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The Role of the Medial Temporal Lobe during Encoding and Retrieval of Relational Face Memory – an fMRI Study

DISSERTATION

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Universität Hamburg
vorgelegt von

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aus Duisburg

Hamburg 2009

Angenommen von der Medizinischen Fakultät
der Universität Hamburg am: 17.12.2009
Veröffentlicht mit Genehmigung der Medizinischen
Fakultät der Universität Hamburg
Prüfungsausschuss, der/die Vorsitzende: Prof. Dr. D. Naber
Prüfungsausschuss: 2. Gutachter/in: Prof. Dr. C. Buechel
Prüfungsausschuss: 3. Gutachter/in: PD. Dr. C. Otte

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ABBREVIATIONS

AHC	Anterior Hippocampus
ANOVA	Analyses of Variance
APHG	Anterior Parahippocampal Gyrus
BF	Post-hoc Bonferroni's Multiple Comparison Test
BOLD	Blood Oxygenation Level Dependent
CHR	Corrected Hit Rate
CR	Correct Rejections (New Faces correctly recognized)
EEG	Electroencephalography
EPI	Echo planar imaging
ERP	Event-related Potentials
FFA	Fusiform Face Area
Fix	Fixation Cross/Baseline condition
fMRI	Functional magnet resonance imaging
FOV	Field of View
FP	False Positives (New Faces incorrectly categorized as Old)
HC	Hippocampus
HRF	Hemodynamic Response Function
ISI	Inter Stimulus Intervall
K	Know/Familiarity response
LI	Lateralization Index
M	Misses (Forgotten Faces)
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
MTL	Medial Temporal Lobe
PET	Positron emission tomography

PHC	Posterior Hippocampus
R	Remember/Recollection response
ROI	Region of Interest
RT	Reaction Time
sK	subsequent Familiarity
sM	subsequent Misses
sR	subsequent Recollection
SUR	Single Unit Recording
SVC	Small Volume Correction
TLE	Temporal Lobe Epilepsy

PUBLICATION

Parts of this work will be submitted to “Hippocampus” for publication as a peer-reviewed full paper.

Further, parts will be presented at the Human Brain Mapping Conference in San Francisco in June 2009.

1 LITERATURE REVIEW

The following chapter will review the current literature on human memory, recollection, familiarity and face memory. The focus of this review will be on the engagement of the medial temporal lobe in relational memory.

The first part will introduce the general theme of this study and its relevance to clinical memory disorders. Specific definitions of memory subsystems are given in the second section of this chapter.

1.1 Introduction

The study of human memory and its neural correlates has a long tradition of research. Around 50 years ago, Brenda Milner established the importance of structures within the medial temporal lobe (MTL) to declarative episodic memory (for a brief definition see Sec. 1.2.1) (Milner 1968). One of the most famous neuropsychological cases, studied by Milner and colleagues, is that of the epilepsy patient H.M. who lost his declarative memory as the result of a bilateral temporal lobotomy in the 1950s. Similarly, patients with temporal lobe lesions (e.g. caused by hippocampal sclerosis, stroke, epilepsy, Korsakow-Syndrome, tumour or trauma) develop impairments in declarative memory whereas non-declarative memory and often semantic memory are spared (Gazzainiga 2002; Murphy, Troyer et al. 2008).

Behaviourally, the examination of recognition memory indicates that there are two separate processes underlying episodic memory; recollection and familiarity (Tulving 1985; Eichenbaum, Yonelinas et al. 2007). Recollection describes the conscious recovery of contextual information surrounding a previous encounter with the item. Familiarity, by contrast, describes the sensation that an item was encountered previously but does not involve related contextual associations (Yonelinas 2001; Moscovitch, Rosenbaum et al. 2005; Yonelinas, Otten et al. 2005). A growing body of neuroimaging studies supports an anatomical differentiation between those two processes. The emerging consensus is that the hippocampus supports relational processing, particularly where multi-modal input is involved, whereas adjacent cortices mediate non-associative aspects of declarative memory (Eichenbaum, Yonelinas et al. 2007). In accordance with this, patients with hippocampal lesions and intact adjacent cortices show impaired recollection but spared familiarity (Moscovitch and McAndrews 2002). While the hippocampus supports memory for relational information, it is unclear whether encoding and retrieval of this information engage the same circuitry. Here, we used event-related fMRI to examine these processes in a face memory paradigm.

1.2 Fractionation of Human Memory

The following section will briefly introduce the common theories about human memory. Because of the focus of the current study, the following sections will be concerned primarily with episodic memory. First, episodic memory will be explained within the context of other memory systems, followed by the description of temporal memory processes, such as processing, encoding and retrieval. At the end of this overview, material-specific memory such as verbal and non-verbal memory will be discussed.

