THE INTEGRATION OF MEMORY AND VISUAL PERCEPTION IN
THE HUMAN MEDIAL TEMPORAL LOBE

by

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This research was conducted at the Department of Neuropsychology, within the Faculty of Psychology of the Ruhr University under the supervision of Prof. Dr. Boris Suchan.

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Statement

I certify herewith that the dissertation included here was completed and written independently by me and without outside assistance. References to the work and theories of others have been cited and acknowledged completely and correctly. The “Guidelines for Good Scientific Practice” according to § 9, Sec. 3 of the PhD regulations of the International Graduate School of Neuroscience were adhered to. This work has never been submitted in this, or a similar form, at this or any other domestic or foreign institution of higher learning as a dissertation.

The abovementioned statement was made as a solemn declaration. I conscientiously believe and state it to be true and declare that it is of the same legal significance and value as if it were made under oath.

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<td>ANOVA</td>
<td>analysis of variance</td>
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<td>BIC</td>
<td>binding of item and context</td>
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<td>BOLD</td>
<td>blood oxygen level dependency</td>
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<td>CA</td>
<td>cornu ammonis</td>
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<td>DG</td>
<td>dentate gyrus</td>
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<td>EC</td>
<td>entorhinal cortex</td>
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<td>FDR</td>
<td>false discovery rate</td>
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<td>FFA</td>
<td>fusiform face area</td>
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<td>FWHM</td>
<td>full-width half-maximum</td>
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<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<td>HC</td>
<td>hippocampus</td>
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<tr>
<td>HR-fMRI</td>
<td>high resolution functional magnetic resonance imaging</td>
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<tr>
<td>MTL</td>
<td>medial temporal lobe</td>
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<td>MTLMS</td>
<td>medial temporal lobe memory system</td>
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<td>MTLRS</td>
<td>medial temporal lobe representational system</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MVPA</td>
<td>multi-voxel pattern analysis</td>
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<td>PFC</td>
<td>prefrontal cortex</td>
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<td>PHC</td>
<td>parahippocampal cortex</td>
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<td>PRC</td>
<td>perirhinal cortex</td>
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<tr>
<td>PSC</td>
<td>percent signal change</td>
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<td>ROI</td>
<td>region of interest</td>
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<td>RT</td>
<td>reaction time</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>SEM</td>
<td>standard error of the mean</td>
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<td>TE</td>
<td>echo time</td>
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<td>repetition time</td>
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Abstract

The structures of the medial temporal lobe, including the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex, have been known to be essential for long-term memory processing for many decades. However, more recent research has demonstrated that the medial temporal lobe can also be needed for other cognitive processes apart from memory. It has been shown that higher level visual tasks can recruit structures like the hippocampus and the perirhinal cortex in order to successfully perform complex visual discriminations. Four studies were carried out in this doctoral thesis in order to investigate how the human medial temporal lobe does process mnemonic and perceptual tasks and to find a model that is suitable to account for all of the results.

In Study 1 a complex visual discrimination task and a recognition task were directly compared in an fMRI design with 20 participants. Both the processing of faces and the processing of scenes activated the hippocampus, regardless of the task type. Furthermore, stimulus-specific processing could be shown: While the left hippocampus was more strongly involved in the recognition of scenes, the right hippocampus showed stronger activation for the recognition of faces. Further analyses of the parahippocampal cortex and fusiform gyrus also showed stimulus specific processing in visual stream structures that propagate the information to the hippocampus. Overall, the results were in line with a perceptual-mnemonic theory of the medial temporal lobe and demonstrated hippocampal contributions to complex perception.

Study 2 employed the same behavioral paradigm and could demonstrate visual discrimination deficits in two patients suffering from brain lesions with differing location and origin. Both patients, one with extensive medial temporal lobe lesions (VG) and one with a small lesion of the anterior fornix (HJK), did show deficits in complex discriminations when compared to their matched control groups. VG was strongly impaired in discriminating scenes and faces with high feature ambiguity and in recollecting verbal and non-verbal information, while showing otherwise intact cognitive functions. Patient HJK was only clearly impaired in discriminating faces with high feature ambiguity, and did also show slight deficits in attention and working
memory in the neuropsychological tests. Study 2 confirmed the previous results and also extended the perceptual-mnemonic theory to the main output structure of the hippocampus, the fornix.

In Study 3, the neural correlates of category learning in medial temporal lobe were investigated in 28 participants. A paradigm that has been employed previously in humans and pigeons was adapted for this fMRI study, with two possible learning strategies, prototype-based and exception-based categorization. Results showed that the former strategy mainly recruited the fusiform gyrus, while latter was more dependent on hippocampal activations. Correlation analyses showed that these results were not based on a complete dichotomy or specialization of both structures, but rather on a temporal delay of processing in both structures. Study 3 demonstrated the contribution of medial temporal lobe structures to a perceptual learning task, establishing the basal neural underpinnings needed for a comparison of visual category learning and visual discrimination.

Finally, the aim of Study 4 was to integrate the results from all previous studies by investigating a potential overlap of mnemonic and perceptual tasks. For this, a visual category learning paradigm and a complex visual discrimination paradigm were employed in an fMRI design with 28 participants. Overall, the findings from all previous studies could be replicated. Furthermore, visual categorization learning and complex visual discriminations activated voxels within the same region, the left posterior hippocampus. This result is a strong support of a representational view of the medial temporal lobe, which focuses on the type of stimulus that is being processed at a time, and not on the underlying cognitive processes.

The results of the current thesis suggest that the medial temporal lobe is involved in a wide variety of cognitive processes, not limited to the mere encoding or retrieval of memory. The hippocampus, standing at the top of the processing hierarchy, is also needed for high level visual discriminations as well as for the categorization of visual stimuli, integrating complex visual conjunctions. After integrating all of the findings, the medial temporal lobe representational system was proposed, in which the medial temporal lobe is concerned with a domain preferential processing of various stimulus types, regardless of the task that has to be performed.
Chapter 1

General Introduction

1.1 Traditional models of the medial temporal lobe

Since the case of Henry Gustav Molaison, widely known in the classic scientific literature as patient H.M., the medial temporal lobe (MTL) has been functionally linked to long-term memory (Scoville & Milner, 1957). In order to alleviate his otherwise untreatable epilepsy, H.M. underwent a bilateral removal of the hippocampus (HC). During the procedure, large parts of the adjacent structures, like the entorhinal cortex (EC) and the medial temporal pole, were damaged as well. Following the procedure, he suffered from severe anterograde amnesia with an additional temporally graded retrograde amnesia (Squire, 2009), showing the importance of the MTL and especially the HC to human long-term memory.

1.1.1 The medial temporal lobe memory system

One classical theoretical view, the medial temporal lobe memory system (MTLMS), assumes that a subset of structures of the MTL (see also Figure 1.1) is concerned with purely mnemonic functions, especially with declarative memory for facts, events and relations (Squire, Stark, & Clark, 2004). These structures include the HC, the EC and perirhinal (PRC) as well as the parahippocampal (PHC) cortices (Eichenbaum & Cohen, 2001; Squire & Zola-Morgan, 1991). On the other hand, the theory does not assume an

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1 For reasons of simplicity, the term “hippocampal formation”, which – disputably – encompasses the dentate gyrus, CA fields, subiculum, presubiculum, and parasubiculum, will be referred to as “hippocampus”, abbreviated “HC”.

3
involvement of the MTL structures in other cognitive processes, such as perception (Clark, Reinagel, Broadbent, Flister, & Squire, 2011; Kim et al., 2011; Squire & Wixted, 2011). Furthermore, within the framework of this system, the various MTL structures are assumed to have no clear functional differences, resulting in similar deficits when either one of the structures is damaged (Squire et al., 2004; Squire & Wixted, 2011).

Figure 1.1: A schematic sagittal view of the human brain, with a focus on the MTL and associated structures. In the sagittal view, the EC would not be normally visible, since it is situated medial with respect to HC and PRC. For the sake of giving an overview, the EC is presented here as being situated anterior of the PRC. The HC receives inputs from its surrounding structures and conveys them via the fornix to the mammillary bodies, which are also connected to the anterior thalamus.
1.1.2 Functional segregations within the MTL

Other theoretical views propose that there are indeed functional segregations between these structures, with the HC sitting on top of a hierarchical structure (Lavenex & Amaral, 2000), receiving and integrating sensory inputs from two sources. While the PRC receives more inputs from ventral visual (“What”) pathways, the PHC processes inputs from the dorsal visual (“Where”) stream, with both structures further projecting to the EC and finally the HC (Eichenbaum & Lipton, 2008).

One model of recognition memory that assumes a functional segregation is the so-called two component model of recognition memory, in which the two processes recollection and familiarity can be distinguished (Diana, Yonelinas, & Ranganath, 2007; Yonelinas, 2001; Yonelinas, Aly, Wang, & Koen, 2010). Several different models of recognition memory have been put forward, but there has been a considerable amount of controversy around the question whether this distinction reflects one singular or two different processes, and whether these two processes are based on and processed by different anatomical structures.

There is, however, consensus on the definition of both processes: Through recollection, subjects can consciously retrieve previously learned information with a high degree of certainty, including its detailed temporal and spatial context. The structure enabling recollection is thought to be the HC (Moscovitch et al., 2005; Squire et al., 2004). Opposed to that, familiarity represents a feeling of knowing some contents about a previously encountered stimulus, with less certainty about its correctness and without further information about the context in which it was encountered. This process is thought to be based on processing in the PRC (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Ranganath et al., 2004).

Another debate surrounding the structures that enable our memory is the question if they are involved in episodic memory over longer periods of time. One theory, the multiple trace theory, assumes that the HC is required for retention and retrieval of episodic memories over extended periods of time, long after the initial encoding of said memories (Moscovitch et al., 2005; Nadel & Moscovitch, 1997).
Other theories, e.g. the consolidation theory, argue that the involvement of the HC is temporally limited, with the HC gradually transferring information to neocortical regions (Squire et al., 2004). There are only a few studies investigating the changes in the neural correlates of familiarity over extended periods of time, but it is assumed to fade quickly (Eichenbaum, Otto, & Cohen, 1994). More supporting data in favor of an anatomical separation of familiarity and recollection processes has been found in patient studies. Patients with ischemic damage to the right HC demonstrated an isolated impairment in recollection with intact familiarity (Peters, Thoma, Koch, Schwarz, & Daum, 2009). This evidence does support the view that familiarity and recollection are mediated by distinct structures of the MTL, because otherwise this double dissociation would not be possible.

In order to further investigate the contributions of HC and PRC to recollection and familiarity and their respective development over time, Suchan et al. (Suchan, Gayk, Schmid, Köster, & Daum, 2008) conducted a prospective study over a time period of six weeks. In this study, subjects had to encode three sets of colored everyday life objects. One subset was later on presented alongside new distractor images. In this retrieval phase, subjects had to first decide whether they recognized an item. Immediately after that, for the familiarity/recollection rating, they had to indicate whether they specifically remembered the particular item, or whether it just seemed familiar. This retrieval was performed immediately after studying the items, three weeks after the encoding, as well as six weeks after encoding. The results from this study support the notion that familiarity and recollection are two distinct processes mediated by different brain structures. While the HC showed activations for the recollection ratings, the PRC showed deactivations for familiarity ratings. Furthermore, these activation patterns persisted over an extended period of time (up to six weeks). Overall, these results are in line with the multiple trace theory (Moscovitch et al., 2005), showing an anatomical and temporal separation of recollection and familiarity.

There has also been contrary evidence, showing no differential involvement of the HC for familiarity or recollection (Wais, Wixted, Hopkins, & Squire, 2006; Wixted & Mickes, 2010). Therefore it has been suggested that evidence in support of a functional segregation might often be confounded with other cognitive processes, e.g. the effects
of memory strength (Squire, Wixted, & Clark, 2007; Wais, 2008; Wais, Squire, & Wixted, 2010). Taken together, there is still no consensus on the question if familiarity and recollection are part of the same process or two anatomically and functionally separable processes (Eichenbaum, Yonelinas, & Ranganath, 2007; Squire et al., 2007).

Another cognitive function mediated by the MTL that is assumed to be functionally segregated, is the processing of different stimulus types: Different approaches yield evidence for spatial memory being mediated by the PHC (Epstein & Kanwisher, 1998), whereas associative/relational memory is associated with the HC (Davachi, 2006; Eichenbaum et al., 2007). As mentioned above, the PRC is strongly connected with inferior temporal regions of the ventral visual processing stream, while the PHC is strongly connected to the dorsal visual stream (Lavenex, Suzuki, & Amaral, 2002; Suzuki & Amaral, 1994), making a specialized processing at least plausible. But yet again, it remains unclear how exactly items and context are being processed by the different MTL structures (Buffalo, Bellgowan, & Martin, 2006; Diana et al., 2007; Taylor, Henson, & Graham, 2007).

With the MTL being of central importance for memory processes, other structures that may be involved in memory have been identified. Recent research has shown that hippocampal-anterior thalamic connections are vital for human episodic memory (Aggleton et al., 2010; Pergola, Ranft, Mathias, & Suchan, 2013), together with more indirect pathways involving the mammillary bodies (see also Figure 1.1). The fornix connects the HC with the mammillary bodies and conveys most of the input and output of the hippocampal formation. It is therefore considered as part of the episodic memory system (Aggleton & Brown, 1999; Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011). It has been shown previously that fornix lesions can lead to memory deficits that are very similar to deficits resulting from HC lesions (Tucker, Roeltgen, Tully, Hartmann, & Boxell, 1988). Etiologies of fornix lesions can differ, but there have been a few cases in which specific infarctions of the anterior part lead to amnesia (Moudgil, Azzouz, Al-Azzaz, Haut, & Gutmann, 2000; Saito, Matsumura, & Shimizu, 2006). These cases are very rare and deficits can be alleviated after as much as one month. Furthermore, animal research has shown that a transection of the fornix can disrupt the learning of food-reward locations (Buckley, Charles, Browning, Philip, &
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Gaffan, 2004) as well as object discrimination learning in specific contexts (Gaffan, 1994), emphasizing its role in spatial processing as part of the Papez circuit (Bird & Burgess, 2008).

1.2 A perceptual role of the MTL

While the MTLMS posits that the MTL is exclusively involved in long-term declarative memory (Squire et al., 2004), recent studies have proposed an “emergent memory account” (Graham, Barense, & Lee, 2010) or a “perceptual-mnemonic theory” (Bussey & Saksida, 2005) of the MTL. These theories question the view that the MTL is only concerned with memory processing and suggest that its structures are also involved in visual discrimination tasks that put a high demand on the visual system (a so-called “high-feature ambiguity” or simply visual overlap). The first piece of evidence for putative perceptual functions of the MTL comes from a study investigating monkeys (Eacott, Gaffan, & Murray, 1994). Here, lesions to the monkey perirhinal cortex have led to deficits in a visual discrimination task with varying inter-stimulus intervals. The finding that perirhinal lesions in non-human primates lead to visual impairments for complex objects with many overlapping features supported the hypothesis that the PRC might act as a continuation of the ventral visual processing stream (Ungerleider & Mishkin, 1982), where it might represent complex visual conjunctions (Bussey & Saksida, 2005). On the other hand, studies investigating human subjects proposed that the HC is involved in the visual perception and processing of visual scenes, as opposed to the role of the PRC in object perception (Lee, Buckley et al., 2005).

1.2.1 The effect of MTL lesions on visual discrimination

Studies investigating human patients with lesions to the MTL show contradictory results. Amnesic patients performing in a visual discrimination task did not show any of the deficits that were found in monkeys (Stark & Squire, 2000). Interestingly, Lee,
Buckley et al. (2005) could show that patients with MTL damage can indeed exhibit perceptual deficits in visual discrimination tasks with morphed stimuli. Using images of faces, objects, outdoor scenes, as well as art, they provided evidence for impairments in scene processing after HC lesions. Furthermore, when patients suffered from larger MTL lesions including the HC and PRC, they were additionally impaired in face and object perception. Similar perceptual deficits in patients with MTL lesions could also be shown (Barense, Gaffan, & Graham, 2007). However, these results could not be replicated in another study using the same experimental paradigm (Shrager, Gold, Hopkins, & Squire, 2006). This might be explained by differing lesion assessments in the aforementioned studies (Suzuki, 2009).

Another possible explanation for a diminished performance of some patients in these discrimination tasks might be that healthy controls have an advantage through their use of episodic memory. Since the stimuli are shown in several trials over the course of the experiment, learning processes might help in these discrimination tasks. One way to overcome this possible confound is to use trial-unique stimuli. These stimuli are only shown in one trial over the course of the experiment and therefore healthy control subjects have no benefit from learning them. In a study employing this paradigm (Barense et al., 2007) it could be shown that patients suffering from PRC lesions performed on a normal level when objects were discriminable by differences in single features. However, when conjunctions of features had to be discriminated, their performance decreased significantly. One point of critique was that the lesions had a very heterogeneous etiology, ranging from virus encephalitis, over CO poisoning, to anoxia. These differing etiologies might have affected other brain regions and influenced the performance to a varying degree, which was also apparent by the variance of performance scores in the neuropsychological assessment. Yet another alternative explanation for the performance decline of patients in visual discrimination tasks might be the involvement of working memory. It has been shown that patients fail in discrimination tasks only if the size of the stimulus displays does extend the working memory capacity (Knutson, Hopkins, & Squire, 2012).
1.2.2 fMRI studies of visual discrimination in the MTL

Besides the investigation of patients with MTL lesions, there have been several fMRI studies employing visual discrimination tasks. Using a task without demands on declarative memory, it could be demonstrated that the right PRC is involved in perceiving and discriminating object identity changes (Lee, Bandelow, Schwarzbauer, Henson, & Graham, 2006). For this task, objects were placed on a 3 by 3 matrix and either their spatial arrangement or the objects themselves could vary. The spatial rearrangements did not yield any significant brain activation. Although there was no HC activation, which would have been expected in the first place, the authors concluded that the perirhinal cortex might be involved in higher order visual perception, which would be in line with a perceptual-mnemonic theory of the MTL. Additionally, the missing HC activation might have been caused by the low demands of the spatial rearrangement task (Lee et al., 2006).

HC activation in a discrimination task was found in a second study by the same group (Lee, Scahill, & Graham, 2008). An oddity task with faces and scenes shown from various viewing angles was employed in a block design. The discrimination of scenes resulted in significant posterior hippocampal and parahippocampal activation, while the face discriminations yielded significant activation of the anterior HC and PRC. This raised the question if different parts of the HC, along its longitudinal axis, are concerned with the processing of different stimulus types. Another finding was the decreased activation for stimuli that were presented repeatedly. Unfortunately, the block design that was employed in this study did not allow separating recollected and non-recollected stimuli in the analysis, so that activation of the PRC due to the novelty of a stimulus and activation of the HC due to recollection could not be estimated. Overall, the results of this study could not show a completely distinct involvement of HC for spatial processing and the PRC for object processing.

One problem shared by both fMRI studies is the fact that memory demands could not be eliminated completely. For one, both studies did not use trial-unique stimuli, so that a potential learning effect might have been present over the course of the experiments. Also, the discrimination tasks both included spatial manipulations (e.g. the spatial re-
arrangement of objects) alongside the perceptual task, which might have required working memory to some extent.

