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The Parahippocampal-Hippocampal Region: Differentiation in Structure and Function

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2009

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citation for published version (APA)

van Strien, N. M. (2009). *The Parahippocampal-Hippocampal Region: Differentiation in Structure and Function*. s.n.

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chapter

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General discussion

The general aim of this thesis was to identify individual contributions of sub-regions of HF – PHR using a combination of anatomical and functional approaches. First, we provide an overview of the results, which will then be discussed in the light of current models of HF – PHR function. Finally, two key issues will be addressed that remain to be solved in future research.

Summary of aims and results

In chapter 2, the extensive anatomical literature on HF – PHR connectivity was reviewed, aiming to include all documented connections in the rat. We argued that current theories of HF – PHR function could benefit from such detailed anatomical knowledge since this is a necessary requirement to understand function. Moreover, this may eventually lead to theories that have greater biological plausibility than current ones. We showed that many currently known anatomical details are not included into the circuit-diagrams as used in the standard model. In addition to providing a practically useful tool to consider all known connections, we have also emphasized that for many connections topological information is available. These details are often not fully appreciated, due to the already overwhelming complexity of the network. A novel approach was presented to interactively display all known HF – PHR connections of the rat and their topological organization. Although the interactive diagram has its own limits, for example the absence of information about connection strength or the excitatory and inhibitory nature of connections, it is to our knowledge the first attempt to create an interactive diagram of the full circuitry.

In chapter 3, we challenged the prevailing view that the association of different elements that constitute a memory is exclusively mediated by HF. We examined if an associative network exists outside HF that could combine neocortical information that is directed towards HF by way of the perirhinal and postrhinal cortices. Eventually, the separate input from the perirhinal cortex and postrhinal cortex has to be associated in order to encode, consolidate or retrieve the combined representation. We predicted that convergence would occur in the entorhinal cortex, based on the observation that both cortical areas send overlapping projections to the entorhinal cortex (Burwell and Amaral, 1998). Additionally, a recent report suggested that LEA is involved in odor-place associations (Mayeaux and Johnston, 2004), which supports the idea that the entorhinal cortex contains a network for association. We used an advanced anatomical approach (Wouterlood, 2006) to examine if projections from perirhinal and postrhinal cortices converge onto entorhinal cells that are identified as neurons projecting to HF. Although we observed the previously described intermingling of perirhinal and postrhinal fibers in the entorhinal cortex, we did not find evidence for convergence of these projections

onto entorhinal-to-hippocampal projection neurons. However, our results currently do not rule out that convergence of perirhinal and postrhinal projections occurs outside HF, since other extra-hippocampal pathways may exist, for example in PER, that were currently not examined.

In the next chapter, the topic changes from studies about the organization of HF – PHR circuitry to functions of the region using functional MRI in healthy human volunteers. In chapter 4, we examined the possibility that the HF – PHR circuitry is involved in non-mnemonic information processing, such as visual perception. Based on the perceptual mnemonic feature conjunction model (Bussey et al., 2005); see chapter 1 and 4), we predicted that HF – PHR would be more activated by viewing a stereoscopic stimulus, compared to a highly similar monoscopic stimulus. This proved to be the case, especially for the perirhinal cortex. Our results support the perceptual mnemonic feature conjunction model and consequently, indicate that both HF and PHR are involved in mnemonic as well as in non-mnemonic information processing. Moreover, the data support a functional differentiation between sub-regions of the PHR on the one hand and HF on the other, in that visual complexity is preferentially dealt with in the perirhinal cortex.