1.2.1 Fractionation of Memory Systems

Perhaps the most widely-accepted fractionation of memory is the declarative/non-declarative distinction. Studies of people with amnesia have provided evidence for the dissociation between declarative or consciously-accessible memory and a set of memory systems referred to as non-declarative or procedural memory that are not consciously accessible (Tulving 1983). People with medial temporal lobe (MTL) damage display impairment in declarative but not in non-declarative memory (Squire, Knowlton et al. 1993). Within the declarative memory system, Tulving (1983) further distinguishes episodic from semantic memory. Episodic memory contains information about temporally-dated episodes or events and temporal-spatial relations between them (Tulving 1983), e.g. the own biography. Semantic memory, by contrast, refers to abstract knowledge about the world, i.e. generic information that is acquired across many different contexts and stored independently from the learning situation, e.g. capitals of European countries. This fractionation of declarative memory is supported by evidence of different neural processes underlying episodic and semantic memory. For example, patients with mild unilateral MTL damage show impaired personal episodic recall, such as the own wedding day, leaving semantic memory intact (Viskontas, McAndrews et al. 2000). In contrast, semantic dementia, also known as the temporal lobe variant of fronto-temporal dementia, results in a progressive and relatively pure loss of semantic knowledge about words, objects and people, and is associated with asymmetric, focal atrophy of the antero-lateral temporal lobes (Hodges and Graham 2001).

1.2.2 Fractionation of Memory Processes

Several contemporary models of MTL function have been drawn upon the data described above to propose biological mechanisms underlying episodic memory.

Nadel and Moscovitch (1997) proposed the "Multiple Trace Theory" (MTT) as an extension to the "standard model of consolidation" developed by Marr et al. (1971). The MTT states that encoding (formation), consolidation (maintenance) and retrieval (recovery/recognition) of episodic memory always require the participation of MTL structures:

First, the hippocampal complex rapidly (and obligatorily) encodes all information that is attended or consciously apprehended. Neocortical (or other) neurons that represent the attended information and corresponding hippocampal neurons are bound into a coherent memory trace, which represents consolidation. The entire hippocampal-neocortical ensemble constitutes the memory trace for this episode. Because the hippocampal complex obligatorily encodes all information that is attended, the re-activation or retrieval of this information results in the creation of a newly encoded hippocampal trace, which is related to the original one. The spatial-temporal contextual information that conveys the episodic quality to memory depends therefore always upon the continuing involvement of the hippocampal complex (Nadel and Moscovitch 1997). For example, to encode an object within its context requires hippocampal activation which then forms a memory trace. Encoding the same object in a different context also requires the hippocampus which then forms another memory trace. During retrieval those traces are re-activated and bound to hippocampal activation. In accordance to this theory, recent studies show that episodic memory relies on the hippocampus, regardless how old the memories are (Ryan, Nadel et al. 2001; Rekkas and Constable 2005; Moscovitch, Nadel et al. 2006) .

1.2.3 Fractionation of Material-Specific Memory

According to material-specific memory theories, different types of declarative information (i.e., verbal, nonverbal and spatial information) are processed in different, specialised brain areas. Verbal memory is defined as recall for language and words. fMRI and lesion studies show that most right-handed persons process verbal information within the left temporal lobe (Kelley, Miezin et al. 1998; Lee, Yip et al. 2002; Moscovitch and McAndrews 2002; Coleshill, Binnie et al. 2004; Helmstaedter, Brosch et al. 2004). Nonverbal information, e.g. abstract images or faces, and spatial information, such as positions on a screen, are processed predominantly in the right temporal lobe (Milner 1968; Trahan, Larrabee et al. 1990; Dade and Jones-Gotman 2001; Crane and Milner 2002; Lee, Yip et al. 2002; Moscovitch and McAndrews 2002; Coleshill, Binnie et al. 2004; Vaz 2004; Gillespie, Bowen et al. 2006). However, some studies could not confirm the right hemispherical dominance for nonverbal information (McGlone 1994; Vaz 2004). The latter studies contained images of objects, which can be easier remembered using verbal mnemonic strategies. Therefore it remains unclear whether the stimuli used by McGlone and Vaz can be categorized as exclusively nonverbal. As a recent study showed, differences in verbal mnemonic strategies can significantly affect the magnitude of hemispheric asymmetries in a non-verbal task (Clapp, Kirk et al. 2007). The non-confirmation of right-hemispheric dominance could thus be an effect of the choice of stimuli. Images of objects represent a mixture of verbal and nonverbal information, as one study nicely illustrates the bilateral activation of the medial temporal lobes for object processing (Kelley, Miezin et al. 1998). On the other hand, human faces are difficult to verbalize. Therefore, they are valuable nonverbal items for neuropsychological testing procedures. Studies that use faces as test stimuli almost consistently suggest right hemispherical dominance (Milner 1968; Kelley, Miezin et al. 1998; Dade and Jones-Gotman 2001; Crane and Milner 2002; Moscovitch and McAndrews 2002; Coleshill, Binnie et al. 2004; Glogau, Ellgring et al. 2004; Vaz 2004).