Additional support for a PRC involvement in the visual processing of faces and objects has been shown by Barense et al. (Barense, Henson, Lee, & Graham, 2010). Faces, scenes and artificial objects (so-called “greebles”, see also Gauthier & Tarr, 1997) were used in a discrimination task with varying stimulus views. The authors could show that the PRC was activated for the processing of faces and objects, while the posterior HC was activated for both faces and scenes. In a more recent study, they could also show an effect of stimulus familiarity, with stronger activations of the PRC and HC for familiar stimuli (Barense, Henson, & Graham, 2011).

Another common problem in fMRI studies investigating the MTL is the signal dropout due to local distortions of the magnetic field that are caused by air/tissue and bone/tissue interfaces (Olman, Davachi, Inati, & García, 2009). One study (O'Neil, Cate, & Köhler, 2009) tried to address this problem by employing high resolution fMRI (HR-fMRI) in a visual discrimination study. They applied a perceptual oddball paradigm and a forced choice recognition task with morphed face stimuli (resulting in stimuli with a high feature overlap). Comparing the activations from both tasks, they found significant activation in the right PRC for both of them, which suggests an overlap of perceptual and mnemonic processing in the MTL.

### 1.2.3 The importance of working memory

Another cognitive process that might be in part responsible for MTL activations in discrimination tasks is working memory. It is still under debate to what extent working memory is reliant on MTL structures. However, it has been shown that the HC is at least involved in certain working memory tasks (Hartley et al., 2007; Olson, Moore, Stark, & Chatterjee, 2006). Adding to this, studies with patients suffering from amnesia have shown that MTL damage does not only lead to long-term memory deficits, but also to short-term memory impairments (Hannula, Tranel, & Cohen, 2006; Ryan & Cohen, 2004). In contrast, working memory for relational information can also be unimpaired.
Chapter 1: General Introduction

after MTL lesions (Jeneson, Mauldin, & Squire, 2010). Studies using fMRI have also demonstrated that the HC can be activated in working memory tasks (Oztekin, Davachi, & McElree, 2010), also in interaction with parietal lobe structures (Oztekin, McElree, Staresina, & Davachi, 2009). Opposing to this, there is also evidence speaking against a general involvement of the HC in working memory (Baddeley, Jarrold, & Vargha-Khadem, 2011). In this study, a patient with lesions of both hippocampi did show a normal performance on a range of different complex working memory tasks.

Taken together, the role of the HC in working memory is still under debate and it is questionable how much working memory demands could be contributing to visual discrimination tasks, especially since Lee & Rudebeck (2010a) could show that the judgment of a single object in a discrimination task can be also impaired in patients with damage to the HC.

1.2.4 The role of the fornix

The role of the fornix in visual discrimination tasks without memory demands is yet unclear, since case studies with anterior fornix lesions usually focused on memory deficits. Taking into account its role in episodic memory (Aggleton & Brown, 1999; Metzler-Baddeley et al., 2011) and the evidence showing that the HC is involved in visual discrimination (Barense et al., 2007; Lee et al., 2008), it is highly probable that the fornix might also play a role in visual discrimination, since the fornix is a major output structure of the HC. Hence, if the HC is processing higher order visual information, the fornix is as well.
1.3 MTL and category learning

Another cognitive process that is at least partially mediated by the MTL is category learning. Enabled by this vitally important process (Ashby & Maddox, 2005), human and non-human animals can adequately react to their environment and hence avoid potentially noxious or lethal objects/situations (Smith et al., 2012). One example for successful categorization would be the correct differentiation of toxic and non-toxic plants, another one the correct identification of dangerous animals, as opposed to harmless ones. Categorization is not limited to objects; Abstract concepts can be learned and differentiated into groups as well (Smith & Minda, 1998).

One model of category learning assumes that categorization is based on two separate processes (Medin & Schaffer, 1978; Posner & Keele, 1968): Prototype-based strategies are used by successfully abstracting the central tendencies of stimuli belonging to one category (Smith & Minda, 1998; Smith & Minda, 2001). Exemplar-based strategies are storing the individual instances of one category, and when confronted with a new stimulus from the same category, are performing a generalization (Medin & Schaffer, 1978; Medin & Schwanenflugel, 1981). This example of a multiple systems model assumes that two single system models (prototype- and exemplar-based category learning) can address and explain previous data from categorization studies. Apart from that, various cluster-based models have been proposed. These assume that categorization is based on representations suitable for a specific learning context.

1.3.1 The SUSTAIN model

One example of a cluster model is the “Supervised and Unsupervised STratified Adaptive Incremental Network” model, abbreviated “SUSTAIN” (Davis, Love, & Preston, 2012; Love, Medin, & Gureckis, 2004). Within this model, category learning is explained by assuming an initial single cluster within the brain, which can code categories and features. This cluster can only represent a very simple category structure on its own. When it is confronted with a surprising event, i.e. a stimulus that does not fit
its initial representation, it recruits additional clusters. After several encounters with stimuli, this process results in a set of clusters that are competitively representing one category each (Love et al., 2004).

Another cluster model that is very similar to “SUSTAIN” is the rule-plus-exception model, abbreviated “RULEX” (Nosofsky, Palmeri, & McKinley, 1994). RULEX assumes that subjects are able to classify objects using a stochastic process. For this, they form simple classification rules with the occasional addition of exceptions, when new stimuli do not fit these rules. These two models do differ in one main aspect: In the RULEX model, categorization is explained by being based on two mutually exclusive categories. SUSTAIN on the other hand is able to be used as a much more general learning model (Love et al., 2004).

1.3.2 Neural correlates of category learning

There has been a considerable amount of research regarding the brain structures that participate in various forms of category learning. It has been shown that, depending on the experimental paradigm, different structures can be involved, e.g. the visual association areas, the MTL, the PFC, as well as the basal ganglia (Ashby & Maddox, 2005). But it is yet unclear which structures are exactly contributing to prototype- and exemplar-based category learning.

Prototype-based learning strategies might be mediated at least in part by the fusiform gyrus. This could be shown in categorization studies, in which the learning about the category membership of different objects changed the activation of the fusiform gyrus (Folstein, Palmeri, & Gauthier, 2013). The fusiform face area (FFA), which is located within the fusiform gyrus, is usually seen as being specifically responsible for face processing (Kanwisher, 2000; Kanwisher, McDermott, & Chun, 1997). However, it might also represent an area that is generally underlying visual expertise for various stimuli (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Pernet, Celsis, & Demonet, 2005; Tong, Joyce, & Cottrell, 2008).
The explicit memorization of individual stimuli that is performed in exemplar-based learning strategies might be processed by the MTL, since it would need memory systems that are tuned to sparse coding properties (Quiroga, Reddy, Kreiman, Koch, & Fried, 2005). In line with this, it has been shown that single neurons in the HC can be activated for category-specific visual responses (Kreiman, Koch, & Fried, 2000; Olshausen & Field, 2004; Quiroga et al., 2005). Furthermore, the cell firing within the HC can correlate with the performance in category learning (Hampson, Pons, Stanford, & Deadwyler, 2004).

Further evidence for a participation of MTL structures in category learning comes from studies using formal modeling within the framework of the SUSTAIN model. Here, in a rule-plus-exception learning task, the MTL was needed for the overall successful learning, showing the importance for the mastering of category rule exceptions (Davis et al., 2012).

1.4 A representational view of the MTL

As shown above, various cognitive processes are attributed to the MTL, e.g. memory processing, visual discrimination, and category learning. To explain these processes and their neural underpinnings, it might be helpful to focus on neural representations rather than on cognitive processes (Lee, Yeung, & Barense, 2012). Especially the HC, PRC, as well as the PHC would be of interest for this view, with their strong and differential connections that enable their interplay (Libby, Ekstrom, Ragland, & Ranganath, 2012).

One example of a model that focuses on the type of information that is being processed is the binding of items and context model (BIC), in which specific MTL regions are activated depending on the type of stimulus (Diana et al., 2007; Ranganath & D'Esposito, 2010). In this model, the PRC processes items, while the PHC processes their context. This information is then integrated (or bound) in the top layer of this hierarchical system, the HC. The EC might have domain-specific subregions, which receive non-spatial perirhinal input or spatial parahippocampal input, as has been shown recently (Schultz, Sommer, & Peters, 2012). Further support comes from studies
assuming that the HC might bridge representational gaps (Staresina & Davachi, 2009). It then acts as a “convergence zone” with again domain-specific inputs from the PRC and PHC (Staresina, Duncan, & Davachi, 2011).

Although initially a model for the understanding of recognition memory processing, the assumptions of the BIC model may be extended to other cognitive domains, like visual perception and working memory (Lee et al., 2012).

Taken together, MTL activity is very heterogeneous and dependent on different factors like strategies, task requirements and the type of processed information (Pustina, Gizewski, Forsting, Daum, & Suchan, 2012), and all of these findings are in favor of a representational model of the MTL.

1.5 Aims of the thesis

The present work aimed at investigating the contributions of the human MTL to various cognitive functions, including recognition memory, visual discrimination, as well as category learning, in order to explore its functional organization. In the past few years, there has been a lot of controversy about the involvement of MTL structures in certain processes, how these processes might interact with each other, and if there is indeed a partial or full functional segregation of the various MTL structures. The parallelism of organization of various cognitive processes does at least suggest that the underlying theoretical questions might be related, and that they might indeed address parts of the same problem.

This leads to the following central questions:

- How are memory and visual perception integrated in the MTL?
- Would it be more suitable to view the function of the MTL in the light of representations, rather than descriptive cognitive processes?
- What kind of model would be suitable to explain the processing of memory and perception within the MTL?
1.5.1 Studies

**Study 1:** Neuroimaging studies with human participants have been focusing on investigating visual perception in the MTL on its own, showing inconclusive results and not comparing it to memory processing (section 1.2). *The aim of Study 1* was to directly compare mnemonic and visual processing in a within-subjects fMRI study, employing a full factorial design with both tasks and different stimulus types (faces and scenes).

**Study 2:** It has been known for several decades that damage to the MTL leads to a disruption of long-term memory (section 1.1). Furthermore, single case patient studies have shown that damage to the anterior fornix can lead to memory deficits as well (section 1.1.2), but the effect of fornix lesions on visual processing has not been studied so far. *The aim of Study 2* was to test patients with lesions to the MTL and fornix with an established visual discrimination paradigm from Study 1, to show if they are similarly affected by lesions with different locations and etiologies.

**Study 3:** Categorization is a visual learning process that is in part reliant on MTL structures. Recent research has shown that category learning can be explained with different models. One of these models assumes that there are two learning strategies that are used by humans and animals, namely prototype- and exemplar-based strategies. The neural correlates of these strategies are yet unclear (section 1.3). *The aim of Study 3* was to find the underlying neural processes of prototype- and exemplar-based categorization strategies, by using a within-subjects fMRI study in which the learning over time is investigated.

**Study 4:** Given the fact that the MTL has been shown to be involved in both visual discrimination tasks (Study 1) as well as categorization tasks (Study 3), the question remains how both processes are represented in the MTL and if they overlap to some extent. After establishing the general categorization networks in Study 3, *the aim of Study 4* was to compare both category learning and visual discrimination in a within-subjects fMRI study and to show the degree of overlap that activations from both tasks might exhibit. For this, previously successfully employed paradigms (Study 1 to 3) were used and compared.
Chapter 2

Study 1: A comparison of MTL involvement in memory and visual discrimination

2.1 Introduction

As described previously in the general introduction (see section 1.2), the involvement of the human MTL (including the HC and the PRC) in perceptual tasks is not understood completely so far. Recent imaging and lesion studies suggest that the MTL is also involved in processing and discrimination of complex visual stimuli (with a high feature ambiguity) as opposed to less complex visual stimuli. These findings led to an “emergent memory account” (Graham et al., 2010) or a “perceptual-mnemonic theory” (Bussey, Saksida, & Murray, 2005) of the MTL.

Several studies could demonstrate hippocampal and perirhinal activation for mnemonic and perceptual tasks (Barense, Henson et al., 2010; Devlin & Price, 2007; Lee et al., 2008; O'Neil et al., 2009). Barense et al. (Barense, Henson et al., 2010) could demonstrate perirhinal cortex activation for the discrimination of faces and artificial objects (so-called “greebles”) and posterior hippocampal activation for scene and face processing. Besides, there also seems to be an effect of familiar (famous faces and real world objects) versus unfamiliar (novel faces and artificial objects) stimuli, with increased activation in PRC and HC for familiar stimuli (Barense et al., 2011).

These findings also suggest that there is a double dissociation of the putative perceptual functions of the HC and the PRC, with parallels to the well-established memory functions of these areas (Ranganath & D'Esposito, 2010). Based on the fact that the HC is an allocortical structure that evolved very early in vertebrate history (Bussey
& Saksida, 2005), it seems highly unlikely that the neocortical (and therefore anatomically highly dissimilar) PRC has identical or similar functions (see also Murray & Wise, 2004).

However, other studies with similar designs (Hampton, 2005; Levy, Shrager, & Squire, 2005; Shrager et al., 2006; Stark & Squire, 2000) could not show any visual discrimination deficits resulting from hippocampal or perirhinal damage.

Everything considered, the exact role of the MTL in high-level visual processing is not determined yet. Furthermore, it remains unclear how the perceptual processing in the MTL can be distinguished and separated from memory processes.

### 2.1.1 Aims and hypotheses

So far, there has been no study that has directly compared the activations of HC and PRC during memory and perception tasks in a within-subjects full factorial design using different stimulus types. The aim of this study was to use functional magnetic resonance imaging in healthy subjects to further elucidate the contributions of different MTL structures to perceptual and mnemonic processing of faces and scenes, by directly comparing the activation in a visual discrimination and a recognition task (one week after encoding).

The following hypotheses were formulated:

- The HC should be activated for the correct recognition of previously learned stimuli.
- Both HC and PRC should be activated for discriminations involving stimuli with high feature ambiguity.
- There should be a functional specialization for the processing of different stimulus types, with the HC and PHC mainly being involved in the processing of scenes, and the PRC in the processing of faces.
2.2 Methods

2.2.1 Participants

Twenty right-handed and neurologically healthy human subjects (10 male and 10 female; mean age: 23.06 years; range: 18-29) participated in this study. All subjects had normal or corrected-to-normal vision. Three of the subjects had to be excluded from the data analysis because of a very low number of recognized items in the memory task or because of excessive movement in the MRI scanner. All participants gave informed written consent after a detailed written and oral explanation of the procedure.

2.2.2 Experimental design

The experiment was divided into two sessions that were performed inside of a magnetic resonance imaging (MRI) scanner. There was a delay of exactly seven days between both sessions. In the first session, the participants performed in a visual discrimination task, followed by an encoding task. In the second session, they carried out a recognition task.

The computerized tasks were presented and performed using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA) and MRI-safe LCD video goggles (Resonance Technology Company, Inc., Northridge, CA, USA). The experiment was presented in a resolution of 800 x 600 pixels, and responses were recorded using an MRI-safe keypad.

The discrimination task used three stimulus types in an oddity paradigm (O'Neil et al., 2009): faces, scenes, and black rectangles (the black rectangles were used as a baseline condition in the fMRI analysis). 180 pictures of each stimulus type were used in two difficulty conditions (“easy” and “hard”), with a simultaneous presentation of three stimuli in each trial, resulting in overall 216 trials (see also Figure 2.1). The stimuli were presented simultaneously for four seconds, in order to minimize working memory demands. Participants had to indicate with a button press which one of the presented
pictures was the “odd-one-out”. In the “easy” condition, the task was easily solvable by comparing single features. Pictures in the “hard” condition however had a high feature ambiguity that resulted in a higher difficulty, which is supposed to recruit MTL structures for a successful processing. “Easy” and “hard” conditions were balanced for all stimulus types and across all subjects, in order to prevent effects of order or training.

To achieve this, the stimuli for “easy” and “hard” conditions were constructed differently: For the “easy” condition, only two different pictures were used per trial (two different frontal view faces, scenes, or two black rectangles with different sizes). The target (the “odd-one-out”) was presented at a random position and the non-target on the remaining two positions.

A previously used panoramic technique (Park & Chun, 2009) was adapted to create the scene stimuli for the “hard” condition. Stimulus triplets (with an overlap of 75% or 90% between the pictures) were created, employing a “sliding window” procedure (see also Pustina et al., 2012). The target was defined as having the smallest overlap with the other two pictures. Face stimuli for the “hard” condition were constructed by using face photographs from various viewing angles (ranging from -60° to 60°, in steps of 30°). The hair was masked and only the faces were shown, to increase the overall similarity between the faces. The “hard” stimuli for the baseline condition were created by using very small size differences (ranging from 5 to 10 pixels, while “easy” stimuli differences ranged from 30 to 40 pixels). Additionally, the rectangles were presented with a small random position jitter, to ensure that they would not align and that they would be harder to discriminate.

Similar error rates for all stimulus types in “easy” or “hard” conditions were achieved by an extensive piloting, in which different degrees of overlap and size differences were tested.
After performing in the discrimination task, subjects had to encode 36 faces and scenes. They were instructed beforehand that they would need to remember the items for the recognition task in the second session. During the testing, subjects had to indicate if they perceived a stimulus as having a positive or negative valence, in order to increase the depth of processing. All pictures that were used in the first session were novel to the subjects. They also were trial unique, in order to prevent repetition suppression or
learning effects. The second session took place seven days later. Subjects were instructed that they would have to perform in a recognition task in which they would have to recognize faces and scenes from the first session (see Figure 2.2). The pictures were presented one at a time. Overall, four different types of pictures were included and presented one at a time: Familiar pictures from the encoding task, new distractor pictures, familiar targets from the discrimination task, and familiar non-targets from the discrimination task. Stimuli from the discrimination task (only from the easy conditions) were included to examine incidental encoding that might have occurred. In both sessions, all pictures were presented for a duration of 4 seconds, with a variable inter-trial interval (ITI) ranging from 1 to 3 seconds, in which a fixation cross was presented.

The study received ethical approval by the local Ethics Committee of the Medical Faculty of the Ruhr University Bochum, which conforms to the Declaration of Helsinki.
2.2.3 Scanning parameters

MRI and fMRI during both sessions was performed using a Philips 3T Achieva MRI scanner with a 32 channel SENSE head coil. A T1 weighted structural scan was acquired for every participant at the start of the first experimental session, with 220 slices, a voxel size of 1 x 1 x 1 mm, an echo time of 3.8 ms, and a flip angle of 8°. T2* weighted echo-planar MR images (EPI) were acquired in all three experimental conditions in an ascending sequence of 30 slices (voxel size = 1.65 x 1.65 x 3 mm, TR = 2200 ms, TE = 35 ms). Five dummy images were acquired at the start of each session to allow for MRI signal stabilization, and discarded immediately afterwards.

2.2.4 Data analysis

For the analysis of the behavioral data, several repeated measures ANOVAs (with Greenhouse Geisser correction) were applied for discrimination and recognition tasks. All statistical analyses were performed using SPSS Statistics 20 (IBM Inc.)

All functional and structural images were pre-processed using the latest release of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The pre-processing consisted of the following steps: Slice-time correction, realigning and unwarping, co-registering the EPIs with the corresponding structural scan, segmenting the structural scan into grey and white matter, and normalizing the EPIs to MNI space with DARTEL (Ashburner, 2007). Unwarping was employed to reduce distortions caused by magnetic field inhomogeneity, which can result from the participants’ movements. During normalization, all EPI images were re-sliced into 1 x 1 x 1 mm voxels. Afterwards, a smoothing was performed, using a Gaussian kernel of 3mm full-width half-maximum (FWHM). The small voxel size and smoothing kernel was chosen in order to increase sensitivity in the investigated brain structures, which are of relatively small size.

