinal activity. The authors speculate as to whether the PrC may be involved in the unitization process itself or whether the PrC exploits other functions, drawing on unitized representations.

There may be differences between mere perceptual, imagery-based and conceptual unitization (Rubin et al., 2013; Staresina & Davachi, 2010). In Staresina and Davachi's experiment, participants needed to form perceptual units by moving the pieces of objects mentally together (i.e. using visual imagery), however, no new concept was created (see also Delhaye et al., 2019). In contrast to such unitization by imagery-from-perception, Haskins et al. (2008) required participants to unitize the meaning of two words and thereby form a novel conceptual entity (e.g. 'book' and 'worm' becomes 'bookworm'). The latter thus refers to a higher-level cognitive task that unitizes information by attributing (novel) meaning. Presumably, the human PrC is specifically involved in the latter. Indeed, human fMRI studies on the PrC stress its particular involvement when semantic meaning is relevant (for a related conceptual model see Miyashita, 2019). Specifically, the medial human PrC (segmented following Taylor & Probst, 2008; but note Berron et al., 2017; S.-L. L. Ding & Van Hoesen, 2010) may help to dissociate confusable objects, e.g. objects that share perceptual features but also meanings (Kivisaari et al., 2012). These results align with numerous human data indicating a PrC function in semantic cognition. Conceptual learning, semantic processing and semantic priming have been associated with perirhinal functional activity and perirhinal damage leads to an inability in making fine semantic discriminations (Bowles et al., 2016; Bruffaerts et al., 2013; Clarke & Tyler, 2014, 2015; Dew & Cabeza, 2013; Kivisaari et al., 2012; Ranganath & Ritchey, 2012; Taylor et al., 2006; Tyler et al., 2004; W.-C. Wang et al., 2014; Wright et al., 2015). For example, Bruffaerts et al. (2013) presented words that were previously clustered semantically and whose semantic distances were determined. Interestingly, when analyzing multivariate representational similarities of the fMRI voxel patterns evoked by presented words, the PrC reflected the semantic distances. That is, words with a more distinct meaning were associated with a multivoxel activity pattern that was likewise more distinct and vice versa. This ability to make semantic discriminations is compromised by perirhinal damage and related to perirhinal functional activity in healthy humans (Tyler et al., 2004). Moreover, prior exposition to a semantically similar word usually improves performance on a memory task that uses conceptual retrieval cues ("conceptual priming"). Conceptual priming is impaired by extended medial temporal lobe lesions that incorporate the perirhinal and, in healthy participants, conceptual priming is associated with an increase in perirhinal activity (W.-C. Wang et al., 2010, 2014). These human data add to a perirhinal function in unitization, suggesting a multidimensional role in integrating conceptual information attributed to encountered objects.

3.5 DISCUSSION

Across species, evidence relates the PrC to item recognition and familiarity but also to the unitization of more diverse types of task-relevant information. The extent and precise conditions of PrC contributions to various types of conjunction are, however, still unclear. Different task demands may have led to diverse results in the PrC literature. Bos et al. (2017), for instance, found item-related responses and the previously reported spatial responses, sometimes even in the same neuron. The extent towards which the PrC processes item-related information merged with contextual aspects may thus depend on the task at hand. This matches a more general role in representing unitized meaningful entities. Another complication for our understanding of PrC functionality is the region's heterogeneity and thus differences between targeted PrC subregions, or, in human fMRI, to averaging over subdivisions. Differences in functional and anatomical connectivity profiles between Brodmann Area 36 and 35 have been described in rodents and monkeys (Burwell, 2001; Burwell et al., 1995; Burwell & Amaral, 1998a, 1998b; Deacon et al., 1983; Furtak et al., 2007). In fact, Fujimichi et al. (2010) reported an increasing strengthened integration of two paired visual stimuli when going up the cortical hierarchy of the macaque PrC, leading from Area 36 to Area 35. Hints for a functional gradient also exist in humans (Kafkas et al., 2017; Liang et al., 2013; Litman et al., 2009; Zhuo et al., 2016).

Future studies on human PrC function will benefit from recent methodological advances in high resolution imaging that allow to segment the structure with a fundamentally higher level of detail and to delineate PrC subregions (Berron et al., 2017).

An intriguing mechanism that may draw on unitized representations is the proposed function of the PrC as an "inhibitory wall" that regulates the information flow between the neocortex and hippocampus (Biella et al., 2001, 2002; De Curtis & Paré, 2004; Martina et al., 2001; Nilssen et al., 2019; Pelletier et al., 2004; Willems et al., 2016). That means, information may only flow from PrC to the lateral EC and hippocampus when convergent input from different distant regions reduces local inhibition in the PrC (De Curtis & Paré, 2004; Unal et al., 2012). This gating pattern may facilitate task-dependent integrative functions of the PrC across information types. To select which task-relevant information is transferred to the hippocampal system, a gating system such as PrC needs information on, for instance, which elements from the sensorium belong together and are collectively predictive of outcome (e.g. reward) and which do not. In that sense, task-relevant mnemonic gating without any form of unitization seems difficult to realize. The interactions between gating and execution of unitizing operations in PrC remain to be investigated, as well as how PrC gating and firing may depend on hippocampal feedback, which in behaving animals may be expressed in phase locking of PrC neurons to the hippocampal theta rhythm (Ahn et al., 2019; Bos et al., 2017).

Two hypotheses may explain the mechansims of unitized represenations in the PrC. First, as I layed out in the General Introduction, the recurrent networks in the hippocampus are thought to implement pattern completion (e.g. in area CA3 as I show in the Chapter IV of this thesis; Grande et al., 2019; Hopfield, 1982; K. Nakazawa et al., 2002; Treves & Rolls, 1992). Representations in the hippocampal system may become conjunctive, simple, amodal patterns that can be fully retrieved upon partial cue information. Reinstated conjunctive hippocampal representations (via pattern completion) may flow downstream towards lateral EC and PrC and, via big-loop recurreny, multiple simple representations may be merged into more complex ones. Second, unitization can be an extended form of predictive processing. Hence the reciprocal interaction of lower sensory cortices with higher areas to generate predictions about the causes of sensory input (Friston, 2005; Pennartz et al., 2019; Rao & Ballard, 1999). Higher sensory areas may interact with PrC and other parahippocampal structures to integrate low-level predictions into high-level representations that combine features within and across modalities (Olcese et al., 2018; Struckmeier et al., 2019). These unitized representations can influence, and are influenced by more agnostic, conceptual hippocampal representations (Buzsáki & Moser, 2013; O'Keefe & Dostrovsky, 1971; Pennartz, 2015; Quiroga, 2012). Clearly, these two computational hypotheses are not mutually exclusive. In combination with the "gating" function of the PrC, we hypothesize that unitized representations in the PrC are evoked and reinstated when sufficient bottom-up sensory evidence comes in through lower-level cortical areas. The completion to a unitized pattern then may act as a prerequisite for further information flow towards the hippocampal circuitry. These computational hypotheses will require further development by multi-area computational modelling as well as empirical testing.

In conclusion, the rodent iterature indicates an item-related processing bias under no task demands while also emphasizing the representation of context information and task contingencies studies. Non-human primates support a perirhinal role in representing sensory information that is unitized into meaningful perceptual and conceptual entities (cf. feature ambiguity tasks and representations of stimulus-outcome pairings). Finally, human studies underline a perirhinal role in representing unitized items based on related semantics. Thus, empirical evidence across species and paradigms strongly suggest that the PrC represents different types of item-related information, including contextual aspects, in unitized entities.

CHAPTER IV

ACCESSING DISTRIBUTED CORTICAL REPRESENTATIONS INVOLVES HIPPOCAMPAL CA3

IV. REINSTATING DISTRIBUTED CORTICAL REPRESENTATIONS VIA PATTERN COMPLETION INVOLVES HIPPOCAMPAL CA3

The previous two chapters addressed the organization of memory representations in the parahippocampal-hippocampal system. Here now, I focus on the access and reinstatement of distributed cortical representations for holistic recollection. Accessing memory representations is thought to be driven by a pattern completion mechanism that often has been associated with hippocampal subregion CA3, however lacking empirical support in humans. In this chapter of the thesis, I investigate how episodic recollection emerges from the architecture of the hippocampal circuitry, more specific how hippocampal subregion CA3 relates to pattern completion mechanisms. This Chapter IV has been published in the *Journal of Neuroscience* (Grande et al., 2019) and with minor edits, I integrated the manuscript into the current thesis.

4.1 INTRODUCTION

As mentioned before, episodic memories bind multiple elements into a cohesive representation. Later recollection may be triggered by any one of these elements. Asked, for example, about whether we had been to a certain restaurant before, we may recall meeting a friend there lately. Remarkably, the "restaurant" cue may even initiate *holistic* recollection: Another guest's dog or the piano in the restaurant may come to our mind. Holistic recollection thus refers to comprehensive recall of the elements an event encompasses, even though incidental to the current situation (Tulving, 1983).

Successful pattern completion is considered a prerequisite for such holistic recollection. The cue information needs to be completed towards the whole event to produce comprehensive recall (Marr, 1971; McClelland et al., 1995; Treves & Rolls, 1994). As indicated in the General Introduction, a corresponding feature of recollective experiences is the reinstatement of the encoding-related cortical activity (Bosch et al., 2014; Gordon et al., 2014; Liang & Preston, 2017; Staresina et al., 2012, 2013). Cortical reinstatement of incidentally recalled event elements is related to functional activity in the hippocampus (Horner et al., 2015). However, the spatial resolution in that study was not sufficient to dissect the specific involvement of hippocampal subregions.

Anatomically inspired computational and theoretical models attribute different information processing mechanisms to different hippocampal subregions, as I introduced in Chapter I. Unique recurrent collaterals in subregion CA3 provide an effective condition for the implementation of pattern completion (Marr, 1971; Treves & Rolls, 1991). Consequently, computational models suggest subregion CA3 to guide the incidental recall of additional event elements based on pattern completion (McClelland et al., 1995; Treves & Rolls, 1994).

The empirical support for the functional role of CA3 in pattern completion mainly originates from animal research (Fellini et al., 2009; Gold & Kesner, 2005; I. Lee & Kesner, 2004; K. Nakazawa et al., 2002; Neunuebel & Knierim, 2014; Vazdarjanova & Guzowski, 2004). For long the resolution of human fMRI did not allow to separate subregion CA3 from DG. Therefore, most fMRI studies indiscriminately attribute pattern completion to human subregion CA3/DG (J. Chen et al., 2011; Dimsdale-Zucker et al., 2018; Dudukovic et al., 2011; Hindy et al., 2016; Newmark et al., 2013; Schapiro et al., 2012). Solely Bonnici et al. (2012) and also Chadwick et al. (2014) demonstrated a generalization function selectively in CA3. Evidence for explicit functional engagement of (the human) CA3 in holistic recollection and thus mnemonic pattern completion is still pending.

Here, I aim to provide first empirical evidence at the hippocampal subregion level for the functional underpinnings of holistic recollection via pattern completion in humans using ultra-high field fMRI

data at 7 Tesla. I used the same task as Horner and colleagues (2015) during which multi-element events were learned as overlapping pairs of associations between elements (places, people and objects), and subsequently retrieved as paired associations. This task allowed me to assess holistic recollection in terms of neural activity. That is, I measured the extent of incidental retrieval of event elements that were neither the cue nor target of retrieval in terms of regional activity during retrieval corresponding to the nontarget element category (e.g. place, people or object). Fully overlapping associations (closed-loops), which appear to create coherent, whole events with holistic recollection, were compared with partially overlapping associations (open-loops), see Horner et al. (2015) for details. I hypothesized that cortical reinstatement of incidental elements during holistic recollection would be associated with activity in hippocampal subregion CA3 but not DG.

4.2 METHODS

4.2.1 Participants

In total, 30 participants (12 female, mean (standard deviation) age: 27 (4)) were recruited from the campus of Otto-von-Guericke University Magdeburg and the Leibniz Institute for Neurobiology Magdeburg. All participants reported to be right-handed and without any neurological or psychiatric illness. If necessary, vision was corrected to normal. Minimum educational level of all participants was the German Abitur (A-level). The participants received an allowance of 30 €. The study was approved by the local Ethics Committee of the Otto-von-Guericke University Magdeburg.

4.2.2 Materials and Procedure

Regarding materials and procedure I followed Horner et al.'s, (2015) set up closely. In the following sections the main features of the design are outlined and adjustments that were necessary are specified.

Materials

Stimuli consisted of written words that belonged to four categories: locations (e.g. kitchen), objects (e.g. hammer), animals (e.g. mouse) and famous people (e.g. Obama). The words were taken from Horner et al. (2015) and translated into German. To assure a similar level of familiarity within the German sample, several people-stimuli were changed based on preceding behavioral pilot results. In total, 36 events were created by associating one example out of each category with another. Initially, four event sets were built and randomized across participants. For each participant, 18 events were assigned randomly to consist of four categories (location – object – people – animal). These events will be referred to as open-loop structure events in the following. The remaining 18 events consisted of three categories. Within these closed-loop structure events, 9 events were randomly selected to encompass the categories location – object – people and 9 events to encompass the categories location – animal – people.

Words were presented in white font on a black background to the center of a screen (font size = 30) and via a mirror mounted on the head coil, participants could watch the projected screen with a visual angle of +/- 3° x +/- 2 °.

Task Procedure

Prior to the scanning session, participants received task instructions. The task was described as an associative learning paradigm. They were told to imagine each displayed associative word pair together in one scene as vividly as possible. Importantly, the underlying associative event structure of the stimuli was not revealed and remained implicit.

During the scanned encoding phase, participants learned the 36 events in a pair-wise associative manner. The encoding phase consisted of three blocks with 36 trials each, adding up to a total of 108 encoding trials. In each block, one associative pair of each event was presented for 6 seconds (e.g. kitchen – hammer out of the event kitchen – hammer – Obama – dog, Figure 12 [C]). Following that procedure, one element within an event overlapped between the first and the second encoding block. At the third block, some events remained as an associative chain and followed an "open-loop" event structure (Figure 12 [B]). Thus, in the last encoding block, the third associative pair from these events overlapped again with one element from previously encoded associates of the respective event (AB – BC – CD). In contrast, "closed-loop" events were structured such that at the last encoding block both elements of the currently encoded associate overlapped with previously encoded elements from the respective event (AB – BC – CA; Figure 12 [A]).

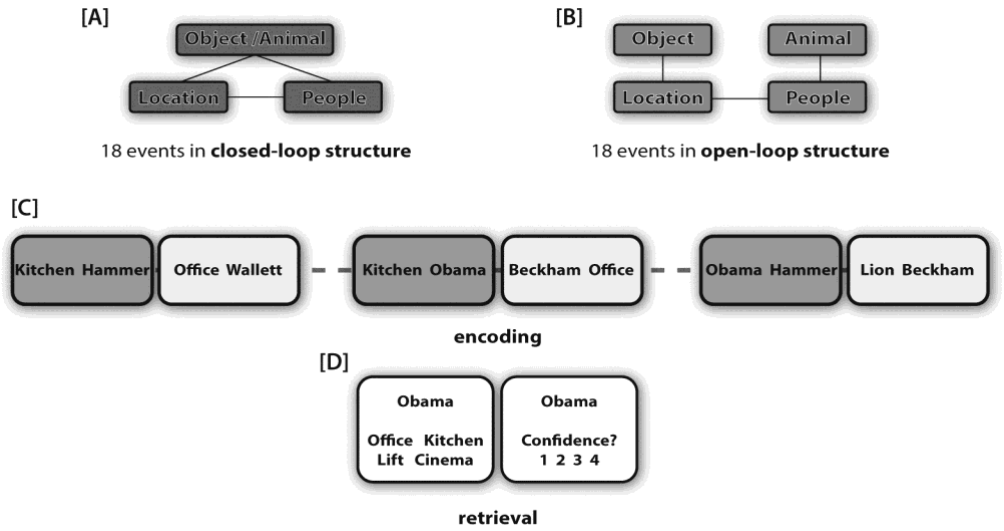

Figure 12. Multi-element event paradigm. *Participants learned 36 events that consisted of multiple elements, with each element belonging to the location, people or object/animal category. All events followed either a closed-loop structure [A] or an open-loop structure [B]. [C] At encoding, events were learned in three blocks in a pairwise associative manner, one associative pair at each block. [D] At retrieval, all three pairwise associations within each event were tested bidirectionally. The 4-alternative forced choice recognition trial was followed by a confidence rating.*

The specific category pairing at each block was randomized. However, the third encoding block was restricted to a location – object/animal or a people – object/animal category pair. Further details about the randomization procedure can be found in Horner et al. (2015). No responses were required by the participants. The interstimulus interval was 1500 ms and each encoding trial was initiated with a fixation cross of 500 ms.

The scanned retrieval phase followed encoding immediately. Here, each pairwise association within an event was tested. This yielded 6 retrieval trials per event and 215 retrieval trials in total. The 6 retrieval trials were distributed over 6 blocks. During each block one associative pair from each event was tested - each pair bidirectionally. On each trial, participants were cued with one element from an event and instructed to retrieve an associated element by means of a 4-alternative forced choice recognition procedure (Figure 12 [D]). The displayed lures belonged to the same category as the target but were taken from other encoded events. Cue and response options were presented until a response was made but with a maximum of 6 seconds. See Horner et al., 2015 for further details on the randomization procedure at retrieval. Each retrieval trial was followed by a 1 – 4 confidence rating for 6 seconds. The interstimulus interval was 1500 ms and each retrieval trial was initiated with a 500 ms fixation cross.

A debriefing phase of approximately 30 min immediately followed the scanning session. More details regarding the administered questions can be found in Horner et al. (2015).

Scanning procedure

The scanning was performed with a 7 Tesla MRI Siemens machine. A 32-channel head coil was used. Participants received earplugs and ear defenders to protect against noise. Prior to functional data acquisition, structural images were acquired. First, a whole-brain T1-weighted volume was obtained (TR = 2300 ms; TE = 2.73 ms; flip angle = 5°; resolution = 0.8 mm isotropic; matrix size = 320 x 320). Second, a partial high-resolution T2-weighted volume was acquired with an orientation aligned orthogonally to the hippocampal main axis (TR = 8000 ms; TE = 76 ms; slice thickness = 1 mm with 1.1 mm slice spacing; in-plane resolution = 0.4375 mm x 0.4375 mm; 55 coronal slices; FOV = 256 mm x 256 mm; matrix size = 512 x 512).

Succeeding the structural data acquisition, two runs of functional data were obtained. Both runs consisted of T2*-weighted EPIs, oriented in parallel to the hippocampal long axis (28 axial slices; TR = 2000 ms; TE = 22ms; matrix size 1536 x 1536; FOV = 256mm x 256 mm; resolution= 0.8 mm, odd-even interleaved slice acquisition). First, functional data regarding the encoding phase was obtained (440 volumes). Second, the functional data regarding the retrieval phase was obtained (approximately 700 volumes, depending on response times). Responses were recorded using a scanner-compatible 4-choice button box. The complete scanning procedure took approximately 80 min.

The functional data was distortion corrected by means of a point spread function (Zaitsev et al., 2004) and online motion corrected during image reconstruction.

4.2.3 Behavioral data analyses

The overall accuracy per participant was calculated as the percentage of correct retrieval trials. Note that there are 6 retrieval trials for each of the 36 events. I calculated accuracy separately for closed- and open-loop events. With a paired samples t-test, I tested for significant differences in performance between loop conditions (closed- versus open-loop events). I also evaluated the amount of retrieval dependency among the elements within an event, separately for closed- and open-loop events. This measure reflects the likelihood that an element is successfully retrieved, given successful retrieval of the other elements that belong to the same event. The dependency measures were calculated by means of participant-specific contingency tables. In total, six contingency table were created per participant, one for each category (location (A), people (B), object (C)) being either cue or target. The cue-based tables reflect the retrieval dependency of two elements from the same event across separate retrieval trials, given the trials used the same cue element from the respective event (AbAc). The target-based tables reflect the retrieval dependency of the same target element across separate retrieval trials, given the trials used different cue elements belonging to the same event (BaCa). Each table's cells contain the retrieval performance across events for the respective condition. The dependency measure based on observed data is defined as the proportion of events for which both overlapping associations related to a common element (either being cue or target) are retrieved successfully or unsuccessfully.

To assess the dependency measures from the data, I compared them with both a model that assumes full retrieval dependency, and a model that assumes full retrieval independency among all elements of an event. The expected dependency based on the independent model was estimated by multiplying the probabilities of separately retrieving either of the two items of an event within the contingency tables. The dependent model is based on the independent model but estimates the expected dependency by accounting for the level of guessing and inserting an "episodic factor". This

"episodic factor" weights the performance for a certain event by a factor that captures the difference between the respective event's performance across separate retrieval trials versus general performance across all events. Note, that the measure of observed dependency scales with accuracy. Therefore, only comparisons between observed dependency measures and model-based expected dependency values are informative. Comparisons between dependency measures were made using paired-samples t-tests for both event structure conditions (open-loop and closed-loop), separately. For further details on the calculation of dependency measures based on the data and based on the two models, see Horner et al. (2015) and Horner & Burgess (2013).

To gain an impression of dependency differences that might be masked due to high accuracy levels in both loop conditions (88.55% and 86.27% for closed- and open-loop, respectively), the confidence level was taken into account. Dependency measures were evaluated in the above described manner. However, instead of calculating dependency measures based on contingency tables that refer to correct versus incorrect retrieval, now the contingency tables were refined to reflect high confidence (score 4 or 3) versus low confidence (score 1 or 2) or incorrect retrieval. Statistical comparisons between dependency scores in different event loop conditions were made with paired-samples t-test. As indicated above, these comparisons involve the differences in observed dependency and expected dependency based on the independent model in respective conditions.

4.2.4 Functional data analyses

Preprocessing

All preprocessing steps were performed with SPM12 ((Penny et al., 2011). The raw functional data was distortion and motion corrected already (see fMRI acquisition). First, the raw data was converted from DICOM into NifTi format. Second, slice timing correction was applied and the data was smoothed with a full-width half-maximum Gaussian kernel of 2x2x2 mm. The size of the kernel was chosen based on previous reports to preserve high specificity but increase sensitivity at the same time (Berron et al., 2016; Maass et al., 2015).

Outliers based on motion (threshold 2 mm) or global signal (threshold 9.0) were detected by the ARTifact detection Tool software package (Mozes & Whitfield-Gabrieli, 2011). The fully preprocessed data was used for outlier detection. The procedure resulted in a vector for each participant that indicated outlier scans. They were entered as separate regressors into all univariate analyses (see below).

Structural template calculation (T1 weighted)

To calculate and visualize functional analyses results on group level, a sample-specific template was created for the T1-weighted structural volumes. This assures optimal alignment of the functional data across participant (Avants et al., 2011). I used the nonlinear diffeomorphic mapping procedure called "buildtemplateparallel.sh" provided by Advanced Normalization Tools (ANTS) to construct a T1-template based on the 30 whole-brain T1-weighted volumes obtained from all participants (Avants et al., 2010).

Hippocampal segmentation

The current study aimed to examine specific functional activity patterns in the hippocampus. Thus, I restricted several functional analyses (indicated below) to hippocampal regions of interest (ROI). Using ITK-SNAP (Yushkevich et al., 2006) I manually segmented the bilateral hippocampus in all 30 participants on their specific T2-weighted structural volume. Therein I followed the segmentation protocol by Berron et al. (2017). This yielded participant-specific masks for hippocampal subregions CA1, CA2, CA3, Subiculum and DG, one for each hemisphere.

To use these masks as anatomical regions of interests in the functional analyses, each participant-specific T2-weighted hippocampal subregion mask was coregistered to the participant's EPI-space and resampled to the EPI-resolution. This was accomplished in two steps. First, SPM12 was used to coregister and resample the T2-weighted hippocampal subregions masks to the individual T1 space by applying "spm_coreg" (Penny et al., 2011). Second, these masks where coregistered from the individual T1 space to the EPI space using FSL flirt (Greve & Fischl, 2009; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001).