As described above, there is abundant evidence for material-specific memory processes, including verbal, nonverbal and spatial information. However, it is not yet known which memory process depends on which hemisphere. For example, are all stages in the processing of verbal information (e.g. encoding, consolidation and retrieval) exclusively dependent on the left hemisphere? Is face memory processing exclusively right hemispheric? As it will be described in section 1.4 of this chapter, different stages of face memory are thought to be dependent on different hemispheres.

1.2.4 Summary

Episodic memory is a subsystem of declarative memory, which contains information about temporally-dated episodes or events and temporal-spatial relations between them. In accordance to the Multiple Trace Theory, encoding and retrieval for episodic memory are both dependent on medial temporal lobe structures, such as the hippocampus. Non-verbal information, e.g. faces, is mostly processed within the right hemisphere, although it remains unclear whether different stages of face memory are exclusively located right hemispheric.

1.3 Recollection and Familiarity

Imagine a scene when you are walking across a city and see somebody who seems vaguely familiar. When she greets you, you are quite sure that you know this person but you cannot remember where you have met her or why you know her. During the following casual conversation you are searching for clues. At one point, she says something about a party last week and all of the sudden, you remember her name and some aspects of the discussion at this party.

This scene illustrates the two subjective experiences underlying recognition memory, recollection and familiarity. Recollection refers to memory retrieval accompanied by the recovery of specific contextual details, whereas familiarity refers to the feeling that an event is old in the absence of confirmatory contextual information (Yonelinas 2002).

Two dominant approaches try to explain these two experiences; the Dual- and Single-Process-Theories. Dual-process models propose that recollection and familiarity reflect two independent memory processes, while single-process models claim only one common process which supports both aspects of retrieval. Evidence for the dual-process view comes from various experimental studies, such as patients studies (Brown and Aggleton 2001; Moscovitch and McAndrews 2002), receiver-operating characteristics (Yonelinas 2002; Glanzer, Hilford et al. 2004; Healy, Light et al. 2005), event-related potential (ERP) studies (Yovel and Paller 2004; MacKenzie and Donaldson 2007) as well as functional imaging studies (Davachi, Mitchell et al. 2003; Ranganath, Yonelinas et al. 2003; Daselaar, Fleck et al. 2006). These studies show that some variables preferentially influence recollection, whereas other variables influence familiarity. For example, recollection is slower, requires more attention, and increases more with encoding depth and study time than familiarity. On the other hand, familiarity is influenced by interference, perceptual match and delay in recognition (for a review see Eichenbaum, Yonelinas et al. 2007). Further, neuoimaging studies are beginning to elucidate that the hippocampus is engaged during recollection whereas other medial temporal regions reflect recognition based on item familiarity in the absence of retrieval of context.

In contrast, the single-process theory proposes that recollection and familiarity are the same phenomenon and only the memory strength is different in both processes (Squire, Wixted et al. 2007). According to this view, damage to the MTL should lead to equivalent deficits in recollection and familiarity. However, patients with MTL amnesia can discriminate between new and old items relatively well, but are profoundly impaired in distinguishing between recollection and familiarity (Mayes, Baddeley et al. 1989). Furthermore, evidence from imaging studies show that confidence ratings alone, as a measure of memory strength, do not support a single network for recollection and familiarty (Daselaar, Fleck et al. 2006). In this study, only recollection activated the hippocampus, whereas even familiarity responses with a strong confidence rating did not (see Sec. 1.3.2.2, Fig. 4). A study by Vilberg and Rugg (2007) also failed to show any effect of the same neuronal structure for increasing memory strength.