After the pre-processing, all functional images were submitted into a first level GLM analysis. The blood oxygenation level dependency (BOLD) signal was modeled with
the canonical hemodynamic response function (HRF). A high-pass filter at 128 s was used to remove low frequency drifts.

The model for the discrimination task encompassed seven regressors, one for correct responses to each stimulus type in both difficulties (“easy baseline”, “hard baseline”, “easy faces”, “hard faces”, “easy scenes”, “hard scenes”), with an additional regressor for fixation periods. Contrasts were defined by subtracting the correct “hard baseline” responses from the correct “hard face” or “hard scene” responses. The model for the recognition task included the following regressors: “correct recognition”, “correct rejection”, “false alarms”, and “misses” for face and scene stimuli, as well as a fixation regressor. For the contrasts, “correct rejection” was subtracted from “correct recognition” for both stimulus types. The fixation regressors in the discrimination and recognition task were added in order to increase the amount of explained variance. They were not used in any subsequent analysis.

All resulting contrasts (“face discrimination”, “scene discrimination”, “face recognition”, and “scene recognition”) were then used for group inference in the second level random effects analysis. A within-subjects full factorial model with two factors was applied to the data from the discrimination and recognition task. The model included the factors “task” (discrimination; recognition) and “stimulus type” (faces; scenes). Main effects for both factors were used as contrasts of interest, alongside the resulting interactions. Significant activation clusters in the full factorial analysis were then used to extract mean signal changes (in percent) with MarsBaR software (http://marsbar.sourceforge.net/) and were then fed into paired t-tests.

All reported statistics refer to whole brain analyses. Due to a strong a priori hypothesis about the involvement of the MTL in visual perception, the statistical maps were initially analyzed using an uncorrected threshold of \( p < 0.001 \) with a minimum of 10 voxels per cluster (Ashburner, 2007; Pustina et al., 2012). To reduce type II errors while keeping type I errors low (Lieberman & Cunningham, 2009), a Monte Carlo simulation with 10,000 iterations was used (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Slotnick, Moo, Segal, & Hart, 2003; Slotnick & Schacter, 2006; Zaki, Davis, & Ochsner, 2012), defining the threshold at \( p < 0.05 \), corrected for multiple comparisons.
This simulation yielded a cluster extent threshold of 33 resampled voxels while assuming an individual voxel type I error of $p = 0.001$.

For the localization of the resulting activations, bilateral ROIs were defined using hippocampal, parahippocampal, and perirhinal masks. The hippocampal and parahippocampal masks were taken from the Automated Anatomical Labeling Toolbox (Tzourio-Mazoyer et al., 2002). For the perirhinal mask, two perirhinal maps used in previous studies were additively combined (Devlin & Price, 2007; Holdstock, Hocking, Notley, Devlin, & Price, 2009), resulting in a map derived from 28 subjects. Only activations in these structures were reported.

All statistical analyses of the behavioral data and mean signal changes were performed using SPSS Statistics 20 (IBM Inc.).

### 2.3 Results

#### 2.3.1 Behavioral data

For the discrimination task, RTs and accuracy (correct responses – false alarms) were analyzed. For this, the factors stimulus (“faces”, “scenes”, and “baseline”) and difficulty (“easy”, “hard”) were used. For RTs, significant results were found for the factors stimulus ($F_{2,32} = 12.375; p < 0.002$) and difficulty ($F_{1,16} = 332.365; p < 0.0001$), as well as the interaction of both ($F_{2,32} = 12.803; p < 0.0001$). Paired t-tests revealed that the interaction was based on an overall increase of RTs in the “hard” condition as opposed to the “easy” condition. For easy discriminations, the RTs were slowest for faces, as opposed to easy scenes and baseline stimuli (see Table 2.1). In regard to accuracy, there were also significant effects for the factors stimulus ($F_{2,32} = 12.42; p < 0.0001$), difficulty ($F_{1,16} = 313.308; p < 0.0001$) and the interaction of both ($F_{2,32} = 11.331; p < 0.0001$). Here, the interaction was based on a reduced accuracy for “hard” baseline stimuli compared to the other stimulus types. For the recognition task, RTs were analyzed using the factors stimulus (“faces”, “scenes”) and response type (“correct recognition”, “correct rejection”, “miss”, “false alarm”). The analysis revealed a main
effect for the factor response type ($F_{2,32} = 7.765; p < 0.002$), with correct recognition ratings being faster than correct rejections, misses and false alarms (see Table 2.1). There was no main effect of the factor stimulus and no significant interaction of stimulus and response type. There was also no significant difference in accuracy between face and scene stimuli.

Table 2.1: Behavioral results from discrimination and recognition tasks. Mean reaction times (in ms) and mean performance scores with standard deviations (SDs) for all stimulus types in the discrimination and recognition task. Note that only faces and scenes were used in the recognition task (where correct recognition plus misses or correct rejections plus false alarms do not add up to 1, participants did not respond for the respective number of trials).

<table>
<thead>
<tr>
<th>Discrimination</th>
<th>Baseline</th>
<th>faces</th>
<th>scenes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT</td>
<td>Accuracy</td>
<td>RT</td>
</tr>
<tr>
<td>Easy discriminations</td>
<td>1169 (304)</td>
<td>0.93 (0.12)</td>
<td>1786 (403)</td>
</tr>
<tr>
<td>Hard discriminations</td>
<td>2117 (636)</td>
<td>0.43 (0.14)</td>
<td>2414 (311)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recognition</th>
<th>Baseline</th>
<th>faces</th>
<th>scenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct recognition</td>
<td>/ /</td>
<td>1655 (334)</td>
<td>0.44 (0.14)</td>
</tr>
<tr>
<td>Misses</td>
<td>/ /</td>
<td>1831 (407)</td>
<td>0.52 (0.16)</td>
</tr>
<tr>
<td>Correct rejection</td>
<td>/ /</td>
<td>1843 (502)</td>
<td>0.69 (0.16)</td>
</tr>
<tr>
<td>False alarms</td>
<td>/ /</td>
<td>1881 (411)</td>
<td>0.27 (0.16)</td>
</tr>
</tbody>
</table>
Figure 2.3: Mean reaction times and percentage of correct responses in the recognition task. Explicitly encoded items were recognized faster (top) and with a higher accuracy (bottom) than implicitly encoded items (p<0.05). There was no difference between stimulus types or discrimination targets vs. non-targets. Error bars represent the standard error of the mean (SEM).
To test for incidental encoding in the discrimination task, the number of recognized items and the RTs from both discrimination and encoding task were compared. For this, stimuli from the discrimination task were additionally separated into two categories, discrimination targets and discrimination non-targets. A repeated measures ANOVA with the factors stimulus (“faces”, “scenes”) and encoding condition (“explicit”, “discrimination target”, “discrimination non-target”) revealed a main effect of the encoding condition for both correct responses ($F_{2,32} = 5.693; p < 0.01$) and RTs ($F_{2,32} = 51.116; p < 0.0001$), showing that implicitly encoded stimuli were remembered to a smaller degree and elicited increased RTs (see Figure 2.3).

### 2.3.2 Imaging data

The full factorial analysis yielded four activation clusters in the HC and one cluster spanning the fusiform and parahippocampal gyrus (see Table 2.2 and Figure 2.4).

For the main effect of “task”, two activation clusters were found, one for the contrast recognition > discrimination, located in the right posterior HC (39 -31 -10; 47 voxels), and another one for the contrast discrimination > recognition in the left anterior HC (-29 -9 -21; 40 voxels). For the main effect of “stimulus type”, one significant cluster was found: The contrast faces > scenes yielded an activation cluster spanning across the right fusiform to the parahippocampal gyrus (25 -39 -14; 104 voxels). Furthermore, for the interaction of the two main factors, two clusters showed significant activations, one in the left posterior HC (-29 -37 -3; 10 voxels), and one in the right anterior HC (35 -14 -14; 10 voxels). These interaction clusters have to be regarded with caution, since they only reached significance with a threshold of $p < 0.001$, uncorrected for multiple comparisons.
Figure 2.4: **Significant activations from the full factorial model.** Only the main factor “task” (p<0.05 corr.) and the interaction of “task” and “stimulus type” (p<0.001, k=10) yielded significant activation in the HC. One additional cluster in the fusiform gyrus (extending to the parahippocampal gyrus) showed significant activation for the main effect of “stimulus type”, in the contrast faces > scenes (p<0.05 corr.). All activations projected on the mean structural image of all participants.

Surprisingly, no significant activations were found in the perirhinal cortex, even with an uncorrected threshold of p < 0.001 and a reduced cluster extent of 10 contiguous voxels. Furthermore, separate t-tests (easy faces, hard faces, easy scenes, and hard scenes, all contrasted against the respective baseline discrimination in the first level) were calculated for the two tasks in order to investigate a possible masking of stimulus specificity by task-specific effects. Again, no significant perirhinal activations were found. In order to search for weaker effects the threshold was lowered to p < 0.01, but yet again, no significant activation of the perirhinal cortex was found.

In order to further investigate stimulus specific effects, which were inconclusive in the full factorial analysis, the parahippocampal and fusiform gyrus were also used as ROIs in the separate t-tests. For the hard discrimination of faces, two large clusters were found in the left (-48 -54 -15, 712 voxels) and right (43 -44 -19, 916 voxels) fusiform gyrus. Three additional clusters were found for hard discriminations of scenes in the left (-22 -43 -7, 142 voxels) and right (31 -45 -6, 118 voxels; 32 -33 -15, 68 voxels) parahippocampal gyrus (see also Table 2.2).
Table 2.2: Imaging results. The table shows significant activations for the two main effects (p<0.05 corr.) and interactions (p<0.001 uncorr.) in the full factorial analysis. Additionally, significant clusters resulting from the separate t-tests of the discrimination task are listed. Each line represents one cluster.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>MNI coordinates (x, y, z)</th>
<th>Cluster size</th>
<th>T-score</th>
<th>Anatomical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognition &gt; Discrimination</td>
<td>39 -31 -10</td>
<td>47</td>
<td>4.74</td>
<td>right posterior hippocampus</td>
</tr>
<tr>
<td>Discrimination &gt; Recognition</td>
<td>-29 -9 -21</td>
<td>40</td>
<td>4.61</td>
<td>left anterior hippocampus</td>
</tr>
<tr>
<td>Faces &gt; Scenes</td>
<td>25 -39 -14</td>
<td>104</td>
<td>4.54</td>
<td>right fusiform gyrus / parahippocampal gyrus</td>
</tr>
<tr>
<td>Interactions</td>
<td>-29 -37 -3</td>
<td>10</td>
<td>5.26</td>
<td>left posterior hippocampus</td>
</tr>
<tr>
<td></td>
<td>35 -14 -14</td>
<td>10</td>
<td>4.37</td>
<td>right anterior hippocampus</td>
</tr>
<tr>
<td>T-test hard scenes</td>
<td>-22 -43 -7</td>
<td>142</td>
<td>7.75</td>
<td>left parahippocampal gyrus</td>
</tr>
<tr>
<td></td>
<td>31 -45 -6</td>
<td>118</td>
<td>6.11</td>
<td>right parahippocampal gyrus</td>
</tr>
<tr>
<td></td>
<td>32 -33 -15</td>
<td>68</td>
<td>5.62</td>
<td>right parahippocampal gyrus</td>
</tr>
<tr>
<td>T-test hard faces</td>
<td>43 -44 -19</td>
<td>916</td>
<td>9.95</td>
<td>right fusiform gyrus</td>
</tr>
<tr>
<td></td>
<td>-48 -54 -15</td>
<td>712</td>
<td>7.95</td>
<td>left fusiform gyrus</td>
</tr>
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</table>
The signal changes and paired t-tests for the interaction clusters revealed that both interactions were based on a difference between the activation for faces and scenes in the recognition task. There was no significant difference between stimulus types in the discrimination task. While the left HC showed a stronger activation for scenes and a deactivation for faces in the recognition task, the right HC showed the opposite pattern, with a stronger activation for faces and a deactivation for scenes (see Figure 2.5). As mentioned above, these results have to be interpreted carefully, since the interaction clusters did not reach the cluster extent threshold of 33 voxels and hence represent activations with an uncorrected threshold.

The mean signal changes in the hippocampal clusters, active for the main effect of “task”, did confirm a task-specific involvement of each cluster. The signal change in the fusiform/parahippocampal gyrus however showed a more differential involvement, with a stronger signal change for the recognition of faces and the discrimination of scenes, respectively.
Figure 2.5: Percent signal change in clusters active for main effects and interaction contrasts. Analogue to the first level analysis, the baseline condition was subtracted from hard discriminations of faces and scenes for the discrimination PSCs. For recognition PSCs, the correct rejections were subtracted from correct recognition responses. This analysis confirmed the task-specific involvement of the two hippocampal clusters active for the main effect of “task”, as well as a differential involvement of the fusiform/parahippocampal cluster in the processing of different stimulus types. Furthermore, both interactions were based on a difference between the activation for faces and scenes in the recognition task, with no significant difference between stimulus types in the discrimination task. Error bars represent the SEM.
2.4 Discussion

Study 1 investigated the contribution of MTL structures to mnemonic and visual processing. Visual discrimination and recognition tasks were directly compared in a within-subjects full factorial design.

As hypothesized, the HC showed significant activation for the correct recognition of previously encoded stimuli. A cluster in the right HC was activated during the recognition task, for both faces and scenes. Additionally, as formulated in the second hypothesis, the visual discrimination of stimuli with high feature ambiguity elicited significant activation in the left HC. Parallel to the recognition task, this region was activated for both faces and scenes. There was no confirmation of the second part of hypothesis 2, since the PRC was not activated in the visual discrimination task. This null result could be caused by signal dropout in the MTL (Olman et al., 2009), which may have led to missing signal in parts of the PRC. Further analyses using separate t-tests for the two different tasks and a reduction of the threshold in the fMRI analyses also failed to show any activation in the PRC, supporting this explanation.

Regarding the stimulus-specific processing within the MTL, the third hypothesis could not be fully confirmed. The main effect of “stimulus type” revealed a significant activation, with the cluster extending over the right parahippocampal gyrus to the right fusiform gyrus. The extraction of mean signal changes in this cluster revealed that it was involved in the recognition of both stimulus types. However, this result might have been caused by the large extent of this cluster, with the mean signal change combining contributions from both structures. Furthermore, the analysis of the significant interaction yielded differences in the stimulus specific processing in the recognition task.

The results of Study 1 do contribute to the question if and how the human MTL is involved in high-level visual processing. They support the notion that visual discrimination tasks using stimuli with high feature ambiguity engage the MTL in order to successfully process and discriminate the presented stimuli, as has been shown previously in various studies (Barense, Henson et al., 2010; Bussey et al., 2005; Devlin & Price, 2007; Graham et al., 2010; Lee et al., 2008; Murray, Bussey, & Saksida, 2007;
O'Neil et al., 2009). These results are in disagreement with the notion that the MTL is specialized only for memory processing (Hampton, 2005; Levy et al., 2005; Shrager et al., 2006; Squire et al., 2004; Stark & Squire, 2000).

A common counter-point in regards to visual processing in the MTL is the argument, that a confound with working memory might be responsible for significant activation during discrimination tasks, since there is evidence that the HC can be active during certain types of working memory tasks (Hartley et al., 2007; Olson et al., 2006). In Study 1, this potential problem has been addressed by a simultaneous presentation of the stimuli in the discrimination task, keeping the working memory demands to a minimum. Additionally, the experimental condition was contrasted with a similar baseline condition that used the same task.

Another potential flaw might be the comparison of three-stimulus displays in the discrimination task with the single-stimulus displays in the recognition task, which may rely on working memory to varying degrees. This problem has been alleviated again by choosing appropriate contrasts (hard discrimination > hard baseline; correct recognition > correct rejection) that subtracted similar experimental conditions with the same type of stimulus display, respectively.

Furthermore, previous patient studies could show that visual discrimination deficits cannot be explained by working memory impairments alone. Patients with MTL lesions have shown deficits even when deciding if a single object is geometrically possible or not (Lee & Rudebeck, 2010a).

Another criticism might be that the activation of the HC in the discrimination task might stem from an incidental encoding of the stimuli. However, the behavioral data from Study 1 shows that the discrimination targets and non-targets were recollected to a significantly smaller degree than the stimuli from the encoding task. All of these stimuli were presented for the same amount of time, with the exception that participants were explicitly instructed to memorize the stimuli from the encoding task.

The only hypothesis that could not be fully confirmed in Study 1 was the assumption that there would be a functional specialization of MTL structures, as has been shown in many other studies for memory and visual discrimination tasks (Barense et al., 2005;
Barense et al., 2007; Eldridge et al., 2000; Lee, Bussey et al., 2005, Lee, Buckley et al., 2005, 2005, Ranganath et al., 2004; Suchan et al., 2008). Here, the HC was involved in the processing of both stimulus types. The only small hint for functional differences was apparent in the interaction clusters in the left and right HC. These results have to be regarded carefully, since the activations in the interaction clusters did not survive a corrected statistical threshold. Additionally, the missing perirhinal activation contributed to a missing functional specialization. But since this could be caused by signal dropout (see above), the data do not indicate that the PRC is not involved in visual or mnemonic processing. For future studies, the scanning parameters should be adapted to prevent signal loss in the MTL, in order to make assertions about the exact role of the PRC.

Furthermore, the absence of bilateral HC activations in both tasks should be interpreted carefully as well, since this could be caused by a lack of statistical power and does not imply a lateralization of functions. Taken together, the observed activation patterns in Study 1 cannot be explained by traditional models that view the HC as being specialized for the processing of spatial stimuli. Rather, the HC seems to be involved in both tasks (mnemonic and visual) and processes both types of stimuli.

Moreover, studies using multi-voxel pattern analysis (MVPA) showed that single memories can be represented distinctively in the HC (Chadwick, Hassabis, & Maguire, 2011). This suggests that the subfields of the HC might be specifically involved in different aspects of the formation and maintenance of representations. This shows the need for a much finer analysis of the MTL (with a higher resolution) in order to explain the observed activation clusters. Different parts of the HC may be concerned with different representations, as implicated by the current findings.

In summary, Study 1 does present strong evidence for a perceptual involvement of the MTL (and especially the HC), by directly comparing mnemonic and visual tasks in a full factorial fMRI design. The results show that the HC is not only enabling long-term memory processing, it is also needed in high level visual processing. This is in line with a perceptual-mnemonic theory of the MTL and in disagreement with an exclusively mnemonic theory. They also show that there is a need for a comprehensive MTL model that incorporates various task and stimulus types. This can only be achieved by
controlling all aspects of the tasks and stimuli that are being processed in any given experimental paradigm, together with an analysis tailored for smaller structures like the HC. Furthermore, the results of Study 1 suggest that it might be favorable to regard the functioning of the MTL in the light of representations, as opposed to descriptive cognitive functions.
Chapter 3

Study 2: Lesions of the hippocampus and anterior fornix lead to perceptual deficits in a visual discrimination task

3.1 Introduction

As has been shown in Study 1 and in other previous studies using fMRI in healthy humans (Barense, Henson et al., 2010; Devlin & Price, 2007; Lee et al., 2008; O'Neil et al., 2009), the HC is strongly involved in the discrimination of visual stimuli with high feature ambiguity. Additionally, lesion studies demonstrate that patients with MTL lesions, including HC and PRC, fail in visual discrimination tasks for specific stimuli, depending on the location of the lesion (Barense et al., 2005; Barense et al., 2007; Lee, Bussey et al., 2005; Lee, Buckley et al., 2005). While selective hippocampal damage leads to impaired visual discrimination of morphed scenes, extensive MTL lesions impair the ability to discriminate scenes and faces (Lee, Buckley et al., 2005). Additionally, patients with perirhinal lesions show deficits for the visual discrimination of complex objects (Barense et al., 2007).