In the last chapter, we addressed the mnemonic component of HF and PHR in more detail, focusing on their role in crossmodal memory. Although crossmodal memory is a characteristic feature of declarative memory, to date only few studies have examined it. We predicted that either the HF or the perirhinal cortex might take a key role in associating information from different modalities. As already mentioned, HF is considered the typical brain region in which different elements that are part of a single experience are associated. However, the perirhinal cortex is a main recipient of multiple types of sensory information (Suzuki and Amaral, 1994) and has been implicated in crossmodal memory (Goulet and Murray, 2001; Lee et al., 1988; Murray and Gaffan, 1994; Murray and Mishkin, 1985; Taylor et al., 2006). By comparing brain activation between a crossmodal retrieval condition and a baseline task, we observed that HF and PHR are both active when retrieving crossmodal information. However, when crossmodal retrieval was compared to unimodal retrieval, only the (left) perirhinal cortex showed increased activation. This suggests that both HF and perirhinal cortex are active during crossmodal memory retrieval, but that the perirhinal cortex is critically and selectively involved in the process of retrieving information on associated sensory information in different modalities.

A second question that could be addressed using the same experimental paradigm is whether HF and PHR activation in crossmodal retrieval depends on modality. We expected HF and PHR to be involved in crossmodal memory for multiple modalities, since this had been shown in separate experiments for auditory (Tanabe et al., 2005) and tac-

tile (Goulet and Murray, 2001) information. However, it was never addressed whether HF and PHR would be similarly involved in auditory-visual or tactile-visual associations. One reason to expect a difference is that different types of sensory information may be of different relevance. Comparing brain activation between auditory-visual and tactile-visual retrieval yielded increased activation in both HF and PHR when auditory information was presented. These results indicate that HF and PHR are differentially activated in crossmodal retrieval of different modalities.

A third question that was examined concerned whether HF and PHR activation is dependent on inferential distance of retrieval. Contemporary theory predicts increased HF activation when stimuli are only indirectly associated (Moses and Ryan, 2006), compared to when they are directly linked. Therefore, we expected to see increased HF activation in the inferential condition compared to the learned condition. This was only the case in the comparison of tactile-visual inferred over tactile-visual learned retrieval. This provides only partial support for a role of HF in inferred crossmodal retrieval.

The HF and PHR: conclusions and perspective on structure and function

The examples of HF – PHR structural and functional research given in this thesis, allow for two general conclusions that will be discussed in this section. The first is that the HF and PHR sub-regions can functionally be differentiated. Our data (van Strien et al., 2008) support previous suggestions that the perirhinal cortex is specifically involved in visual perception of objects (Bartko et al., 2007). Using a similar approach, it was recently shown that when comparing spatial scenes of low and high complexity, increased activation occurs mainly in the parahippocampal cortex, which was related to increased complexity (Bar et al., 2008). Furthermore, our data support a preferential involvement of HF in inferred learning protocols, in line with earlier suggestions.

We also observed that the HF and PHR sub-regions do not act as uniform modules. The fact that sub-regions are not functionally homogenous could be related to connectional observations discussed in chapter 2. Often, within a sub-region a connectional topology exists such that different parts within a sub-region can be distinguished. Data, not only in the rat, but also in for example monkeys and cats (see Witter et al., 2000 for a review), show for example that the septal half of HF receives stronger cortical input from the dorsolateral part of the entorhinal cortex, whereas the temporal half of HF receives stronger input from the ventromedial parts of the entorhinal cortex. In turn, the dorsolateral entorhinal cortex receives prominent input from neocortical regions (Kerr et al., 2007), whereas the ventromedial entorhinal cortex receives strong input from the hypothalamus and the amygdala (Petrovich et al., 2001; Witter and Amaral, 2004). This topology has been shown to have functional relevance. Lesions of septal HF

and the connectionally related dorsolateral portions of entorhinal cortex results in striking navigational deficits. In contrast, lesions in the temporal hippocampus and related ventromedial portion of the entorhinal cortex do not yield strong navigational deficits, but result in strong alterations in fear related behavior (Kjelstrup et al., 2002; Moser and Moser, 1998). Moreover, it was recently suggested in humans that activation in the anterior HF predicted memory for emotional items, whereas posterior activation predicted memory for neutral items (Dolcos et al., 2004). Alternatively, it was suggested that episodic and semantic memory are connected to different regions along the longitudinal axis of the HF (Giovanello et al., 2008). The posterior (septal) HF is more closely related to episodic memory, whereas the anterior (temporal) HF is more related to semantic memory. Finally, it was suggested that the posterior HF is related to recollection and the anterior half of the HF and the rhinal regions to novelty (Daselaar et al., 2006). Therefore, evidence from functional MRI studies in humans are in line with the outcome of anatomical, electrophysiological and behavioral studies in animals and suggest that in addition to ascribing functional differentiation within the HF - PHR to individual sub-regions, functional differentiation might also be mediated at a smaller scale, i.e. within individual sub-regions.