Several neuropychological methods have been developed in order to experimentally separate recollection and familiarity (see Sec. 1.3.2, Tab. 1 and 2) (for a review see (Mayes, Montaldi et al. 2007)). One body of research focuses on the subjective distinction between recollection and familiarity, which is operationally defined by whether the participant can retrieve information regarding the encoding experience (i.e. remember/recollection) or is only aware of the prior occurrence of the target without retrieving additional context (i.e. know/familiarity) (Moscovitch and McAndrews 2002; Otten 2007). Another body of research uses objective measurements, such as associative recognition or the source memory paradigm. In associative recognition, participants are asked to study associations (e.g. face-name pairs) and at recognition, retrieve those pairs (e.g. pair correct versus pair incorrect) (Sperling, Chua et al. 2003; Kirwan and Stark 2004). In the source memory paradigm, participants are presented with two types of stimuli (e.g. words written in green or blue) which they should encode differently (e.g. green=mentally visualize or blue=read backwards). At recognition, they then indicate if they recognize the word and if yes, whether they remember the colour (i.e. source correct) or not (i.e. source incorrected) (Davachi, Mitchell et al. 2003; Ranganath, Yonelinas et al. 2004). Another method is to obtain recognition confidence ratings. Because recollection reflects retrieval of specific details of the study event, it is expected to lead to higher confidence. Familiarity, on the other hand, should contribute across a wide range of confidence responses, because all items should elicit some confidence strength (Gonsalves, Kahn et al. 2005; Daselaar, Fleck et al. 2006). In general, results from contrasts that differentiate between remember and know, between pair correct and pair incorrect, between source correct and source incorrect, and between the hightest and lower confidence ratings can be considered as recollection. Familiarity contrasts examine typically differences between recognized but non-recollected items and forgotten items (i.e. misses), and between decreasing confidence responses.

In conclusion, recollection clearly requires the formation, retention and retrieval of relational information, but it is unknown whether the processes and underlying neuronal networks involved in retrieval are the same as those involved in encoding. To aid further discussion, the functional organization of the MTL will be described in the next section. Afterwards, the important literature on fMRI studies on recollection and familiarity will be discussed.

1.3.1 Neuroanatomy of Recollection and Familiarity within the Medial Temporal Lobe

At least 50 years of evidence has established the importance of structures within the medial temporal lobe (MTL) to memory (Milner 1968; Squire, Knowlton et al. 1993; Tulving and Markowitsch 1998; Zola, Squire et al. 2000; Squire, Stark et al. 2004; Eldridge, Engel et al. 2005; Moscovitch, Rosenbaum et al. 2005; Diana, Yonelinas et al. 2007).

The MTL can be divided into the perirhinal cortex, the parahippocampal cortex and entorhinal cortex (together known as parahippocampal region), and the hippocampus (including dentate gyrus, Ammon's horn and subiculum) (see Fig. 1).

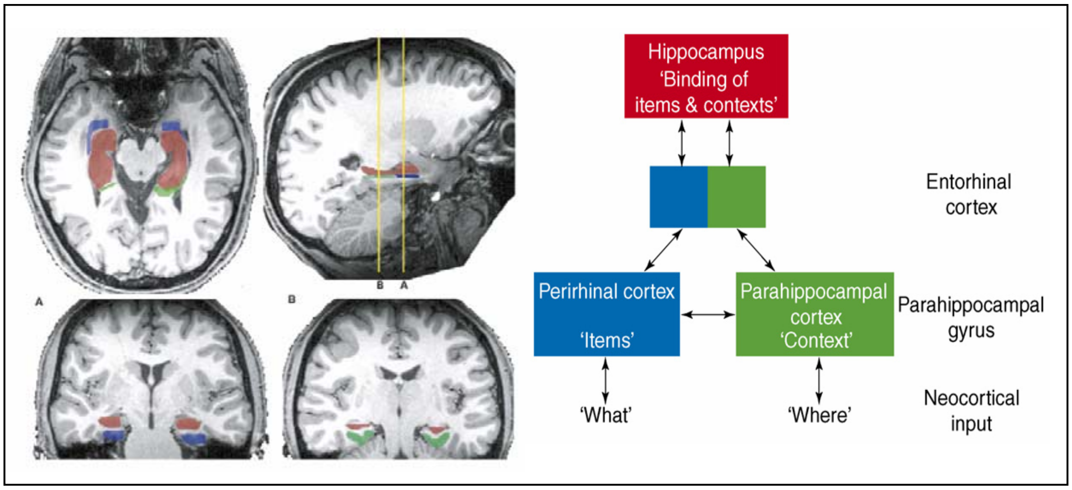

Figure 1. Functional organization of the MTL memory system (Diana et al., 2007)

Left: Approximate locations of the hippocampus (red), the perirhinal cortex (PRc, blue) and the parahippocampal cortex (PHc, green) shown on T1-weighted MRI, A: transveral and coronal MRI of the anterior MTL, B: sagittal and coronal MRI of the posterior MTL.