Following up on this research, another structure that might be of interest for the study of high level visual perception is the fornix. Lesions of this structure cause memory deficits comparable to deficits caused by HC lesions (Tucker et al., 1988). Especially lesions of the anterior part of the fornix lead to a very transient form of amnesia (Moudgil et al., 2000; Saito et al., 2006). These findings fit the view, that the fornix, as part of the Papez circuit (Bird & Burgess, 2008), acts as a main output structure of the HC (see also section 1.1.2).
3.1.1 Aims and hypotheses

While previous studies dealing with patients that suffered from lesions to the MTL or fornix have focused on the resulting memory deficits, Study 2 was designed to investigate the patients’ ability to visually discriminate stimuli with high feature ambiguity. The aim was to further corroborate the results of Study 1 by testing patients with lesions of the HC and hippocampal output structures. For this, two different patients were tested: VG, suffering from lesions of the MTL and HJK, suffering from a small focal lesion of the anterior fornix.

Our hypotheses in this study were as follows:

- Damage to the HC (or the MTL in general) should lead to episodic memory deficits as well as to deficits in the discrimination of visual stimuli with high feature ambiguity.
- Damage to the fornix, as a main output structure of the HC, should also lead to deficits in episodic memory and visual discrimination.
- There should be no other cognitive deficits apart from amnesia and visual discrimination deficits.

3.2 Methods

3.2.1 Participants

Given the importance of an undamaged visual system for the performance in a visual discrimination task, only patients with circumscribed damage were chosen for this study, resulting in two patients that were investigated: Patient VG (male, 54 years old, education of 13 years) was involved in a bicycle accident in July 2001 (10 years before the testing took place), followed by a coma of approximately 6 months. He was identified as having bilateral HC lesions, medial temporal lobe lesions as well as a slight enlargement of the ventricle in the right frontal lobe. Patient HJK (male, 82 years old,
education of 13 years) suffered from a small infarction of the anterior fornices in December 2012 and was tested seven days after being admitted to the hospital.

Healthy control subjects with matching age and education levels were tested for behavioral comparison. Eight subjects (2 male and 6 female; mean age: 56.25; range: 52-59) were recruited as controls for patient VG, another eleven subjects (6 male and 5 female; mean age: 77.75; range: 77-84) were controls for patient HJK. All participants in the control groups were right-handed, neurologically healthy, and had normal or corrected-to-normal vision. All participants gave informed written consent after a detailed explanation of the procedure.

3.2.2 Structural MRI

Magnetic resonance imaging (MRI) of both patients was performed on a 3T GE Medical Systems scanner (General Electric Company). For patient VG, a high resolution T1-weighted volume was obtained, with an in-plane resolution of 1mm x 1mm and a slice thickness of 1.2mm. For patient HJK, a diffusion-weighted image (DWI) was obtained (with an in-plane resolution of 1.02mm x 1.02mm, and a slice thickness of 5mm), in order to detect the small infarct at an early stage. An additional T1-weighted coronal volume was obtained for HJK, with a coronal in-plane resolution of 0.43mm x 0.43mm, and a slice thickness of 5.5mm.

3.2.3 Experimental design

For the patients, the experiment took place at home or in the clinic. Control subjects were tested at a laboratory at the Ruhr University in Bochum, Germany. The computer based part of the experiment was performed using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA).
All participants had to perform in a discrimination task, in which 180 greyscale pictures of faces and scenes each were presented in separate blocks in an oddity task (O’Neil et al., 2009). The task was adapted from Study 1, but only two stimulus types (faces, scenes) and two difficulty conditions (“easy” and “hard”) were employed (for examples of face and scene stimuli, see Figure 2.1 in section 2.2.2), resulting in 144 trials overall. As in the previous study, three pictures were shown simultaneously to minimize working memory demands. Additionally, all pictures were trial unique. Subjects were asked which picture was the “odd-one-out” and had to respond by pressing one of three buttons (for further details regarding the stimuli, see section 2.2.2). There was no size oddity judgment task this time, since there was no need for an fMRI baseline condition.

To assess the overall cognitive functioning of both patients, the following standardized neuropsychological (paper and pencil) tests were conducted: The Wechsler Memory Scale – Revised (WMS-R; Subscale “Attention and Concentration”, including digit and block span) was used to assess attention as well as short-term and working memory for visual and verbal stimuli. The Trail Making Test (TMT) was used to test visual search, attention and mental flexibility. The Rey-Osterrieth Complex Figure (ROCF; only copy and delayed recall conditions were used) was employed to investigate visuospatial processing and anterograde visual memory. Finally, the “Verbaler Lern- und Merkfähigkeitstest” (Verbal Learning and Memory Test, abbreviated VLMT) was used to assess verbal learning as well as anterograde recall and recognition memory. Patient HJK was additionally screened for dementia, using the Mini Mental State Examination (MMST). A detailed description of all applied tests can be found in the Appendix, in section A.1. The performance of both patients was evaluated by comparing their scores to the normative data from respective manuals (Folstein, Folstein, & MacHugh, 2000; Helmstaedter, Lendt, & Lux, 2001; Osterrieth, 1944; Reitan, 1992; Wechsler, 2004).

The study received ethical approval by the local Ethics Committee of the Medical Faculty of the Ruhr University Bochum, which conforms to the Declaration of Helsinki.
### 3.2.4 Data analysis

Statistical analysis was performed using SPSS Statistics 20 (IBM Inc.). Several ANOVAs were calculated in order to find effects of stimulus type or difficulty. For comparison of patients and their respective control group, Singlims_ES.exe was used (Crawford & Garthwaite, 2002; Crawford, Garthwaite, & Porter, 2010). This program allows performing a modified t-test for single case analysis. Structural images were inspected and reoriented using the latest release version of SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8).

### 3.3 Results

#### 3.3.1 Structural MR images of both patients

The lesions of both patients were evaluated by a qualitative visual rating performed by a trained neurologist. The recent structural images of patient VG show large lesions of the MTL, with a bilateral atrophy of the HC and adjacent structures. Additionally, the white matter of both temporal lobes is damaged. Frontal and occipital lobes are intact and show no signs of damage (see Figure 3.2A). The DWI recordings of patient HJK show a small infarction of the anterior fornix, with no additional damage to other brain structures.

#### 3.3.2 Neuropsychological assessment of the patients

The analysis of the standard neuropsychological tests revealed that patient VG did not show any deficits in attention, short-term memory, visuospatial processing, or mental flexibility. However, he was severely impaired in anterograde memory for verbal and non-verbal stimuli. Patient HJK’s data revealed memory impairments comparable to patient VG, but with more widespread deficits. HJK had a diminished performance in tests of attention, mental flexibility and motor function. However, there were no signs
of dementia or deficits in visuospatial processing (see table 3.1). It has to be mentioned that several tests did not have normative data for people of HJK’s age (only the ROCF and MMST had appropriate normative samples). In these cases, HJK’s performance was compared to the oldest available group, which may have resulted in very conservative judgments and an underestimation of his performance.

Figure 3.1: Structural MR-images of patients VG and HJK. (A) The coronal and sagittal section of patient VG’s brain show that he has a severe atrophy of both hippocampi, alongside further lesions of the medial and lateral temporal lobe. (B) The coronal section of patient HJK’s DWI recording shows a small infarction in the anterior part of the fornix.
Table 3.1: Neuropsychological assessment of patients VG and HJK. Raw scores of both patients are presented alongside possible maximum scores (where feasible). Note that scores from the Trail Making Test represent the time that was needed to finish the test. Also note that in the evaluation column “o” represents normal performance, “-” represents below-average performance, and “+” represents above-average performance, as assessed by comparison with normative data, where possible.

<table>
<thead>
<tr>
<th></th>
<th>Patient VG</th>
<th>Patient HJK</th>
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<tr>
<td></td>
<td>Score</td>
<td>Evaluation</td>
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<td><strong>Wechsler Memory Scale – Revised – Subscale: Attention &amp; Concentration</strong></td>
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<tr>
<td>Mental Control</td>
<td>5/6</td>
<td>o</td>
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<tr>
<td>Digit Span</td>
<td>14/24</td>
<td>o</td>
</tr>
<tr>
<td>Block Span</td>
<td>13/24</td>
<td>o</td>
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<tr>
<td><strong>Trail Making Test</strong></td>
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<td>Version A</td>
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<td>o</td>
</tr>
<tr>
<td>Version B</td>
<td>85</td>
<td>o</td>
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<td><strong>Rey – Osterrieth Complex Figure</strong></td>
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<tr>
<td>Direct copy</td>
<td>35/36</td>
<td>+</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>12/36</td>
<td>-</td>
</tr>
<tr>
<td><strong>Verbal Learning and Memory Test</strong></td>
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<td></td>
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<tr>
<td>Immediate recall</td>
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<td>-</td>
</tr>
<tr>
<td>Recognition</td>
<td>3/15</td>
<td>-</td>
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<tr>
<td><strong>Mini Mental State Exam</strong></td>
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</table>
3.3.2 Behavioral data in the computerized test

For the analysis of the behavioral data in the discrimination task, two analyses were performed. First, repeated measures ANOVAs were performed separately for both control groups, to assess the effect of task difficulty (“easy” and “hard”) as well as stimulus type (“faces” and “scenes”) on correct responses and RTs.

VG’s control group did show a significant main effect of difficulty on correct responses ($F_{1,7} = 129.574; \ p < 0.0001$), with less correct responses in both hard task conditions. For their RTs, the main effects of difficulty ($F_{1,7} = 153.476; \ p < 0.0001$) and stimulus ($F_{1,7} = 28.432; \ p < 0.001$), as well as the interaction of both ($F_{1,7} = 14.474; \ p < 0.007$) became significant. This interaction was based on much faster responses in the “scenes easy” condition, with overall faster RTs in easy conditions.

The analysis HJK’s control group also yielded a significant main effect of difficulty on correct responses ($F_{1,10} = 266.192; \ p < 0.0001$), with an additional significant interaction of difficulty and stimulus type ($F_{1,10} = 17.797; \ p < 0.002$). This interaction was based on a worse performance for “faces easy”, in comparison with “scenes easy”. For the RTs, the data were comparable to the other control group. Main effects of difficulty ($F_{1,10} = 184.020; \ p < 0.0001$) and stimulus ($F_{1,10} = 41.220; \ p < 0.0001$), as well as the interaction of both factors ($F_{1,10} = 54.420; \ p < 0.0001$) became significant. This interaction was also based on faster responses in the “scenes easy” condition.

Secondly, the patient’s performance was compared to their respective control group, using modified one-tailed t-tests. For VG, almost all performance measures were comparable to his control group. Only the comparison of correct responses in the task conditions “faces hard” ($t_7 = -2.247; \ p = 0.030$) and “scenes hard” ($t_7 = -1.787; \ p = 0.046$) yielded significant differences (see also Figure 3.2 and Figure 3.3).
**Figure 3.2: Percentage of correct responses in the discrimination task.** The comparison of correct responses for patients VG and HJK and their respective control group shows that VG’s performance in the hard conditions was significantly diminished (top row). For patient HJK, only the discrimination of faces in the hard condition yielded significant differences in comparison to his control group (bottom row). Error bars represent the SEM.

For patient HJK, correct responses did only significantly differ in the condition “faces hard” ($t_{10} = -1.928; p = 0.041$). Additionally, HJK’s reaction times were significantly slower for “scenes easy” ($t_{10} = 1.951; p = 0.040$). Correct responses in the “scenes hard” condition did not differ significantly from the control group, probably caused by an overall lower performance of the control group in this condition (see also Figure 3.2 and Figure 3.3).
Figure 3.3: Reaction times in the discrimination task. The comparison of reaction times shows that both patients did not differ significantly from their respective control group in most conditions. Patient HJK however did show significantly higher RTs for “scenes easy”. Overall, the reactions in the “scenes easy” condition were faster for both patients and control groups in comparison to the other stimuli and difficulties. Error bars represent the SEM.

3.4 Discussion

The present study aimed to contribute to the question if and how the MTL is involved in visual discrimination of stimuli with high feature ambiguity, apart from its well-studied memory processing contributions. For this, a visual discrimination paradigm that has been previously used in healthy participants (see Study 1) was applied to two patients, one with lesions to the HC and surrounding structures (VG), and one with a small infarction of the anterior fornix (HJK).

As hypothesized, the damage to patient VG’s HC and adjacent MTL structures caused a diminished performance in memory tasks in the neuropsychological test battery. He was
significantly impaired in the learning and recollection of verbal and non-verbal stimuli, as has been shown with the ROCF and VLMT. Additionally, he showed deficits in the discrimination of faces and scenes. Patient VG’s RTs for both stimulus types in both difficulties did not differ from the RTs of his matched control group, showing that his processing of the stimuli was not slowed. Also, his number of correct responses to easy face and scene discriminations was comparable to the control group, reaching over 90% correct responses for easy discriminations in total. He only failed in successfully discriminating stimuli with a high feature ambiguity in the hard conditions, reaching only about chance level (as opposed to his control group that had almost twice as many correct responses). Taken together, his memory and visual discrimination deficits fully support the first hypothesis.

Regarding the second hypothesis, a similar pattern was observable, but the results were more mixed. Patient HJK did also display similar memory deficits in the ROCF and VLMT tests, with an impairment of learning and recollecting verbal and non-verbal information. In the discrimination task, he also showed significant deficits. As for patient VG, patient HJK’s RTs were mostly comparable to his control group, with the difference that he was significantly slower in correctly discriminating easy scenes. Regarding his correct responses, he was only significantly impaired in the discrimination of hard faces, although both hard conditions were at about chance level. The hard discriminations of scenes did not significantly differ from his control group, because the healthy controls did also show a weaker performance in the discrimination of hard scenes. Overall, the second hypothesis could be confirmed to some extent, with the exception that the discrimination of scenes with high feature ambiguity was not impaired in comparison with age-matched controls.

The third hypothesis could be partially confirmed. Patient VG did not show any wider cognitive deficits, apart from his impairments in long-term memory and visual discrimination. He performed normally in all other neuropsychological assessments, and he did even show an above-average performance in the direct copy of the ROCF, demonstrating his intact visuospatial processing and motor skills. Patient HJK’s neuropsychological assessment did again show more mixed results. While demonstrating the same memory impairments as patient VG, he was also impaired in
working-memory and attention. These deficits may have resulted from the fact that he was still in the acute phase of his hospitalization. However, he did not show any signs of dementia in the MMST screening, despite his advanced age.

In the same way as the results from Study 1, the current results do support the notion that visual discrimination tasks using stimuli with high feature ambiguity engage the MTL, as has been shown many times before (Barense, Henson et al., 2010; Bussey et al., 2005; Devlin & Price, 2007; Graham et al., 2010; Lee et al., 2008; Murray et al., 2007; O'Neil et al., 2009). Again, the data are contrary the assumption that the MTL is specialized for memory processing (Hampton, 2005; Levy et al., 2005; Shrager et al., 2006; Squire et al., 2004; Stark & Squire, 2000).

Furthermore, Study 2 has for the first time demonstrated that lesions of the fornix do also lead to visual discrimination deficits that are very similar to the ones caused by MTL lesions. Previous studies dealing with anterior fornix lesions were more concerned with the resulting memory deficits (Buckley et al., 2004; Moudgil et al., 2000; Saito et al., 2006), showing that this main output structure of the HC is vital for episodic memory, probably through its projections to the anterior thalamus (Aggleton et al., 2010; Pergola et al., 2013). But by demonstrating the visual discrimination impairments resulting from a minor fornix lesion, the data of HJK show the importance of the fornix for the higher-level visual processing. These results also indirectly show that the output of the HC is of major importance for visual discrimination tasks, emphasizing the role of the MTL in perceptual processing.

One problem with the results of Study 2 is that the behavioral data of patient HJK were not as conclusive as patient VG’s data. The fact that HJK was not significantly worse in the discrimination of scenes with high-feature ambiguity might have been caused by the low performance and the advanced age of the controls. It has been shown that the fornix degenerates throughout the lifespan (Gunbey et al., 2014; Jang, Cho, & Chang, 2011). Studies on primates have also suggested that this progressive degeneration might be associated with the disconnection of HC and Thalamus as well as HC and the medial frontal cortex (Peters, Sethares, & Moss, 2010). The slower RTs in easy scene discriminations might be related to the fact that the HC is generally involved in spatial
processing (Bird & Burgess, 2008; Lee et al., 2012; O'Keefe & Nadel, 1978), so that patient HJK’s spatial abilities were more broadly impaired.

A common criticism regarding an MTL involvement in complex visual processing is the possibility that working memory processes are involved in the visual discrimination task. As mentioned before, this can be ruled out, since even the judgment of a single object can be impaired in patients with MTL lesions (Lee & Rudebeck, 2010a). The fact that HJK showed deficits in attention and working memory tests might have contributed to his impairments to some degree, but it cannot completely account for his diminished performance, especially since not all of his working memory functions were impaired (e.g. the digit span test in the WMS-R).

Another argument might be that the patients in Study 2 might have been impaired in visual discrimination because of their general learning impairment as apparent in the verbal and non-verbal learning and memory tasks. Assuming this, the healthy controls would benefit from their intact memory and hence be able to show a better performance in the discrimination task. This explanation can be ruled out on the basis that only trial-unique stimuli were used and that controls could not benefit from learning over the course of the experiment.

Future research might try to find more patients with similar focal lesions and let them perform in visual discrimination tasks. In the case of the very transient anterior fornix infarctions it might also prove useful to design a second task that is performed several weeks or months after the stroke, in order to assess if the performance in visual discrimination and other cognitive tests does improve over time. Furthermore, diffusion tensor imaging (DTI) studies might be of benefit by showing a possible relation between fornix microstructure and visual discrimination performance in healthy subjects. It might also prove useful to investigate age-related changes in visual discrimination performance due to structural changes of the fornix and MTL structures.

Taken together, the results of Study 2 are in line with previous research and with the findings from Study 1. Furthermore, the perceptual-mnemonic view of the MTL has been extended to the main output structure of the HC, the fornix, showing that it may be useful to incorporate a more extended network of structures into the research dealing
with a perceptual role of the MTL. The current study also dismisses the MTLMS as a sufficient model to explain the function of the MTL and yet again shows, that a representational model of the MTL might provide useful to explain the contributions of the MTL the processing of various stimuli in differing tasks.
Chapter 4

Study 3: Fusiform gyrus and hippocampus enable prototype- and exemplar-based category learning

4.1 Introduction

As described in section 1.3, category learning is a vital learning mechanism that has been the focus of various research approaches and models and it has been shown that the MTL is one of the key structures that enables successful category learning (Ashby & Maddox, 2005). One view does propose two different learning strategies, prototype- and exemplar-based category learning (Medin & Schaffer, 1978; Posner & Keele, 1968).