All masks were divided in an anterior and a posterior part. To that end, the main hippocampal extension in each hemisphere was defined for each individual by taking the outer parts of the z-dimension. All hippocampal subregions of that participant within that hemisphere were split in two at the border identified by half the length of the total hippocampus in z direction.

General functional analyses approach

All functional analyses were performed with SPM12 (Penny et al., 2011) on single participant and group level.

Functional analysis at the participant level. At the first level, a general linear model was fit to each participant's functional data in native space. Therefore, the underlying neural data was modelled by a boxcar function at stimulus onset for each condition of interest (dependent on the respective analysis). The resulting neural model was convolved by a canonical hemodynamic response function to predict the functional data. Besides the regressors predicting the functional data related to each condition of interest, each general linear model also included one intercept regressor and six motion correction parameters as regressor of no interest. The motion-correction parameters were added to capture variability related to task-correlated motion and reduce the amount of false-positive activity in task conditions (Johnstone et al., 2006). If applicable, a regressor of no interest was added to capture variance in the functional data related to the outlier scans. Each general linear model was fit to the acquired functional data to obtain parameter estimates for each condition of interest. To examine differences in BOLD activity related to the conditions of interest, contrast maps were calculated for each participant in native space (specific contrasts dependent on respective analysis).

Normalization. To be able to assess consistent contrast effects at group level, I normalized each participant's contrast maps to the group T1 template. Therefore, I first normalized each participant's mean functional EPI to the participant's structural T1 image and then to the T1 group template by using FSL "epi_reg" (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001) and ANTS "WarpImageMultiTransform.sh" respectively (Avants et al., 2010, 2011). This procedure resulted in participant-specific transformation matrices that could then be used for the spatial normalization of the contrast maps.

Second level group analyses. For group analyses, I assessed consistent differences in functional activity across participants. Therefore, the spatially normalized contrast maps from each participant were entered into a general linear model using SPM12 (Penny et al., 2011). Unless stated otherwise, group results are reported with an initial cluster defining threshold of $p < .005$.

Functional analyses in detail

Two participants were excluded from all functional analyses due to an amount of outlier scans exceeding 10 % of the total scans at retrieval. Outliers were determined by excessive motion (threshold 2 mm) or global signal changes (threshold 9.0). In addition, all ROI analyses within hippocampal subregions were conducted with one participant less due to motion in the T2 image of that participant which made hippocampal subregion segmentation impossible.

For all analyses the object and animal conditions were merged (see Horner et al., 2015). Note, that I did not see any specific functional activity for animals in the 'retrieval phase – element specific activity' analysis (see below). When lowering the threshold ($p < .005$, uncorrected), however, functional clusters were comparable to the object condition (in lateral occipital cortex). As I did not see qualitative differences in functional activity, I collapsed object and animal conditions to assure comparability of results with Horner et al. (2015). The animal and the object condition will both be referred to as the object category in the following.

Retrieval phase – element specific activity. To examine significant clusters of functional activity related to specific categories of event elements, I set up a general linear model with 7 regressors of interest. Each regressor included the boxcar convolved stimulus onsets for one type of cue-target association (location – object; object – location; object – people; people – object; people – location; location – people). Each trial duration was determined by the response time. An additional regressor was included that modelled the interstimulus interval with a duration of 1.5 seconds. To assess differences in functional activity related to the three element categories, contrast maps were obtained between the parameter estimates related to the regressors that contained the respective category and those that did not contain the respective category. For instance, to obtain location related clusters of significant functional activity, I contrasted the parameter estimates obtained for the location-object, object-location, location-people and people-location regressors with the parameter estimates for the object-people and people-object regressors.

To examine consistent clusters of significant functional activity at group level, the normalized contrast maps were entered into a one sample t-test on second level. All results are reported with family-wise error correction after applying an initial cluster defining threshold of $p < .001$.

Cortical reinstatement at retrieval. Here, we initially evaluated whether the function an element occupies at retrieval (cue, target or nontarget) entails differences in the overall amount of cortical reinstatement. Subsequently, differences in cortical reinstatement of cues, targets and nontargets between closed- and open-loop events were explored.

To begin with, the amount of cortical reinstatement was assessed for each function an element could take (cue, target and nontarget), across event loop conditions. This yielded an overall cortical reinstatement score per element function and participant (Figure 13 [A]). Based on the previous analysis (retrieval phase - element specific activity) we obtained a significant cortical functional cluster for each category (location, people and object) at the group level (Figure 13 [A](ii)). In the case of multiple significant functional clusters, I focused on the element-specific ROI that was identified by Horner et al. (2015) to assure comparability of results (note that we obtained comparable results when using all our identified clusters). The corresponding functional masks were coregistered to each participant's native space with FSL flirt (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001). Using REX toolbox (Whitfield-Gabrieli, 2009), I then extracted participant-specific parameter estimates for each regressor of interest in the element specific activity analysis out of each element-specific ROI. Parameter estimates within each ROI were z-standardized. To obtain a participant specific value for the amount of cortical reinstatement related to each element function, I took the parameter estimates out of each ROI, first for the condition that the respective ROI was related to the category of the cue ("cue cortical reinstatement"), second for the condition that the respective ROI was related to the category of the target ("target cortical reinstatement"), and third for the condition that the respective ROI was neither related to the category of the cue or the target but only related to the nontarget category ("nontarget cortical reinstatement", Figure 3 [A]). For instance, the previous analysis (element-specific activity at retrieval) found a significant cluster of increased functional activity in the parahippocampal cortex for location category stimuli. Now, I took

the parameter estimate regarding the people-object and object-people condition out of the parahippocampal cortex to obtain a measure for the nontarget cortical reinstatement for when the location was nontarget. Similarly, I proceeded for the remaining two categories (people, object) to obtain nontarget cortical reinstatement values for each category. The normalized parameter estimates were averaged across ROIs (i.e. categories) for each participant, separately for cue, target and nontarget cortical reinstatement (Figure 13 [A](iii)). Differences in the amount of overall cortical reinstatement between element functions (cue, target, nontarget) were tested using a repeated measures ANOVA.

To further explore the differences in cortical reinstatement between closed- and open-loop events, I then evaluated cortical functional activity for both event loop conditions. To compare cortical reinstatement between event loop conditions, I had to delineate functional cortical activity for closed- and open-loop events. Therefore, the above described univariate analysis (element-specific activity at retrieval) was performed again. Instead of 7 regressors of interest, 14 were created, they contained the same information as the 7 in the analysis before, now split up into trials that belonged to closed-loop and open-loop events. Then, the same procedure was followed as described above to acquire element-related cortical activity values for cue, target and nontargets per participant. Now however, calculated for closed-loop events and open-loop events separately. Subsequently, obtained difference scores for cortical reinstatement between event loop conditions were tested for significant deviation from zero by using one-sample t-tests to assess whether cortical reinstatement was higher in closed-loop events.

Hippocampal activity and cortical reinstatement. The following analyses were aimed to identify activity clusters in the hippocampus that functionally relate to holistic recollection and to delineate their subregion-specific localization. As holistic recollection is conceptualized to be measurable by the amount of nontarget cortical reinstatement, I assessed hippocampal functional correlates of increased nontarget cortical reinstatement in closed-loop events.

First, I followed an exploratory parametric analysis approach to assess whether any hippocampal cluster correlates with nontarget cortical reinstatement under conditions of increased holistic recollection. Therefore, initially a univariate first level analysis was performed. The general linear model encompassed three regressors of interest. One contained the boxcar function convolved stimulus onsets for trials that are part of closed-loop events (duration equaled response time). The second regressor contained the boxcar function convolved stimulus onsets for trials that belong to open-loop events (duration equaled response time). The third regressor contained the boxcar convolved onsets of the inter stimulus intervals (duration 1.5 seconds). Contrast maps were obtained for each participant for closed-loop versus open-loop event retrieval trials.

To investigate hippocampal involvement in holistic recollection, that is particularly the cortical reinstatement of nontargets, I used the first level contrast maps that indicated for each individual where in the hippocampus BOLD activity was greater for closed-loop than open-loop event retrieval (Figure 13 [B]). With the second level group analysis, I investigated which of the functional activity clusters that related to closed-loop retrieval correlate with the amount of nontarget cortical reinstatement across participants (Figure 13 [B]). To assess the functional specificity of the revealed significant cluster at nontarget cortical reinstatement, the second level group analysis was performed two more times, additionally for cue cortical reinstatement and target cortical reinstatement. Each general linear model included the normalized contrast maps for the contrast closed > open-loop retrieval of each participant as a first regressor. The second regressor included the respective participant-specific value for cue, target or nontarget reinstatement, obtained by the independent analysis of element-category related cortical activity at retrieval (Figure 13 [A]). All results are

reported with an initial cluster defining threshold of $p < .005$. Small volume correction with a bilateral hippocampal mask was applied at second level.

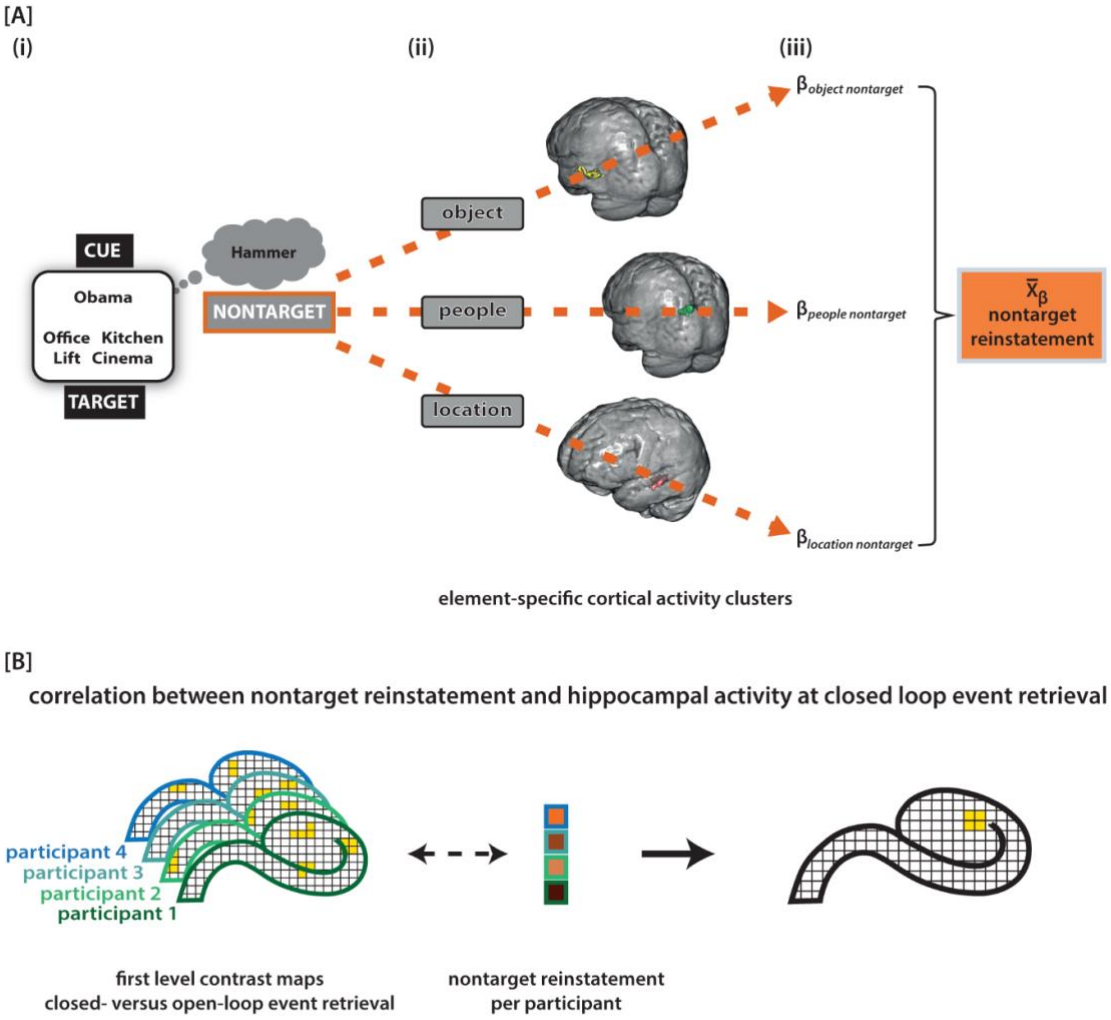

Figure 13. Overview "hippocampal activity – nontarget reinstatement" analysis procedure. *[A] Calculation of participant-specific nontarget reinstatement values. At each retrieval trial one event element served as a cue and one is the target. The additional element remained incidental to that task trial - that is the nontarget (i). From the previous "element-specific activity at retrieval" analysis, cortical clusters have been identified that specifically relate to the respective element categories (i.e. PhC for location, MPC for people, LOC for object) (ii). For each participant, beta values are extracted from the respective cluster for the condition that the category's function at retrieval is to be a nontarget (iii). Z-standardized beta values are averaged subsequently to obtain an overall nontarget reinstatement value per participant. [B] Correlations between nontarget cortical reinstatement and hippocampal activity. With a univariate first level GLM analysis, participant-specific contrast maps are obtained that indicate the difference in hippocampal activity between the closed- and open-loop retrieval condition. At group level that hippocampal activity pattern was correlated with the participant specific nontarget reinstatement values. This yielded a statistical map, indicating hippocampal activity at closed-loop retrieval that was scaled by the amount of nontarget reinstatement across participants. PhC – parahippocampal cortex; MPC – medial parietal cortex; LOC – lateral occipital cortex; GLM – general linear model.*

To assess whether the identified hippocampal cluster correlated more with nontarget cortical reinstatement than with cue or target reinstatement, participant-specific mean functional activity was extracted from the respective cluster for the contrast closed > open-loop retrieval with REX (Whitfield-Gabrieli, 2009). Pearson correlation coefficients for each cortical reinstatement type (cue,

target and nontarget) with the extracted functional cluster activity were obtained. With a one-tailed z-test I tested whether the obtained Pearson correlation coefficients were significantly higher for nontarget reinstatement than for cue and target reinstatement respectively (Diedenhofen & Musch, 2015; Rosenthal et al., 1992).

The clusters identified by the above described analyses can only be attributed to a specific subregion by visual inspection. As they were considered to be located close to the right anterior CA3-DG border, a subsequent ROI analysis was performed to delineate functional involvement of CA3 versus DG. Therefore, mean beta values from the first level analyses were extracted using REX (Whitfield-Gabrieli, 2009) for each individual out of the manually segmented hippocampal subregions masks for right anterior CA3 and right anterior DG. Beta values were extracted referring to the closed-loop regressor and to the open-loop regressor. Pearson correlation coefficients and corresponding significance values were obtained for the relationship between the difference in beta values (closed- versus open-loop) and the amount of nontarget reinstatement across participants. With a one-tailed z-test I tested whether the obtained Pearson correlation coefficient was significantly higher for right anterior CA3 than right anterior DG (Diedenhofen & Musch, 2015; Rosenthal et al., 1992).

4.3 RESULTS

4.3.1 Behavioral results

On average 87.41% (SD = 9.78%) of all trials in the recall phase were answered correctly by the 30 participants. There was no significant difference in accuracy between closed-loop (mean = 88.55%, SD = 8.96%) and open-loop events (mean = 86.27%, SD = 10.60%).

Also I investigated the amount of dependency among event elements. Note, that the dependency measure I calculated scales with accuracy. Therefore, the evidence for dependency is defined as the difference between data-based dependency and the expected dependency based on the independent model. The evidence for dependency is not significantly higher for closed- than open-loop events ($t(29) = 1.162$; $p = .255$). The higher the overall accuracy, the more dependency values approach 1 (also see Horner et al., 2015). The very high accuracy may thus have led to ceiling levels in the estimated dependency measures, making it impossible to detect differences between open- and closed-loop event dependency.

To test whether the high overall accuracy may have obscured stronger dependency among closed-loop elements, we calculated dependency again by taking the confidence level into account. That is, instead of classifying the retrieval trials by correct versus incorrect, I split them into high and low confidence trials and collapsed incorrect and low confidence trials. The evidence for dependency is not significantly different between loop conditions ($t(29) = 1.978$; $p = .058$). However, open-loop events but not closed-loop events showed significantly lower dependency than the dependent model ($t(29) = -2.59$; $p = .015$ and $t(29) = -1.47$; $p = .152$). In general, the results are consistent with previous results (Horner et al., 2014; Horner et al., 2015). That is, retrieval at closed-loop events entails more dependency among event elements than retrieval at open-loop events.

4.3.2 Univariate results

Element-specific cortical activity at retrieval

The aim of this analysis was to identify element-specific cortical functional activity patterns at retrieval. Therefore, category associations that contained a respective element were contrasted with category associations that did not contain the respective element (e.g. identify location activity by contrasting location – object and location – people with people – object trials).

People-related activity was found in the medial parietal lobe (cluster size k = 1172, $p < .001$, see Figure 13 [A](i)), in a left inferior temporal cluster (cluster size k = 103, $p = .006$) and in a right lateral parietal cluster (cluster size k = 126, $p = .001$). Object-related activity was found in the left lateral occipital lobe (separated into three clusters, first cluster size k = 864, $p < .001$, see Figure 13 [A](i); second cluster size k = 101, $p = .006$, third cluster size k = 75, $p = .041$). Location-related activity was found in bilateral clusters in the parahippocampal cortex (left cluster size k = 2242, $p < .001$, right cluster size k = 883, $p < .001$, see Figure 13 [A](i)), bilateral retrosplenial cortex (cluster size k = 7786, $p < .001$) and bilateral lateral parietal cortex (left cluster size k = 698, $p < .001$, right cluster size k = 418, $p < .001$).

Cortical reinstatement during closed-loop event retrieval

The identification of element-specific activity patterns at retrieval allowed us to obtain participant-specific values for the amount of cortical reinstatement at retrieval (Figure 13 [A]). Therefore, parameter estimates were extracted from each element-specific cortical region when the respective element functioned as a cue, target or nontarget. I averaged these values across element categories. Note that, when multiple element-specific clusters have been identified, I extracted parameter estimates exclusively from the region selected by Horner et al. (2015) to assure comparability of results (i.e. people: medial parietal cluster, animal/object: left lateral occipital cluster, location: bilateral parahippocampal cluster). Thus, I obtained three values per participant that reflect the element-related cortical activity at retrieval: First, the cue cortical reinstatement, thus the functional cortical activity induced by cues, second, the target cortical reinstatement, that is functional cortical activity induced by targets and third, the cortical reinstatement of nontargets, i.e. the cortical reinstatement of event elements currently incidental to the task.

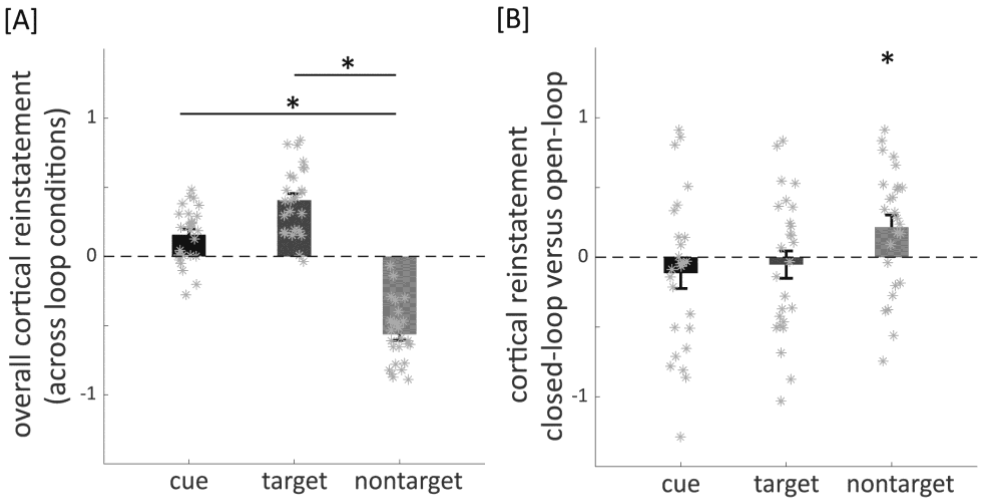

Figure 14. Difference in cortical reinstatement between element functions (i.e. cue, target, nontarget) *[A] across loop conditions ("overall" cortical reinstatement) and [B] subtracting cortical reinstatement at open-loop from closed-loop retrieval. [A] *denotes significant difference (p < .05), [B] *denotes significant difference from zero (p < .05)*

Over all experimental conditions, cue and target cortical reinstatement was significantly higher than nontarget cortical reinstatement, and targets induced significantly more cortical activity than cue elements (Figure 14; main effect of element function $F(2,75) = 111.35$; $p < .001$, ANOVA). Note that the displayed beta values are not in relationship to an explicit baseline but rather the overall mean parameter estimate. Differences are thus not absolute but relative to each other. Here holistic recollection was operationalized as the amount of incidental reinstatement, i.e. reactivation corresponding to nontarget elements. To test whether closed-loop event retrieval entails more

holistic recollection, I investigated whether more nontarget cortical reinstatement took place for closed-loop than open-loop event retrieval (see Figure 13 [B]). Indeed, the difference between the amount of element-related cortical activity in closed- and open-loop conditions is only significantly higher than zero for nontargets ($t(25) = 2.46$, $p = .02$), not so for cues ($t(25) = -1.04$, $p > .05$) or targets ($t(25) = -.05$, $p > .05$; Figure 14 [B]; one-sample t-tests). Thus, cortical reinstatement of nontargets was higher for closed-loop than open-loop retrieval.

Anterior CA3, but not DG activity during closed-loop retrieval correlates with overall nontarget reinstatement

Phenomenological differences between closed- and open-loop retrieval in terms of holistic recollection, i.e. the amount of nontarget cortical reinstatement, are apparent based on the previous analyses. I therefore examined whether there are specific hippocampal functional correlates of closed-loop event retrieval. When functional differences between closed- and open-loop event retrieval are related to holistic recollection, they should scale with the amount of nontarget reinstatement a participant engages in.

First, I contrasted BOLD activity during closed- and open-loop event retrieval within each participant. This yielded participant-specific statistical maps indicating functional activity differences between both loop structures. At the group level these contrast maps were then correlated with the participant-specific amount of nontarget cortical reinstatement. This explorative approach yields clusters within the hippocampus that display increased functional involvement during closed-loop event retrieval when overall nontarget cortical reinstatement, i.e. holistic recollection, is high (Figure 15 [A]). An anterior right hippocampal cluster (cluster size k = 35; *p(cluster)* = .028 (uncorr)), located in subregion CA3, was revealed that scales its functional activity during closed-loop event retrieval with the participant's amount of overall nontarget cortical reinstatement (Figure 15 [B]). Note, that no significant clusters could be identified for the reverse correlation and when correlating individual contrast maps for open > closed-loop retrieval with the overall nontarget cortical reinstatement across individuals.

To test whether the identified cluster was specific for nontarget reinstatement, i.e. holistic recollection, and not related to other retrieval processes, I first tested whether the respective cluster correlated with cue and target reinstatement as well. Pearson correlations between cluster activity (i.e. extracted beta values for the closed – open-loop contrast) and cue as well as target reinstatement were significantly lower than the previously identified correlation of the right anterior CA3 cluster with nontarget reinstatement ($z = -2.584$, $p = .005$ and $z = -3.226$, $p = .001$ for the difference in correlations between p(nontarget reinstatement, cluster activity) and p(cue reinstatement, cluster activity) or p(target reinstatement, cluster activity), respectively). Second, I investigated whether additional anterior hippocampal activity is related to cue or target induced cortical activity. Therefore, the same parametric analyses approach was adopted at group level as we applied for the identification of hippocampal activity related to nontarget reinstatement. Now, however I correlated the difference in functional activity between loop conditions with cue and target cortical reinstatement respectively. No anterior hippocampal cluster showed increased involvement during closed-loop event retrieval with higher amounts of cue or target cortical reinstatement.