Right: Representation of the anatomical connections among and the proposed roles of the hippocampus, PRc and PHc in episodic memory. The arrow between PRc and PHc indicates the anatomic connection between the two regions; the PRc receives more inputs from the PHc than vice versa.

Most of the neocortical input to the perirhinal cortex comes from association areas that process unimodal sensory information about qualities of objects (i.e. "what" information), whereas most of the neocortical input to the parahippocampal cortex comes from areas that process polymodal (i.e. "context" information). The "what" and "context" streams of processing remain largely segregated as the perirhinal cortex projects primarily to the lateral entorhinal area, whereas the parahippocampal cortex projects mainly to the medial entorhinal area. Some connections exist between the perirhinal and parahippocampal cortices and between the entorhinal areas, but the "what" and "context" information converges mainly within the hippocampus. The cortical outputs of the hippocampal processing involve feedback connections from the hippocampus successively back to the entorhinal, then perirhinal and parahippocampal cortices, and finally, neocortical areas from which the inputs to the MTL originated (Diana, Reder et al. 2006; Eichenbaum 2006; Eichenbaum, Yonelinas et al. 2007).

This anatomical evidence suggests the following hypothesis about how information is encoded and retrieved during memory processing. During encoding, representations of distinct items (e.g. people, objects, events) are formed within the perirhinal cortex and lateral entorhinal area. These representations along with back projections to the "what" pathways of the neocortex can then support subsequent judgements of familiarity. In addition, during encoding, item information is combined with contextual representations that are formed in the parahippocampal cortex and medial entorhinal area, whereas the hippocampus associates items and their context. When an item is subsequently presented as a memory cue, the hippocampus completes the full pattern and mediates a recovery of the contextual representation in the parahippocampal cortex and medial entorhinal area. Hippocampal processing may also recover specific item associations of the cue and reactivate those representations in the perirhinal cortex and lateral entorhinal area. The recovery of context and item associations constitutes the experience of recollection.

1.3.2 Functional Imaging of Recollection and Familiarity

Functional magnetic resonance imaging (fMRI) studies are beginning to elucidate the crucial role of the hippocampus in relational memory during encoding and retrieval (Davachi 2006; Eichenbaum, Yonelinas et al. 2007). However, hippocampal activation is almost always associated with activation of a network of other regions that include the retrosplenial cortex, posterior cingulate gyrus, posterior parietal cortex, precuneus, anterior temporal cortex, ventromedial and ventrolateral prefrontal cortex, and sometimes the frontal pole (Cansino, Maquet et al. 2002; Kirwan and Stark 2004; Prince, Daselaar et al. 2005). The current study focusses on the MTL, especially the hippocampus. Therefore, next section will discuss fMRI studies, which examine activity in different MTL regions correlated with recollection and/or familiarity.

1.3.2.1 Encoding

It is well established that the MTL is essential for successful encoding of episodic memory (Milner 1968; Eichenbaum, Yonelinas et al. 2007). An important question for this study is whether recollection and familiarity differs already at the stage of encoding. A useful technique to study this question is the "subsequent memory effect" or "Dm effect" (Difference due to memory) (Paller, Kutas et al. 1987). In this paradigm, brain activity is measured while participants study a list of items. Later, participants receive a recognition memory test. Brain activity associated with items that will later be remembered can then be compared to brain activity associated with items that will later be forgotten. In the same way it is possible to examine activation reflecting the formation of representation that supports recollection, familiarity, or both processes. Some imaging studies found greater activation in the hippocampus for subsequent remember than for subsequent know responses (Davachi and Wagner 2002; Sperling, Chua et al. 2003; Kirwan and Stark 2004; Ranganath, Yonelinas et al. 2004; Prince, Daselaar et al. 2005; Uncapher and Rugg 2005; Kensinger and Schacter 2006; Chua, Schacter et al. 2007; Otten 2007) (see Tab. 1, Fig. 2). Some studies suggest a somewhat more anterior hippocampal area that is crucial for relational binding (Davachi, Mitchell et al. 2003; Chua, Schacter et al. 2007), whereas another study found activation in more posterior hippocampal regions (Ranganath, Yonelinas et al. 2004). However, there are no reliable differentiations in anterior-posterior locations of these activations related to encoding (Diana, Yonelinas et al. 2007). Other studies could not confirm the hippocampal role in subsequent recollection processes (Henson, Rugg et al. 1999; Cansino, Maquet et al. 2002; Henson, Hornberger et al. 2005; Gold, Smith et al. 2006). Gold et al. (2006) found greater brain activity in the hippocampus, perirhinal cortex and parahippocampal cortex which was associated with words that would later be remembered. However, activity in these regions did not predict the difference between recollection and familiarity (Gold, Smith et al. 2006).