Although these types of learning have been studied previously in human and non-human animals (Cook & Smith, 2006), the neural correlates are not clear as of yet. One structure of interest might be the fusiform gyrus (especially the FFA), which is known to be involved in tasks with a demand for visual expertise (Gauthier et al., 1999; Pernet et al., 2005; Tong et al., 2008) and also to be involved in category learning (Folstein et al., 2013). While the FFA might be responsible for prototype-based learning, the HC might be important for exemplar-based learning, given its responses to specific categories of stimuli (Kreiman et al., 2000; Quiroga et al., 2005). As of now, it is not clear if prototype- and exemplar-based category learning strategies are two separate processes with separate neural representations, or if they might just represent two parts of the same process.
4.1.1 Aims and hypotheses

In order to investigate complex visual processing in the MTL it is first required to establish the basal neural processes that enable visual category learning. These neural correlates can then be used to compare categorization (which requires memory) and visual discrimination (which does not require memory) within the MTL (see Study 4).

Study 3 aimed to replicate the behavioral results of Cook and Smith (2006) and to establish the neural correlates for both categorization strategies, in order to contribute to the question if both learning types are part of the same process or two individual and distinct cognitive processes. For this, the same behavioral paradigm as used by Cook and Smith (2006) has been employed, using the same well-tested stimuli. Participants had to categorize unfamiliar abstract stimuli into two groups by means of direct feedback after every trial. The categories consisted of a prototype, five typical stimuli and an exception (which shared more features with the opposing prototype).

Based on previous findings, the following hypotheses were formulated:

- Differential activation patterns for prototype-based and exemplar-based learning do exist and are in part mediated by the MTL.
- While prototype-based learning should be mediated by the fusiform gyrus, exemplar-based learning should be heavily reliant on the MTL, especially the HC.
- Behaviorally, the learning of exceptions should be diminished in the beginning and should progressively increase over the course of the experiment, when participants realize that their prototype-based learning strategy does not work for the exceptions.
4.2 Methods

4.2.1 Participants

Twenty-eight right-handed and neurologically healthy subjects (12 male and 16 female subjects; mean age: 24.61 years; range: 20-30) with normal or corrected-to-normal vision participated in the experiment. All subjects gave informed written consent after a detailed explanation of the procedure.

4.2.2 Experimental design

The experiment took place inside of an MRI scanner and was performed using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA) and MRI-safe LCD video goggles (Resonance Technology Company, Inc., Northridge, CA, USA) with a resolution of 800 x 600 pixels, registering the responses with an MRI-suitable keypad. Participants had to perform a visual categorization task, which was adapted from Cook and Smith (2006). In this task, circular stimuli (400 x 400 pixels) with six binary color dimensions had to be categorized into one of two stimulus “families”, with the participants having no prior knowledge about the stimuli or categories. The stimuli were similar in their structure but differed in the color combinations. Each category consisted of a prototype, alongside five typical stimuli that shared five colors with the prototype, as well as an exception that shared five colors with the prototype of the other category (see Figure 4.1). This design prevented the usage of a prototype-based strategy for the exceptions, since this strategy would lead to a miscategorization.

Stimuli were presented centrally on a white background. The responses were recorded using two buttons, with each button corresponding to one of the two categories. Immediately after the response a feedback was given: “correct” or “incorrect”. Alternatively, the feedback was “please react faster!” if the participant did not press a button within 2.2 seconds of stimulus presentation.
Chapter 4: Study 3

Figure 4.1: Stimuli from both categories. All stimuli were constructed with 3.88 shared colors within and 2.12 shared colors between categories. Additionally, the stimuli of one category shared 4.57 colors with their own prototype and 1.43 with the prototype of the other category (see also Cook & Smith, 2006).

The feedback was presented for 1 second, followed by a fixation cross that was presented for another second before the next trial started. The experiment consisted of five blocks, with each block being composed of 98 trials, resulting in 490 trials over the course of the experiment. All stimuli were randomly presented in seven trials of each block; therefore each block contained 14 prototypes, 70 typical stimuli and 14 exceptions. Participants were allowed to take a (self-paced) break after every block.

The study received ethical approval by the local Ethics Committee of the Medical Faculty of the Ruhr University Bochum, which conforms to the Declaration of Helsinki.

4.2.3 Scanning parameters

The experiment was performed using a Philips 3T Achieva MRI scanner with a 32 channel SENSE head coil. A T1 weighted structural scan was acquired for every participant at the start of the first experimental session, with 220 slices, a voxel size of 1 x 1 x 1 mm, an echo time of 3.8 ms, and a flip angle of 8°. T2* weighted EPIs were acquired in all five blocks in an ascending sequence of 30 slices (voxel size = 1.65 x 1.65 x 5 mm, TR = 2200 ms, TE = 35 ms). The first five images at the start of each session were discarded to allow for MRI signal stabilization.
### 4.2.4 Data analysis

After a first inspection of the behavioral data, participants were divided into two separate groups: learners, who reached a correct response rate of at least 70% for all stimulus types in the last block, and non-learners with less than 70% correct responses for at least one stimulus type. Additional t-tests were calculated to ensure that the behavioral performance of the non-learners did not differ significantly from the 50% chance level.

For all further analyses, prototypical and typical stimuli were combined and were both treated as “prototypes”, since each of the typical stimuli could structurally represent the prototype for the other stimuli from the same category (see also Figure 4.1). A repeated measures ANOVA (with Greenhouse Geisser correction) with the factors “stimulus” (ProTyp vs. Exc), “block” (1; 2; 3; 4; 5), and the inner-subject factor “learner” (yes vs. no) was calculated for the correct responses.

The imaging data was preprocessed using the latest release of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The preprocessing consisted of slice-time correction, realignment (with unwarping), co-registration of the EPIs with the structural scan, segmentation of the structural scans into grey and white matter, and normalization to MNI space using DARTEL (Ashburner, 2007). The unwarping procedure was used in order to reduce distortions caused by magnetic field inhomogeneities, which may result from the participants’ movements. EPIs were resliced into 2 x 2 x 2 mm voxels, and finally smoothed with a Gaussian kernel of 8 mm full-width half-maximum (FWHM). The preprocessed images were then submitted into a first level GLM analysis, where the blood oxygenation level dependency (BOLD) signal was modeled with the canonical hemodynamic response function. A high-pass filter at 128 s was used to remove low frequency drifts.

The statistical maps were thresholded at p < 0.05 using false discovery rate (FDR) correction for multiple comparisons, with a minimum of 15 contiguous voxels per cluster. All reported statistics refer to whole brain analyses. Anatomical labeling was performed using the automated anatomical labeling toolbox (AAL) (Tzourio-Mazoyer et al., 2002).
For the first level analysis, 7 regressors were defined per block, representing correct and incorrect responses for the three stimulus types (“correct prototypes”, “incorrect prototypes”, “correct typical”, “incorrect typical”, “correct exception”, “incorrect exception”) as well as a regressor for the fixation period. For the contrasts of interest, prototypical and typical stimuli were combined (“ProTyp”). Correct responses were contrasted against the fixation regressor, separate for block 1 (before learning) and block 5 (after learning), resulting in the contrasts “ProTyp untrained”, “ProTyp trained”, “Exc untrained”, and “Exc trained”. These four contrasts were then used for group inference in the second level analysis.

In the group-level random effects analysis, a within-subjects full factorial model with 3 factors was employed. The model included the factors “group” (learners vs. non-learners), “stimulus” (ProTyp vs. Exc), and “block” (1 vs. 5). Main effects for all factors and interactions were used as contrasts of interest. Selected significant activation foci from interaction contrasts were used to extract mean signal changes (in percent) with MarsBaR software (http://marsbar.sourceforge.net/), and were then fed into paired t-tests.

To further examine the course of activation in different brain structures, Pearson correlations were computed for the mean signal changes in the ROIs that were defined in the previous analyses. Correlations were computed for learners and non-learners and for both stimulus types separately for the course of five blocks.

All statistical analyses of the behavioral data, mean signal changes, and Pearson correlations were performed using SPSS Statistics 20 (IBM Inc.).
4.3 Results

4.3.1 Behavioral data

The above mentioned post hoc differentiation of the participants into two groups yielded 17 learners and 11 non-learners. The non-learner’s performance did not differ significantly from the chance level of 50%. The repeated measures ANOVA revealed significant main effects for the factors “stimulus” ($F_{1,26} = 4.502; p < 0.05$) and “block” ($F_{4,104} = 15.138; p < 0.0001$), and a significant interaction between the factors “block” and “learner” ($F_{4,104} = 8.055; p < 0.0001$). Paired t-tests showed that the interaction resulted from the different learning curves of both groups (Figure 4.2). While the learners showed an increase of correct responses for both stimulus types over the five blocks, the non-learners remained at chance level.

![Correct responses](image)

**Figure 4.2: Correct responses in the categorization task.** Learners show an increase in correct responses over the five experimental blocks for both stimulus types, while non-learners do not show any change. Error bars represent SEM.
4.3.2 Imaging data

The second level full factorial analysis yielded significant activation clusters for the main effects “block” and “group”. The factor “block” yielded activations spanning the entire brain and will not be considered here (see Table A.1 in the appendix for details).

For the main effect of “group”, three activation clusters were found with the contrast learners > non-learners (see Figure 4.3): one in the right (14 -50 0, 208 voxels, \( T = 6.18 \)) and the left lingual gyrus (-16 -60 4, 66 voxels, \( T = 4.82 \)) as well as one in the left inferior frontal gyrus, extending to the insula and temporal pole (-46 16 -4, 53 voxels, \( T = 4.85 \)).

![Figure 4.3: Significant activations for the main effect of “group” in the full factorial design.](image)

Figure 4.3: Significant activations for the main effect of “group” in the full factorial design. Note that the main effect of “stimulus” did not yield any significant activation. All activations are FDR corrected for multiple comparisons (\( p < 0.05 \)) and are projected on the mean structural image of all participants.

Additionally, the interaction contrast of “block” x “group” yielded significant activations (see Figure 4.4 and Table A.1 in the appendix), with clusters in the left (-40 12 -16, 64 voxels, \( T = 4.73 \)) and right temporal pole (34 10 -26, 100 voxels, \( T = 4.70 \)), the pars triangularis of the left inferior frontal gyrus (-54 20 -2, 44 voxels, \( T = 4.65 \)), and the left fusiform gyrus (-42 -48 -22, 24 voxels, \( T = 4.23 \)).
Figure 4.4: Significant activations for two interactions. Note that the interaction “block” x “group” for prototype stimuli did not yield any significant activation. All activations are FDR corrected for multiple comparisons (p < 0.05) and are projected on the mean structural image of all participants.

For further analysis, the interaction was divided into separate contrasts for each of the stimulus types, resulting in an additional significant cluster in the right HC (30 -24 -10, 23 voxels, T = 3.97) and left parietal lobe (-50 -60 40, 76 voxels, T = 3.94) for exceptions (see Table A.1 in the appendix for a detailed listing). The interaction contrast for prototype stimuli did not show any significant activation. Mean signal changes were extracted for the left fusiform gyrus and the right HC. T-tests revealed that the interactions were based on a higher activation for learners in the last block compared to the first block, with a significantly higher signal change difference for prototype stimuli in the fusiform gyrus and a trend for the signal change difference of exceptions in the right HC (see Figure 4.5). The percent signal change of non-learners did not show any significant differences between the blocks or stimulus types.
Figure 4.5: Percent signal change of two significant activation clusters. For both ROIs, t-tests revealed significant differences for learners between the first and last learning session, as well as higher signal change differences for prototype stimuli in the left fusiform gyrus and a trend for exceptions in the right HC.
The analysis of correlations of the mean signal change in the right HC and left fusiform gyrus revealed that successful learners showed an early correlation of signal change between both structures for the learning of prototypes. For exceptions, the correlation only became significant in the last part of the experiment (see Figure 4.6). Notably, there was a drop of correlation in the second block of the experiment, resulting in approximately zero correlation between both structures and for both stimulus types. This drop occurred due to an earlier positivity of the hippocampal signal change for both stimulus types in comparison with the left fusiform gyrus. Signal changes in the fusiform gyrus showed a time displaced course for prototype and exception learners with later involvement for exception learners. Additionally, there was almost no significant correlation for the non-learners, with only a small correlation (p<0.05) for exceptions in the last block of the experiment.
Figure 4.6: Correlations of percent signal change in HC and fusiform gyrus. Pearson correlations were calculated separately for learners and non-learners, with one asterisk representing a significance threshold of \( p<0.05 \) and two asterisks representing \( p<0.01 \).
4.4 Discussion

The aim of Study 3 was to reveal the neural correlates of prototype-based and exemplar-based category learning in humans, in order to find the basal neural networks that are involved in a visual learning task. For this a categorization task similar to the design employed by Cook and Smith (2006) was used in an fMRI design.

The behavioral data replicated previous results (Cook & Smith, 2006), confirming the third hypothesis. Overall, the performance was slightly poorer, although it has to be noted that the original study tested only nine participants. Here, 11 out of 28 subjects were classified as non-learners, based on a correct response count of less than 70% in the last experimental block. One possible explanation might be the unusual environment or the noise caused by the MRI scanner. Nevertheless, learners showed a good performance for prototype stimuli early on, with a steady increase over the five experimental blocks. Correct categorizations of exceptions started at chance level in the first block but showed a rapid increase after the second block, with a comparable performance to prototype stimuli in the last block.

The imaging showed significant activations of the lingual gyrus and the left inferior frontal gyrus for the comparison of learners and non-learners, independent of block or stimulus type. Thus, learners possibly performed at a higher level since they successfully activated the lingual gyrus, an area that is involved in analyzing and memorizing visual color stimuli (Wang et al., 2013). The activation of Broca’s area is very likely related to inner verbalizations (Shergill et al., 2001) in a possible attempt to acquire knowledge about category membership.

The mean signal change of significant activations in the interaction contrasts was extracted to provide insight into the neural processes involved in the categorization of different stimulus types at different time points. Distinct neural correlates for the two categorization strategies emerged: While the left fusiform gyrus was more involved in prototype-based learning, the right HC was activated in exemplar-based learning of exceptions, confirming hypotheses one and two.
These results are in line with previous findings. Gauthier et al. (1999) showed that an extensive training with novel objects (“greebles”) leads to activation of a “greeble”-specific area in the fusiform gyrus. Also, expertise for other objects can lead to activations in the fusiform gyrus and occipital lobe (Gauthier, Skudlarski, Gore, & Anderson, 2000). This may be related to local changes of synaptic strengths, lowering thresholds for recognizing target stimulus elements and thereby increasing classification of a coherent object “family”, regardless of individual stimuli (Soto & Wasserman, 2012). These changes likely involve a population coding account of object configurations (Hirabayashi & Miyashita, 2005). It is a matter of debate if the represented aspects involve holistic face representations (Zhang, Li, Song, & Liu, 2012), or single parts of faces (Harris & Aguirre, 2010). It is also controversial if non-faces are processed configurally in the same way as faces (Beeck, Baker, DiCarlo, & Kanwisher, 2006) - an alternative interpretation of the discovery of greeble-specific areas in the fusiform gyrus might be that the greebles were perceived as humans or faces (Beeck et al., 2006) - an interpretation that is highly improbable with the present stimulus set. However, the current stimuli contain considerable configural features resulting from the spatial arrangement of the different colors.

More proof for the importance of the left visual ventral stream was found in the examination of patients with lesions to the left posterior hemisphere. They did show more deficits in generalization and visual category learning than patients with right posterior cerebral lesions (Langguth, Jüttner, Landis, Regard, & Rentschler, 2009).

The hippocampal activation, also present in the main effect of “block” (see Table 4.1), did distinguish between successful learners of the exceptions in the last block. After a few blocks, the participants realized that their prototype-based strategy used for 12 of 14 stimuli does not work for the two exceptions and switched to an exemplar-based strategy, as previously shown by Cook & Smith (2006). This strategy required an explicit memorization of the exceptions, which was possibly enabled by the category-sensitive cells in the MTL, especially the HC (Hampson et al., 2004; Kreiman et al., 2000). Indeed, MTL neurons in monkeys and humans show selective responses to classes of visual stimuli and to specific individuals (Mormann et al., 2008). These results suggest an invariant, sparse and explicit code (Quiroga et al., 2005). Coding
properties of hippocampal neurons are highly flexible and quickly learn to categorize visual stimuli by extracting unique combination of features that are relevant for discrimination (Hampson et al., 2004). These experiments reveal that hippocampal neurons are able to code for individual items using a multitude of different representations. Even if there are doubts about the assumption of extremely specialized “grandmother cells”, these neurons are sparse in the sense that they fire after the presentation of only very few stimuli (Quiroga, Kreiman, Koch, & Fried, 2008). It is probable that the sparse coding is supported by the firing of inhibitory neurons, resulting in an increase of the hemodynamic response and hence the BOLD signal (Viskontas, Knowlton, Steinmetz, & Fried, 2006). Inhibition could modify synaptic connections in the MTL via long-term depression and lead to more specific neural representations (Axmacher, Elger, & Fell, 2008).

Although the functional data seemed to show a differential processing of prototypes and exceptions at a first glance, further analyses have shown that there was no complete dichotomy in regards to the processing of the different stimulus types. The correlation of the mean signal changes over time revealed a synchronization of activation changes between right HC and left fusiform gyrus. The activations were synchronized in the first block, with the learners showing negative signal changes for both stimulus types. The desynchronization after the first block revealed a different progression for the signal changes of both structures, with the HC showing more positive signal changes than the fusiform gyrus in the second block. In the third block, the correlation of both structures became significant again for prototypes, followed by exceptions in the last block. In general, the hippocampal activation showed a parallel, but time displaced activation course for exception and prototype learners. The activation of the fusiform gyrus, which might reflect the representation of the stimulus, emerged later for the exceptions than the prototype, which is also reflected by the behavioral data. Taken together, the population coding properties of the fusiform gyrus enabled the learners to build representations of the stimulus families with shared similarities among their features. The increase of activation over time corresponded to the ability to successfully categorize prototype stimuli early on during the experiment. Furthermore, it also enabled participants to discriminate the exceptions from the rule, in interplay with the sparse coding properties of the HC, which coded the representation of exceptions.
Taken together, results from the current study reveal two neural substrates that are associated with a prototypical stimulus that shares a large number of common elements with other members of a class and an exceptional exemplar that represents a unique cue. While the former seems to require object-based processes of the ventral visual stream, the latter additionally needs the HC to create a sparse code for a stand-alone representation of the exceptions. In order to further elucidate the underlying systems, future research might focus on formal modeling of the initial assumptions and the validation of these models by using MVPA to disentangle the patterns of activation that enable successful category learning. Overall, the MTL is of central importance for both strategies that enable visual category learning.
Chapter 5

Study 4: Overlap of visual discrimination and categorization processes in the medial temporal lobe

5.1 Introduction

As described in the general introduction, the MTL is involved in a variety of cognitive functions. The results obtained in Study 1 and Study 2 are in line with the view that it is not only enabling memory (Squire et al., 2004), but that its structures are also involved in complex visual discrimination tasks (Graham et al., 2010; Lee et al., 2012) in which the stimuli have a high feature ambiguity.