A second general conclusion is that the HF and the PHR both associate information, but they do so at different levels of complexity. Based on observations in the literature and this thesis, three processing levels can be distinguished. When looking at the HF – PHR network, the first, least complex level of association is likely to occur within the perirhinal and parahippocampal (postrhinal) cortices. At this level, information can be associated directly between stimuli, such as we observed for stimuli from multiple modalities, but also for complex conjunctions of visual features. At this level, non-spatial and spatial information are still relatively separated. For example, a recent study examined functional differences by comparing brain activation in spatial and non-spatial contextual associations. It was found that the anterior parahippocampal gyrus, which includes the perirhinal cortex, is activated in non-spatial contextual associations, whereas the posterior parahippocampal gyrus, consisting of the parahippocampal cortex, is involved in spatial contextual associations (Aminoff et al., 2007; Bar et al., 2008). At the next level of association, the non-spatial and spatial information may become associated. This association is likely to occur in the entorhinal cortex, possibly by way of the intrinsic connections between the lateral and medial entorhinal cortex. Cells in MEA are strongly spatially modulated whereas those in LEA are not (Hargreaves et al., 2005), but the latter are involved in odor-place associations (Mayeaux and Johnston, 2004). Finally, the highest level of associational complexity occurs in the HF. Here, information

from neocortical and subcortical regions are combined to form episodic representations in which elements that were not directly linked, such as observed in tactile inferential crossmodal retrieval, may become coupled (Giovanello et al., 2008). At this level of association, highly similar information can be transformed into unique, nonoverlapping complex representations (Bakker et al., 2008). Together, these findings support the idea that both the HF and PHR are involved in associative information processing at distinct levels of complexity.

Key issues for future research

Taking the results of the present thesis under consideration, at least two issues remain, that need to be addressed in future studies of HF – PHR connectivity and function.

The first concerns whether our current level of anatomical knowledge is sufficient. Currently, almost no objective information is available on the density of connections and even less is known about the functional efficacy of connections. Combinations of quantitative anatomical approaches and *in vivo* and *in vitro* electrophysiological approaches may be instrumental in this respect. Similarly, the restricted knowledge of the excitatory and inhibitory aspects of the circuitry limits functional thinking. The balance between excitation and inhibition sets the temporal dynamics of the system (Klausberger and Somogyi, 2008) and has been proposed to be critical for switching between the encoding and consolidating phase of episodic memory (Dragoi and Buzsaki, 2006). Although many current theories of HF – PHR function do not use the anatomical detailed information that is currently available, the aim is to advance understanding of both the HF – PHR structure and function, based on the assumption that anatomical detail will also provide valuable functional clues. Therefore, it would appear reasonable to accept the contention that the current level of connectional knowledge is insufficient.

The second issue concerns the question if the current functional terminology that is used when describing HF – PHR functions, hampers a fine-grained examination of the relation between the HF - PHR structure and functions. Current functional terminology is often vague, and when looking at brain activation studies, seemingly contradicting or isolated findings of regional function are reported. The previously described examples of anterior and posterior differences within the HF illustrate this point. It seems useful to aim to define what elements these seemingly different functions have in common and try to name these elements as part of a to be developed theory of HF-PHR functions.

Concluding remarks

The intricately connected networks of HF and PHR support a marvelous set of functions that are related to memory, navigation and perception. To define detailed models of HF – PHR functions that permit both theoretical and network level explanations is a major aim for future research. This requires objective techniques, meticulously defined theoretical concepts, but most importantly, inventive and inspired researchers.