Table 1: Literature review of subsequent recollection and familiarity

Encoding

Subsequent Recollection

Study	Method	Materials	Contrast	Hippocampus	PHG
Chua et al. 2007	Pair association	face/names	PC>PIC	L: -28 -4 -24	
				Ri: 20 -8 -16	
Otten et al., 2007	R/K/M	words/pics	R>M	Ri: 33 -39 -3	none
Kensinger et al., 2006	Source decision	words/pics	SC>SIC	L: -31 -13 -16	none
				Ri: 39 -21 -12	none
Gold et al. 2005	Source decision	words	SC>SIC	none	none
Henson et al., 2005	R/K/M	words	R > K	none	L: -30 -30 -24
					Ri: 27 -33 -21
Uncapher et al. 2005	Source decision	words	SC>SIC	L: -21 -15 -15	none
Kirwan et al., 2004	Pair association	face/names	PC>PIC	Ri: 35 -24 -12	Ri: 36 -40 -6
Ranganath et al, 2004	Source decision	words	SC>SIC	Ri: 26 -30 -4	Ri: 30 -40 -16
Davachi et al. 2003	Source decision	words	SC>SIC	L: -33 -21 -21	L: -33 -39 -18
				Ri: 30 -9 -24	
Sperling et al. 2003	Pair association	face/names	PC>PIC	L: -30 -21 -18	
Cansino et al., 2002	Source decision	objects	SC>SIC	none	none
Henson et al., 1999	R/K/M	words	R > K	none	none

Subsequent Familiarity

Study	Method	Materials	Contrast	PPHG	APHG
Chua et al. 2007	Pair association	face/names	PIC>M	L: -24 -14 -24	none
Otten et al., 2007	R/K/M	words/pics	K>M	none	none
Kensinger et al., 2006	Source decision	words/pics	SIC>SC	none	L: -39 -12 -31
Gold et al. 2005	Source decision	verbal	SIC>M		Ri (no coord.)
Henson et al., 2005	R/K/M	words	K > R	none	RI (no coord.)
Uncapher et al. 2005	Source decision	words	SIC>M	none	Ri: 30 -24 -24
Kirwan et al., 2004	Pair association	face/names	not reported		
Davachi et al. 2003	Source decision	verbal	SIC>M	none	L (no coord.)
Ranganath et al, 2003	Source decision	verbal	SIC>SC	none	L: -18 6 -34
Sperling et al. 2003	Source decision	face/names	not reported		
Cansino et al., 2002	Source decision	objects	SIC>SC	none	None
Henson et al., 1999	R/K/M	words	K > R	Ri: 20 - 17 -30	RI (no coord.)

Ri=right; L=left; SC=source correct; SIC=source incorrect; R=remember; K=know; M=misses; PC=pair correct; PIC=pair incorrect; PHG=parahippocampal gyrus; PPHG=posterior PHG; APHG=anterior PHG

In order to directly compare MTL regions across studies, all reported Talairach & Tournoux (1988) coordinates were transformed into MNI space, using the non-linear matlab function tal2mni authored by M. Brett (available at http://brainmap. org/ale/index.html).