Additionally, Study 3 could show the fundamental MTL structures that are involved in a visual category learning task. Categorization can be based on two differing learning strategies (Medin & Schaffer, 1978; Posner & Keele, 1968): Using an experimental paradigm that was adapted from a previous behavioral study (Cook & Smith, 2006), it could be shown that prototype-based learning, in which stimuli are categorized based on a large number of shared common elements with a prototype, is mostly based on neural processes in the fusiform gyrus or the ventral visual stream in general. Exception-based learning on the other hand is based on the learning of unique cues, which was represented by hippocampal activations. However, this apparent dichotomy was not complete, as correlation analyses have shown that the HC and fusiform gyrus both participate in these learning strategies, but in a time displaced manner.
5.1.1 Aims and hypotheses

As of yet, there has been no study comparing visual discrimination and category learning in the MTL. Therefore, the aim of Study 4 was to use functional magnetic resonance imaging in healthy subjects to investigate the contributions of the medial temporal lobe to the processing of abstract three-dimensional stimuli by directly comparing the activation in a visual discrimination and a category learning task. Previously developed paradigms were used for this in a within-subject fMRI design - a visual discrimination task (adapted from Study 1) and a visual category learning task (adapted from Study 3). Abstract artificial 3D stimuli were used for both tasks, in order to prevent face or scene specific processes and to make both tasks comparable.

Based on the findings from the previous three studies, the following hypotheses were formulated:

- The HC should be activated for discriminations involving stimuli with high feature ambiguity.
- There should be differential activation patterns for prototype-based and exemplar-based learning.
- Both learning strategies should be associated with activations in the fusiform gyrus and HC.
- If the MTL is processing representations of stimuli regardless of the task or cognitive process, the neural activations for both tasks should overlap within the MTL.
5.2 Methods

5.2.1 Participants

28 healthy human subjects participated in this study. Five participants had to be excluded from the analysis because of technical difficulties or because the participants did not understand the tasks, leaving 23 participants in the analysis (10 male and 13 female; mean age: 24.04 years; range: 19-33). All participants were right-handed, neurologically healthy and had normal or corrected-to-normal vision. All subjects gave informed written consent after a detailed explanation of the procedure.

5.2.2 Experimental design

The experiment took place inside of an MRI scanner and was performed using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA) and MRI-suitable LCD video goggles (Resonance Technology Company, Inc., Northridge, CA, USA) with a resolution of 800 x 600 pixels, registering the responses with an MRI-suitable keypad.

Two different tasks were applied: First, they had to perform in a discrimination task, in which 180 pictures of artificial 3D stimuli were presented in an oddity task (O'Neil et al., 2009). The task was again adapted from Study 1 and Study 2, but this time only one stimulus type in two difficulty conditions (“easy” and “hard”) was presented, resulting in 36 easy and 36 hard trials. Additionally, 180 black rectangles in varying sizes were used as a baseline condition, with 36 easy and 36 hard trials. Similar to the previous studies, three trial-unique pictures were shown simultaneously for four seconds in each trial in order minimize the working memory demands. Subjects had to decide which picture was the “odd-one-out” and had to respond by pressing one of three buttons.

All artificial stimuli were created with the free version of SketchUp (Trimble Navigation, Ltd., Sunnyvale, CA, USA) and consisted of one unique “body” and four appendages or features. These features were then manipulated in order to achieve
different degrees of overlap. In the “easy” condition, the “odd-one-out” differed in 3 out of 4 features (color and/or shape). For the “hard” condition, stimuli shared 3 out of 4 features, resulting in a higher overlap (see Figure 5.1). These stimuli were piloted extensively to achieve similar error rates for both difficulties as in the previous studies. The black rectangles for the baseline condition were constructed in the same way as in Study 1. For further information on the presentation of the stimuli in the discrimination task, see section 2.2.2.

Figure 5.1: Examples of stimulus displays from the discrimination task. Easy discriminations of both stimulus types are displayed on the left and hard discriminations on the right. Each of these 4 conditions was presented 36 times over the course of the experiment, with trial-unique stimuli. Note that the black rectangles were used as a baseline condition for the analysis of discrimination related activations.
Following the discrimination task, the participants had to perform in a categorization task, which was structurally similar to the paradigm used in Study 3 (Cook & Smith, 2006). This time the stimuli consisted of artificial 3D stimuli, created in SketchUp. As before, the stimuli were similar in structure (sharing the same main body), but differed in the combination of 6 binary features. Participants had no knowledge about or prior experience with these stimuli, and had to categorize them into one of two “families”. Each category consisted of a prototype, alongside five typical stimuli that shared five features with the prototype, as well as an exception that shared five features with the prototype of the opposing category (see Figure 5.2). For more information regarding the presentation of the stimuli, see section 4.2.2.

The study received ethical approval by the local Ethics Committee of the Medical Faculty of the Ruhr University Bochum, which conforms to the Declaration of Helsinki.

Figure 5.2: Artificial stimuli that were used in the categorization task. Stimuli from both categories were constructed with 3.88 shared features within and 2.12 shared features between categories. Additionally, the stimuli of one category shared 4.57 features with their own prototype and 1.43 with the prototype of the other category (see also Cook & Smith, 2006 and Study 3).
5.2.3 Scanning parameters

The experiment was performed using a Philips 3T Achieva MRI scanner with a 32 channel SENSE head coil. A T1 weighted structural scan was acquired for every participant at the start of the first experimental session (220 slices, voxel size = 1 x 1 x 1 mm, TE = 3.8 ms, flip angle = 8°) in order to create a mean structural image and to overlay activations. T2* weighted EPIs were acquired during both tasks in an ascending sequence of 30 slices (voxel size = 1.65 x 1.65 x 5 mm, TR = 2200 ms, TE = 35 ms). The first five dummy images at the start of each scanning session were discarded to allow for MRI signal stabilization.

5.2.4 Data analysis

The functional and structural images were pre-processed using the latest release of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The pre-processing consisted of a slice-time correction, realigning and unwarping, co-registering the EPIs with the structural scan, segmenting the structural scan into grey and white matter, and normalizing the EPIs to MNI space. The unwarping was employed in order to reduce the distortions that can be caused by magnetic field inhomogeneities resulting from movement. All images were re-sliced into 1.5 x 1.5 x 1.5 mm voxels and then smoothed with a Gaussian kernel of 8 mm full-width half-maximum (FWHM). The pre-processed images then were submitted into a first level GLM analysis, where the blood oxygenation level dependency (BOLD) signal was modeled with the canonical hemodynamic response function. A high-pass filter at 128 s was used to remove low frequency drifts.

For the discrimination task, five regressors were defined on the first level: one for the presentation of artificial stimuli and baseline stimuli in both difficulties (“easy baseline”, “hard baseline”, “easy discrimination”, “hard discrimination”), and one additional fixation regressor (to increase the amount of explained variance). First level contrasts were then defined by subtracting “hard baseline” from “hard discrimination” as well as “easy baseline” from “easy discrimination”. The resulting discrimination
contrasts were then used for group inference in the second level random effects analysis. A within-subjects full factorial model with one factor (“stimulus”) was used.

For the categorization task, 7 regressors were defined per block on the first level: correct and incorrect responses for the three stimulus types (“correct prototypes”, “incorrect prototypes”, “correct typical”, “incorrect typical”, “correct exception”, “incorrect exception”), and a fixation regressor. As before, prototypical and typical stimuli were combined (“ProTyp”) for the following contrasts: Correct responses were contrasted against the fixation regressor, separate for block 1 (before learning) and block 3 (after reaching a learning plateau, see below), resulting in the contrasts “ProTyp untrained”, “ProTyp trained”, “Exc untrained”, and “Exc trained”. These four contrasts were then used for group inference in the second level analysis. In the group-level random effects analysis, a within-subjects full factorial model with 2 factors was used, including the factors “stimulus” (ProTyp vs. Exc), and “block” (1 vs. 3).

Main effects for all factors in both tasks were used as contrasts of interest, together with the resulting interactions. Significant interaction clusters in the full factorial analyses were then used to extract mean signal changes (in percent) with MarsBaR software (http://marsbar.sourceforge.net/). Afterwards, these were fed into paired t-tests.

All reported statistics refer to whole brain analyses. As in Study 1, the statistical maps were initially analyzed using an uncorrected threshold of p < 0.001 with a minimum of 10 voxels per cluster. To reduce type II errors while keeping type I errors low (Lieberman & Cunningham, 2009), a Monte Carlo simulation with 10,000 iterations was used (Johnstone et al., 2007; Slotnick et al., 2003; Slotnick & Schacter, 2006; Zaki et al., 2012), defining the threshold at p < 0.05, corrected for multiple comparisons. This simulation yielded a cluster extent threshold of 65 resampled voxels while assuming an individual voxel type I error of p = 0.001.

MarsBaR software was also used in order to extract single ROIs for the overlaying of activations from both tasks performed with the freely available MRIcro software (http://www.mccauslandcenter.sc.edu/mricro/).

All statistical analyses of the behavioral data and mean signal changes were performed using SPSS Statistics 20 (IBM Inc.).
5.3 Results

5.3.1 Behavioral data

The data from the visual discrimination task could not be analyzed in its entirety. Due to a technical problem one third of the data was missing for 14 participants. For these, only 96 (4 x 24) trials could be analyzed, balanced across all conditions. For 8 participants, the data was complete and was therefore based on 144 (4 x 36) trials. The responses of one participant were not recorded at all.

For the reaction times, the repeated measures ANOVA yielded a significant main effect for the factor “difficulty” ($F(1,21) = 189.130; p < 0.0001$) as well as a significant interaction between “difficulty” and “stimulus” ($F_{1,21} = 4.531; p < 0.045$). The main effect of “difficulty” resulted from the significantly faster RTs for easy stimuli. Paired t-tests revealed that this interaction was the result of faster reactions for easy baseline stimuli as opposed to easy artificial objects (see Figure 5.3).

For the hits, the repeated measures ANOVA yielded a significant main effect only for the factor “difficulty” ($F_{1,21} = 161.050; p < 0.0001$), which was based on the higher amount of correct responses for the easy difficulty (see Figure 5.3).

Regarding the categorization task, the data for all 23 participants was available. In contrast to Study 3, which used a similar category structure and paradigm, all of the participants included in the analysis did successfully learn to categorize prototypes and exceptions correctly. The repeated measures ANOVA revealed significant main effects for the factors “stimulus” ($F_{1,22} = 18.292; p < 0.0001$) and “block” ($F_{4,88} = 22.585; p < 0.0001$), as well as a significant interaction between both factors ($F_{4,88} = 16.390; p < 0.0001$). Paired t-tests revealed that this interaction resulted from the different learning curves for both stimulus types (Figure 5.4). In the first block, the correct responses for prototypes and exceptions differed significantly, with a much worse performance for exceptions. In block 3, correct responses for both stimulus types reached the same level and did not improve any further.
Figure 5.3: RTs, hits, and FAs in the visual discrimination task. The upper graph shows the RTs in the discrimination task, with significantly faster RTs in the easy condition, and especially for baseline stimuli. The lower graph depicts the hits in the discrimination task, with a significantly higher hit rate for easy conditions. Error bars represent SEM. Note that only data from 22 participants was used in the behavioral analyses. For 14 of these, only two thirds of all trials were available.
Figure 5.4: Correct responses in the categorization task. All participants show an increase in correct responses over the five experimental blocks for both stimulus types. Successful categorization of prototypical stimuli starts out on a higher level than the categorization of exceptions, but both curves reach their peak after the third block. Error bars represent SEM.

5.3.2 Imaging data

The results from the full factorial group analyses will focus on hippocampal and fusiform activations, based on the findings from Study 3 (see Figure 5.5 for these activations). A detailed listing of all activations can be found in the Appendix (Table A.2).

The second level analysis of the discrimination task yielded a significant main effect for “stimulus” (i.e. the contrast of discrimination > baseline) in the left posterior HC (-27 -28 -11, 75 voxels, T = 4.03).

For the categorization task, several clusters in the HC and fusiform gyrus were found. The main effect of “stimulus” yielded an extensive cluster in the right anterior HC (21 -15 -15, 310 voxels, T = 4.83), for the contrast exceptions > prototypes. Furthermore, the main effect of “block” yielded three clusters: for the contrast block 1 > block 3, one cluster in the right fusiform gyrus was found (33 -49 -8, 415 voxels, T = 4.34). The contrast block 3 > block 1 yielded one cluster in the left fusiform gyrus (-42 -43 -18, 14
voxels, $T = 5.20$) and one cluster in the left posterior HC (-29 -31 -9, 155 voxels, $T = 5.05$).

Additionally, the interaction contrast of “stimulus” x “block” yielded activation clusters in the left (-26 -34 -8, 64 voxels, $T = 4.31$) and right posterior HC (24 -30 -8, 20 voxels, $T = 3.50$). These interaction clusters have to be interpreted carefully, since they did not reach the Monte Carlo corrected threshold of 65 contiguous voxels and hence represent uncorrected ($p<0.001$) data. Mean signal changes were extracted for these ROIs resulting from the interaction contrast.
Figure 5.5: Significant activations in categorization and discrimination tasks. Only significant activations (p<0.05, corrected) in the HC and fusiform gyrus are depicted. Note that the activations from the interaction contrast did not reach the Monte Carlo corrected threshold of 65 contiguous voxels. All activations are projected on the mean structural image of all participants.

Consecutive t-tests revealed that the interactions were based on a higher difference for prototype stimuli between the first and the last block (see Figure 5.6). The percent signal change of exceptions did not show this difference.
Figure 5.6: Percent signal change in clusters active for interaction contrasts in the categorization task. For both ROIs, t-tests revealed significant differences for prototype stimuli between the first block (before learning) and the third block (after learning). For exceptions, the PSC did not change significantly between both blocks. Error bars represent the SEM.
For further visualization of the data and in order to see investigate the overlap of activations in the discrimination and categorization task, the activations found in the left posterior HC were projected onto one structural image (see Figure 5.7). This projection shows that the activations from both tasks did overlap in the left posterior HC. Nevertheless, this left sided focus needs to be regarded carefully, since a null finding in the right HC does not ultimately indicate that the right HC was not involved in these processes.

Figure 5.7: Overlap of activations from the discrimination and categorization task. The ROIs that were extracted from the contrast discrimination > baseline and categorization block 3 > block 1 do partially overlap in the left posterior HC. Note that the activation clusters were overlaid on the colin27brain included in the MRICro software package.
5.4 Discussion

The goal of this study was to investigate how visual discrimination and category learning, both cognitive functions that are in part mediated by the MTL, are represented within the MTL structures. A paradigm that was successfully employed in Study 3 was used to investigate if both types of tasks do overlap in the MTL.

The behavioral data in Study 4 could overall replicate the results of the previous three studies. For the discrimination task, the complex stimuli with a high feature ambiguity did cause lower hit rates and slower RTs than the easy stimuli. The RTs for baseline stimuli were significantly faster in the easy condition, which indicates that the artificial 3D stimuli were a bit harder to discriminate than the baseline stimuli. This effect is similar to the effects found for faces in Study 1. While the hit rate was the same for faces, scenes and baseline stimuli, the RTs for faces were slower. This shows that the artificial stimuli as well as the faces were not completely matched with the other stimulus types in regards to difficulty.

For the categorization task, the behavioral results showed a very similar learning curve as in the original study from which the paradigm was adapted (Cook & Smith, 2006), with participants being mostly successful using a prototype-based strategy and then switching to an exemplar-based strategy in order to enhance their performance for the two exceptions. The learning curve was also very similar to the performance for the abstract circular stimuli in Study 3. One difference was that all of the participants that were included in the analysis showed similar learning curves. There was no post-hoc differentiation of learners and non-learners as in Study 3. Another slight difference was that the learning curves did not improve after the third block. These results indicate that the categorization of abstract 3D stimuli was apparently easier than the categorization of circular stimuli for most participants, although the stimuli from both studies were structurally identical.

The imaging results from the categorization task overall replicated the findings from Study 3, with both fusiform gyrus and HC being involved in the learning of prototypes and exceptions. It could be shown that the right posterior HC is activated in the contrast exception > prototypes, again suggesting that this might reflect the creation of stand-
alone representation of the exceptions. The contrasting of block 3 against block 1 (or learned vs. not-learned) regardless of the stimulus type, yielded hippocampal and fusiform activations, again supporting the view that both structures are involved in this categorization paradigm and confirming hypotheses 2 and 3.

These results are also in line with previous studies, showing that the fusiform gyrus is involved in the learning and representation of novel objects (Gauthier et al., 2000; Gauthier et al., 1999). Since the behavioral data in the discrimination task were very similar to the discrimination performance for faces in Study 1, one possible explanation might be that the current artificial stimuli – much like “greebles” (Gauthier et al., 1999) – are being perceived as faces (Beeck et al., 2006). Here, the fusiform activation was found in the first as well as in the last block, showing a prolonged involvement in learning and categorizing stimuli. The HC was active in the contrast block 3 > block 1, but also explicitly in the contrast exception > prototype. This might again reflect the explicit memorization that was needed in order to successfully categorize exceptions. It has been shown previously that the HC does comprise category-sensitive cells (Hampson et al., 2004; Kreiman et al., 2000), and that single MTL neurons can exhibit selective responses to specific stimuli (Mormann et al., 2008).

Moreover, it could be shown that the HC was again involved in a complex visual discrimination task that was not reliant on memory processes, thus confirming the first hypothesis. The contrast discrimination > baseline resulted in a left sided hippocampal activation. In order to verify the fourth hypothesis, the hippocampal activations resulting from both visual discrimination and categorization were overlaid onto the same brain. The resulting overlap showed that both tasks activated voxels in the same part of the left posterior HC, with a clear overlap of both activation clusters. These results confirmed the fourth hypothesis and showed that the MTL (or to be more precise, the HC, as part of the MTL) was involved in processing representations of artificial 3D stimuli, regardless of the task that had to be solved by the participants of this study.

This does further contribute to the question if and how the MTL is involved in complex visual discrimination tasks. As in Study 1 and Study 2, the results show that discriminating stimuli with high feature ambiguity does recruit the MTL, again
supporting previous findings (Barense, Henson et al., 2010; Bussey et al., 2005; Devlin & Price, 2007; Graham et al., 2010; Lee et al., 2008; Murray et al., 2007; O’Neil et al., 2009). Unfortunately, as in Study 1, the current findings failed to find any perirhinal activations. Nevertheless, only one stimulus type was used in Study 4, so that it would have been impossible to demonstrate a putative functional specialization for different stimulus types (Barense et al., 2005; Barense et al., 2007; Eldridge et al., 2000; Lee, Bussey et al., 2005; Lee, Buckley et al., 2005, 2005, Ranganath et al., 2004; Suchan et al., 2008). Furthermore, the data are again in disagreement with the notion that the MTL is specialized only for memory processing (Hampton, 2005; Levy et al., 2005; Shrager et al., 2006; Squire et al., 2004).

Besides replicating and corroborating the findings of the previous three studies, Study 4 does also show that two very different tasks (visual categorization and discrimination) that are supposedly engaging differing cognitive processes both yield large activations of the same neuronal population in the HC. These findings are not in line with data from a patient study that shows that the type of stimulus is the main cause of categorization deficits (Graham et al., 2006). However, it does support the idea that representational accounts of the MTL (Graham et al., 2010; Saksida & Bussey, 2010) might be more fitting to explain the data from various studies, with the MTL having a broader role in different cognitive processes. One important driving factor in these representational models might be the complexity of stimulus conjunctions/features, with the HC and PRC being especially sensitive for stimuli with high feature ambiguity (Cowell, Bussey, & Saksida, 2010; Mundy, Downing, & Graham, 2012). This is also supported by findings that show the HC as being able to flexibly and quickly categorize stimuli by extracting their unique feature combinations (Hampson et al., 2004).