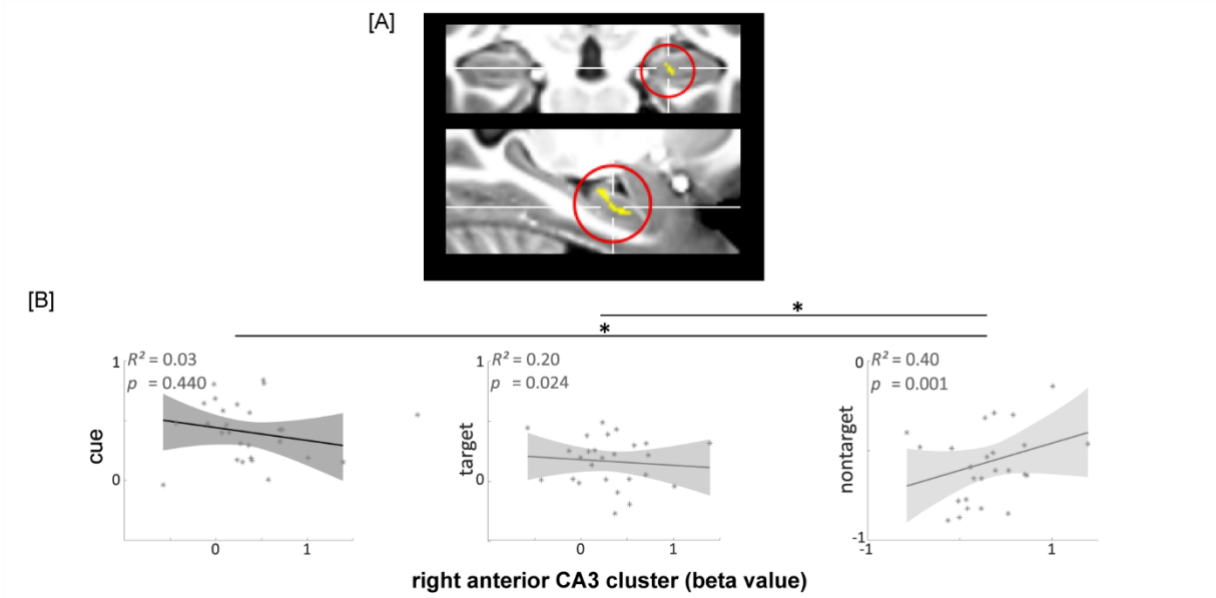

Figure 15. Functional hippocampal activity correlations at closed-loop retrieval with overall nontarget cortical reinstatement. *[A] Hippocampal cluster whose difference in activity between retrieval of closed- versus open-loop events correlates with amount of non-target reinstatement across participants (cluster size k = 35; p(cluster) = .028 (uncorr)). [B] Correlations between cue, target and nontarget cortical reinstatement and the extracted beta values for closed- versus open-loop retrievals from the identified hippocampal cluster, respectively. * denotes significant differences between correlations (p < .05).*

Taken together, I identified a cluster, located in anterior right hippocampal subregion CA3, where activity during closed-loop retrieval correlates with the amount of overall nontarget cortical reinstatement in each participant.

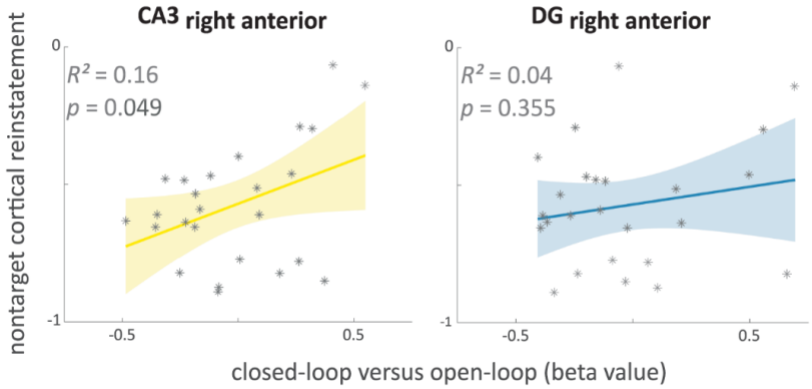

Figure 16. Functional activity correlations of subregions of interest at closed-loop retrieval with overall nontarget cortical reinstatement. *Differences in activity between closed- and open-loop retrieval were extracted as mean values from manually segmented hippocampal subregions CA3 and DG (right anterior) and subsequently correlated with the amount of overall nontarget cortical reinstatement. CA – cornu ammonis; DG – dentate gyrus.*

So far, only by visual inspection I assigned the identified right anterior hippocampal cluster to subregion CA3. As the cluster is in close vicinity to the DG, I aimed to disentangle the specific contributions. Therefore, an ROI approach was adopted. I extracted functional activity (beta values) from manually segmented right anterior subregion CA3 and DG respectively for the loop condition contrast (closed > open-loop event retrieval). The mean functional activity within ROIs was correlated with the amount of nontarget cortical reinstatement across participants. Indeed, only for the right anterior CA3 but not for the right anterior DG the mean functional activity was correlated with the

overall amount of nontarget cortical reinstatement across participants (Figure 16; $R^2 = 0.16$, $p = 0.049$ and $R^2 = 0.04$, $p = 0.355$ for the correlation nontarget cortical reinstatement – right anterior CA3 and DG, respectively). The correlation between nontarget cortical reinstatement and right anterior CA3 was, however, not significantly higher than with right anterior DG ($z = 1.088$, $p = .138$). The ROI results are further evidence for a trend towards specific functional involvement of subregion CA3 (right anterior) but less of adjacent subregion DG in closed-loop event retrieval when participants generally entail more nontarget cortical reinstatement.

4.4 DISCUSSION

Using ultra-high field 7 Tesla fMRI, I provide first empirical evidence for the involvement of human hippocampal subregion CA3 in holistic recollection via pattern completion. Therein I go beyond a replication of the main findings by Horner et al. (2015) and unpack the functional involvement of hippocampal subregions at recollection of multi-element events. This provides insight into how distributed memory representations are accessed via the hippocampus.

The paradigm relies upon the assumption that multi-element events composed as a closed-loop entail more holistic recollection at retrieval than events with an open-loop structure. Extensive previous research provides support for an increased dependency among event elements that are encoded in an all-to-all associative manner (Horner et al., 2015; Horner & Burgess, 2013, 2014). The likelihood to incidentally retrieve event elements when cued with one element, i.e. for holistic recollection is therefore increased in closed-loop events. Consequently, cortical reinstatement of incidental event elements has been shown and here again been confirmed to be higher when retrieving closed-loop events (Horner et al., 2015; Figure 14 and 15). Additionally, I demonstrated increased functional involvement of right anterior subregion CA3 at closed-loop event retrieval in relation to cortical reinstatement of incidental elements (Figure 16 [A]). The data indicate that anterior CA3 activity is related to successful pattern completion associated with holistic recollection. The results contribute to recent efforts in empirically addressing the functional subregion architecture of the human hippocampus.

While models of the functional organization of hippocampal subregions (Amaral & Witter, 1989; Hunsaker & Kesner, 2013; Lisman, 1999) have been informed by anatomical and animal research, the translation of these insights to humans has been limited by the resolution of fMRI, particularly in distinguishing functional activity in CA3 and DG. Here, I was able to acquire functional images with a submillimeter resolution (0.8 mm isotropic) allowing me to segment CA3 and DG separately and to examine specific functional patterns of both subregions (Berron et al., 2016). Indeed, the anatomical ROI analysis confirms that the association between functional subregional activity and the amount of holistic recollection particularly holds for anterior CA3 but less for the adjacent DG (Figure 7). The association between subregion CA3 and a condition that entails more pattern completion is in accordance with previous animal research (Fellini et al., 2009; Gold & Kesner, 2005; I. Lee & Kesner, 2004; K. Nakazawa et al., 2002; Neunuebel & Knierim, 2014; Vazdarjanova & Guzowski, 2004).

Along the transversal axis of the hippocampus considerable heterogeneity has been suggested, beyond the representational differences shown in Chapter II of this thesis. Importantly, the anatomical transition between subregions is not decisive but rather graded (Amaral & Witter, 1989). This renders it difficult to strictly examine functional activity of CA3 and DG independently. Moreover, despite the usage of ultra-high resolution functional imaging, 2 mm smoothing was applied which blurs functional data at the border of segmented subregions. Nevertheless, the current anatomical ROI analysis averages functional signal across whole subregions that extend more than the 2 mm smoothing radius. The observed significant correlation between CA3 activity and holistic recollection

is thus, even though not completely independent from DG activity, a confirmation of CA3 being significantly involved at successful holistic recollection.

Particularly in the anterior medial part (i.e. uncal region), hippocampal anatomy is highly complex and variable between individuals (Ding & Van Hoesen, 2015). Therefore, some subregion segmentation protocols decided to spare this region (e.g. Dalton et al. 2017). Indeed, subregion specific interpretations in the hippocampal head should be drawn with caution. However, the segmentation protocol, that I have applied, leveraged the higher resolution at 7 Tesla (i.e. 1 mm slice thickness) to translate recent findings on subregion boundaries in the hippocampal head from neuroanatomy to MRI (Ding & Van Hoesen, 2015; Berron et al., 2017).

Note again, that the cortical reinstatement of incidental elements ("nontargets", Figure 13) is an indirect measure for hippocampal pattern completion. Theoretical models propose that successful retrieval is initiated by completing a cue pattern towards the full event representation in the hippocampus (Marr, 1971; McClelland, 1995; Treves & Rolls, 1994). Pattern completion may go beyond the required target and include nontargets, particularly if the event representation binds multiple elements tightly together (as e.g. in closed-loop events, Horner et al., 2015; Horner & Burgess, 2014). The elements of the completed event representation are subsequently reinstated in the cortex, which then creates a recollective experience (Bosch et al., 2014; Gordon et al., 2014; Liang & Preston, 2017; Staresina et al., 2012; Thakral et al., 2015)). Thus, the observation of increased cortical activity associated with incidental event elements upon retrieval, and its correlation with activity in CA3 supports these models and implicates CA3 in hippocampal pattern completion and holistic recollection.

Even though here the measure of pattern completion is indirect, several aspects of the results support the specific involvement of anterior CA3 in holistic recollection. First, the anterior CA3 cluster related to cortical reinstatement of nontargets could not be identified in relationship to cue or target cortical activity and functional activity within the CA3 cluster was not correlated with reinstatement of cues or targets (Figure 16 [B]). As cues and targets are presented on screen, successful pattern completion is less relevant for the retrieval of these elements. The increased activity of anterior CA3 at closed-loop event recollection when nontarget cortical reinstatement is high, can thus be referred back to the increased engagement of a pattern completion mechanism (Horner et al., 2015). Second, the anterior CA3 involvement at closed-loop event retrieval cannot be explained by mere recall success. Despite more holistic recollection at closed-loop events (i.e. higher retrieval dependency and more nontarget reinstatement), accuracy levels in both event structure conditions are similar. This rules out performance to be a driving factor in the functional activity pattern of anterior CA3. Importantly, CA3 activity was observed here in relation to the amount of holistic recollection during the whole task, averaged across both event loop conditions (i.e. in relation to *overall* holistic recollection). Thus, participants that generally engaged in more holistic recollection, showed more CA3 activity when retrieving closed-loop events. In contrast, Horner and colleagues (2015) observed that hippocampal involvement at retrieval of closed-loop events increased with the *difference* in holistic recollection between closed and open-loop events. Small variations in the data may explain the subtle differences in results. Even though I similarly observed higher nontarget reinstatement at retrieval of closed-loop events (Figure 15), the difference to nontarget reinstatement at open-loop events was smaller than in Horner et al. (2015). In the current data, performance in both loop conditions was higher and there was more holistic recollection in open-loop events (perhaps due to higher performing participants inferring the missing associations), so that differences between closed- and open-loop events were reduced.

While I leveraged the closed- versus open-loop contrast to examine specific hippocampal involvement during holistic recollection via pattern completion, I do not claim that the hippocampus is not involved in the recollection of open-loop associations. The hippocampus likely mediates the associative memory required to answer the paired-associate questions regarding both open- and closed-loop events. However, the open-loop events serve as a strict control condition, as the current data and previous literature indicate that there will be greater pattern completion for closed-loop events, resulting in tighter dependency among elements and greater incidental reactivation of nontarget elements (Horner et al., 2015; Horner & Burgess, 2014). Pattern completion is defined as a computational mechanism on representational level (McClelland et al., 1995; Treves & Rolls, 1994). However, the approach here was univariate. Moreover, as I averaged across trials and restricted the cortical reinstatement analysis to ROIs, I may not have captured the full variety in the functional activity pattern at holistic recollection. Future studies need to verify pattern completion mechanisms in the human CA3 on trial-specific level as well as directly on representational level by multivariate approaches (as e.g. in Trelle et al. (2020) who, however, took CA3/DG together). The hippocampal effects need to be related to cortical reinstatement beyond restricted ROIs.

Here functional data in ultra-high resolution was acquired with 7 Tesla fMRI using the established multi-element event paradigm by Horner and colleagues (2015). In accordance with anatomical and animal research, the results yield first compelling empirical evidence for a functional involvement of the human hippocampal subregion CA3 (but less pronounced in DG) in holistic recollection via pattern completion. This investigation contributes to our understanding of the heterogeneous functional architecture within the human hippocampus. It shows how distributed cortical memory representations can be accessed and holistically recollected via specific hippocampal subregions.

CHAPTER V

THE VULNERABILITY OF MEMORY REPRESENTATIONS

V. EPISODIC MEMORY REPRESENTATIONS IN ALZHEIMER'S DISEASE SHOW INFORMATION-SPECIFIC VULNERABILITY

Memory representations and their holistic recollection depend on the integrity of their supporting brain architecture. So far, this thesis focused on unraveling this functional architecture in the parahippocampal-hippocampal system. Here now, I discuss the implications that these insights have for the nature of episodic memories, their memorability and the decline of episodic memory function under Alzheimer's pathology. Critically, I explore the interplay between the vulnerability of episodic memories and our understanding of how they emerge from the functional architecture of the parahippocampal-hippocampal system. This chapter has been published in *Neuropsychologia* (Grande et al., 2021) and is integrated into the current thesis with minor edits.

5.1 INTRODUCTION

I introduced this thesis by referring to our memories of experienced episodes as conglomerates of many type of information. This definition of episodic memory as a faculty that captures rich, multi-modal personal events in coherent recollective experiences indeed has stood the test of time. Thereby episodic memory was defined as distinct from semantic memory, which Tulving described as "a mental thesaurus [that] organize[s] knowledge a person possess[es]" (Tulving 1972). In clinical research (and for long in basic research) this conceptual distinction of episodic and semantic memory has remained hugely influential to unravel the neural processes that allow memories to be remembered. Throughout this chapter, I will show how this framework has driven the evaluation of recent memories in clinical settings and research. Here, I propose, however that it is time to develop the assessment of memories based on their experiential nature further towards a focus on the explicit information that a memory represents to understand how remembrance is affected by disease.

The coherent experiential nature of episodic memory is an important component of Tulving's theory which he developed further in the 1980's and 1990's (Düzel et al., 1997; Schacter & Tulving, 1994; Tulving, 1985). He posited that episodic memory is governed by a particular type of conscious awareness of information about previously experienced events: autonoetic awareness (Tulving, 1985; Wheeler et al., 1997). "It is the kind of awareness that characterizes mental 're-living' of happenings from one's personal past. It is phenomenologically known to all healthy people who can "travel back in time in their own minds."(Düzel et al., 1997). In contrast, noetic awareness (knowing) accompanies an individual's interaction with its environment in the present.

This concept led to a particular form of memory assessment in clinical diagnostics and research, namely the Remember/Know paradigm (Gardiner, 1988; Tulving, 1985). A major support for Tulving's concept came from clinical observations of impaired memory for personal experiences but preserved memory for learned facts. Notably, patients with developmental amnesia showed a striking impairment of episodic memory while semantic memory appeared to be intact (Gardiner et al., 2008; Vargha-Khadem et al., 1997, 2001). Impaired autonoetic awareness of events was reflected in the inability to remember, that is mentally 're-live' information, and the rather selective impairment of neural signatures reflecting remembering (Düzel et al., 2001).

The proposition of a coherent experiential nature underpinning episodic memories permeates how scientists and clinicians evaluate its impairment. This is illustrated in the fact that the diagnostic assessment of episodic memory is performed largely independent of the representational content of memoranda that I focused on in the previous chapters (Costa et al., 2017). Tests for memory function entail a large variety of different types of stimuli, administered in many different tasks requiring some

form of recollection or recall. Faces, words and images, visual and auditory as well as story content can be found as memoranda in different standard tests, as for example the "Doors and People Test" (Baddeley, Emslie, & Nimmo-Smith, 1994), the "Verbal Learning and Memory Test" (Helmstaedter & Durwen, 1990), the Wechsler Memory Scale (Wechsler, 1987), the "Face – Name Associative Memory Exam" (Rentz et al., 2011) or the "Free and Cued Selective Reminding Test" (Buschke, 1984). In practice, any of these tests are employed to evaluate memory function, with the tests being agnostic for the assessed content (Costa et al., 2017). This reflects an overarching conception in neuropsychological assessment that when episodic memory is impaired, the ability to remember recent events equally fades for all types of information due to their convergence in a multimodal processing hierarchy (Costa et al., 2017; Mishkin et al., 1998). Memory function is thus evaluated so far without careful consideration of the to-be-remembered material. Meanwhile and given the previous chapters of the thesis another possibility is emerging, namely that impaired episodic memory can be associated with a discrete loss of specific representations.

According to this idea, in a progressive neurodegenerative condition such as Alzheimer's disease, the ability to remember certain mnemonic information could fade before other types of information are affected. Especially in early stages of the disease when the impairment is not yet complete, an accumulating body of research suggests that individuals may have preserved memory for certain representations. The intriguing possibility is that the information-type of this selective impairment may be hard-wired into the anatomy of episodic memory and therefore constant across individuals and situations. This alternative conception of episodic memory impairment has been barely considered so far.

This proposal refers to recent episodic memories, thus memories before systems-consolidation took place. The focus is on a phenomenon that takes place during encoding and presumably early molecular synaptic consolidation (Lisman et al., 2011), thus in the early hours of a memory trace. As such, within this chapter I do not address autobiographical memories that define a person's biography and the memory profile a person with Alzheimer's dementia still experiences about the personal past. These autobiographical memories are amalgamates of episodic, semantic and personal semantic information that have been acquired in the past (Kopelman et al., 1989). Research on autobiographical memories has had a long-standing focus on content-specific aspects of memory (cf. Kopelman et al., 1989; Levine et al., 2002). The contents of autobiographical memories traces are shaped by hippocampal-neocortical or neocortical-neocortical interactions and re-consolidation, ensuing content-specific vulnerability and stability (Moscovitch et al., 2005; Nadel et al., 2000; Nadel and Moscovitch, 1997; Winocur and Moscovitch, 2011). While these systems consolidation processes may well be influenced by the initial shape of a memory trace, they are not the focus of the current proposal. Here, the aim is to increase awareness for the phenomenon of information-specific vulnerability of episodic memories apparent shortly after encoding and prior to systems level consolidation processes.

In that light, I here discuss the possibility that fading memories may affect certain representations more strongly than others, creating "islands of relatively intact recollection" (note, this term has been used in relation to remote memory impairment in transient epileptic amnesia e.g. by Butler & Zeman, 2008)whose representational building bricks are consistently reproducible across individuals. In the following, I briefly highlight aspects of the functional architecture of memory representationsthat show how specific information are processed in the brain. I discussed these aspects in depth in the previous chapters. Thereafter I will illustrate the vulnerability of episodic memories as the leading symptom in acute hippocampal injuries causing amnesia and progressive conditions such as Alzheimer's disease. I continue to review the recent attempts in advancing the classical investigation

and description of episodic memory in terms of experiential nature and processes focusing on the content of episodic memories. I present recent insights into a high consistency across episodic memories in their likelihood to be remembered—regardless of the observer and the situation, certain memories are intrinsically more *memorable* than others. I will show how the functional architecture of memory representations and memorability may relate to each other and conclude this chapter by discussing the implications of these observations for future research and our understanding of impaired memory.

5.2 RECENT INSIGHTS INTO THE FUNCTIONAL ARCHITECTURE OF EPISODIC MEMORY

For decades, researchers aimed to identify the processes that underlie the formation and experiential nature of episodic memory and unravel which brain structures give rise to our awareness of past experiences. As I showed in Chapter II, in the hippocampus, multiple cortical information processing streams converge, rendering it essential to create and relive a coherent memory of rich multimodal events (Mishkin et al., 1998). As indicated in Chapter IV, the holistic experience of episodic memory is however not only accomplished by medial temporal lobe structures but by a widespread network of interacting brain regions that also spans frontal and parietal cortices (Cabeza et al., 1997; Nyberg et al., 2000, 2001; Nyberg, McIntosh, Houles, et al., 1996; Nyberg, McIntosh, Cabeza, et al., 1996; Simons & Spiers, 2003; Wagner et al., 2005).

One recent achievement in understanding the functional architecture of episodic memory is the refinement of the structure-function mapping within the hippocampus. The previously described empirical evidence for CA3 involvement in pattern completion (Chapter IV) is one example therefore. The hypothesis that anatomical features of subregions within the hippocampal circuitry map onto different memory processes had already been formulated (Marr, 1971) at around the same time that Tulving introduced the episodic memory concept. However, as I layed out in the General Introduction, it required considerable advances in high resolution imaging to make the investigation of these processes and computations in humans feasible.

As previously described (see General Introduction and Chapter IV), the hippocampal subregions dentate gyrus (DG), CA3 and CA1 act via distinct mechanisms on incoming information (and recurrently interact with each other). In DG, a pattern separation mechanism distinguishes similar inputs into distinct representations (Berron et al., 2016; J. K. Leutgeb et al., 2007; Neunuebel & Knierim, 2014). In CA3, however, a pattern completion mechanism completes a partial memory cue to previously stored whole representations (Chapter IV, Grande et al., 2019; K. Nakazawa et al., 2002; Neunuebel & Knierim, 2014). The completed representation is then transferred to CA1 and reinstated in cortical areas for a holistic recollective experience as illustrated in Chapter IV (Bartsch et al., 2011; J. Chen et al., 2011; Dimsdale-Zucker et al., 2018; Duncan et al., 2012; Maass et al., 2014; Schlichting et al., 2014). Here it was also evident, that the anatomical organization of cortical reinstatement, in turn, seems to depend on sensory domain or type of information (Cabeza et al., 1997; Horner et al., 2015; Nyberg et al., 2000; Nyberg, McIntosh, Houles et al., 1996). The perspective of structure-process mapping thus revealed how multifaceted memory representations become differentiated from another and how the experiential nature of episodic memory may relate to cortical reinstatement.