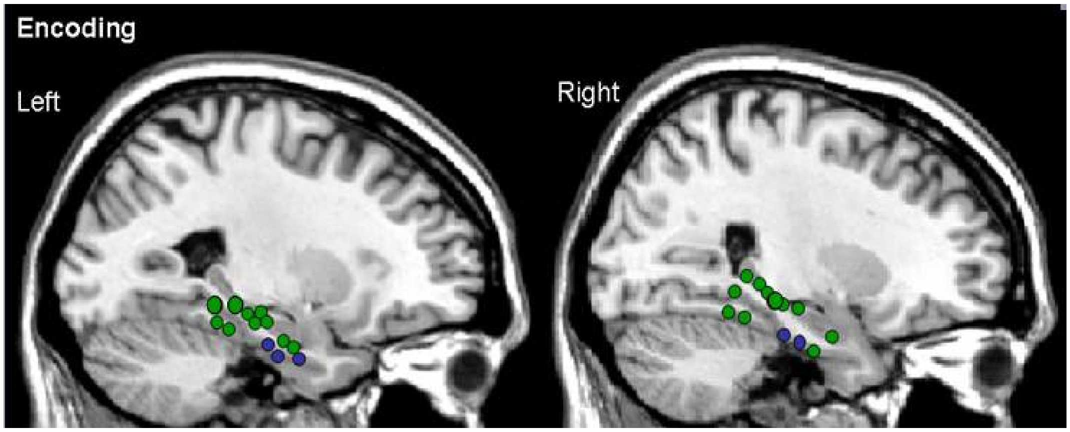

Figure 2: Literature review of subsequent recollection and familiarity
Summary of studies during encoding for subsequent recollection (green) and subsequent familiarity (blue), displayed on a T1-weighted MRI. In order to directly compare MTL regions across studies, all Talairach&Tournoux coordinates were transformed into MNI space using the non-linear matlab function tal2mni authored by M. Brett. Note that these points demonstrate approximate locations. Some studies reported several peak voxels which are all represented by separate points. Data from: Chua et al., 2007; Davachi et al., 2002; Henson et al., 2005; Kensinger et al., 2006; Kirwan et al., 2004; Ranganath et al., 2003; Sperling et al., 2003.

Experimental manipulations of encoding have a profound effect on successful recall, especially subsequent recollection. Davachi et al. (2003) examined activity during a deep (visual imagery) encoding task that elicited high levels of recognition memory and a shallow (word pronunciation) encoding task that elicited relatively poor memory. Their results show that hippocampal activation for deeply encoded items was selectively enhanced if the subject correctly recalled encountering the item in the deep encoding task. Therefore, deep encoding is associated with greater hippocampal activation than shallow encoding.

Activation in the perirhinal area is rarely associated with recollection, however, it is consistently correlated to subsequent familiarity (Davachi, Mitchell et al. 2003; Ranganath, Yonelinas et al. 2004; Henson 2005; Uncapher and Rugg 2005; Gold, Smith et al. 2006; Kensinger and Schacter 2006; Uncapher and Rugg 2008).

During encoding, activity in the perirhinal area is increased for items which are later judged as familiar in comparison to items that are recollected or forgotten.

1.3.2.2 Retrieval

The anatomical characteristics of the MTL (see Sec. 1.3.1, Fig. 1), suggest that the hippocampus, the perirhinal cortex and the parahippocampal cortex each form unique representations that support recognition memory. In this scheme the hippocampus plays a key role in the retrieval of item-context associations. In accordance with this, many fMRI studies (see Tab. 2, Fig. 3) have shown greater hippocampal activation for verbal stimulus and scenes in recollection than in familiarity (Eldridge, Knowlton et al. 2000; Cansino, Maquet et al. 2002; Dobbins, Rice et al. 2003; Kahn, Davachi et al. 2004; Weis, Specht et al. 2004; Wheeler and Buckner 2004; Dolcos, LaBar et al. 2005; Woodruff, Johnson et al. 2005; Yonelinas, Otten et al. 2005; Daselaar, Fleck et al. 2006; Montaldi, Spencer et al. 2006; Vilberg and Rugg 2007). A few studies have failed to show a recollection effect within the hippocampus (Henson, Rugg et al. 1999; Sharot, Delgado et al. 2004; Gonsalves, Kahn et al. 2005; Henson, Hornberger et al. 2005).

Table 2. Literature review of recollection and familiarity

Recollection

Study	Method	Materials	Contrast	Hippocampus	PHG
Vilberg et al., 2007	Source decision	Pictures	SC > SIC	L (no coordinates)	None
				Ri (no coordinates)	None
Daselaar et al., 2006	1-6 confidence	Words	6 > 1-5	L: -26 -26 -11	None
				Ri: 30 -23 -11	None
Montaldi et al., 2006	1- 4 confidence	Scenes	4 > 1-3	L: -12 -33 -3	None
				Ri: 21 -33 -3	None
Dolcos et al., 2005	R/K/N	Pictures	R > K	L (no coordinates)	L (no coordinates)
				Ri (no coordinates)	Ri (no coordinates)
Gonsalves et al., 2005	R/K/N	Faces	R > K	None	None
Henson et al., 2005	R/K/N	Words	R > K	None	None