One drawback of the current study is the fact that discrimination and categorization tasks were tested separately, hence leading to a comparison of events that are distant in time. Future research might develop a design in which categorization and discrimination of similar stimuli is intermixed and can be ultimately compared without any temporal delay, in order to validate the current findings.

In summary, the results presented in Study 4 have replicated the findings from Study 1 and 3 and extended them by showing how a visual category learning task and a complex
visual discrimination task can overlap in the human HC. These findings again disagree with the MTLMS model (Squire & Zola-Morgan, 1991), which assumes that the MTL is involved in memory processing but not in any other cognitive processes. They are in support of a representational view of the MTL (Graham et al., 2010; Lee et al., 2012; Saksida & Bussey, 2010) though, demonstrating that similar stimuli (abstract 3D stimuli) lead to a similar activation pattern in the HC, although two very different tasks were being used.
Chapter 6

General Discussion

The investigation of perceptual processes in the MTL is still at the beginning (with the first studies having been performed in the nineties of the last century) and the studies dealing with this topic do often yield contradictory results. The current thesis aimed at contributing to this young field of research by investigating how the structures of the human MTL are involved in the processing of visual stimuli in various paradigms and with respect to differing cognitive demands.

To achieve this, performance and brain activations in a complex visual discrimination paradigm were directly compared with memory related activations (Study 1). The same paradigm was also applied in a behavioral patient study, in order to demonstrate how two very different brain lesions can contribute to visual discrimination deficits, apart from the expected memory deficits (Study 2). The neural correlates of visual category learning were also investigated (Study 3) and afterwards compared to the established visual discrimination paradigm (Study 4), in order to show a potential overlap of complex visual discrimination and visual category learning processes.

A detailed discussion of the results from all four studies can be found at the end of each respective study chapter (see sections 2.4, 3.4, 4.4, and 5.4). Section 6.1 will briefly summarize these results before integrating the findings from these four studies into the current research and deriving a new model of the MTL. Afterwards, the implications for our view of the MTL will be discussed, and possible future directions for human MTL research will be proposed.
6.1 Summary of the main results

All four studies that were conducted for the current thesis dealt with the contributions of the human MTL (and especially the HC) to complex visual discrimination as well as learning and memory. Three of the studies focused on brain activations as measured by fMRI (Study 1, Study 3, and Study 4) and one study focused on the behavioral level, investigating patients and matched healthy controls (Study 2).

6.1.1 Study 1

The direct comparison of a complex visual discrimination task and a recognition task in a within-subject full factorial fMRI design showed that the processing of faces and scenes activates the HC, regardless of the task that has to be performed. Unfortunately, no perirhinal activation could be demonstrated in this study, which may have been caused by signal dropout in the MTL. Nevertheless, stimulus-specific processing could be shown to some degree in the interaction analysis. While the left HC was more strongly involved in the recognition of scenes, the right HC showed stronger activation for the recognition of faces. Further analyses of the interactions incorporating the PHC and fusiform gyrus also showed stimulus specific processing in visual stream structures that propagate the information to the HC. Taken together, these results supported a perceptual-mnemonic theory of the MTL (Bussey & Saksida, 2005; Graham et al., 2010), by showing that the HC is involved in the processing of faces and scenes in both mnemonic as well as complex visual discrimination tasks.

6.1.2 Study 2

Using the same established behavioral paradigm as in Study 1, Study 2 could demonstrate visual discrimination deficits in two patients suffering from brain lesions with differing location and origin. Both patients, one with extensive MTL lesions (VG) and one with a small lesion of the anterior fornix (HJK) did show deficits in a visual
discrimination task when compared to age and education matched control groups. Patient VG was strongly impaired in discriminating scenes and faces with high feature ambiguity and in recollecting verbal and non-verbal information, while showing otherwise intact cognitive functions. Patient HJK was only clearly impaired in discriminating faces with high feature ambiguity, and did also show slight deficits in attention and working memory in the neuropsychological tests. These effects may be in part explained by his higher age (and also the higher age of his control group) or by the fact that he was still in the acute phase of his hospitalization. Taken together, Study 2 confirmed the results that were shown for healthy participants in Study 1 and also extended the perceptual-mnemonic theory of the MTL to the main output structure of the HC, the fornix, a brain structure that has been previously connected to episodic memory (Aggleton & Brown, 1999; Metzler-Baddeley et al., 2011).

6.1.3 Study 3

Study 3 demonstrated the fundamental neural correlates of category learning in the human MTL, with two underlying learning strategies, prototype-based and exception-based categorization. A paradigm that has been employed previously in humans and pigeons (Cook & Smith, 2006) was adapted for this fMRI study, in a within subject full factorial design. Results showed that prototype-based categorizations mainly recruited the fusiform gyrus, while exception-based categorizations were more dependent on hippocampal activations. Further correlation analyses showed that these results were not based on a complete dichotomy or specialization of both structures, but rather on a temporal delay of processing in both structures. Taken together, Study 3 for the first time demonstrated the neural correlates of prototype- and exception-based category learning, and in general the contribution of MTL and related structures to a perceptual learning task, establishing the basal neural underpinnings needed for a comparison of visual category learning and visual discrimination.
6.1.4 Study 4

After showing the neural basis of prototype-based and exception-based category learning in Study 3, Study 4 aimed at integrating the results from all previous studies, by investigating a potential overlap of mnemonic and perceptual tasks. For this, a visual category learning paradigm (adapted from Study 3) and a complex visual discrimination paradigm (adapted from Study 1 and 2) were employed in a within subject full factorial fMRI design with healthy human participants. Overall, the findings from all previous studies could be replicated. The findings could also be extended by showing that visual categorization learning and complex visual discriminations activated voxels within the same region of the MTL, or to be more specific the left posterior HC. This result is a strong support of a representational view of the MTL (see below), which focuses on the type of stimulus that is being processed at a time, and not on the underlying cognitive processes.

6.2 Complex visual discrimination in the light of traditional MTL models

In the past 70 years, research dealing with the human MTL has almost exclusively dealt with its role in memory, or in the case of patient studies, the implications for amnesia and related disabilities. The traditional models that were derived from decades of memory research do posit that the HC and surrounding MTL structures (e.g. the PRC and PHC, as well as the EC) do form the major memory system in the human brain (Squire et al., 2004; Squire & Wixted, 2011; Squire & Zola-Morgan, 1991). In the MTLMS (see section 1.1.1), the MTL is exclusively involved in long-term declarative memory, with damage leading to deficits in all related declarative memory processes.

While this classical model is in line with the memory task results from Study 1 as well as the memory deficits demonstrated by the patients in Study 2, the discrimination task results cannot be accounted for easily, since cognitive processes apart from memory are
excluded from the MTLMS (Clark et al., 2011; Kim et al., 2011; Squire & Wixted, 2011).

Furthermore, the differential processing of various stimulus types that could be shown to some degree in Study 1 would not fit the MTLMS, since it posits that there are no clear functional differences between the different MTL structures (Squire et al., 2004; Squire & Wixted, 2011; Squire & Zola-Morgan, 1991).

The results from the discrimination task in Study 1 as well as Study 2 and Study 4 can only be explained in the light of models that assume that stimuli with high feature ambiguity and without a need for memory processing do engage the MTL, as shown previously on many occasions (Barense, Henson et al., 2010; Bussey et al., 2005; Devlin & Price, 2007; Graham et al., 2010; Lee et al., 2008; Murray et al., 2007; O'Neil et al., 2009).

Additionally, the results shown in Study 2 demonstrated that the fornix is not only vital for human episodic memory (Aggleton et al., 2010; Metzler-Baddeley et al., 2011; Pergola et al., 2013), but also for complex visual discriminations that do not require memory: A very minor lesion of the anterior fornix of Patient HJK did lead to severe results in both mnemonic and perceptual tasks (see section 3.3).

6.3 Distinguishing memory and perception in the MTL

There is still a considerable amount of controversy regarding the role of the MTL in higher-order visual perception (Baxter, 2009; Suzuki, 2009; Suzuki & Baxter, 2009): As mentioned earlier, the most common criticism regarding perception in the MTL is that the employed discrimination paradigms are to some degree confounded with memory processes.

The effects of long-term memory and a potential learning benefit have been omitted in the visual discrimination studies of this thesis by exclusively using trial-unique stimuli.
However, patient studies using complex discrimination paradigms have shown that patients with selective hippocampal lesions or more extensive MTL lesions can perform as good as their healthy controls, as long as the controls are prevented from learning the stimuli (Shrager et al., 2006). A more recent study has also confirmed these results, using trial-unique stimuli and showing no impairment after HC lesion (Kim et al., 2011). Lee et al. (2012) point out that these differences, which are in stark contrast to their previous findings (Lee, Bussey et al., 2005), are showing a pattern that is too inconsistent to refute a perceptual role of the MTL and to assume that learning processes are important for complex discrimination tasks. For example, there was an apparent early difference between patients and controls in the early trials of the experiment, at a time point, at which the controls could not have benefitted from learning (Kim et al., 2011). The authors also argue that the findings from several other studies, which used trial-unique stimuli, are not explainable in the view of a learning-based explanation of discrimination deficits (Lee, Buckley et al., 2005; Lee et al., 2006). In the same way, the current results disagree with a learning-based explanation, since only trial-unique stimuli were used in Study 2. Furthermore, in Study 1, incidental encoding was controlled by including stimuli from the discrimination task in the recognition task. The results showed that these stimuli were encoded only to a very small degree (see section 2.3.1). Adding to this, recent findings demonstrated that hippocampal activation in discrimination tasks is unrelated to subsequent recognition memory performance (Lee, Brodersen, & Rudebeck, 2013), showing that encoding does not play an important role in these tasks and that it does not explain the activations.

The same study has also compared univariate and multivariate fMRI analyses in a design that was investigating spatial memory and perception in the HC (Lee et al., 2013). The authors found that the HC is involved in long-term declarative memory as well as complex spatial perception, demonstrating that it can be beneficial to use various statistical approaches in the analysis of fMRI data to successfully distinguish mnemonic and perceptual processes.

As mentioned earlier, it has been shown in several studies that the HC can be also involved in specific types of working memory tasks (Hartley et al., 2007; Olson et al., 2006). This problem has been addressed in all current studies that employed the visual
discrimination paradigm (Study 1, Study 2, and Study 4) by presenting all stimuli simultaneously in each trial. Additionally, by choosing a baseline condition that was structurally identical (size oddity judgements with black rectangles) in the fMRI studies (Study 1 and Study 4), possible activations resulting from visual search have been omitted.

Furthermore, Patient VG in Study 2 did perform normally in working memory tests during the neuropsychological assessment, although suffering from extensive MTL lesions, showing that his damage to the MTL and more specifically to the HC did not impair his working memory performance. This is also in line with a study by Lee & Rudebeck (2010a), in which patients showed deficits in a discrimination task that used only a single stimulus.

6.4 Alternative models and explanations for the category learning results

The results of Study 3 and Study 4 did show that the fusiform gyrus as well as the HC plays a major role in prototype-based and exemplar-based category learning. An explanation of the fusiform gyrus’ participation in these learning processes is rather straightforward: As stated above, it is heavily involved in building expertise for faces (Kanwisher, 2000; Kanwisher et al., 1997) or other objects (Gauthier et al., 1999; Tong et al., 2008). It has also been previously shown to be involved in the learning of categories (Folstein et al., 2013), which could also be supported by patient studies investigating subjects with lesions to the left posterior hemisphere (Langguth et al., 2009).

A complementary explanation for the involvement of the HC in categorization might be the attempt to discriminate the exceptions from the other similar objects by means of pattern separation (Bakker, Kirwan, Miller, & Stark, 2008). One argument against a vital contribution of the HC to categorization learning are the findings that show that categorization learning can be intact although the HC is damaged and recognition
memory is impaired in patients (Bozoki, Grossman, & Smith, 2006; Knowlton & Squire, 1993; Squire & Knowlton, 1995). However, this dissociation may also be based on differential memory demands and possibly on residual resources (Nosofsky, Denton, Zaki, Murphy-Knudsen, & Unverzagt, 2012; Nosofsky & Zaki, 1998; Zaki & Nosofsky, 2001).

Study 3 and Study 4 were conceived and conducted within a framework of theories that assume prototype-based and exemplar-based processes as different constituents of category learning (Ashby & Maddox, 2005; Medin & Schaffer, 1978; Medin & Schwanenflugel, 1981; Posner & Keele, 1968; Smith & Minda, 1998; Smith & Minda, 2001). In contrast, common element models (see Soto & Wasserman, 2010 for a review and mathematical formulation) assume that most stimuli have some common elements that can make them similar. In these models, perceptual similarity between two stimuli is a direct function of the proportion of shared elements. Conversely, non-shared features drive dissimilarity between those stimuli. The common elements model can be extended to the results of Study 3 and 4 as well as the study of Cook & Smith (2006) by assuming that “exceptions” represent nothing else than a unique cue within the common elements framework. Accordingly, each stimulus feature employed in a categorization task is associated independently with an outcome. It then activates an individual configural unit which represents this unique combination (Gluck, 1991). Such an account would predict faster learning of stimuli with more common elements due to shared associative strength and slower learning of exception stimuli (Soto & Wasserman, 2010).

Alternatively, the results from the categorization tasks in Study 3 and 4 could also be regarded in the light of the SUSTAIN model (see section 1.3.1). A single representational cluster, enabled by MTL engagement, would suffice to categorize the 6 similar prototype stimuli from one category. As soon as the exception is shown and incorrectly categorized, the network is in need of a new cluster, in order to represent the exception. The SUSTAIN model assumes that if a category structure is complex enough, SUSTAIN will act as an exemplar model and store every category member in its own cluster (Davis et al., 2012; Love et al., 2004). However, a recent study using MVPA (Mack, Preston, & Love, 2013) demonstrated that exemplar-based models
cannot be dismissed as of yet, since the MVPA did reveal activation patterns that are best explained by exemplar-based models.

Traditional memory models like the MTLMS (Squire et al., 2004; Squire & Wixted, 2011; Squire & Zola-Morgan, 1991) would support the view that the HC (or more generally speaking, the MTL) is involved in the encoding of stimulus properties and retrieval of category membership. Nevertheless, a functional segregation enabling differing learning strategies would not be compatible with the model (see above, section 6.2), since the MTLMS does not assume a functional segregation of the MTL structures.

6.5 Integrating the results with representational accounts

Having demonstrated that traditional models of the MTL cannot sufficiently explain the results that have been obtained in Study 1 to Study 4, there is a need to find alternative models capable of encompassing all of the available data. As shortly mentioned in the general introduction (see section 1.4), one solution might be to employ a representational model of the MTL. Below, existing representational models as well as a new representational model (derived from the BIC, see below) will be discussed.

6.5.1 Integration with the BIC model

Contrary to classical memory models of the MTL (e.g. the MTLMS), which assume no functional segregation of the MTL, the BIC model (Diana et al., 2007; Ranganath & D'Esposito, 2010) does suggest an alternative view: In this memory model, which is originally based on anatomical findings in monkeys and rodents (Eichenbaum et al., 2007), the participation of specific MTL structures is dependent on the type of information that is being processed. The authors propose that the HC sits on top of the hierarchical processing structure in the MTL, receiving and integrating information.
about items and the context in which they are presented. This information initially comes from the ventral and dorsal visual stream, and is being propagated by the PRC (items) and PHC (context) on to the HC. This model is able to explain results from various studies investigating memory (and especially familiarity and recollection) for different stimulus types (Barense et al., 2005; Barense et al., 2007; Eldridge et al., 2000; Lee, Bussey et al., 2005, Lee, Buckley et al., 2005, 2005, Ranganath et al., 2004; Suchan et al., 2008), with the HC showing activations related to recollection. It has to be mentioned though that “context” in the BIC does not need to be spatial context (Diana et al., 2007). As Diana et al. point out, the “context” that is being processed in the PHC could also relate to semantic or schematic types of context.

6.5.2 The medial temporal lobe representational system - MTLRS

Although the BIC was originally conceived as a model in order to explain memory processing within the MTL (Diana et al., 2007; Ranganath & D'Esposito, 2010), the results from the current studies can be integrated into the BIC model. The only adjustment that needs to be made is to leave out the assumption that the model does solely account for recognition memory processes. Instead, the assumption put forward here will be that this model explains in a more general fashion how stimuli are being processed regardless of the task that needs to be performed and regardless of the underlying cognitive process. For the sake of simplicity, this adjusted model will be now called the “Medial Temporal Lobe Representational System” (MTLRS, see Figure 6.1).
Figure 6.1: Representational model of MTL processing. This schematic overview is based on the BIC model (Diana et al., 2007) but it does differ in one main aspect: while the original model was focused on explaining the processing of familiarity and recollection memory processes in the MTL, this adjusted model (the medial temporal lobe representational model – in short: MTLRS) makes no assumptions about the underlying cognitive processes. It is solely focused on the type of stimulus that is being processed by the MTL, regardless of the task that has to be performed. Note that the MTLRS does also extend the original finding by including the fornix as a main output structure, as a result of the findings in Study 3. However, many additional connections to the PFC and thalamus are not depicted in this figure. See the upper right figure (or Figure 1.1) for anatomical locations. EC: Entorhinal cortex; PRC: Perirhinal cortex; PHC: Parahippocampal cortex.
Extended to visual processing, the model could help to explain and integrate all of the findings in the current thesis: The HC, standing at the top of the processing hierarchy within the MTL (Saksida & Bussey, 2010), is needed for the integration of information about objects and spatial relations\(^2\) in terms of recollection (Peters et al., 2009; Ranganath et al., 2004; Suchan et al., 2008). Apart from that, the HC is also involved in visual discrimination of faces and scenes with high-feature overlap (Barense, Henson et al., 2010; Lee et al., 2008). For this, it receives input from the PRC (“items” or objects) and the PHC “context” or spatial information) via the lateral and medial EC.

Being a very general model that incorporates all kinds of input independent of the putative cognitive process, the MTLRS model would be able to explain the results obtained in Study 1 (see section 2.3.2), although there was an absence of strongly differential activation for differing stimulus domains: No activation was found in the PRC, a structure that would be normally concerned with the processing of items within this model. This may have been caused by a signal dropout in the MTL. Local distortions of the magnetic field that are caused by air/tissue and bone/tissue interfaces (Olman et al., 2009) may have led to the problem that most of the PRC was not scanned properly.

The fusiform gyrus, which was active for the processing of faces, is not directly part of the model. Nevertheless, as a part of the ventral visual stream, it is known to be of major importance for face perception (Kanwisher, 2000; Kanwisher et al., 1997) or, more generally speaking, in building visual expertise for objects other than faces (Gauthier et al., 1999; Tong et al., 2008). It is directly connected with and propagates information to the PRC, which can be regarded as the continuation of the ventral visual stream (Bussey & Saksida, 2007).

Additionally, it could be shown that the PHC was activated by the processing of scenes (or context within the model). Assuming that the face/object-specific information that was passed on from the fusiform gyrus to the PRC did not yield any perirhinal activation only due to signal loss, the HC was then activated regardless of stimulus

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\(^2\) As mentioned above, the definition of “context” within the BIC model is not limited to spatial processing. However, for initial MTLRS model we will assume that spatial information and context are interchangeable.
domain, showing that it might have integrated the information about single objects (faces) and context (scenes) coming from PRC and PHC. This was the case for both mnemonic and perceptual tasks, confirming that the model is applicable regardless of the experimental paradigm, and only being based on the nature of the stimulus that is being presented at a time.