Besides the information-specificity in cortical reinstatement, the process-oriented perspective on memory makes no structural distinction for various types of information. This view is challenged by representation-based models, in which mnemonic informaiton co-determines the anatomical anchoring in the brain. Thus, one recent achievement in understanding the functional architecture of episodic memory is the consideration of a structure – *information* mapping. It originates in the debate about mapping mnemonic experiences, i.e. familiarity versus recollection (related to remember/know

but also see Gardiner, 2001 for a more differentiated view) to structures in the medial temporal lobe. Initially, dual-process accounts interpreted reports about patients with hippocampal lesions but preserved recognition ability as evidence for a functional dissociation between the PrC and hippocampus in underpinning familiarity versus recollection experiences (Yonelinas et al., 2005). Familiarity, in this context, described retrieval based on a general sense of knowing whereas retrieval via recollection entailed remembrance of the context in which the memory was acquired. A fundamentally different perspective on functional dissociations within the medial temporal lobe was however taken by Eichenbaum and later by Graham and Ranganath (Eichenbaum, 2000; Graham et al., 2010; Ranganath & Ritchey, 2012). It is the idea that has been central throughout the first half of my thesis: Different regions of the parahippocampal-hippocampal system and further neocortical regions specifically process item-related and context information. As noted earlier, this idea was formulated within the influential posterior medial – anterior temporal framework (Ranganath & Ritchey, 2012; Ritchey et al., 2015). Thus, irrespective of the task at hand, item-related information (but as I discussed in Chapter III this may also include spatial features), is preferentially processed in the PrC (and connected structures of the anterior temporal system) whereas contextual information are preferentially processed in the parahippocampal cortex (A. C. H. Lee, Buckley, et al., 2005; Liang et al., 2013; Litman et al., 2009; Ross et al., 2018; Staresina et al., 2011). This representational segregation partially continues within the EC and the hippocampal transversal axis (see also Beer et al., 2018; Flasbeck et al., 2018; Henriksen et al., 2010; Maass et al., 2015; Nakamura et al., 2013; Navarro Schröder et al., 2015; Neunuebel et al., 2013; Schultz et al., 2012; Sun et al., 2017; Syversen et al., 2021). Along the longitudinal axis of the hippocampus, a gradient from coarser anterior representations towards finer posterior representations has been reported (Small, 2002; Poppenk et al., 2013; Strange et al., 2014; Brunec et al., 2018). Overall, a topographical bias to process certain types of information within specific structures is evident across species, critically with the information converging at various locations throughout the processing hierarchy of the parahippocampal-hippocampal system (as discussed in the General Introduction, Chapter II and Chapter III; Doan et al., 2019; Nilssen et al., 2019).

To briefly summarize, the understanding of how memories emerge in the brain is currently advancing by a more finegrained structure – process mapping in the medial temporal lobe and a focus on the interplay of functionally heterogeneous subregions, with the empirical evidence presented in Chapter IV being an example. In addition, recent investigations among which also results presented in Chapter II, acknowledge that information is inherent to the specific functional architecture that gives rise to memory. New accounts merge these process- and content-oriented approaches to understand episodic memory function (Bastin et al., 2019). Here I now take these new insights into the functional architecture from which episodic memory emerges and apply them to understand impairment of episodic memory in disease conditions. Notably, it changes the traditional way of assessing the vulnerability of episodic memories as I illustrate in the following paragraph.

5.3 EPISODIC MEMORY IMPAIRMENT AFTER ACUTE BRAIN INJURY AND UNDER PROGRESSIVE NEURODEGENERATION IN ALZHEIMER'S DISEASE

Clinical research into the nature of impaired episodic memory after acute brain injury has focused on the question whether its impairment can be selective and dissociate from relatively intact semantic memory. Direct assessments of semantic and episodic details in memory functions have been key and also indirect approaches using autonoetic and noetic awareness as proxies for episodic and semantic memory.

As mentioned in the General Introduction, patient H.M. provided the first prominent evidence for the

role of the parahippocampal-hippocampal system in explicit memory, K.C. provided evidence for the semantic-episodic memory distinction. The profile of memory impairment in patient K.C. was striking. His episodic memory was severely impaired while as in H.M., his general intellectual capacity was normal and he was unimpaired in tasks that required a mere knowledge-based usage of memories (Milner et al., 1968; Rosenbaum et al., 2005, 2012). In K.C. new learning of semantic information was explicitly tested and while being slow, found to be possible (Rosenbaum et al., 2005). Three cases of developmental amnesia confirmed that episodic memory can be profoundly impaired while semantic memories can be acquired, even giving amnesic individuals the possibility to attend school with an average range of success (Vargha-Khadem et al., 1997; but see Squire and Zola, 1998 for another interpretation). A main focus of investigations thus became the experiential nature of memories in these and other amnesic patients. Clear evidence for a specific impairment in autonoetic consciousness upon retrieval was provided with the developmental amnesia patient Jon, who showed electrophysiological and behavioral responses compatible with a sense of knowing despite a lack in the experience of recollection and associated electrophysiological signatures (Düzel et al., 1997, 2001). Also more recently, a lack of autonoetic consciousness was shown in a study with 16 patients that suffered from lesions in hippocampal subregion CA1 and transient global amnesia (Bartsch et al., 2011). These amnesia cases show that a decline in awareness may be present but other aspects of a memory may still be preserved (see also Düzel et al., 2001). It is essential to note, however, that the location of lesions is very heterogeneous from patient to patient and so is the profile of the memory impairment.

Unlike acute brain injury, Alzheimer's disease is associated with a progressive and relatively stereotypic memory decline across individuals. I introduced several important aspects of this neurodegenerative disease already in the General Introduction and recapitulate the essential aspects here. The most prominent risk factor for Alzheimer's disease is old age and, as previously decribed, indeed, the aging brain is already subject to widespread neural changes (Buckner, 2004) including frontal (Andrews-Hanna et al., 2007; Daselaar & Cabeza, 2008; Davis et al., 2008) and medial temporal lobe (Leal & Yassa, 2015; Raz et al., 2005) regions. Countless studies have investigated which aspects of memory change with age and which specific processes deteriorate. In the General Introduction I already mentioned impairment in executive components of memory (Shing et al., 2008; Daselaar and Cabeza, 2008), richness of remembered information and binding abilities (Levine et al., 2009; Old and Naveh-Benjamin, 2008; Piolino et al., 2003; St Jacques et al., 2012; Yonelinas et al., 2007). A difficulty to separate memory representations from each other (Reagh et al., 2015, 2018; Yassa, Lacy, et al., 2011; Yassa, Mattfeld, et al., 2011) may go hand in hand with a bias to pattern complete memory cues (Vieweg et al., 2015), resulting in false "memories" (Devitt & Schacter, 2016; Fandakova et al., 2015). While episodic memory is strongly susceptible to decline with age, semantic memory is less affected (Zacks et al., 2000). This leads to a profile of fragmented autobiographical memories, still preserving semantic details and personal semantics while laking episodic content like personal thoughts (e.g. Levine et al., 2002; Piolino et al., 2002).

Briefly be reminded that the core pathologies underlying Alzheimer's disease are neurofibrillary tangles and beta-amyloid plaques (Braak & Braak, 1991, 1995; Braak & Del Trecidi, 2015; Hyman et al., 1989; McKhann et al., 2011). Both are anatomically progressive pathologies with stereotypic spreading patterns in the brain. In human imaging studies, amyloid pathology frequently begins in medial parietal structures, including retrosplenial cortex, posterior cingulate and precuneus as well as medial frontal areas (Grothe et al., 2017; Mattsson et al., 2019; Palmqvist et al., 2017; Villeneuve et al., 2015). Cortical tau pathology, in contrast, frequently begins in the transentorhinal area before spreading to the EC, parts of the hippocampus, then the PrC, the lateral temporal lobe and finally

cortical frontal and parietal regions (Braak et al., 2006; Braak & Braak, 1991).

Thus, the pathology, ultimately concomitant of cell loss in the respective brain regions, affects key brain regions for successful episodic memory (Jagust, 2018; Jagust et al., 2006). Particularly tau pathology in the parahippocampal-hippocampal system predicts episodic memory decline (e.g. Maass et al., 2017, Lowe, et al. 2018, Sperling et al, 2019, Hanseeuw et al, 2019).

Much research investigated the specifics of memory impairment in Alzheimer's disease. The early stages of Alzheimer's disease are associated with episodic memory impairments while semantic processing has been found intact (Morris & Kopelman, 1986). Research points towards increasing reliance on semantic details and gist memory in these stages (El Haj et al., 2017 for an overview). A temporal gradient has been frequently reported with preserved remote memories but impaired formation and retrieval of new memories (Irish, Lawlor et al., 2011; Irish, Hornberger et al., 2011; Kopelman et al., 1989; McKhann et al., 2011; Addis and Tippett, 2004). Information-specific assessment of autobiographical memories however indicates that the temporal gradient could be more pronounced for (personal) semantics while episodic components are impaired throughout (Irish et al., 2011; Piolino et al., 2003), a finding that may depend on the specifics of the assessment method (Barnabe et al., 2012). Moreover, recent preliminary findings show particular impairment on everyday memory under conditions of delayed recall and for associative memories in MCI (Irish, Lawlor et al., 2011). Interestingly, however, certain rich cues, for instance music, odors or pictures (e.g. El Haj et al., 2020, 2012, 2018) may still evoke fragmented autobiographical memories and memories may be enhanced by a focus on self-referential aspects (e.g. Carson et al., 2019; El Haj and Antoine, 2017; Kalenzaga et al., 2013) as well as with emotional cues in early disease stages (e.g. Hamann et al., 2000; Kensinger et al., 2004; Kumfor et al., 2013; Sava et al., 2015). Overall, emotional components of a memory seem preserved despite a general diminished sense of reliving and visual imagery in Alzheimer's dementia (El Haj et al., 2016; El Haj and Antoine, 2017; Rauchs et al., 2007). Indeed, extensive investigations of autobiographical memories (Levine et al., 2002) carved out a specific profile and revealed that within a single remembered autobiographical episode, Alzheimer's dementia is related to specific impairment of the event-related and personal thought related details, and a bias to report more semantic details (Barnabe et al., 2012; Irish et al., 2011; Murphy et al., 2008).

Regarding memory for recent episodes, some studies show particularly impacted free and delayed recall (e.g. Bäckman et al., 2005), while a meta-analysis finds recognition to be only preserved in preclinical Alzheimer's dementia (MCI) not with progressed states of the disease (Koen & Yonelinas, 2014). Comparable to autobiographical memories, it additionally became evident recently that among recent episodic memories certain material shows more vulnerability for memory impairment. As mentioned before, mnemonic discrimination for item information is more impaired than contextual information with beginning tau pathology (Berron et al., 2019; Maass et al., 2019). This observation sets the stage for investigations on the diagnostic value and specific memorability of certain contents within episodic memory with various levels of pathology in the early stages of Alzheimer's disease (Bainbridge, Berron, et al., 2019).

Note that it yet has to be determined, at which point age-related and pathological Alzheimer's processes lead to differential profiles in episodic memory decline (Jack et al., 2010). Irrespective of an ongoing debate about the neuropathological distinction between normal aging and Alzheimer's, diagnostic assessments of memory function in old age and Alzheimer's disease consider episodic memory as an information-independent clinical symptom. Thus, similarly to research on amnesia, the main focus is on the experiential nature of fading memories and the processes that are affected. The recent insights into the functional architecture of memory representations, however, also highlight mnemonic information as an important variable in the evaluation of episodic memory decline.

5.4 THE MEMORABILITY OF EPISODIC MEMORIES

Memorability refers to the observation that irrespective of the testing situation and consistently across individuals, some stimuli are more likely to be remembered than others (Bainbridge et al., 2013; Isola et al., 2011). This memorability of a stimulus has been shown to account for as much as 50% of the variance in memory performance (Bainbridge et al., 2013), and is consistent across different tasks, image contexts, presentation and retention times (Broers et al., 2018; Bylinskii et al., 2015; Goetschalckx et al., 2018). Independent of attention, priming effects or top-down influences, the phenomenon is considered to be "automatic" (Bainbridge et al., 2021), determined already 160 ms after stimulus onset (Mohsenzadeh et al., 2019) and related to functional activity in late visual regions (inferotemporal cortex), the medial temporal lobe and anterior hippocampus (Bainbridge et al., 2017; Bainbridge & Rissman, 2018; Jaegle et al., 2019).

Memorability thus appears to be an inherent feature of episodic memory. Current research seeks to identify the qualities and the specific content information that determines how memorable an episode is likely to be. While several attributes for an image have shown correlations with memorability, no singular attribute has been found that can act as a proxy for memorability. For example, manmade scenes containing many objects tend to be more memorable than outdoor natural scenes (Bainbridge, Berron, et al., 2019; Isola et al., 2014), however these attributes do not explain a high amount of variance in memorability. Low level qualities like color coding or brightness and also the eye fixation time during encoding seem not to be able to explain an image's memorability (Bainbridge et al., 2013; Bainbridge, Berron, et al., 2019; Isola et al., 2011). Other high-level qualities of an image such as its aesthetics, emotional content, and even observer's own ratings of how memorable an image appears do not show strong correlations with memorability (Bainbridge et al., 2013; Isola et al., 2014). Recent work utilizing computational models and neuroimaging techniques have suggested that above all, it may be the composition of the elements an episode consists of, in particular an item's relationship to other items in the representational space of a memory that influences an episode's memorability. For example, research using deep learning methods have found that more sparsely distributed items are more memorable (Lukavský & Děchtěrenko, 2017), and that dissimilarity in low-level visual information may map onto memorability (Koch et al., 2020). At the same time, similarity at the level of conceptual information may relate to memorability (Koch et al., 2020). For instance, highly semantically connected words are more memorable and are reinstated earlier in the anterior temporal lobe (W. Xie et al., 2020) and memorable images show more similar representational patterns in the brain than forgettable images (Bainbridge et al., 2017; Bainbridge & Rissman, 2018). An understanding of the principles that govern the memorability of an episode could reveal the computations performed after perceiving the episode that lead to successful memory encoding.

The memorability feature of episodic memories is especially compelling when it comes to the evaluation of memory decline. A recent behavioral study investigated memorability of photographic images in older adults that were either cognitively normal without memory complaints, cognitively normal but with a subjective memory decline severe enough to seek medical advice (subjective cognitive decline) or with significant (1.5 SDs) memory decline relative to the expected performance in old age (MCI) and showing a profile typical of prodromal Alzheimer's disease (Bainbridge, Berron, et al., 2019). If episodic memory decline from cognitively normal older adults to those with MCI would affect episodic memory irrespective of the representational content of photographic images, the outcome of this study would have been a reduced memory performance proportionally across all images. However, this study observed an asymmetry across images as related to memorability—a

specific set of images remained highly memorable to cognitively normal adults but became forgettable to those with MCI. Looking at memory performance for these images specifically, we could significantly predict whether an individual suffers from MCI, better than any other set of images. Equally intriguingly, some stimuli remained consistently and highly memorable across healthy controls and MCI patients, and performance for those images could be predicted by deep learning models. Thus, while some stimuli seemed to be memorable across everyone (no matter the pathological condition), other stimuli seemed to be of diagnostic value as they were highly forgettable by individuals facing conditions of preclinical dementia but not by healthy controls (Bainbridge, Berron, et al., 2019). These results indicate that certain neural pathways essential for memory processes or for representing mnemonic information may be affected earlier in the course of decline than others, resulting in a specific pattern of episodic forgetting and potential islands of recollection. As they are defined here, these islands refer to certain mnemonic information that remains accessible to episodic memory when other types of information cannot be remembered anymore. Importantly, deliberate selection of the content to be remembered can promise to unveil these differences across neural pathways, and across different stages of cognitive decline.

As I briefly mentioned before, functional imaging in older adults show that the anterior temporal – posterior medial system segregation is less clear than in young adults and they recruit the anterior temporal system less (Berron et al., 2018). Increased tau pathology is related to a specific decrease in memory performance for item information, while contextual information is preserved (Berron et al., 2019). This information-driven difference is also reflected in the observation that man-made scenes with multiple items are the first to show strong differences in memorability between healthy adults and those with MCI (Bainbridge, Berron, et al., 2019). In general, accumulating evidence shows that tau pathology affects anterior temporal regions and possibly isolates the hippocampus from the large-scale anterior temporal network while amyloid leads to a deficit in the posterior medial network function (Adams et al., 2019; Harrison et al., 2019). This may explain information-specific memory impairments in accordance with the preferentially processed information in the affected network (Berron et al., 2019; Maass et al., 2019 and see Berron et al., 2020 for effects on respective network connectivity). Thus far, while decodable patterns of memorability have been observed in parts of the anterior temporal network such as the PrC and anterior temporal lobe, it is less clear whether posterior medial regions show information about the memorability of a stimulus (Bainbridge et al., 2017; Bainbridge & Rissman, 2018). However, other research has shown decodability of other memory content such as the identity or representational information of a memory from posterior medial regions like the retrosplenial and parahippocampal cortex (Bainbridge et al., 2021; Silson et al., 2019).

Initial findings thus point towards a potential relationship between the inherent feature of memorability based on memory information, an underlying functional architecture of biased information-processing in certain brain systems and information-specific memory decline in relation to pathology within these brain systems. An open question however will be how different types of memory content may allow researchers to pinpoint representational differences in the respective brain systems, and how performance on specific stimuli is associated to brain pathologies in certain functional networks.

5.5 DISCUSSION AND FUTURE PERSPECTIVES

While we are still in the early days of understanding memorability, the phenomenon provides an intriguing new way on how we conceptualize episodic memory and interpret and investigate fading episodic memory. The observations that certain recent memories fade more easily than others across people, that the content and composition of episodic memories may drive their memorability, and

that the content of episodic memories determines the specific underlying functional architecture, call for a change of perspective in how episodic memory decline is investigated and evaluated. To understand episodic memory function, we need to understand how the type of information influences episodic memories and why this influence is hard-wired to the human brain so as to render it stable across individuals.

To illustrate these considerations, I here refer to memories as "landscapes" which are affected by erosion. As much as a landscape is defined by the sum of its elements (i.e. mountains and forests), an episodic memory is defined by the sum of different types of information defining the event. Components of the landscape will have different vulnerabilities to erosion; trees and soil are likely to be affected much earlier than mountains composed of granite. Likewise various causes of erosion (e.g. continuous wind, rain, tornados or flooding) exert different forces on the components of a landscape. Similarly, healthy aging processes causes certain memory components to decline while pathological processes may excel these and even carve out a unique shape of the memory landscape. This analogy may help us to conceptualize how the landscape of memories may be affected in disease. The current insights into the functional architecture of the parahippocampal-hippocampal system suggest that different types of information are processed and represented in different functional routes withn the parahippocampal-hippocampal system and wider episodic memory network. Similarly, islands of recollection in the memory landscape of episodic memory may prevail until later stages of neurodegeneration. Thus, rather than speaking of loss or impairment of episodic memory as a whole, it may be more appropriate to consider the possibility of impoverished episodic memory with selective loss of specific types of information.

The illustration of memory landscapes in episodic memory serves to highlight how our understanding of memory is shaped by how we test for episodic memory. If clinical research is guided by a model of episodic memory as a representationally-independent faculty of reliving past events, our discoveries and understanding will remain limited to what the model permits. If clinical research embraces the representational nature of episodic memory decline and evaluates assesses remembrance of recent episodic memories for different types of content, we may gain new insights into the episodic memory experience of patients with Alzheimer's disease.

The potential in investigating progressive impairment of recent episodic memories in neurodegenerative conditions is twofold. First, islands of recollection could provide a unique window into the organization of memory. Information-specific cognitive readouts could provide insights into which aspects of episodic memory are neuroanatomically distinct and thereby contribute to basic research like in Chapter II - IV. In analogy to the early insightful observations on differences in systems consolidation for rather semantic versus rather episodic elements, also the observations on memorability obtained thus far are a first proof of concept that motivate further investigation. The second potential is of a clinical nature. Islands of recollection could be content-specific for certain stages of disease progression thereby enabling tailored tests for diagnostic staging. Moreover, specific strategies may allow us to harness preserved memory abilities to support activities of daily living.

What happens in the early hours of a memory trace that determines its memorability is entirely up to speculation for now. The novelty of memorability findings does not allow yet any firm hypotheses on mechanisms that drive variations in memorability within the population as well as between healthy older adults and older adults with Alzheimer's disease. However, several aspects may play a role that are related to the way content-information is bound together, represented and sorted at encoding. One mechanism that determines memorability may be the level of integration within an item's representation. A word's memorability, for example is determined by its centrality in the semantic

space (W. Xie et al., 2020). Highly memorable item representations may thus closely incorporate multiple features. Likewise, the inherent multimodality of certain content representations may drive memorability. For instance, in contrast to scenes, the representation of isolated objects is intrinsically multimodal, integrating olfactory, gustatory, auditory or tactile information. Note, that also among different items, the level of multimodality changes (consider for instance a lamp versus a cup of coffee). Hence the involved functional architecture differs for multimodal item and context memories due to biased pathways of information processing, as I discussed in Chapter II and III (cf. Fiorilli et al., 2021; Grande et al., 2022; Lee et al., 2021; but note the described profound overlap as well). Under healthy conditions multimodal representations may enhance memorability because a memory can be accessed via multiple ways (e.g. the cup of coffee via a scent or a taste). In Alzheimer's disease particularly multimodal representation areas like the PrC, more precisely Area 35 (cf. Chapter III; Fiorilli et al., 2021; Bussey et al., 2005; Lee et al., 2021), are affected early on, presumably leading to an increased vulnerability for certain object memories. Another appealing mechanism that may determine differential memorability effects in Alzheimer's disease are attentional and perceptual mechanisms. When a stimulus consists of multiple items, a condition may appear that potentially resembles simultanagnosia, that is the inability to perceive and bind multiple items together while their single recognition is unaffected (Chechlacz et al., 2012; Coslett & Saffran, 1991). Whenever there is competition between multiple objects in complex scenes, attention-based deficits may be possible that hinder the binding of mnemonic elements, in particular when Alzheimer's pathology innervates key item-related processing structures along with the visuospatial attention system in posterior brain areas (Chechlacz et al., 2012) as one would typically expect in MCI. Consequently, memorability under Alzheimer's disease may be affected for isolated as well as multiple objects, but potentially being even more impaired for the processing of multiple objects in those with Alzheimer's disease in comparison to healthy individuals. Note that deliberately manipulating overall attention to a stimulus did not change memorability (Bainbridge, 2017), hence we are here referring to attentional dynamics driven by the stimulus itself. Overall, we think that memorability may reflect the order in which perceptual inputs are prioritized for memory encoding (cf. W. Xie et al., 2020), but future studies need to reveal whether this idea holds and unravel the mechanisms by which this prioritization takes place, potentially leading to different levels of integration within an item's representation.

Indeed, careful inspection of the memorability findings so far reveals that the above stated mechanisms may not be the full story and need further elaboration. First, the ideas may predict that in particular highly multimodal items like objects are memorable across people. However, single objects can be among forgettable items as well (Bainbridge, Berron et al., 2019) and memorability effects have also been observed in abstract noise stimuli (Lin et al., 2021). Second, complex images containing multiple items seem to be highly diagnostic, presumably driven by deficits in the parahippocampal-hippocampal system and attentional deficits (Bainbridge et al., 2019). However, not all diagnostic images are cluttered and display a complex assembly of objects (Bainbridge et al., 2019). Third, the finding that a lack of memorable qualities (esthetics, interest) leads to the forgetting of otherwise highly memorable objects under Alzheimer's dementia may follow from competition between items. However, studies on memorability that looked at many singular properties for predicting memorability (e.g. the number and size of objects, esthetics, interestingness etc., see e.g. Bainbridge et al., 2013; Bainbridge, Berron et al., 2019; Isola et al., 2014) were not able to predict large variance in memorability (at least for faces as in Bainbridge et al., 2013). Presumably, our general representations about the larger visual statistical world (innate or learned) play an essential role. Thus, overall the intrinsic, task- and experience-independent nature of memorability is not yet fully explainable and still remains a secret of the brain's functional architecture.

Besides the multidimensionality of episodic memories, a core quality of episodic memory is the autonoetic nature. Some even consider autonoetic consciousness an essential prerequisite of memory (Klein, 2015; Klein & Markowitsch, 2015). A key question that needs to be addressed when considering memorability is to what extent preserved memorability is associated with autonoetic awareness. It may be possible that, similarly to some preserved sense of familiarity in patient Jon (Gardiner et al., 2006), memorable images under conditions of memory decline are associated with diminished autonoetic awareness. However, it may well be possible that preserved components of the hippocampal cortical circuitry may still allow autonoetic awareness to accompany preserved memorability. This alternative is especially plausible given that degeneration seems to affect specific types of representations more than others. Indeed, high memorability often but not always is related to autonoetic consciousness of the retrieved material (Broers & Busch, 2020). In that sense, we see the experiential nature of memories and the content of memories as two scales (whether orthogonal or closely linked to each other) on which memory function needs to be evaluated.

A thorough understanding of the relationship between memorability and autonoetic consciousness allows us to gain insight into daily experience with Alzheimer's dementia, as has been done within the area of autobiographical memory. Accessing sensory and perceptual episodic aspects of an event is also related to a sense of self (Conway, 2001; Conway & Pleydell-Pearce, 2000; Irish, Lawlor, et al., 2011; Piolino et al., 2009). In Alzheimer's disease the self becomes more abstract as highly personal semantic information prevails (Addis and Tippett, 2004; Strikwerda-Brown et al., 2019; Caddell and Clare, 2010; Martinelli et al., 2013). The identification of memorable and autonoetic aspects within a memory may serve to boost the subjective sense of self (Prebble et al., 2013).

While my thesis focusses on the nature of episodic memories (see footnote 1 in the General Introduction), related questions could also be raised about semantic memories. In fact, the interaction between episodic and semantic aspects may contribute to variability in memorability and semantic features remain among those that need to be explored as rendering an image memorable. The research on memorability is still in its infancy, and it will be interesting to address the question of whether memorability applies to semantic memories and their impairment patterns in neurodegenerative conditions as well. While many mechanisms may apply to both episodic and semantic memory and both types of memory closely interact (Renoult et al., 2019; Tulving & Markowitsch, 1998), episodic memory may be special in giving rise to autonoetic consciousness (LeDoux & Lau, 2020). Clarifying the relationship between memorability and autonoetic consciousness will thus also contribute to our understanding of the differences between semantic and episodic memory regarding memorability.

Note that many studies already investigate conditions that make memories stick (under healthy and pathological conditions), whether it is the emotional state, a personally meaningful cue or the extent that the episodic elements are unitized (e.g. (Bastin et al., 2013; Cooper et al., 2019; Diana et al., 2011; El Haj et al., 2012, 2020; El Haj & Antoine, 2017b; Hayes et al., 2007; Kwan et al., 2016; Naveh-Benjamin et al., 2002; and see Yonelinas, 2002 for factors that enhance recognition). These aspects may only partially explain memorability, as memorability is not only context- and task-independent but also experience-independent and similar across people (Bainbridge, 2020). The memorability of a stimulus for healthy individuals can even be predicted by computational algorithms (Needell & Bainbridge, 2021). However, as described earlier, certain esthetic aspects may contribute partially as much as the element's composition, presumably affecting possibilities for unitization. Specific memory assessments that account for the representational nature (e.g. drawings as in Bainbridge et al., 2019; Morgan et al., 2019 or digital memory rebuilds as in Cooper et al., 2019) instead of assessments focused on experimental nature (like the remember/know paradigm) may help to

investigate how conditions of memory enhancement relate to intrinsic memorability.and they are usually studied across different memories with a focus on experiential nature.

Likewise, this is not the first proposal for an information-specific investigation of memory capabilities at a representational level. As indicated already, within autobiographical memory research, it is standard to evaluate the personal past by treating memories as a conglomeration of different types of information that all need to be evaluated separately for a comprehensive memory profile (Levine et al., 2002). Certain aspects of an autobiographical memory or episode can be preserved while other content is impaired and these nuanced memory profiles are consistent within disease groups (Irish et al., 2011). Recent proposals leave categorical approaches to memory content behind and emphasize that a memory is formed and stored in representations of different dimensionalities and levels of abstraction within the functional architecture of memory (Andermane et al., 2021; Brunec et al., 2018; Ekstrom & Yonelinas, 2020; Irish & Vatansever, 2020; Renoult et al., 2019). Different implications of these abstract to specific gradients in memory representations are emphasized. For instance, the amount of semantic versus episodic aspects in a memory is determined by the position of the respective memory representation on a continuum of more or less contextualization (Irish & Vatansever, 2020) and by the need to access specific details versus gist information (Ekstrom & Yonelinas, 2020; Renoult et al., 2019), extending beyond a dichotomy between semantic and episodic memories (Renoult et al., 2019). As the coarseness or precision of representations is rooted in the functional anatomical architecture of memory (Andermane et al., 2021; Brunec et al., 2018; Ekstrom & Yonelinas, 2020; Irish & Vatansever, 2020; Yonelinas, 2013), partial dysfunction of neural substrates does not cause the full memory to fade but rather fragmented memories that draw on remaining representations (Ekstrom & Yonelinas, 2020). Many aspects of the above mentioned representational accounts came together in a recent proposal postulating that episodic memories may fade in a fragmented manner that is compatible to our proposal ((Andermane et al., 2021). They elaborate on distinct behavioral findings regarding the forgetting of memory representations. While item representations seem to fade gradually over time, higher-order representations like narratives seem to be forgotten rather holistically. The underlying representational architecture of episodic memories that we outlined above provides a potential explanation. It will be an exciting avenue for future research to investigate memorability in the light of that concept and link the findings to clinical observations.

The unique angle that the current proposal takes is to refer to the intrinsic memorability of memories. The functional underpinnings of memorability seem to come into play during encoding and during early phases of molecular synaptic consolidation and are not subject to (systems) consolidation mechanisms (Bainbridge & Rissman, 2018; Mohsenzadeh et al., 2019). Notably the same items remain memorable or forgettable, even when memories fade over time (Isola et al., 2014) and memorability is highly specific, even varying within stimulus categories (e.g. Bainbridge et al., 2013; Bainbridge, 2017). Thereby the current perspective is fundamentally different from the previous accounts where memories are shaped over time and strongly influenced by task demands (Andermane et al., 2021; Ekstrom & Yonelinas, 2020; Levine et al., 2002; Renoult et al., 2019) with effects on general categories of mnemonic content (e.g. Irish and Vatansever, 2020; Levine et al., 2002; Strikwerda-Brown et al., 2019). That said, however, the memorability of items may be influenced by specific retrieval tasks (Bainbridge et al., 2019; Broers and Busch, 2020) – an observation that needs further investigation. Finally, I emphasize again that memorability is related to representations of recent experiences. As indicated before, within this Chapter V I propose to reconsider the assessment of recent episodic memory and on mnemonic material that may serve to identify Alzheimer's disease in preclinical and prodromal stages. Likewise, there is also increased interest in the assessment of autobiographical

memory towards individual daily life memories (Palombo et al., 2018) and it will be important to consider how these two approaches can be linked to each other. The current observations together with particularly the recent perspective on forgetting by Andermane and colleagues (2021) show that it is now timely to investigate the fragmented nature and information-specific aspects of recent episodic memories and their decline.

The episodic memory framework inspired decades of research on the experiential nature of memories. The recent findings on episodic memory decline and information-specific processing routes of mnemonic information support an extension of this framework by the concept of memorability. Memories may not fade unitarily but in an information-specific manner, mirroring affected cortical regions and presumably leading to islands of recollection.

CHAPTER VI

GENERAL DISCUSSION

VI. General Discussion

6.1 Summary of current findings

In previous chapters I depicted a highly topographical architecture in the human parahippocampal-hippocampal system wherein various subregions represent and process specific aspects of an episode. I showed how these subregions communicate with each other and with cortical regions, and how the aspects of an experienced episode can be assembled and recollected. When Alzheimer's disease affects the system, I propose that fragmented memories reflect the distorted architecture.

Leveraging ultra-high field functional imaging at 7 Tesla in Chapter II, I provide a comprehensive investigation of the functional connectivity and information processing within the parahippocampal-hippocampal system. I identify selective scene processing, constrained to the preferentially connected posterior-medial entorhinal subregion and distal subiculum. Anterior entorhinal subregions together with the preferentially connected subiculum/CA1 border, show no difference between object and scene conditions. These two functional routes indicate a continuation of segregated cortical information processing streams that innervate the parahippocampal gyrus. Unlike the traditional strictly parallel and segregated scheme, the routes seem consistent with segregated context and converged item-context processing, respectively.

I also lay out a role of the PrC beyond item information processing. Chapter III evaluates current insights from the animal and human literature to propose unitized representations in PrC. The PrC may play a crucial role when item-related features, irrespective of their nature and content, are unitized to reduce dimensionality. This is another indication of information convergence within the traditionally segregated item processing route in the parahippocampal-hippocampal system.

In Chapter IV I use ultra-high resolution fMRI at 7 Tesla to specify that the hippocampal subregion CA3 is involved in the access and reinstatement of cortically distributed memory representations via pattern completion. Thus, while the continuation of information-processing streams (Chapter II) suggests that parts of the hippocampus (subiculum and CA1) represent and process information in a segregated manner, distributed cortical representations can be accessed via hippocampal subregion.

The functional architecture of representations within the parahippocampal-hippocampal system putatively leads to fragmented memories when the system distorts with progressing Alzheimer's pathology. I propose in Chapter V that memorability, a stable quality of mnemonic information across individuals, is not solely determined by the composition of the memory representation itself. The extent of neurodegeneration, in accordance with the information represented in affected brain structure, alters memorability of certain mnemonic information. The consequence is fragmented memory representations that reflect the underlying Alzheimer's pathology.

In this thesis I transfer insights on organizational principles within the parahippocampal-hippocampal system from computational and animal research to the human brain. These findings imply a specific representational architecture that maintains connections among information that belongs together, and allows the flexible segregation and convergence of information (Brunec et al., 2020). Insight into this organizational scaffold has implications for our understanding of episodic memories, their access, and clinical perspectives on neurodegeneration within the parahippocampal-hippocampal system.

6.2 IMPLICATIONS FOR THE MEMORY REPRESENTATIONS IN THE HUMAN PARAHIPPOCAMPAL- HIPPOCAMPAL SYSTEM

6.2.1 Organized segregation and convergence in the parahippocampal-hippocampal system

The functional architecture of the parahippocampal-hippocampal system encompasses multiple representations that both, extract and combine different aspects of an episode. The organization of these representations is determined by two segregated cortical streams for context and item information that come together in the system (Navarro Schröder et al., 2015; Nilssen et al., 2019; Ranganath & Ritchey, 2012). In the following, I will focus on the principles that characterize these representations, as implied by the empirical work and proposals of the previous chapters. Please refer to Figure 17 (page 104) for an illustration.

Segregated context representations in a specific route between parahippocampal cortex and subiculum

Chapter II provides novel empirical evidence for segregated context processing in a specific functional route within the human parahippocampal-hippocampal system. A continuation of the cortical context-specific stream towards the hippocampus was suggested by rodent anatomy and by scattered functional evidence across species (Berron et al., 2018; Cembrowski et al., 2018; Dalton et al., 2018; Knierim et al., 2014; Maass et al., 2015; Navarro Schröder et al., 2015; for reviews see Nilssen et al., 2019; Witter et al., 2014). Chapter II contains the first comprehensive, ultra-high resolution examination of functional connectivity and information processing in the human parahippocampal-hippocampal system. Therein, I identify a route that selectively processes scene information between functionally connected parahippocampal cortex, posterior-medial EC and distal subiculum subregions (Figure 17, [C] and [E]). My data advance functional insight into a possible route that was reported earlier in humans (Maass et al., 2015). I can confirm previous reports on a hub for context processing in the human distal subiculum (Dalton et al., 2018; Zeidman et al., 2015). The findings bring anatomical and functional insights across species together, advance the sparse literature on the subiculum and clearly demonstrate a transversal functional organization of the subiculum. They imply a specific role for segregated context information in the system.

Segregated context information may serve to organize a stream of incoming information into coherent event representations (Sugar & Moser, 2019; Whittington et al., 2020; see Maurer & Nadel, 2021 for a comparable account along the longitudinal hippocampal axis). Context information changes more slowly than item-related information. In rodents, this is mirrored neurally in the contribution of grid cell firing in the medial EC to fairly stable global remapping while the lateral EC input to the hippocampus leads to frequent rate remapping (Colgin et al., 2008; Igarashi, Lu, et al., 2014). Computationally, context information can provide a basic structure and serve as a frame to determine which elements belong to each other (Figure 17 [E]; Whittington et al., 2020). This helps to organize and bind episodic elements into coherent representations (initial evidence in Cholvin et al., 2021). The idea of a spatial frame for memories is not only derived from rodent research. Research in humans on concept acquisition, schemas, event boundaries and scene perception indicates a comparable contextual scaffolding mechanism (Ben-Yakov et al., 2014; Clewett et al., 2019; Collin et al., 2015; Constantinescu et al., 2016; Deuker et al., 2016; Robin, 2018; Robin & Olsen, 2019). However, this has yet to be empirically verified.

The empirical evidence for segregated context information is based on univariate comparisons between independent scene and object processing conditions. This is a valuable first approach, but it precludes further conclusions on the nature of the represented information. A clear definition is pending to understand the role of this specific functional route. The term "context" information, which I use throughout the thesis (while diverse nomenclature is used throughout the literature, e.g.

'where', 'spatial' or 'global' information) captures the presumed global nature of the information in that route and likewise entails the operationalized scene stimuli in Chapter II. Note that context can also be temporal instead of spatial (e.g. DuBrow & Davachi, 2016; Howard & Kahana, 2002). However, temporal context seems to be processed in another functional route encompassing the lateral EC and distal CA1 (i.e. the route I describe below; cf. Beer et al., 2018; Tsao et al., 2018). A fundamental, defining characteristic of the information, specifically processed in the posterior-medial entorhinal – distal subiculum route, may be geometrical structure or dimensionality. More nuanced representational differences than univariate scene versus object contrasts can reveal are likely. The current finding of a specific functional route for segregated context information is an important step that calls for future investigations of its nature.

Unitized item representations in the perirhinal cortex.

While the cortical context stream continues in a segregated manner through the parahippocampal-hippocampal system, this only partially holds for the item processing stream. The timely review in Chapter III proposes unitized item representations in the PrC that can incorporate various types of information. Thus, some context information may converge on the cortical item processing stream in the PrC. Recent rodent anatomy confirmed cross-projections from the cortical context processing stream to the PrC , which belongs to the cortical stream that segregates item information (Nilssen et al., 2019; for related proposals on integration within the PrC see Lavenex & Amaral, 2000 and Naya & Suzuki, 2011) . Extensive empirical evidence across species, however, showed specific and segregated item processing in the PrC (see Brown & Aggleton, 2001; Graham et al., 2010; Miyashita, 2019; Ranganath & Ritchey, 2012 for overviews). In Chapter III, I reconcile these seemingly contradictory reports and propose PrC representations that unitize multidimensional item-related information (Fiorilli et al., 2021; see Figure 17, [D]). These representations help in complex situations of feature ambiguity (e.g. Erez et al., 2016; A. Y. Li et al., 2022 in humans) and unitize critical item-related features of any kind: reward-related, contextual, spatial, multisensoric or semantic (e.g. Bos et al., 2017; Clarke & Tyler, 2014; Haskins et al., 2008; Keene et al., 2016; Kivisaari et al., 2012; Taylor et al., 2006, 2009). Note that a comparable conclusion on PrC representations was reached earlier based on single-neuron data that focused on the integration of item information and temporal context (Naya, 2016). Chapter III critically advances these earlier ideas by reviewing PrC lesion and functional studies across species and by broadening the scope of the unitized information.

Unitization allows higher-level multidimensional feature binding and a meaningful sorting or integration of elements based on current demands (Diana et al., 2008; Graf & Schacter, 1989; Yonelinas, 2002). Unitized representations in the PrC encompass various features to help define an item (see also Naya, 2016), enhance distinctions between similar items, and thereby serve as important shortcuts for perception and novelty detection (i.e. serving decision making; Bussey & Saksida, 2007; Cate & Köhler, 2006). The value of item-related information, the way we act upon items, and their meaning depends on location and context (cf. the fruit basket in Figure 17 [D] and [E]). Notably, a gating mechanism in the PrC supports information transmission towards the hippocampus (De Curtis & Paré, 2004). Under simultaneous amygdala input, the PrC allows information flow from perirhinal Area 35 to the lateral EC (Kajiwara et al., 2003). The PrC is thus an interface for multidimensional item information towards the hippocampus. Unitized representations, carried onward to the hippocampus and funnelled via the PrC and the lateral EC, can benefit the efficient formation of conjunctive memory representations.

While the proposal argues that item representations in PrC can incorporate context information, direct empirical evidence in humans requires a tailored study design. First, unitization may only be required upon ambiguity of when dimensionality reduction helps to solve the task. For example, I find

empirical evidence for increased PrC activity during item rather than context processing in Chapter II (operationalized with object and scene conditions). The conditions were independent, and participants required no contextual knowledge for the items. In such a situation as in Chapter II item representations in PrC may not need to incorporate contextual elements and hence the data show specific item processing. Second, unitized features are tightly bound and may appear item-specific. Analyses on representational level can examine the nature of PrC representations under various task constraints. In addition, not all levels of unitization may involve the PrC. The PrC is not required for mere perceptual unitization of low-level features (Inhoff et al., 2019; Staresina & Davachi, 2010). However, unitization associated with semantic processing and incorporating higher-level properties includes the PrC (Delhaye, Bahri, et al., 2019; Haskins et al., 2008). The PrC interacts with neocortical areas to create distinct multidimensional unitized representations that separate overlapping features (A. Y. Li et al., 2022; Liang et al., 2020; for a similar idea see Olcese et al., 2018). Downstream information flow from higher-order conjunctive representations within the hippocampus likely has a role in unitization as well (see below).

The PrC comprises Area 35 and Area 36, however their functional distinctions are not well understood. The PrC subregions have distinct neocortical and parahippocampal projection profiles (for neocortical projections in rodents: Burwell et al., 1995; Furtak et al., 2007; for parahippocampal projections in monkeys: Lavenex et al., 2004). In the monkey, sparse reports attribute unitized representations to Area 35 in particular (Fujimichi et al., 2010; Kivisaari et al., 2012; note however differences in segmentation rules; see also Naya 2016). In humans, anterior-posterior representational gradients are reported that imply more item-context convergence in posterior PrC (Liang et al., 2013; Litman et al., 2009). These studies do not specifically capture the PrC subregions, though. Chapter III contains the first investigations of human PrC subregions and their functional connectivity and information processing profiles (subregions also addressed separately in Berron et al., 2019, 2021). I noticed variations in Area 35 and Area 36 functional connectivity to the EC and minor differences in item – context functional activity. Selective item processing might be more pronounced in Area 36. A more specialised task design and a systematic comparison of functional profiles between perirhinal subregions can assess functional variability within the PrC.

Item-context convergence in a route between anterior entorhinal subregions and the subiculum/CA1 border

Item – context convergence characterizes the second functional route through the human parahippocampal-hippocampal system that partly continues from the PrC, following first empirical evidence in Chapter II. The conventional scheme of two parallel, segregated item and context processing streams entering the hippocampus became implausible, given the cross-projections from the context processing parahippocampal cortex to the lateral EC (and PrC) in rodents (Nilssen et al., 2019). Whether selective item processing remains within the human parahippocampal-hippocampal system was unclear. Chapter II presents novel evidence in humans for no item or context selectivity (as operationalized by object and scene conditions) in a route of functionally connected anterior entorhinal subregions and the subiculum/CA1 border (see Figure 17 [E] and [F]). Importantly, the cortical sources of that route, perirhinal Area 35 and 36 and the retrosplenial cortex, show largely segregated item and contextual information processing, respectively (see Figure 17 [C] and [D]; please see the above paragraph for an explanation of why I may not see non-selectivity between item and context information inside the PrC in that task). The detailed analysis of functional connectivity and information processing suggests organized item–context convergence along the parahippocampal-hippocampal processing hierarchy. The findings translate insights from the rodent to the human brain that are consistent with convergent representations in rodent lateral EC and CA1 (Ásgeirsdóttir et al.,

2020; Deshmukh & Knierim, 2011; Doan et al., 2019; Vandrey et al., 2021; Wilson, Langston, et al., 2013; Wilson, Watanabe, et al., 2013). Furthermore, the data shed light on the human retrosplenial cortex by showing its functional connection to the subiculum/CA1 border via the EC.

Organized convergence of item and context information before the hippocampus might support the binding of defining context and spatial aspects to items. Depending on the task requirements, certain context features may already be unitized in the PrC (see the previous paragraph) or they may converge further up in the processing hierarchy (note that the current correlational data prevents conclusions on directionality but see for evidence in monkeys H. Chen & Naya, 2020). A growing number of rodent literature shows convergence before the hippocampus. In the rodent lateral EC, single cells integrate PrC and parahippocampal projections (Doan et al., 2019) that thus stem from item and context processing streams. The rodent distal CA1 represents spatial context information together with item information (note that in the distal CA1, cell tuning is more dependent on item information than in the proximal CA1; Vandrey et al., 2021). An earlier proposal described the idea of item-in-location representations along the traditional item processing route based on electrophysiological findings in the rodent lateral EC (Deshmukh & Knierim, 2011; Knierim et al., 2014). Thus, accumulating data shows convergence in traditionally item-attributed 'non-spatial' subregions (structural connectivity data leads to a consistent conclusion; C. C. Huang et al., 2021). The findings in Chapter II give a timely indication of item-context convergence in the human anterior and lateral EC as well as the subiculum/CA1 border.

The absence of a difference between item and context processing conditions is consistent with convergence but does not provide direct evidence. Note, however that the segregated functional profile in cortical source regions shows that noise differences between conditions, for example, cannot explain the absence of a difference. Nevertheless, the current results contrast with reports about segregated item information in the anterior-lateral EC and rodent subiculum/CA1 border (Beer et al., 2018; Berron et al., 2018; Dalton et al., 2018; Henriksen et al., 2010; Keene et al., 2016; Ku et al., 2017; Nakamura et al., 2013; Y. Nakazawa et al., 2016; Navarro Schröder et al., 2015; Neunuebel et al., 2013; Reagh & Yassa, 2014; Schultz et al., 2012). Methodological factors may underlie opposing findings. Firstly, as previously stated, examining context versus item processing by scene and object conditions in a univariate way is a simplification. The variable definition of information within the cortical processing streams leads to a variety of operationalizations in the above-mentioned literature. Item processing was tested with non-spatial, local, temporal or object stimuli. Context processing was examined with spatial, global or scene stimuli. Sometimes both conditions were assessed within the same set of stimuli, sometimes in distinct task blocks. The contrasting condition or baseline impacts whether a specific operationalization, such as temporal context or object-in-location (as in e.g. Beer et al., 2018; Reagh & Yassa, 2014), appears as item or context processing. Similarly, univariate contrasts between conditions, are insufficient to assess degrees of convergence. Secondly, task constraints can cause different results. The general functional architecture is flexibly adjusted to serve various task demands (e.g. Deshmukh, 2021; Duncan et al., 2014; O'Neil et al., 2012; Roy et al., 2017). In the future, systematic examination of various types of information and their representation along subregions in diverse settings, can reconcile previous data on item–context segregation with the current findings.

The aim in Chapter II was to reveal how segregated functional routes through the system are while this method concealed some specifics about converging routes. To examine the unique mapping of cortical processing streams within the parahippocampal-hippocampal system, a non-hierarchical and exclusive approach treated all cortical sources equally and ruled out influences from other sources or non-preferential connections. The internal anatomical hierarchy within the parahippocampal gyrus

with strong parahippocampal projects to the PrC (Lavenex et al., 2004; Nilssen et al., 2019) could thus not be captured. Convergence in overlapping functional connections could only be shown in information processing. Both the retrosplenial-based and the PrC-based EC subregions functionally connect to the subiculum/CA1 border. They are based respectively on connectivity to cortical context (retrosplenial) versus item (PrC) processing streams, making the anterior EC subregions and the subiculum/CA1 border a key convergence point (cf. Dalton & Maguire, 2017). Note moreover that rodent anatomy shows that the retrosplenial cortex projects to the output layers of the EC (Czajkowski et al., 2013; Sugar et al., 2011) and then, together with subiculum projections, further to EC input layers (Simonsen et al., 2022). Convergent representations could thus be the result of recurrency within the system (as in Koster et al., 2018) and created over time. The current correlational approach to assess functional connectivity precludes inferences on directionality.