In the same way, the results from Study 2 are very much in line with a representational model of the MTL. Both patients (one with major lesions of the MTL, the other with a small infarction in the anterior part of the fornix) did exhibit deficits in complex visual discrimination, alongside long-term memory deficits as assessed by neuropsychological standard tests (see section 3.3). The model can account for the results, because the disruption of either the HC or its output structure (the fornix) should lead to similar deficits. Furthermore, these deficits should be present for all kinds of cognitive processes, which could also be demonstrated (see section 3.3). The fact that Patient HJK (suffering from the fornix lesion) was not significantly impaired in the hard discrimination condition with scene stimuli might have resulted from the weak performance of his matched control group. Both HJK and his control group might have exhibited age-related deficits in scene discrimination. It has been shown previously that older but otherwise healthy participants can be impaired in complex discriminations (Ryan et al., 2012). Nevertheless, in this study the focus was on structural and functional changes within the PRC, which has been often shown to be involved in the processing of overlapping features or conjunctions in rats (Bartko, Winters, Cowell, Saksida, & Bussey, 2007), monkeys (Bussey, Saksida, & Murray, 2002), and humans (Barense et al., 2007).

The results found in the categorization task in Study 3 and Study 4 can also be explained in the light of this model. Although Study 3 was initially performed with the assumption of two differing learning strategies (prototype-based and exemplar-based categorization), the resulting fusiform gyrus activation as well as the HC activation can also be explained by the MTLRS model.

While the initial analyses in Study 3 showed that the fusiform gyrus was more active for the processing of prototypes and the HC was more active for exceptions, further correlational analyses showed that there was no complete functional dichotomy between
the fusiform gyrus and the HC. Both structures played a major role in the processing of either stimulus type, only in a time displaced manner. According to the MTLRS model, in the same way as for the results in Study 1, the fusiform gyrus was probably activated because of its coding of features of the single stimuli. The activated HC was then needed to process the conjunctions of all features the stimuli consisted of. The interplay of these structures enabled the participants to correctly categorize most of the stimuli after the third block, regardless of the stimulus type (exception or prototype).

A very similar pattern of activation was observable in the categorization task performed in Study 4. Adding to the neural correlates of categorization that were found in Study 3, it could be shown that the activation clusters for complex visual discrimination and for visual categorization of complex artificial 3D stimuli do indeed overlap within the HC. This makes sense in the framework of the MTLRS model, since both tasks require an integration of the employed stimuli and their complex conjunctions in order to successfully discriminate or categorize them, leading to fusiform and hippocampal activations for both cognitive processes.

6.5.3 Bridging of representational gaps within the HC

Further support for representational models in general and specifically for the BIC does come from studies that show that the HC might be a convergence zone that is involved in bridging representational gaps (Staresina & Davachi, 2009), emphasizing its role in spatial and temporal integration by showing that an increase of these representational gaps also results in an increase of hippocampal engagement.

Furthermore, the authors presented a more recent study in which they could demonstrate that the PRC and PHC do provide domain-preferential inputs (in form of representations) to the HC, with the PRC preferentially processing objects, and the PHC being responsible for the processing of scenes (Staresina et al., 2011). Additionally, they could show that the transitional zone between PRC and PHC was involved in the processing of both stimulus types, indicating that there might be a gradient of domain specificity along the MTL. The double dissociation of PRC and PHC processing is seen
by the authors as a support of the view that the different contributions of MTL structures are based on the representational domain of a stimulus (Davachi, 2006). It has to be mentioned though that these studies were performed with a focus on MTL memory processing. However, the logic of the argumentation can be easily applied to the MTLRS, with time being another factor that influences the processing within the MTL. Furthermore, as has been pointed out previously (Pustina et al., 2012), MTL activations in general are very heterogeneous and do depend on various factors, e.g. problem solving strategies, the specific task requirements, and the type of information that is being processed.

6.5.4 The role of pattern separation

Originating in computational models of memory (Lacy, Yassa, Stark, Muftuler, & Stark, 2011), pattern separation is a process that is thought to be mediated by the HC (Bakker et al., 2008; Kirwan & Stark, 2007). It enables the discrimination between similar experiences, by reducing interference between sensory inputs and storing them as non-overlapping representations (Yassa & Stark, 2011). The complementary process, pattern completion, which allows completing degraded representations based on previously stored information, was first suggested by Marr (1971). It allows for accurate generalizations, even if the sensory input is noisy or partially missing (Yassa & Stark, 2011). Both processes allow an accurate storage and retrieval of episodic memories, and they both need the HC when high amount of interference caused by sensory inputs needs to be resolved (Kirwan & Stark, 2007). It has also been shown that pattern separation can be processed differently by CA1 and CA3/DG3 regions within the HC (Lacy et al., 2011), further demonstrating functional segregations within the MTL. Overall, pattern separation and completion allow building and discriminating distinct representations (Lee et al., 2012), which incorporate spatial and temporal information

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3 CA is the abbreviation for “cornu ammonis”, which is the name of the four main divisions within the hippocampus proper, CA1 through CA4. DG is short for the dentate gyrus, another part of the hippocampal formation (for more details on hippocampal subfields and anatomy, see chapter 3 of O'Keefe and Nadel (1978)).
about an event. The HC is of major importance for both processes, and also very well suited because of its connections and neural firing properties (Yassa & Stark, 2011).

In the same way as the representational accounts in the previous section (6.5.3), the idea that the HC might be performing pattern separation and pattern completion is based on memory theories and investigations. However, as before, this idea can be extended to other cognitive processes like perception and therefore is not directly opposed to the MTLRS, assuming that pattern completion and separation do not only help to discriminate visual input with temporal delay, but also objects that are presented at the same time. As the authors of a recent review point out (Yassa & Stark, 2011), a computational framework of HC functioning can help to address important questions regarding MTL functioning, and in the light of the current thesis, this is not limited to memory research.

6.6 Open questions

Since the history of MTL research regarding perceptual processing is rather young (with one of the first studies dealing with this topic being carried out exactly 20 years ago by Eacott et al. (1994)), many questions and concerns still need to be addressed. One issue is the question which methods are suitable to compare mnemonic and perceptual processing in the MTL and will be discussed below. Another issue, the operationalization of “pure” perception without the involvement of memory mechanisms, has been discussed above (see section 6.3).

6.6.1 Methodological considerations

Study 1 and Study 4 did compare memory or learning processes with perceptual discrimination processes. The comparisons that were applied here were based on tasks that were performed consecutively. A better and more direct comparison might be
achieved by employing a design, in which both tasks are performed simultaneously or randomized across all trials (O'Neil et al., 2012).

Another potential issue is the large inter-subject variability of small structures like the HC, PRC, and EC. This might lead to errors and inaccuracies in standard fMRI preprocessing workflows that normalize the structural and functional data to the standard MNI space. However, there are improved normalization methods that try to address this problem and largely increase the accuracy of the normalization. One example is ANTS (Avants et al., 2011), the Advanced Neuroimaging Tools software. With this image registration and segmentation tool, diffeomorphic transformations can be applied to functional images after building a specific template with the acquired structural images. Using high-resolution fMRI together with advanced normalization procedures might also help to identify the contribution of hippocampal subfields to the processing of various stimuli. Early computational models already posited functional specializations within the HC (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995), and recent animal studies have confirmed that hippocampal subfields like CA1 and CA3 can exhibit differential contributions to spatial and non-spatial processing (Beer, Chwiesko, Kitsukawa, & Sauvage, 2013; Beer, Chwiesko, & Sauvage, 2014).

6.6.2 Future directions

After discussing the results in the light of a representational model, considering potential problems and reviewing methodological aspects, the question that remains is what future studies could do to improve their experimental paradigms.

The BIC model was initially conceived in order to explain findings in memory studies, with a focus on recollection and familiarity (Diana et al., 2007; Ranganath & D'Esposito, 2010) and how they might be processed within the MTL. This proposed functional segregation is opposing the view of a unitary long-term declarative memory system such as the MTLMS (Squire & Zola-Morgan, 1991). For future studies it might be interesting to investigate how these memory processes are represented alongside perceptual processes within the MTL.
Furthermore, Study 2 has shown that the research dealing with MTL and perception might need to include other structures as well. In this case it could be shown that minor lesions to the fornix, a major output structure of the HC, can lead to very similar deficits as focal MTL lesions do. Adding to that, it could be worthwhile to include the thalamus into this line of research, since it has been shown that the thalamus is also relevant for memory processing (Aggleton et al., 2010; Pergola et al., 2013), probably through the projections that it receives from the HC. Also, using diffusion tensor imaging (DTI) in imaging studies might help to shed more light on the influence of the afferent and efferent connections that the MTL has. DTI studies of the fornix might help to show how the structural integrity of the fornix is correlated with performance in complex discrimination tasks.

As mentioned on several occasions, MVPA might also help to disentangle the processes within and beyond the MTL (see above in section 6.5.2). With MVPA, it is possible to expand the view from activations in single voxels to the investigation of neural activation patterns spanning numerous voxels (Haxby, 2001; Norman, Polyn, Detre, & Haxby, 2006). This method could greatly contribute to the question how representations are defined by the underlying neural activity of brain networks, and it would also be more sensitive to small changes in activation patterns (Yang, Fang, & Weng, 2012).

Another interesting research question derived from the results in Study 2 might be the influence of age-related structural and functional changes in the human brain on complex visual discrimination tasks. A large body of research has already dealt with the influence of MTL lesions on discrimination performance in humans (Barense et al., 2005; Barense et al., 2007; Barense, Rogers, Bussey, Saksida, & Graham, 2010; Lee & Rudebeck, 2010b; Taylor et al., 2007). There is also general evidence for a disruption of large-scale brain networks due to healthy aging (Andrews-Hanna et al., 2007), but the research on effects of healthy aging on complex visual discrimination is still very young (Ryan et al., 2012). Future research might investigate if only the PRC is involved in these age-related changes, or if the HC might be affected as well.

Another structure that will have to be investigated more closely is the entorhinal cortex (EC). It is part of the MTLRS model but is often neglected in human fMRI studies, since the MTL is object to signal dropout (because of its location in a region of large
susceptibility variations) and especially the PRC and EC often suffer from a low signal-to-noise ratio (Bellgowan, Buffalo, Bodurka, & Martin, 2009; Bellgowan, Patrick S F, Bandettini, van Gelderen, Martin, & Bodurka, 2006). However, recent studies have successfully demonstrated that the EC, which is strongly interconnected with the HC (Canto, Wouterlood, & Witter, 2008), does also exhibit a domain-specificity (Schultz et al., 2012). In an fMRI study conducted by Schultz et al. (2012) an improved spatial normalization and a higher resolution of the functional data was employed in order to show that the functional segregation apparent in PRC and PHC (Awipi & Davachi, 2008; Eichenbaum et al., 2007; Epstein & Kanwisher, 1998) does also extend to the medial and lateral EC. This is also in line with recent models proposing that the two major pathways connecting the HC with the ventral and dorsal visual streams (PRC – lateral EC – HC; PHC – medial EC – HC) do exhibit a functional segregation (Davachi, 2006; Eichenbaum et al., 2007). These results further support the assumption that the structures of the MTL are functionally segregated and they also demonstrate that the EC is another important structure that should be investigated in order to understand the architecture of the MTL.

One final aspect worth considering when talking about representations in the MTL might be time (see also section 6.5.3 for a discussion on the role of the HC in spatiotemporal integration), since the term “context” is defined rather loosely and might also incorporate temporal aspects. Accordingly, the HC has been shown previously to be involved in temporal processing (Devito & Eichenbaum, 2011; Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Fortin, Agster, & Eichenbaum, 2002; Jacobs, Allen, Nguyen, & Fortin, 2013; Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013), demonstrating that the HC (or the MTL in general, see also Howard et al., 2014) might be involved in the integration of not only the “what” and the “where”, but also the “when” (Devito & Eichenbaum, 2010).
6.7 Conclusions

The current thesis aimed at contributing to the question if and how the MTL is involved in complex visual processes, apart from its well-established role in memory processing. Furthermore, the question arose if it is suitable to regard the MTL within a framework that uses descriptive cognitive processes in order to explain its contributions, or whether it might be expedient to investigate representational accounts of the MTL.

As Lee et al. (2012) stated, traditional mnemonic models of the MTL have provided invaluable insight into processing mechanisms, but as the evidence for a perceptual role of the MTL grows, there is a need for new all-encompassing models. For this, the medial temporal lobe representational system (MTLRS) was proposed in the current thesis, based on the BIC model (Diana et al., 2007; Ranganath & D'Esposito, 2010) and on suggestions by other authors (Aggleton, Sanderson, & Pearce, 2007; Lee et al., 2012) who have previously described the HC as being crucial for the processing of stimulus conjunctions.

The results presented here can be explained with the proposed representational model (the MTLRS), in which the MTL is concerned with a domain preferential processing of various stimulus types, regardless of the task that had to be performed. Using functional magnetic resonance imaging in humans and behavioral patient studies it could be shown that the MTL (and especially the HC) as well as the fornix are needed in order to enable visual learning, recollection, and complex visual discrimination.

Future research will have to focus on the question how these representations are formed and what computational mechanisms play a role in these processes. Furthermore, it remains to be seen how big the influence of temporal information is in order to build hippocampal-dependent spatiotemporal representations (Lee et al., 2012). Only then we will be able to achieve a thorough understanding of the human medial temporal lobe.
Bibliography


Murray, E. A., & Wise, S. P. (2004). What, if anything, is the medial temporal lobe, and how can the amygdala be part of it if there is no such thing? *Neurobiology of learning and memory, 82*(3), 178–198.


Appendix
Appendix A.

Supplemental data

A.1 Study 2 - Description of the neuropsychological paper & pencil tests

**Wechsler Memory Scale – Revised:** The subscale “Attention and Concentration”, including Digit Span (forward/backwards) and Block Span (forward/backward), as well as Mental Control were used (Wechsler, 2004). Verbal short-term memory (forward) and working memory (backwards) were assessed using the Digit Span subtest, in which the patients had to reproduce sequences of digits that were read to them by the experimenter. Every second trial was accompanied by an increase in the number of digits that had to be repeated. In the same manner, visual short-term memory and working memory were assessed using the Block Span subtest, only in this condition the experimenter touched a sequence of cubes, which had to be repeated by the patients.

**Trail Making Test:** The Trail Making Tests A and B were used to test visual search, attention and mental flexibility, as well as motor function (Reitan, 1992). In version A of the test, patients had to connect numbers on a sheet of paper as quickly as possible, in an ascending order. In version B, alternating numbers and letters had to be connected in an ascending order, as quickly as possible.

**Rey-Osterrieth Complex Figure:** This complex figure test was employed to investigate visuospatial processing and anterograde visual memory (Osterrieth, 1944). A figure composed of 18 components had to be copied by the patients without a time constraint. Afterwards, they had to reproduce it from memory after a delay of 30 minutes. No immediate recall was performed by the patients.
**Verbaler Lern- und Merkfähigkeitstest**: The Verbal Learning and Memory Test was used to assess verbal learning as well as anterograde recall and recognition memory (Helmstaedter et al., 2001). Fifteen words were read by the experimenter and the patients had to recall as many as possible immediately afterwards. This part of the test was repeated four more times with the same list of words. For the delayed recall, patients had to recall the words without another presentation after 20-30 minutes. As a last test, patients had to recognize the learned words from a list with additional distractors.

**Mini Mental State Examination**: The Mini Mental State Examination is a short test used to screen for dementia (Folstein et al., 2000). It is composed of several subtests, which can sum up to 30 points: Orientation to time, orientation to place, registration (repeating 3 words), attention and calculation, recall (of the 3 learned words), language (naming every-day items), repetition (of a short phrase), complex commands.
A.2 Supplemental data for Study 3

Table A.1: Significant activation clusters in Study 3. Significant activations (p<0.05, FDR-corrected) for main effects and interactions in the full factorial analysis are listed, sorted by respective contrast and T-score. Each line represents one cluster, with anatomical labels from AAL.

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<th>Contrast</th>
<th>MNI coordinates (x, y, z)</th>
<th>Cluster size</th>
<th>T-score</th>
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<td>Y</td>
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A.3 Supplemental data for Study 4

**Table A.2: Significant activation clusters in Study 4.** The table shows significant activations (p<0.05, corrected) for all main effects and interactions in the both full factorial analyses, sorted by respective contrast and T-score. Note that an asterisk represents cluster sizes that did not reach the Monte Carlo corrected threshold of 65 voxels (p<0.001 uncorrected). Each line represents one cluster, with anatomical labels from AAL.

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*Significant at p < 0.05
Appendix B.
Curriculum Vitae

NAME
Robert Kazimierz Lech

DATE OF BIRTH
December 27th, 1983

PLACE OF BIRTH
Gdynia, Poland

MARITAL STATUS
Married

WORK ADDRESS
Institute of Cognitive Neuroscience
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PROFESSIONAL EXPERIENCE

since 07/2010
Institute of Cognitive Neuroscience,
Department of Neuropsychology,
Ruhr University Bochum, Germany
Research Assistant

02/2007 – 09/2009
Work Group Cognitive Psychology,
Faculty of Psychology
Ruhr University Bochum, Germany
Student Assistant
EDUCATION

since 10/2010  International Graduate School of Neuroscience, Ruhr University Bochum, Germany
IGSN associate, PhD thesis at the Institute of Cognitive Neuroscience

10/2004 – 02/2010  Ruhr University Bochum, Germany
Studies of Psychology, Diploma

HONORS & AWARDS

10/2011  NeuroVisionen 7
Awarded with a poster prize for “Involvement of the human medial temporal lobe in a visual discrimination task”

since 12/2010  Ruhr-University Research School, Bochum, Germany
Member
Appendix C.

List of publications

Published articles


Submitted articles


Conference abstracts

- Lech, R. K., Güntürkün, O. & Suchan, B.
  Neural correlates of abstraction and exemplar based category learning.
  Annual Meeting of the Cognitive Neuroscience Society, San Francisco (USA), 2013
- Lech, R. K. & Suchan, B.
  Complex visual discriminations recruit hippocampus and perirhinal cortex – evidence from functional imaging and patient data.
  Annual Meeting of the Society for Neuroscience, New Orleans (USA), 2012
- Lech, R. K. & Suchan, B.
  Involvement of the human medial temporal lobe in a visual discrimination task.
  Annual Meeting of the Cognitive Neuroscience Society, Chicago (USA), 2012
• Lech, R. K. & Suchan, B.
Involvement of the human medial temporal lobe in a visual discrimination task.
*NeuroVisionen 7, Universitätsklinikum Essen (Germany), 2011*
Appendix D.

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I would like to thank

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Jonas Lins for helping me with the programming of my first experiment and for preventing me from a nervous breakdown;

Tobias Otto for always having time to help me with computer- and programming-related questions;

Naima Rüther for sharing all of the good times and all of the bad times, for the laughing and talking, and for all of the conferences we went to;

Elisabeth Schriewer for never being tired of acquiring new subjects and for putting up with the struggle to organize dates with all of them;

Patrizia Thoma for hundreds of coffees, and for always having advice for me;

All other lab members that I did not mention specifically for all of their help on countless occasions;

Janina for everything she has ever done for me, for keeping me motivated and upright, and for being the best wife one could imagine.