Results in Chapter II show a distinct relationship between item and context processing in the human PrC than in the anterior EC subregions and the subiculum/CA1 border. This implies organized convergence along the processing hierarchy, as proposed earlier based on animal anatomical wiring (Lavenex & Amaral, 2000). It is unclear how exactly converged item-context representations along the traditional item-processing route differ from unitized representations in the PrC (i.e. representations in Figure 17 [D], [E] and [F]). Unitized representations in the PrC are rather item-focused and serve efficient semantic classifications and to facilitate object identification in certain situations (Chapter III; Delhaye, Mechanic-Hamilton, et al., 2019; Haskins et al., 2008; A. Y. Li et al., 2022; Liang et al., 2020). The successive convergence of multidimensional item information with further contextual aspects, such as the composition of items in the scene, then can serve the formation of higher-level conjunctive representations towards the hippocampus (McClelland et al., 1995; for an overview of computational ideas see Kahana et al., 2008; for empirical evidence on progressive binding see Cooper & Ritchey, 2020 and Sheldon & Levine, 2015).

Conjunctive representations in the hippocampus beyond the subiculum

The extensive investigation of hippocampal functional architecture in Chapters II and IV shows certain interesting aspects with regard to conjunctive representations upward in the hippocampal CA fields. While more evidence is necessary, I intend to discuss these aspects here because prominent theories see hippocampal binding of information into conjunctive representations as critical for episodic memory and recollection (e.g. Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007; Manns & Eichenbaum, 2006; Montaldi & Mayes, 2010; McClelland & Goddard, 1996; O'Reilly & Rudy, 2001). Conjunctive representations can serve as indexes for later access via pattern completion (Goode et al., 2020; Rolls, 1996; Teyler & DiScenna, 1986; Teyler & Rudy, 2007). Empirical evidence for conjunctive representations exists in rodent CA1 and CA3 (McKenzie et al., 2015; Komorowski et al., 2009; for indicative evidence in DG and CA3 see Neunuebel et al., 2013). Evidence in the human hippocampus only starts to get on subregional level (e.g. for the entire hippocampus: Backus et al., 2016; Chadwick et al., 2010; Huffman & Stark, 2014; LaRocque et al., 2013; see for hints on content-invariance in DG and CA subregions Hrybouski et al., 2019; Preston et al., 2010 and very recently Dimsdale-Zucker et al., 2022)[9]. One observation in Chapter II was that, in contrast to the Subiculum, in CA1 I found no information processing differences along the transversal axis (only differences in

[9] Biases for certain informational content are presumed not to drive subregions DG and CA3 when they process amodal information. A complication for conjunctive representations in DG and CA3 are thus reports of animal researchers that find even further continuation of content-specificity in the information processing route of the hippocampus, similarly dividing subregion CA3 into proximal non-spatial time versus distal spatial information processing (Beer et al., 2018; Flasbeck et al., 2018; Nakamura et al., 2013). Others, however, reported functional differences in pattern separation versus completion mechanisms along the transversal CA3-DG axis that do not contradict the idea of conjunctive representations (S. Leutgeb & Leutgeb, 2007). Future empirical work is needed to reveal how findings on information-specific processing relates to functional differences, in how far they can be translated to the human brain and what they imply for a hippocampal role in information binding and holistic recollection.

functional connectivity). This might be consistent with more convergence and conjunction (see Figure 17 [F]). In addition, the data in Chapter IV shows that hippocampal CA3 is involved in holistic recollection of multi-element event representations via pattern completion. This process is in line with index or conjunctive representations (see Figure 17 [G]).

Representations in CA1 might be particularly complex as CA1 is both embedded in a transversally segregated information route with EC and subiculum ("direct" or temporo-ammonic pathway) and in the trisynaptic loop where the entire transversal CA1 axis receives projections from higher-order CA3 (Nilssen et al., 2019). This may explain why a transversal organization in CA1 is less clear than in the subiculum. In Chapter II, the transversal functional connectivity profile in CA1 shows no interaction regarding preferred seeds but instead a decline in overall seed preference towards the proximal end. No transversal profile is evident in information processing, and CA1 does not selectively activate to item or context information. Recent rodent data is consistent with convergence in CA1 (Vandrey et al., 2021), whereas extensive rodent research shows functional segregation across the transversal CA1 axis (Beer et al., 2018; Henriksen et al., 2010; Y. Nakazawa et al., 2016). Task-related differences in CA1 tuning may explain some discrepancies. In empty environments, for example, rodent data shows segregation of place cell sizes along the transversal CA1 axis (Henriksen et al., 2010). However, the presence of items within a spatial environment may lead to convergent item-context processing throughout CA1 (Vandrey et al., 2021; with presumably transversal differences in degrees of convergence). Critically, largely spread across the full transversal axis, CA1 may hold different types of representations simultaneously. Various groups of CA1 place cells code simultaneously for either spatial layout or the conjunctive experience (the latter reinstating in the retrosplenial; Tanaka et al., 2018; Tanaka, 2021; Tanaka & McHugh, 2018).[10] This is consistent with the view of CA1 as a translator between CA3 index representations and rich representations for cortical reinstatement (see Figure 17 [G], [H] and [B]; McClelland & Goddard, 1996) but testing in humans is required.

The data in Chapter IV suggests conjunctive representations in CA3. Hippocampal pattern completion was computationally defined as a process that acts via autoassociation (Treves & Rolls, 1994). This requires the representations that it acts upon to be conjunctive and one entity (Kahana, 2002). I critically showed higher CA3 activation for retrieval of closed-loop events, specifically those events that consist of fully associated elements in contrast to those whose elements are forming a chain of associated pairs. Hierarchical associative models show how multiple elements can be successively merged into higher-order conjunctive representations (McClelland et al., 1995; see Kahana, Howard & Polyn, 2008 for more of these models). This process may have led to conjunctive entities of the events that were learned via associations (*cf.* Asch & Ebenholtz, 1962). Previous behavioral evidence has shown that elements in the closed-loop condition are more tightly bound together, potentially forming conjunctive representations (Horner et al., 2015; Horner & Burgess, 2013, 2014). Note that the high overall accuracy in my data may have prevented me to detect behaviorally measurable differences between retrieval of elements in open- and closed-loop conditions. Future research should verify, on a representational level and within individuals, whether a conjunctive representation underlies the cue-based recollection via CA3 in the closed-loop condition.

[10] Tanaka (2021) also provides a way to merge two influential theories, the cognitive map and the index theory. Conjunctive, amodal representations as proposed by the index theory do not immediately align with the likewise influential cognitive map theory that does not see the hippocampus as agnostic but attributes a dominance of spatial information to the coding of information within the hippocampus (Goode et al., 2020; Schiller et al., 2015; Teyler & Rudy 2007). The above indicated specific segregation of context information in a dedicated area of the hippocampal subiculum that may support the formation of amodal, abstract patterns can be a way to reconcile both views (as in Whittington et al., 2020). Moreover, the different views are reconciled in the complexity of area CA1 where recent evidence shows that both ways of representing information exist simultaneously (Tanaka, 2021; Tanaka et al., 2018; Tanaka & McHugh, 2018).

6.2.2 Access to distributed cortical memory representations via hippocampal CA3

Chapter IV contains the first evidence in humans that comprehensive recollection and cortical reinstatement of memories via pattern completion involve hippocampal subregion CA3. Computational models introduced pattern completion as a fundamental computation to access stored memories (McNaughton & Morris, 1987; see also Semon's theory in Schacter et al., 1978). To relive an episode (see Figure 17 [A]), all its elements need to be reinstated (see Figure 17 [B]), requiring the completion of a single incoming cue towards the whole memory representation, a computation that particularly recurrent collaterals within CA3 seem to be suitable for (see Figure 17 [G]; Marr, 1971; McNaughton & Morris, 1987; Rolls & Treves, 1994). Direct evidence exists for the involvement of the rodent CA3 in pattern completion (Fellini et al., 2009; Guzowski et al., 2004; Kesner & Warthen, 2009; K. Nakazawa et al., 2002; Neunuebel & Knierim, 2014). In humans, however, the small size of the CA3 subregion has made it difficult to functionally dissociate it from DG. The results in Chapter IV advance current human literature that already could associate the entire hippocampus with pattern completion (e.g. Horner et al., 2015; Staresina et al., 2016) as well as joint subregions CA3/DG and the CA1 (Bonnici et al., 2012; De Shetler & Rissman, 2017; Dimsdale-Zucker et al., 2018; Hindy et al., 2016; Molitor et al., 2021; Stokes et al., 2015; Tompary et al., 2016; Trelle et al., 2020; L. Zheng et al., 2021). Chapter IV bridges the gap between computational attributions of pattern completion in CA3, empirical evidence in rodents, and now subregional functionality in humans.

While the evidence in Chapter IV is of an indirect nature, assessing the cortical reinstatement of a learned event is nevertheless a valuable inferential approach for pattern completion. Numerous models conceptualize that the retrieval cue initiates hippocampal pattern completion, triggering reinstatement of the previously encoded cortical pattern (among many others, Clewett et al., 2019; Davachi & Danker, 2013; Kumaran & McClelland, 2012; McClelland & Goddard, 1996; K. A. Norman & O'Reilly, 2003; O'Reilly & McClelland, 1994; for direct empirical evidence see e.g. Staresina et al., 2019). A core element of the pattern completion definition is completion towards all elements an event encompasses, even unrequired information. My univariate analysis thus tests the direct consequence of that pattern completion process. This is reflected in cortical metabolic activity located in those regions that are associated with those elements of an episode that are implicit to the retrieval task at the very moment (Horner et al., 2015). My results further our understanding of pattern completion in the human brain, linking CA3 involvement specifically to the cortical reinstatement of incidental information. Note that pattern completion is defined as a computational process at the representational level. Thus, future ultra-high resolution studies that employ multivariate analysis may directly show pattern completion in CA3. While several studies have attempted to provide evidence for pattern completion at the representational level in humans, Chapter IV is unique as I was able to link the process to subregion-specific activity.

Successful comprehensive recollection requires the interplay of the full trisynaptic loop, not only the involvement of hippocampal CA3. In order to reactivate the episodic information and elicit a sense of remembrance, subregion CA1 is thought to enrich the stored index representations in CA3 (see the previous paragraph and Figure 17 [G] and [H]). CA1 thus contains the pointer to reinstate the distributed cortical pattern (see Figure [B]; e.g. McClelland & Goddard, 1996; for initial empirical evidence, see Tanaka et al., 2014). This can explain functional activity in CA1 that is closely related to pattern completion processes (e.g. Bonnici et al., 2012; De Shetler & Rissman, 2017; Dimsdale-Zucker et al., 2018; Hindy et al., 2016; Tompary et al., 2016). Moreover, as in any encyclopedia, accessing an entry is only possible when a clear organization separates the entries from each other. A separation between event representations is thus essential for their organization and later access (for a computational model see Kumaran & McClelland, 2012; for related evidence in human hippocampal

subregions see Molitor et al., 2021). The interplay of pattern separation and pattern completion in the trisynaptic loop thereby prevents catastrophic interference (O'Reilly & McClelland, 1994). Future work should exmine the dynamics within the trisynaptic loop between pattern separation and pattern completion as well as the enrichment of index representations in CA1.

[11] ⌈The hippocampus interacts with the neocortex to achieve holistic recollection (Kumaran & McClelland, 2012; McClelland & Goddard, 1996; O'Reilly & Norman, 2002; O'Reilly & Rudy, 2000; Trelle et al., 2020). The view that CA3 triggers cortical reinstatement may be too simplistic. Instead, the neocortex may settle itself into states that are closer to the memory representation in question - thereby acting as an additional generator for pattern completion cues (K. A. Norman & O'Reilly, 2003; O'Reilly et al., 2014). Such a dynamic interaction would be compatible with a more flexible process of pattern completion and models of memory search that describe how cues are specified in an iterative manner for probabilistic sampling during associative retrieval (e.g. in Raaijmakers & Shiffrin, 1980). Future examination of the interaction and recurrency between neocortex and hippocampal subregions in accessing representations can further refine these processes (cf. Koster et al., 2018).⌋

Not all access to cortical memory representations requires hippocampal pattern completion. Conjunctive representations of a full event are related to the hippocampus, but unitized item representations are related to the PrC (Bader et al., 2014; Delhaye, Bahri, et al., 2019; Delhaye, Mechanic-Hamilton, et al., 2019; Diana et al., 2008; Erez et al., 2016; Staresina & Davachi, 2010). Whether a given element is encoded as an item feature or a contextual feature can affect the relative engagement of PrC versus hippocampal processing (Davachi & Wagner, 2002; Diana et al., 2010; Haskins et al., 2008; Quamme et al., 2007; Tu & Diana, 2021). Thus, as I argue in Chapter V, the inherent composition of a memory influences which parts of the parahippocampal-hippocampal system are required and how the information is represented (see the contextual binding account for a related idea: Yonelinas et al., 2019). Depending on the memoranda itself, task demands, and individual resources, shortcut access via the PrC is feasible. Note, however, that extensive research shows a different experiential nature that accompanies access via non-hippocampal regions, that is a feeling of familiarity instead of comprehensive recollection and autonoetic experience (e.g. Düzel et al., 2001; Gardiner et al., 2014; Vargha-Khadem et al., 1997). Ongoing research seeks to determine the border between familiarity and recollection ,and how both relate to the access of specific memory representations (see also the next paragraph; for conceptual accounts see e.g. Bastin et al., 2019; Cowell et al., 2019; Yonelinas et al., 2019; for clinical and cognitive empirical research, see e.g. Broers & Busch, 2020; Ross et al., 2018; Strikwerda-Brown & Irish, 2020; Tu & Diana, 2021).

[11] paragraph between ⌈⌋ symbols is included with minor edits from the draft of a chapter that has been accepted for publication by Oxford University Press in the forthcoming book "Handbook of Human Memory" by Theves[+], Grande[+] et al. ([+] shared first authorship) edited by Michael Kahana and Anthony Wagner due for publication in 2023.

6.2.3 Memory representations reflect vulnerabilities of the parahippocampal-hippocampal system

In Chapter V I provide a novel perspective to conceptualize memories as heterogeneous representations that directly reflect the functional parahippocampal-hippocampal architecture and its vulnerabilities in diseases like Alzheimer's. Particularly in clinical research, the assessment of memory function focused on their experiential nature and episodic memories have been treated as unitary (Costa et al., 2017). This approach overlooks episodic memories as multidimensional composites of information and does not account for the heterogeneous representation of information within the parahippocampal-hippocampal system, that I described previously (see Figure 17). In Chapter V, I therefore illustrate memoranda as a landscape with "islands of recollection" and aspects that are susceptible to erosion (e.g. Figure 17 [D], [E] and [F]). The inherent composition of a memorandum determines its representational landscape which is stable across individuals and hardwired into the brain (Bainbridge, 2017b, 2020). We can therefore examine Alzheimer's disease progression and related memory deficits through the lens of the parahippocampal-hippocampal representational architecture, and vice versa. This novel perspective can accelerate both basic cognitive and clinical insight.

A call to conceptualize memories based on their representational content has been made before; unique, however, is the focus on the inherent nature of memories and related clinical implications. Many accounts describe how memory representations are influenced by task demands, general stimulus categories, or shaped over time (e.g. Andermane et al., 2021; Irish & Vatansever, 2020; Murphy et al., 2008; Renoult et al., 2019; Strikwerda-Brown, Grilli, et al., 2019; Yonelinas et al., 2019). Clinical studies have evaluated memorable aspects of past life experiences, defined as autobiographical memories, to gain insight into the experiential nature of memories (Addis et al., 2009; Kopelman et al., 1989; Levine et al., 2002; Piolino et al., 2002; Rosenbaum et al., 2009; Strikwerda-Brown, Mothakunnel, et al., 2019). In Chapter V, I emphasize the intrinsic profile and thus diagnostic potential of a memory representation that is recently formed. Memories of a specific composition either remain intact or can deteriorate easily, consistently across individuals, largely independent of consolidation processes or situational factors (Bainbridge, 2020; Bainbridge et al., 2013; Bainbridge & Oliva, 2014; Bainbridge & Rissman, 2018; Broers et al., 2018; Bylinskii et al., 2015; Goetschalckx et al., 2018; Isola et al., 2011; Mohsenzadeh et al., 2019). Nevertheless, these accounts are not exclusive. The composition of a memory, its embedding in semantic knowledge, and the required detail and precision for accurate remembrance directly influence the nature of a memory representation (Brunec et al., 2018; Ekstrom & Yonelinas, 2020; Irish & Vatansever, 2020; Renoult et al., 2019; Yonelinas et al., 2019). Further research is necessary to reveal how these factors influence the memory representation, how they determine the unitization of cetain aspects and hence the specific involvement of the parahippocampal-hippocampal architecture (see Andermane et al., 2021 for an initial approach related to forgetting).

When the architecture of the system progressively distorts, specific memory landscapes evolve. Pathology progression affects some representational routes earlier than others. The resulting profile of accessible and deteriorated memory content is consistent across individuals and can identify a clinical group (Bainbridge, Berron, et al., 2019). Empirical evidence, for example, indicates distorted specific item-related processing in preclinical Alzheimer's disease, simultaneously with a the pattern of early cortical tau accumulation (Berron et al., 2019, 2021; Maass et al., 2018, 2019). My thesis, however, calls for a refinement of this profile (based on Chapter II and Chapter III). I concluded that item-context convergence may occur along the route that coincides with early tau progression (Area 35 – anterior-lateral EC – subiculum/CA1 border, Figure 17 [D], [E] and [F]). Strict comparisons between item and context processing can thus fall short in the early detection of cognitive alterations

in preclinical Alzheimer's disease (cf. Yeung et al., 2019). In accordance with early tau-pathology in Area 35 (Adams et al., 2019; Braak & Braak, 1991; Braak & Del Tredici, 2020; Das et al., 2019; Kaufman et al., 2018), impaired memory is, for example, specifically reported for unitized item representations (Delhaye, Bahri, et al., 2019; Delhaye, Mechanic-Hamilton, et al., 2019). These representations are generally well remembered in aging (Ahmad et al., 2014; Bastin et al., 2013; D'Angelo et al., 2016; Memel & Ryan, 2017; Z. Zheng et al., 2016). Critically, my data in Chapter II suggest yet another cognitive phenomenon associated with tau propagation: the dedicated context processing route may become affected later on in the trajectory of tau progression. Thus, a specific failure to integrate multiple items into a contextual scaffold (or cognitive map as in Behrens et al., 2018; see Figure 17 [E]) and to process global layouts may become apparent at a later but still prodromal stage of the disease (indicative evidence in Adams et al., 2022). Indeed, man-made scenes containing multiple items show diagnostic potential instead of general object content (Bainbridge, Berron, et al., 2019). Note also that deficits in contextual representations and putatively grid-cell dependent path integration were reported in genetic risk carriers for Alzheimer's years before onset (note that this has not been linked to individual pathology staging; Bierbrauer et al., 2020; Howett et al., 2019; Kunz et al., 2015). Overall, information that requires a high amount of binding within and across items seems particularly sensitive, as Alzheimer's pathology affects areas of multimodal representations (e.g. Figure 17 [D], Chapter III, for a comparable account see Bastin et al., 2019). In the future, precise associations between the state of pathology and mnemonic content should be established.

Functional connectivity patterns can reveal the vulnerabilities of the parahippocampal-hippocampal system in Alzheimer's disease. Alzheimer's tau pathology is hypothesized to spread along functional hubs and connected regions (Franzmeier et al., 2019; Guye et al., 2010; Jagust, 2018; Vogel et al., 2020). Whether and why functional connections accelerate the spread of pathology is still unclear but animal research indicates that neural activity can enhance tau expression (J. W. Wu et al., 2016). Synaptic connections are more important than spatial proximity for tau propagation, and synaptic dysfunctionality occurs after tau spread (Ahmed et al., 2014; Pickett et al., 2017). Functional connectivity measures can aid to identify and even predict tau pathology progression and related memory decline (Adams et al., 2019; Berron et al., 2021; Franzmeier et al., 2022; Franzmeier, Dewenter, et al., 2020; Franzmeier, Neitzel, et al., 2020; Hoenig et al., 2018; Sintini et al., 2021). Thus, data presented in Chapter II provides critical insight into the assessment of vulnerable routes along via which tau may progress (Chételat, 2018; Franzmeier et al., 2019; Pereira et al., 2019). One influential idea states that both pathologies need to merge to initiate the devastating neurodegenerative cascade related to Alzheimer's dementia (Ittner & Götz, 2011; Vogel et al., 2020). Cortical tau pathology begins in Area 35, the anterior-lateral EC, and then affects the subiculum/CA1 border, while Amyloid pathology progresses along cortical midline regions before reaching the subiculum/CA1 border (Braak & Braak, 1991; Braak & Braak, 1995; Lace et al., 2009; for a relationship to functional networks see J. B. Pereira et al., 2019). From that perspective, the functional connectivity pattern indicated in Chapter II is striking: a retrosplenial – anterior EC route and another Area 35 – anterior EC route both incorporate the subiculum/CA1 border. Recent data show that the retrosplenial cortex guides cortical tau spread via the hippocampus (Ziontz et al., 2020, 2021). It seems that tau can reach neocortical regions and interact with amyloid via the subiculum/CA1 border. The data in Chapter II does not allow directional inferences to inform more detailed hypotheses, as I assessed functional connectivity in a correlational manner. Nevertheless, these considerations show how subregional functional connectivity data aids in deriving and testing hypotheses about pathological distortions in the parahippocampal-hippocampal system and beyond.

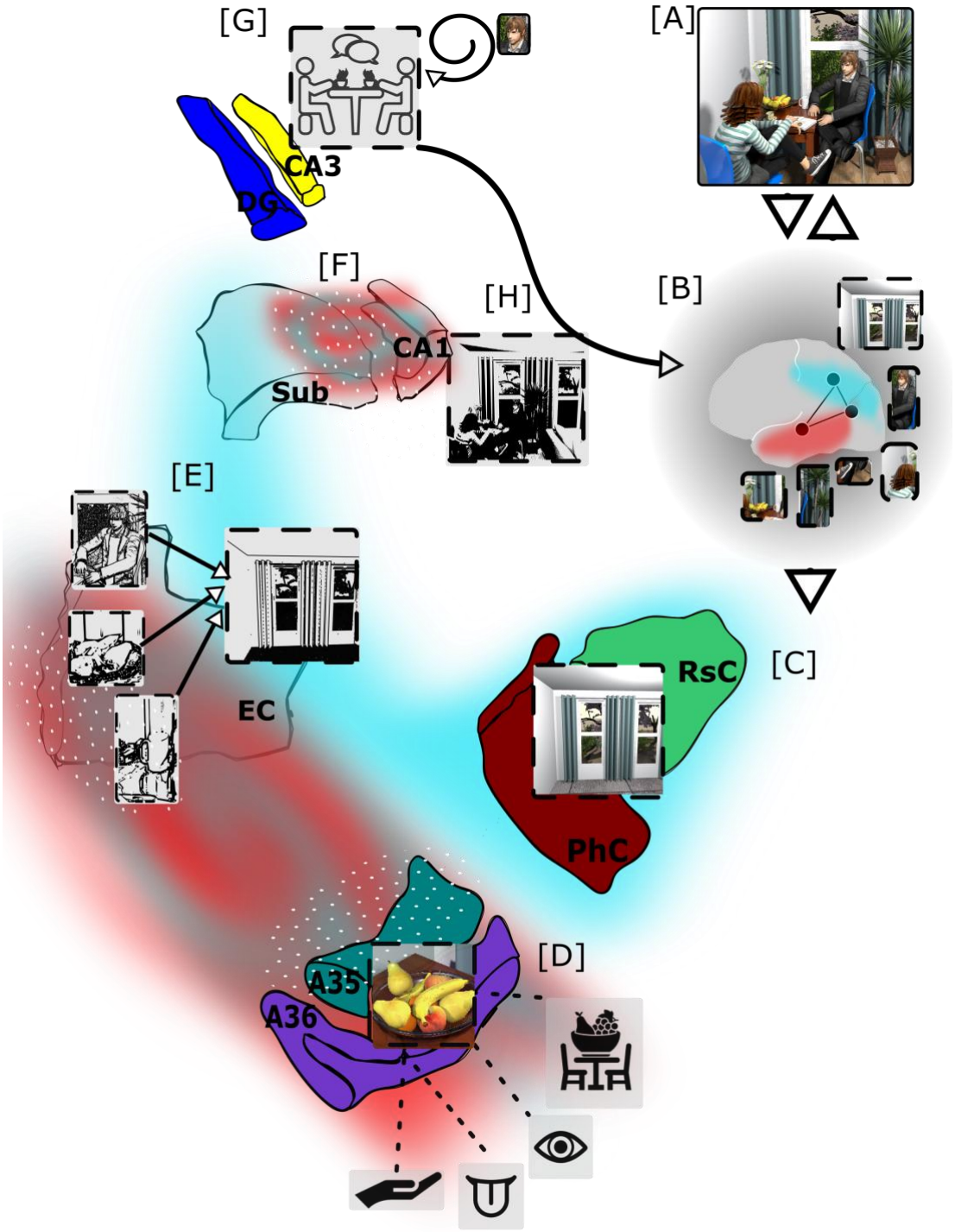

Figure 17. Functional architecture of memory representations as implied by the thesis' findings. *[A] An event is experienced, for example a friend visiting us for a coffee. [B] During that experience, the brain represents different aspects of the situation with a general segregation of contextual aspects (e.g. the living room) and item-related aspects (e.g. the objects on the table; the involved people). To recollect this situation later, the information is processed within the parahippocampal-hippocampal system. [C] Here, contextual information enters via the parahippocampal cortex (PhC) and the retrosplenial cortex (RsC). [D] The perirhinal cortex that consists of Area 35 (A35) and Area 36 (A36) processes the item-related information. Critically, some contextual aspects are integrated into unitized item representations (that may allow shortcut decisions). For example, the taste, shape and colour of a fruit are unitized into the representation of the pear. As it makes a difference whether the pear is in the basket on the table or on the ground, this critical contextual information may likewise be unitized with the item-related aspects. The information, segregated into contextual aspects as well as converged item-context aspects, is communicated to the entorhinal cortex (EC) and further to the subiculum and CA1.* →

(continued from Figure 17) *[E] One theory is that the dedicated context processing route (associated with the PhC) in the posterior-medial EC and proximal subiculum (Sub), provides a slowly changing contextual scaffold into which converged item-context information from the other route can be bound. This other route spans the anterior EC parts that communicate with RsC and PrC and the subiculum/CA1 border, and provides multidimensional item-related information converged with contextual aspects. [F] The subiculum/CA1 border communicates with the anterior EC subregions and the PrC, a route along which item-context information may converge more and more, until in CA3 (and DG) information is represented in a condensed conjunctive manner [G]. In DG the conjunctive representations may become separated from each other (not depicted and beyond the scope of this thesis). CA3 may contain higher order "index" representations. These can serve like an icon, i.e. representations in CA3 may not contain every detail but tag essential aspects. Via these conjunctive index representations, a trigger (e.g. seeing the friend's face on a picture) later may elicit pattern completion towards the full (index) representation. Presumably this index information is then enriched in CA1 [H] which consecutively allows the cortical reinstatement of the distributed representation and a reliving of the episode [B and A]. In Alzheimer's disease earliest cortical tau pathology begins predominantly in A35 then travels to the anterior-lateral EC and the subiculum/CA1 border from where it spreads further throughout the brain. The displayed topography of representations and pathology suggests that when pathology progresses, not all aspects of a memory representations are impaired. Instead, islands of unimpaired recollection may exist that then are specific to the state of pathology progression. Note in this description, I assume directionality that cannot be inferred based on my findings but is suggested based on anatomical projections. Moreover, the representational nature of the processed information was implied by univariate human results and by previous literature across species.*

6.3 FUTURE RESEARCH AVENUES

It is the nature of science that every research contribution raises more questions than it can possibly solve. The work of my thesis leads to numerous questions that create exciting avenues for future research: (1) methodological advances in high-field imaging, anatomical segmentation, multimodal and multivariate approaches; (2) cognitive advances providing a cartography of parahippocampal-hippocampal connectivity and representations; (3) clinical advances in pathology progression and memory representations.

6.3.1. High-field imaging, anatomical segmentation, multimodal and multivariate approaches

Further advances in online movement correction and data acquisition at even higher spatial resolution can improve the precision of functional inferences and lead to better circuit understanding. Current achievements in ultra-high field imaging of the medial temporal lobe enable in vivo studies of the human brain at the mesoscale level with submillimetre resolution (as in Chapter II and Chapter IV of this thesis and in Berron et al., 2016; Koster et al., 2018; Maass et al., 2014, 2015). However, my thesis demonstrated the necessity of studying the system in greater depth *within* subregions, including further layer-specific investigations, in order to increase circuit-level understanding of the parahippocampal-hippocampal system.

Despite ongoing efforts, more work is needed to harmonize segmentation protocols and set up rules for as yet unincluded subregions (Olsen et al., 2019), with a goal of also considering individual differences in brain structure. Atlas-based segmentation of the parahippocampal-hippocampal regions recently eased the tedious work of manual segmentation (Yushkevich et al., 2015; as applied for Chapter II but not yet for Chapter IV). Still, the use of non-harmonized segmentation protocols remains an issue. For instance, some studies examined the EC based on segmentation protocols that included less of the anterior EC, making comparisons across results difficult (e.g. Maass et al., 2015; Syversen et al., 2021 versus Chapter II). Moreover, segmentation protocols do not cover all hippocampal regions. The incorporation of the hippocampal tail, and further refinement of the complex hippocampal head is needed. Future segmentations will likely benefit from additional methods, such as computationally unwinding the tilted hippocampal tail which simplifies the topography of subregions and hence their segmentation (de Flores, Berron, et al., 2020). While segmentation protocols cover individual differences in brain structure, these differences are not yet

in focus for analyses of functional implications. This is surprising given the considerable anatomical heterogeneity between individuals. Not only is the PrC highly variable (L. Xie et al., 2017), the hippocampus shows variable morphological features between individuals with yet unclear relations to function. For example, the hippocampus shows differences in the amount of digitations in the head (Ding & Van Hoesen, 2015; Piccirilli et al., 2020) and variable inferior dentations across individuals (Hove & Poppenk, 2020). Continued analyses in native space, voxel-wise transformations, and analysis of anatomically defined subgroups for later template creation and group-level comparisons are important to relate brain structure and function in a detailed manner.

The more anatomically sophisticated functional studies can become, the more interesting it will be to link functional connectivity findings to structural insights. For instance, the delineation of the human EC based on connectivity to various cortical regions (among which the retrosplenial) needs further examination. Structural studies can not only validate my findings by leveraging high-resolution methods such as polarized light imaging or ex vivo imaging (Adler et al., 2018; Axer et al., 2011; Oltmer et al., 2022). They can also show differences between basic structure and function and importantly structural connectivity studies in vivo may provide insight into the directionality of pathways (Dalton et al., 2022; C.-C. C. Huang et al., 2021; Syversen et al., 2021).

Sophisticated analyses procedures can reveal additional functional aspects of connectivity profiles. Novel analysis methods to study functional connectivity at voxel-to-voxel level could also explain the functional heterogeneity within seed regions (for a recent review see e.g. Basti et al., 2020). Note that also the longitudinal axis of the entorhinal-hippocampal circuitry is organized by representational differences (Brunec et al., 2018, 2020; Collin et al., 2015; Keinath et al., 2014; Maurer & Nadel, 2021; Poppenk et al., 2013; Robin & Moscovitch, 2017; Strange et al., 2014). Voxel-to-voxel analyses can thus also help to understand how cross-axis organizational principles interact (Genon et al., 2021). Likewise, developed methods that allow the study of functional correlation based on information processing patterns are important to examine the complexity of the system (e.g. Coutanche & Thompson-Schill, 2013; Y. Li et al., 2017). The application of multivariate methods to ultra-high field data should be further intensified, especially for investigating representations within medial temporal lobe subregions. This is relevant for the exploration of ideas regarding the parahippocampal-hippocampal functional architecture that have been formulated on representational level and that require the investigation of joint voxel activity patterns (Kragel et al., 2018). In addition, combinations of intrinsic and task-related functional connectivity analyses, preferentially within-subject, can reveal how the general architecture is flexibly drawn upon under different task demands (see e.g. Rissman et al., 2004; Y. Wang et al., 2015 for task-related functional connectivity analyses).

6.3.2. A cartography of parahippocampal-hippocampal representations and connectivity

Future research can aim for a comprehensive cartography of the representational dynamics and connectivity within the parahippocampal-hippocampal system. Systematic assessment of the representational composition below the subregional level is key. Despite the advancements on insights into information-specific processing streams presented in this thesis, the actual nature of the represented information is still debated and requires verification (Knierim et al., 2014). Researchers used 'what versus where' (e.g. Ungerleider & Haxby, 1994), 'object versus spatial' (Reagh & Yassa, 2014), 'item versus context' (e.g. Berron et al., 2018), 'non-spatial versus spatial' (Henriksen et al., 2010), 'temporal versus spatial' (Beer et al., 2018), 'local versus global' (Knierim & Neunuebel, 2015) or 'sensory versus spatial' (Whittington et al., 2020) as descriptions. A systematic manipulation of stimulus material may reveal the type of processed information and, critically, differences in the level of convergence along the processing route. Multivariate analyses of brain activity are crucial to tap into the distributed nature and subtle differences between representational patterns. The obtained

insights may reveal how an episode gets decomposed and successively transformed into conjunctive, accessible representations. A representational cartography would advance functional understanding of the different types of representations, how they serve episodic memory, and additional cognitive functions.

Structural and functional connections among subregions that are flexibly adjusted to match task demands are an important pillar of the representational architecture within the parahippocampal – hippocampal system. Chapter II shows the potential in a combination of connectivity and information processing approaches which can be further advanced. Divergent connectivity patterns within a region may define functional subregions that differentially process and reflect information, as this has been done for the EC (Maass et al., 2015; Navarro Schröder et al., 2015 and Chapter II). Structural connectivity can inform the directionality of information flow. Advances to assess human structural connectivity with high spatial resolution in vivo, combined with functional assessments, are particularly important, given presumed layer-specific and below subregional patterns of organization in the system (e.g. Chapter II; Maass et al., 2014; Soltesz & Losonczy, 2018). Directionality is critical to understand the role of recurrency for conjunctive representations and convergence. Another exciting area for future work concerns task-related changes in functional connectivity that reveal how the basic architecture is tuned for certain task demands. The wiring and networks of communication within the parahippocampal-hippocampal system are the backbone of its functional architecture, and can likewise reveal how the system is flexibly tuned in various situations to bring about episodic memory.

Accessing entorhinal-hippocampal representations supports not only episodic memory but also higher-level functions like abstract reasoning and generalization[12] (see e.g. these accounts: Behrens et al., 2018; Ekstrom & Ranganath, 2018; Igarashi et al., 2022; Kumaran & McClelland, 2012; Morton & Preston, 2021; Zeithamova & Bowman, 2020). An intriguing idea based on the cognitive map theory (O'Keefe & Nadel, 1978; Tolman, 1948) is that these generalizations can be made on any kind of input (Behrens et al., 2018). Thus, the functional architecture of the parahippocampal-hippocampal system can also be drawn upon when representing abstract knowledge (e.g. social maps in Park et al., 2021). Instead of travelling through experiences, we can travel through an imaginative space of abstract concepts (for instance family trees) and perform inferences between their elements (Behrens et al., 2018). Advanced conceptual proposals exist for how the architecture of the parahippocampal-hippocampal system achieves inference of regularities and generalize across different knowledge structures, though with sparse empirical evidence. Functional ultra-high field imaging and multivariate analyses approaches can help to examine how the interplay of segregated context representations and convergence is suitable to extract structure and represent highly abstract information in a map-like structure (Park et al., 2020; for a computational account on structure extraction see Whittington et al., 2020). Further cortical (especially prefrontal and parietal) communication of the parahippocampal-hippocampal system is necessary to consider as recurrencies of information eithin the system and between the system and the neocortex are proposed to be important for the generalization of concepts and the acquisition of representations of abstract information (as in Kumaran & McClelland, 2012; Morton & Preston, 2021; Peer et al., 2021). Future work may reveal how the functional architecture of memory representations in the parahippocampal-hippocampal system serves cognitive functions beyond episodic memory.

[12] Generalization describes the application of past experiences to novel input. There is considerable empirical evidence for hippocampal involvement in inferential tasks. These tasks test the detection of relations between distinct stimuli that are presented in a set of experiences (Barron et al., 2020; Koster et al., 2018; Schlichting et al., 2014; Shohamy & Wagner, 2008).

6.6.3 Pathology progression and memory content

Future research should further integrate clinical and cognitive accounts on the functional architecture of the parahippocampal-hippocampal system. Both perspectives enrich each other. Mapping specific cognitive alterations to pathology progression and a distorted parahippocampal-hippocampal system aids understanding of Alzheimer's disease and preclinical diagnostics. At the same time, it aids understanding of the system itself and of the nature of episodic memories. The specific trajectories in early Alzheimer's pathology then serve as finegrained and progressive lesion model. Investigations will be most revealing with longitudinal approaches, and with the recent advances and continued achievements in PET tracers that allow testing for pathology spread by tau or amyloid (Maass et al., 2017; Mattsson et al., 2019). While multimodal, longitudinal, high-resolution assessments of large cohorts are logistically challenging, current multicenter studies provide early insights (e.g. Berron et al., 2021; Düzel et al., 2022).

The relationship between Alzheimer's pathology and function is still un clear. Tau putatively spreads along functional pathways (Franzmeier et al., 2022; Vogel et al., 2020; J. W. Wu et al., 2016). The forged functional route that encompasses Area 35, anterior EC subregions and the subiculum/CA1 border appears important as it is vulnerable for early Alzheimer's tau pathology progression (Berron et al., 2021; Lace et al., 2009). Via the retrosplenial cortex that I also identify as part of the route, tau may progress towards the neocortex (Ziontz et al., 2020, 2021) and potentially converges with amyloid pathology (for empirical hints on a retrosplenial function - amyloid relationship see George et al., 2014; Poirier et al., 2011). This provides one possibility how early, spatially separated tau and amyloid may merge and cause widespread pathology throughout the brain. Longitudinal evaluations that combine multiple modalities (in vivo tau and amyloid PET, high-resolution functional imaging), and may in very rare cases even include a final histological assessment, can explore this critical idea. Likewise, further specification of the information that is processed along preclinically altered functional routes is critical to differentiate healthy and pathological aging and for cognition-based diagnostic in preclinical stages.

Cognitive staging of preclinical Alzheimer's, moreover, requires memory assessments on representational level, such as drawings, behavioral probing of carefully composed events at multiple informational levels (as e.g. in Andermane et al., 2021; Bainbridge, Hall, et al., 2019; Morgan et al., 2019), and functional assessment with multivariate methods (Diedrichsen & Kriegeskorte, 2017; Haynes, 2015). Furthermore, the dynamics among elements within and across memoranda seem to affect memorability. Replayed information after learning (Momennejad, 2020; X. Wu & Foster, 2014) could be one exciting way to probe which aspect of a memorandum is salient during higher-level processing, how elements become internally structured and how these processes relate to disease stage and cognition. These efforts can reveal memorable aspects, thus islands of recollection and their underpinning mechanisms.

As an event is represented at multiple levels across the parahippocampal-hippocampal system, questions arise regarding whether preserved 'islands of recollection' may help to access memories and their resulting experiential nature. When certain mnemonic aspects withstand decline, cognitive strategies may be tailored towards these intact memory representations to deliberately make memories memorable and accessible (Bastin et al., 2013; Kirk & Berntsen, 2018). A sense of reliving is associated with holistic recollection (Gardiner, 2001; Tulving, 1985). Future work should examine which aspects of a memory representation are essential for a sense of reliving, and if reliving can be elicited by fragmented memories, promoting a sense of self (El Haj et al., 2019; Prebble et al., 2013; Strikwerda-Brown, Grilli, et al., 2019; but see Irish, Lawlor, et al., 2011;).

In conclusion, this doctoral thesis contributes to our understanding of the complex functional architecture of memory representations in the human brain. The human brain recollects memories with an astonishing level of detail, binding together the many elements that compose an episode. Critical for episodic memory is the parahippocampal-hippocampal system. Rodent research and computational models have inspired theories about organizational principles in the system's functional architecture. I here investigated and discussed these principles in the human parahippocampal-hippocampal system, notably on a subregional level. I conclude that (1) subregional dynamics within the system and their interaction with neocortical structures provide key insights into memory function and that (2) specific aspects of information are dissected in an organized manner within the system, with implications for the nature of memory representations.

Based on empirical evidence and translational literature reviews, I identify routes for information communication and processing, as well as memory access in the parahippocampal-hippocampal system. My findings reveal a highly topographical organization. This structure segregates and converges context and item-related aspects of experiences, and communicates these aspects from cortical regions along specific functional routes through the parahippocampal gyrus and hippocampus. While cortical streams process item and context information in a largely segregated manner, I show for the first time that item and context information may converge before the hippocampus along a specific functional route. In addition, I identify another functional route that specifically segregates contextual scene information. These two processing routes are consistent with recent rodent literature and functionally split the EC and the transversal sub/CA1 axis in the hippocampus. I discuss the benefits of an interplay of segregation and convergence for the formation and organization of memory representations and for their access and recollection. In addition, I show for the first time in humans what computational and rodent models have long indicated: cortical reinstatement and comprehensive recollection of full episodes specifically involve hippocampal subregion CA3. Finally, I provided a clinical perspective on my findings. The outlined functional architecture, together with reports on the inherent memorability of certain mnemonic information, conceptually leads to landscapes of memories. Critically, in early Alzheimer's disease, these landscape memory representations may fragment in a way that directly reflects distorted aspects of the underlying parahippocampal-hippocampal system.

This thesis illustrates the benefit of translational approaches that connect animal, computational and human findings, and the need to investigate the functional architecture at subregional level. I advanced the field with a combined methodological approach of functional connectivity and information processing analyses on ultra-high field functional data, together with translational literature insights. This provides comprehensive insight into the functionality of the human parahippocampal-hippocampal system at a rare level of subregional detail.

This work also provides a fundamental basis for future research that could further specify the nature of various representations within the system, show their implications for cognition beyond episodic memory, and examine how humans can flexibly draw upon this scaffold of functional architecture under various task conditions. Likewise, investigating the effects of Alzheimer's pathology within the functional architecture of memory representations may have implications for early diagnostics and for our basic understanding of episodic memories. My thesis is a step forward in understanding the emergence of cognitive functions from the brain's architecture, and unravelling this miracle of human nature.

VII. REFERENCES

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APPENDIX

SUPPLEMENTARY INFORMATION TO CHAPTER II

Similar to Chapter II, the supplementary is part of a peer-reviewed publication in *eLIFE* (Grande et al., 2022 *eLIFE*). With minor edits the supplement is integrated into the thesis.

I. Left hemisphere results

Four cortical sources divide the left entorhinal cortex in retrosplenial-, parahippocampal-, Area 35- and Area 36-based seeds

Based on functional connectivity preferences to the sources parahippocampal cortex, retrosplenial cortex, Area 36 and Area 35, I obtained four leftentorhinal seeds. The majority of voxels can roughly be described as clustering in the posterior-medial entorhinal portion for the $EC_{PhC\text{-}based}$, the anterior-medial (and posterior-medial) portion for the $EC_{RsC\text{-}based}$ seed, the anterior-lateral portion for the $EC_{Area35\text{-}based}$ and the posterior-lateral portion for the $EC_{Area36\text{-}based}$ seed (see supplementary II for exact voxel counts). Note that both perirhinal-based entorhinal seeds extended along the anterior to posterior axis such that the $EC_{Area35\text{-}based}$ progresses more along deep entorhinal portions (with a main focus anteriorly) and the $EC_{Area36\text{-}based}$ along superficial entorhinal portions (with a main focus posteriorly, see Figure S1 and the medial reflection of the EC seeds).

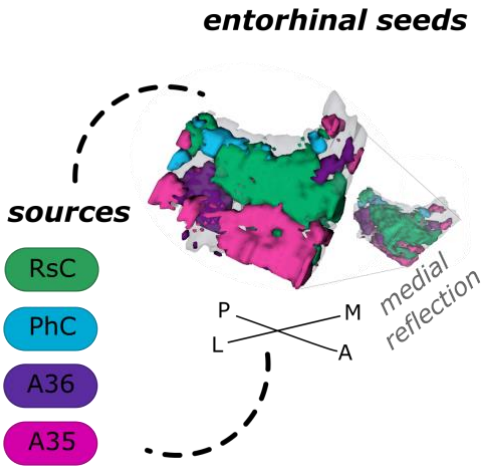

Figure 18. Left entorhinal seed regions based on connectivity preferences to cortical regions. *Displayed is the left entorhinal cortex (EC) as a 3D image with colored seed regions. The seed regions have been identified based on a source-to-voxel functional connectivity analysis and resulting connectivity preference to either the left retrosplenial cortex (RsC, green), parahippocampal cortex (PhC, blue), Area 36 (A36, purple) or Area 35 (A35, pink) sources. Note that preferences to Area 36 are best visible from a medial perspective on the EC as depicted in the medial reflection. Seed regions have been determined based on the maximum voxels across four one-sample t-tests at group level, one per source. M – medial; L – lateral; A – anterior; P – posterior.*

Left distal subiculum is functionally connected with the $EC_{PhC\text{-}based}$ seed and the subiculum/CA1 border to $EC_{RsC\text{-}based}$ and $EC_{Area35\text{-}based}$ seeds

When extracting estimates of connectivity preferences across individuals from proximal and distal hippocampal subregion segments for either entorhinal seed, repeated measures ANOVAs revealed significant seed X segments interaction effects along the transversal axis of the left subiculum and CA1 (subiculum: $F(12,372) = 4.609$; $p < .001$; CA1: $F(6,186) = 2.458$; $p = .047$; see Figure S2).

In the left subiculum, additional repeated measures ANOVAs showed that the $EC_{Area35\text{-}based}$ ($F(4,124) = 4.489$; $p_{FDR} = .025$), and $EC_{PhC\text{-}based}$ ($F(4,124) = 8.701$; $p_{FDR} < .001$) seeds displayed a significant main effect across the transversal subiculum axis. Here, the transversal preference to the $EC_{RsC\text{-}based}$ entorhinal seed does not survive FDR correction ($F(4,124) = 4.489$; Huynh-Field uncorrected $p = .05$), shows however the same tendency as in the right hemisphere. The differential functional connectivity preferences for the $EC_{Area35\text{-}based}$ and $EC_{PhC\text{-}based}$ seed interacted significantly across the transversal axis, as shown in a subsequent repeated measures ANOVA ($F(4,124) = 10.795$; $p_{FDR} < .001$).

In the left CA1, additional repeated measures ANOVAs showed that the connectivity preference towards the $EC_{RsC\text{-}based}$ seed displayed a significant main effect across the transversal CA1 axis ($F(2,62) = 6.753$; $p = .024$). In the distal CA1, the preferential functional connectivity with the $EC_{PhC\text{-}based}$ seed was higher than in the proximal portion of CA1. In the left CA1 a similar but weaker transversal pattern

was observed for connectivity preferences with the $EC_{Area36\text{-}based}$ ($F(2,62) = 3.841$; $p_{FDR} = .051$) and $EC_{PhC\text{-}based}$ seed regions ($F(2,62) = 3.468$; $p_{FDR} = .051$).

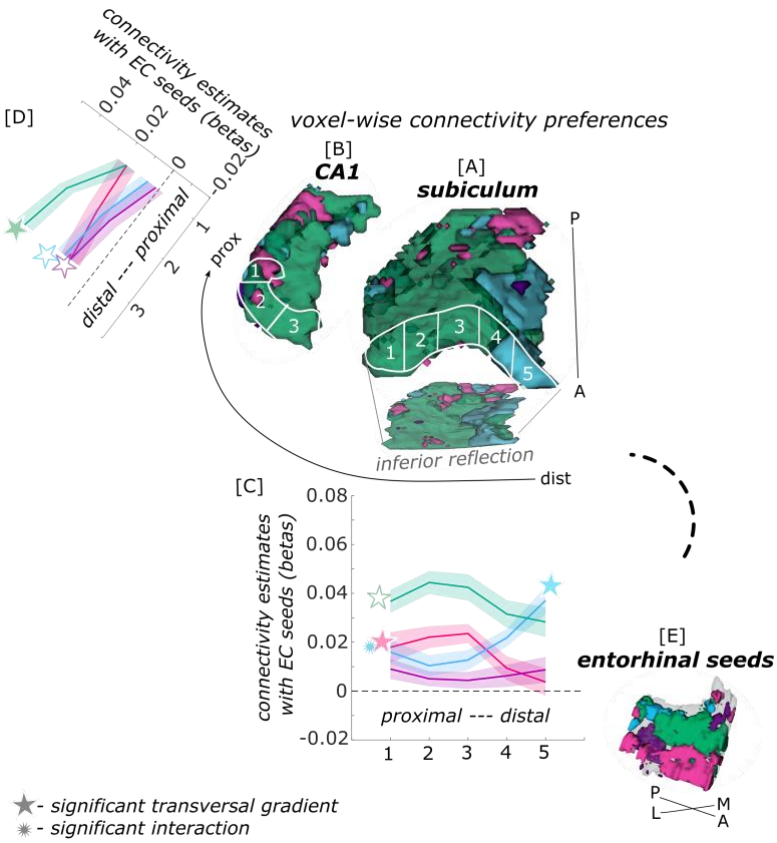

Figure 19. Functional connectivity preferences to entorhinal seeds along the subiculum and CA1 transversal axis, left hemisphere. *Displayed are the results of a seed-to-voxel functional connectivity analysis between the displayed left entorhinal seeds and the left subiculum and CA1 subregion. The 3D figure shows voxel-wise connectivity preferences to the entorhinal seeds (color coded to refer to the respective entorhinal seed [E]) on group level ([A] - subiculum; [B] - CA1). Note that preferences to the $EC_{Area35\text{-}based}$ seed (pink) are located mainly in the inferior subiculum and CA1 and are therefore visible in the inferior reflection. To display mean connectivity preferences across participants along the transversal axis, beta estimates were extracted and averaged from equally sized segments from proximal to distal ends (five segments in subiculum [A], three segments in CA1 [B]; schematized in white on the 3D figures) on each coronal slice and averaged along the longitudinal axis. Repeated measures ANOVAs revealed significant differences in connectivity estimates along the transversal axis in CA1 [D] and subiculum [C] with interaction effects in the subiculum. Displayed significances obtained by FDR-corrected post-hoc tests and refer to $p < .05$. Empty asterisks refer to effects that did not reach significance under FDR-correction. Shaded areas in the graphs refer to standard errors of the mean. EC – entorhinal; M – medial; L – lateral; A – anterior; P – posterior; prox – proximal; dist – distal.*

Left distal subiculum and $EC_{PhC\text{-}based}$ exhibit higher functional activity in the scene condition while other subregions show no difference between conditions

For the characteristics of information processing, I first focus on the left entorhinal seed regions. When extracting task-related parameter estimates for object and scene information conditions (operationalizing item and context information, respectively), a repeated measures ANOVA showed a significant interaction between region and information type (object versus scene; $F(3,93) = 9.772$; $p < .001$). Post-hoc t-tests revealed that only in the $EC_{PhC\text{-}based}$ seed region functional activity for scene information was significantly higher than for object information ($p_{FDR} = .003$), while in the remaining three left entorhinal seed regions no significant difference between object and scene conditions existed (see Figure S3).

In the left hippocampal subregions, extracting the task-related parameter estimates for object and scene conditions from proximal and distal segments within each participant showed a significant interaction between transversal segments and information type in the subiculum ($F(4,124) = 7.697$; $p < .001$), not however in CA1 as revealed by a repeated measures ANOVA. Post-hoc t-tests showed that only in the distal subiculum segments and in the middle segment significantly more scene than object information was processed ($p_{FDR} < .001$; $p_{FDR} = .0015$; $p_{FDR} = .027$ from distal to medial, respectively). In all other segments along the transversal axis, no significant difference in functional activity related to item and scene conditions existed (see Figure S4).

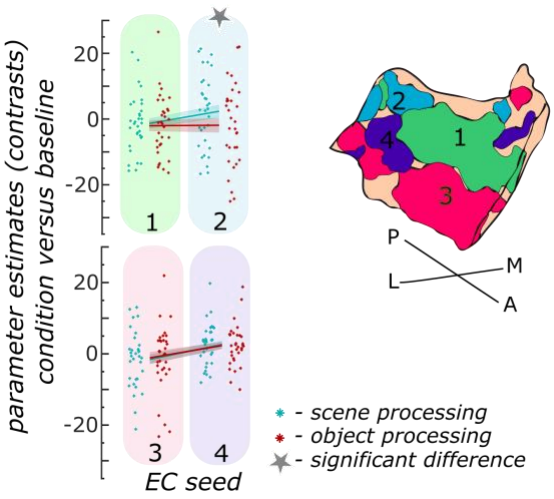

Figure 20. Functional activity during scene and object conditions in left entorhinal seed regions. *Displayed are the extracted parameter estimates for the object versus baseline contrast (red) and the scene versus baseline contrast (cyan) from each left entorhinal seed region per individual (dots) and summarized across individuals (lines). A schematic depiction of the respective entorhinal seed regions is displayed by a 3D drawing of the right EC. A repeated measures ANOVA revealed a significant interaction between condition and seed region. The displayed significant difference is obtained with FDR-corrected post-hoc tests and refers to p < .05. During the object condition, participants were presented with 3D rendered objects on screen, during the scene condition with 3D rendered rooms and during the baseline condition they saw scrambled pictures. The shaded area around the lines refers to standard errors of the mean. EC – entorhinal; M – medial; L – lateral; A – anterior; P – posterior.*

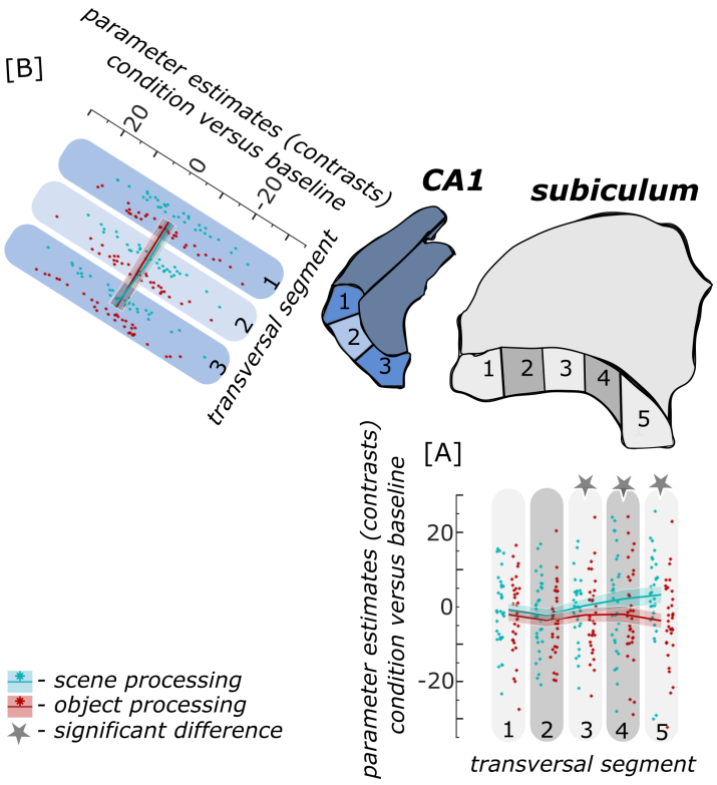

Figure 21. Functional activity during scene and object conditions along the transversal axis of left subiculum and CA1. *Displayed are the extracted parameter estimates for the object versus baseline contrast (red) and the scene versus baseline contrast (cyan) from the respective transversal segments in the subiculum ([A] grey) and CA1 ([B] blue) per individual (dots) and summarized across individuals (lines). A schematic depiction of the respective transversal segment is displayed by a 3D drawing of the right subiculum and CA1 subregions. Repeated measures ANOVAs revealed a significant interaction between condition and transversal segment in the subiculum only. The displayed significant difference is obtained with FDR-corrected post-hoc tests and refers to p < .05. During the object condition, participants were presented with 3D rendered objects on screen, during the scene condition with 3D rendered rooms and during the baseline condition they saw scrambled pictures. The shaded area around the lines refers to standard errors of the mean.*

II. Quantitative assessment of entorhinal seeds

To assess the main location of each cortical source preference within the EC, I cut the left and right EC in four quadrants. This was performed in T1 template space. First, the middle slice of all coronal slices that capture the EC was determined separately for each hemisphere. This slice was used to cut the EC in quadrants I, III and II, IV. Second, the middle slice of all axial slices that capture the EC was determined. This slice served to cut the EC in quadrants I, II and III, IV (see Figure S5). Note, to determine the most superior axial slice, the most posterior coronal level of the EC was used. Subsequently, I counted the number of voxels that have been assigned to each of the four cortical source regions after the initial functional connectivity analyses (that served to determined EC seeds). Averaged across hemispheres, most voxels assigned to the retrosplenial source are in EC quadrant I, most voxels assigned to the Area 35 source in EC quadrant II, most voxels assigned to the parahippocampal cortex in EC quadrant III and most voxels assigned to Area 36 in EC quadrant IV (see Table S1 for detailed voxel counts). Note that these quadrants do not refer to anatomically defined EC subregions.

Figure 22. Entorhinal cortex cut in four quadrants. *Illustrated is the schematic entorhinal cutting in four quadrants (I, II, III and IV) in the right hemisphere. Stippled lines illustrate approximate cuts. M – medial, L – lateral, A – anterior, P – posterior.*

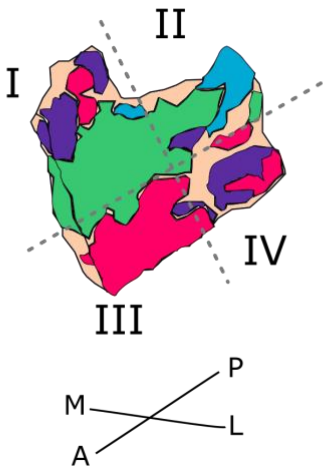

Table S1. *Number of voxels attributed to have a preferred functional connectivity to either cortical source within each EC quadrant (I.-IV.). Bold voxel numbers refer to the highest number across EC quadrants. EC – entorhinal cortex, RsC – retrosplenial cortex, PhC – parahippocampal cortex, A35 – perirhinal Area 35, A36 – perirhinal Area 36.*

EC quadrant	I.	II.	III.	IV.
RsC-source	**599**	421	337	173
PhC-source	13	**132**	0	0
A35-source	71	80	**433**	167
A36-source	103	51	39	**201**

III. Functional connectivity gradients by source and seed region

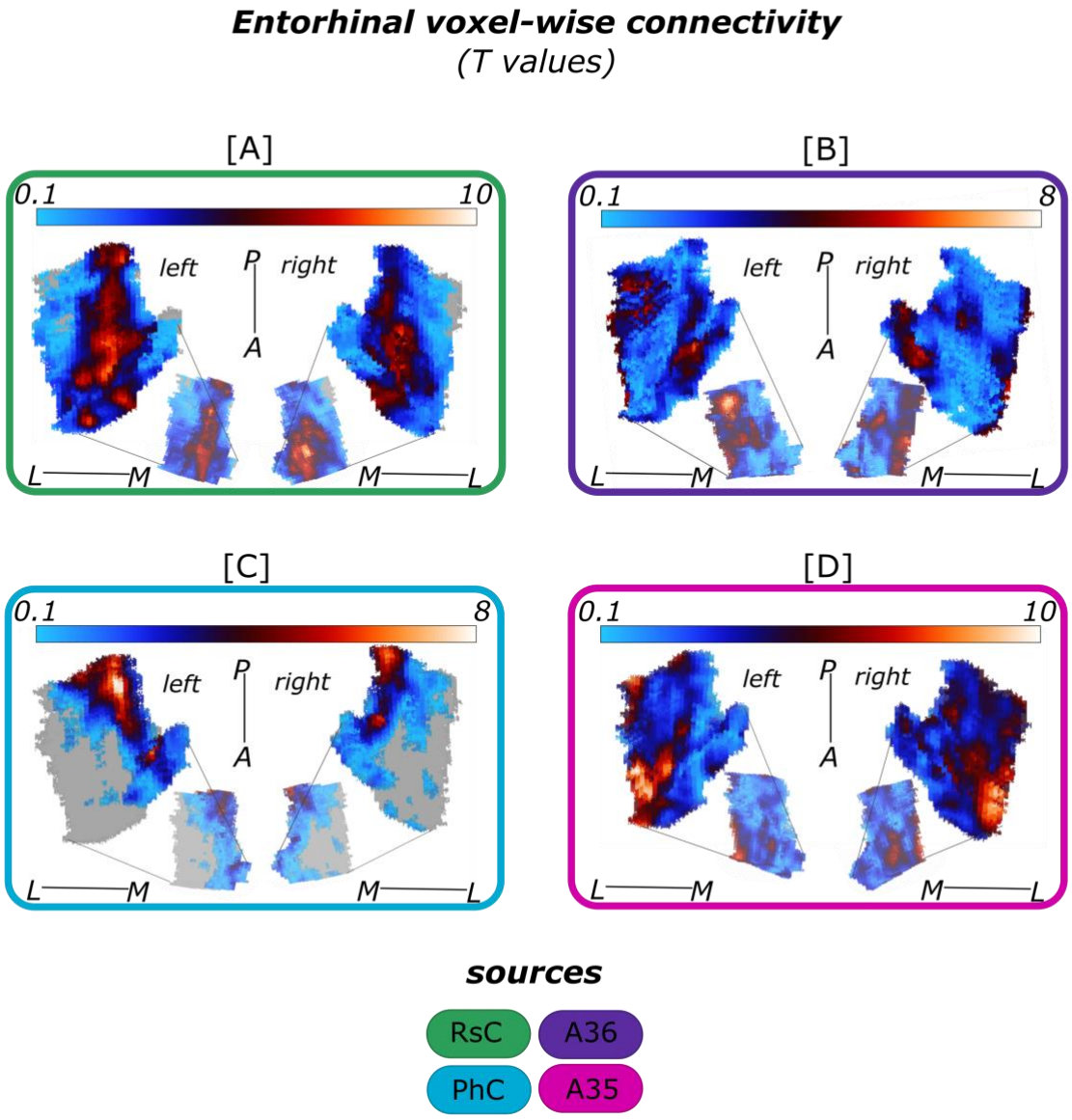

Figure 23. Entorhinal functional connectivity with isolated cortical sources. *Displayed are the voxel-wise functional connectivity values (T values) of the entorhinal cortex (EC) with the respective cortical sources [A] retrosplenial cortex (RsC, green), [B] perirhinal Area 36 (A36, purple), [C] parahippocampal cortex (PhC, cyan) and [D] perirhinal Area 35 (A35, pink). Results from left and right hemisphere one-sample t-tests for the functional connectivity with the respective source are displayed alongside each other for each cortical source. The smaller EC maps in the middle of each rectangle are medial reflections of the respective results. Colorbars reflect the range of T values. Grey areas refer to T values of T < 0.1. L – lateral; M – medial; A – anterior; P – posterior.*

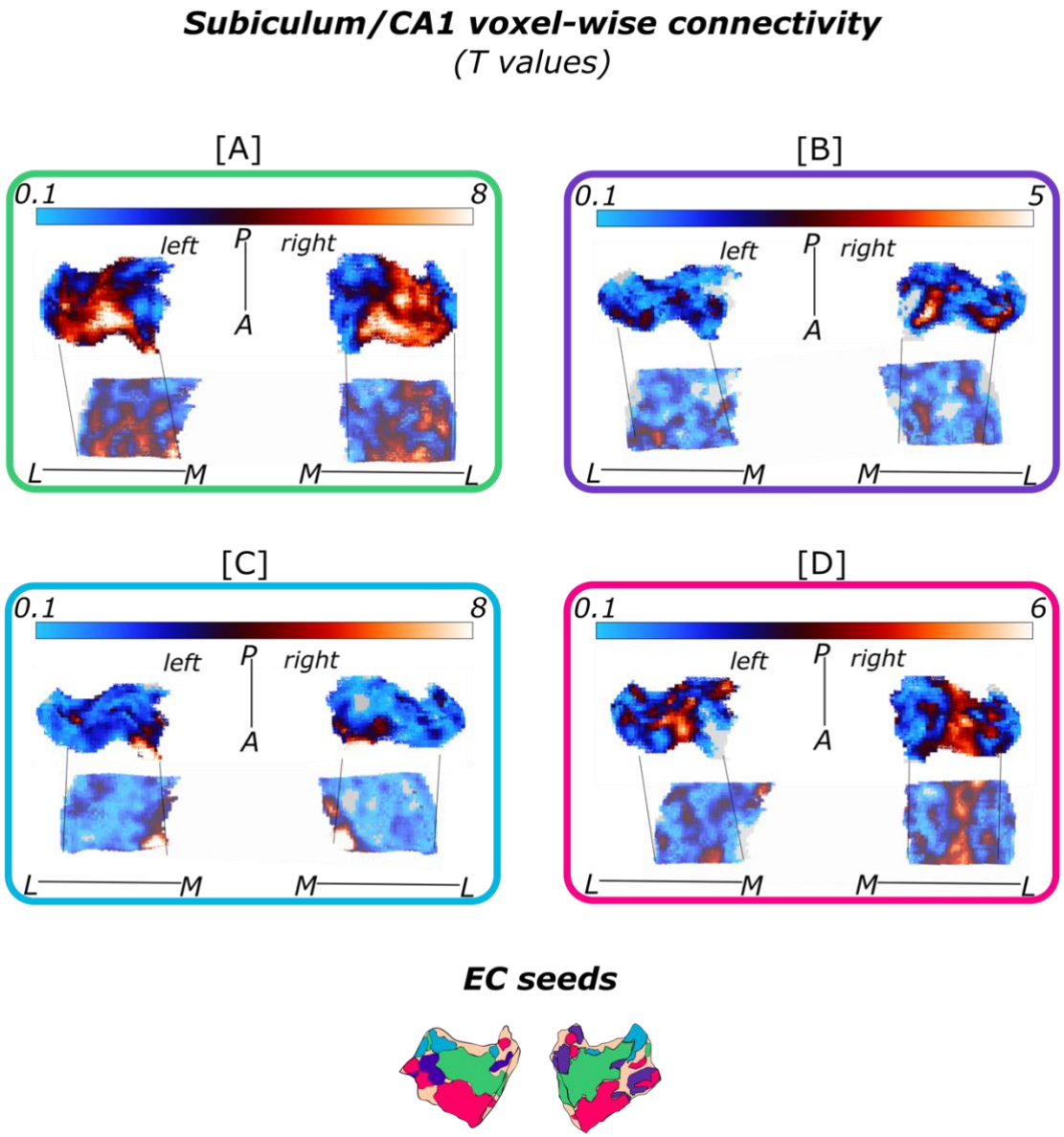

Figure 24. Subiculum/CA1 functional connectivity with isolated entorhinal seeds. *Displayed are the voxel-wise functional connectivity values (T values) of the subiculum and CA1 to the respective [A] green ($EC_{RsC\text{-}based}$) [B] purple ($EC_{Area36\text{-}based}$), [C] blue ($EC_{PhC\text{-}based}$) and [D] pink ($EC_{Area35\text{-}based}$) EC seeds. The respective seeds are illustrated in the lower panel. Results from left and right hemisphere one-sample t-test for the functional connectivity with the respective seed are displayed alongside each other. The lower subiculum/CA1 maps within each rectangle are inferior reflections of the respective results. Colorbars reflect the range of T values. Grey areas refer to T values of T < 0.1. L – lateral; M – medial; A – anterior; P – posterior.*

IV. Quality assurance measures of manually segmented regions-of-interest

The individual regions of interest were segmented by the same two experienced raters that also segmented a subsample of the data (24 hemispheres of 22 participants) for a previous publication (Berron et al., 2017). Quality assurance measures were calculated for that subsample. Regarding intra-rater reliability, the dice similarity coefficients are above 0.88 for all segmented regions (region-specific means (SD) are as follows: parahippocampal cortex 0.93 (0.03); Area 36 0.91 (0.02); Area 35 0.88 (0.02); EC 0.91 (0.01)). The intraclass-correlation coefficients for intra-rater reliability are all above 0.95 (parahippocampal cortex 0.99; Area 36 0.96; Area 35 0.97; EC 0.98). For the inter-rater reliability, dice similarity coefficients are above 0.84 for all segmented regions (region-specific means (SD) are as follows: parahippocampal cortex 0.86 (0.12); Area 36 0.91 (0.02); Area 35 0.84 (0.05); EC 0.87 (0.02)). The intraclass-correlation coefficients for inter-rater reliability are all above 0.78 (parahippocampal cortex 0.94; Area 36 0.88; Area 35 0.87; EC 0.94; see Berron et al., 2017).

V. Metrics for transversal subiculum and CA1 segments

Transversal subiculum and CA1 segments were cut on the group template T1 images. The average number of voxels contained in each subiculum segment was 460.8 voxels for the left subiculum (SD 104.36) and 458 voxels for the right subiculum (standard deviation 75.09). For the left CA1 the average equals 360 voxels (standard deviation 27.58) and 335 voxels for the right CA1 segments (standard deviation 3.56, see Table S2 for segment-specific values and Figure S11 for an illustration).

Table S2. *Number of voxels in transversal subiculum and CA1 segments for each hemisphere.*

	left hemisphere (distal to proximal segments)					*right hemisphere (distal to proximal segments)*				
subiculum	340	419	511	396	638	338	465	451	460	575
CA1	399		341		340	337		330		338

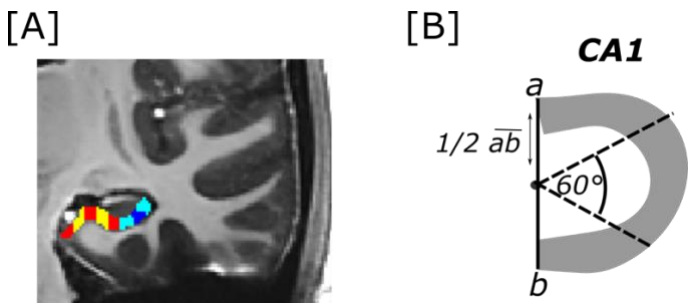

Figure 25. Transversal subiculum and CA1 segments. *[A] Displayed are segments cut along the transversal subiculum (red and yellow) and CA1 (cyan and dark blue) axis in the right hemisphere. Segments were cut on coronal images (as displayed in the example image) on the study-specific T1 template. [B] To cut CA1 segments the endpoints of the transversal CA1 axis (a and b) were connected. From the middle point of that line CA1 was cut into three segments by two lines oriented in 60° angles from the line that connected a and b*

LIST OF ABBREVIATIONS

CA – cornu ammonis

DG – dentate gyrus

PrC – perirhinal cortex

EC – entorhinal cortex

transversal Sub/CA1 axis – transversal axis of hippocampal subiculum and CA1

SRLM – stratum radiatum, lacunosum and moleculare

CSF – cerebrospinal fluid

(f)MRI – (functional) magnetic resonance imaging

PET – positron emission tomography

EPI – echo-planar imaging

MPRAGE – magnetization-prepared rapid gradient-echo

FOV – field of view

TR – repetition time

TE – echo time

ROI – region-of-interest

FDR – false-discovery-rate

GLM – general linear model

ANOVA – analysis of variance

SD – standard deviation

MCI – mild cognitive impairment

SPM – Statistic Parametric Mapping package (Wellcome Trust Centre for Neuroimaging, London)

FSL – FMRIB Software Library (Oxford Centre for Functional MRI of the Brain)

ANTS – Advanced Normalization Tools

LIST OF FIGURES AND TABLES

DECLARATION OF HONOR

I hereby declare that I prepared this thesis without impermissible help of third parties and that none other than the indicated tools have been used; all sources of information are clearly marked, including my own publications.

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- Fabricated data or rejected undesired results
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