Woodruff et al, 2005	R/K/N	words/pics	R > K	Ri: 30 -30 -9	Ri: 32 -36 -10
Yonelinas et al., 2005	1-5 confidence	Words	5 > 1-4	L: -24 -21 -21	L: -15 -51 -15
				Ri: 30 -21 -21	Ri: 15 -60 -15
Kahn et al., 2004	Source decision	Words	SC > SIC	L: -21 -3 -24	L: -24 -33 -15
Sharot et al., 2004	R/K/N	Scenes	R > K	None	Ri: 31 -43 -18
Weis et al., 2004	Source decision	Scenes	SC > SIC	L: -16 -6 -23	Ri: 27 -1 -24
				Ri (no coordinates)	
Wheeler et al., 2004	R/K/N	Words	R > K	L (no coordinates)	None
				Ri (no coordinates)	None
Dobbins et al., 2003	Source decision	Words	SC > SIC	L: -25 -19 -19	L: -35 -32 -18
				Ri: 30 -14 -33	None
Cansino et al., 2002	Source decision	Words	SC>SIC	Ri: 26 -16 -14	L: -14 -44 -4
Eldridge et al., 2000	R/K/N	Words	R > K	L: -34 -24 -13	Ri: 24 -40 -12
Henson et al., 1999	R/K/N	Words	R > K	None	None

Familiarity

Study	**Method**	**Materials**	**Contrast**	**PPHG**	**APHG**
Vilberg et al., 2007	Source decision	Pictures	not reported		
Daselaar et al., 2006	1-6 confidence	Words	1-6, increase	L: -34 -41 -8	None
Montaldi et al., 2006	1- 4 confidence	Scenes	1-3, decrease	None	L: -33 -3 -36
				None	Ri: 36 -9 -33
Dolcos et al., 2005	R/K/CR/M	Pictures	not reported		
Gonsalves et al., 2005	R/K/CR/M	Faces	K > R > M	L: -27 -15 -30	L:-24 -15 -30
				None	Ri: 21 -3 -33
Henson et al., 2005	R/K/CR/M	Words	K > R	None	None
Woodruff et al, 2005	R/K/CR/M	words/pics	not reported		
Yonelinas et al., 2005	1-5 confidence	Words	4-1, decrease	L: -18 -18 -21 (Hippocampus)	
Kahn et al., 2004	Source decision	Words	not reported		
Sharot et al., 2004	R/K/CR/M	Scenes	K > R	None	None
Weis et al., 2004	Source decision	Scenes	K > M	None	L (no coordinates)
					Ri: 31 -17 -30
Wheeler et al., 2004	R/K/CR/M	Words	K > R	None	None
Dobbins et al., 2003	Source decision	Words	SC > SIC	None	None
Cansino et al., 2002	Source decision	Words	SIC>SC	None	None
Eldridge et al., 2000	R/K/CR/M	Words	K > R	None	None
Henson et al., 1999	R/K/CR/M	Words	K > R	None	None

Ri=right; L=left; SC=source correct; SIC=source incorrect; R=remember; K=know; CR=correct rejections; M=misses; 1-6 confidence=confidence judgements from 1 (definitely new) to 6 (definitely old).

In order to directly compare MTL regions across studies, all reported Talairach & Tournoux (1988) coordinates were transformed into MNI space, using the non-linear matlab function tal2mni authored by M. Brett (available at http://brainmap. org/ale/index.html).

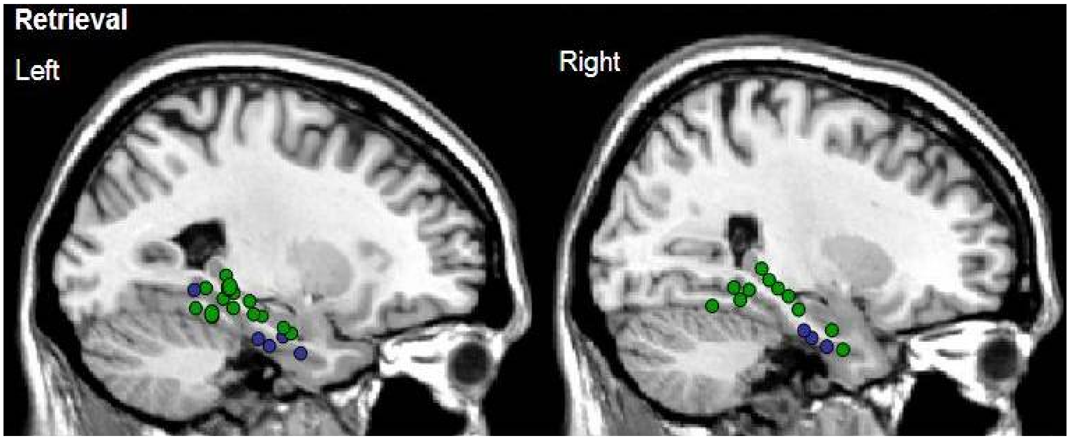

Figure 3: Literature review of recollection and familiarity.
Summary of studies during retrieval for recollection (green) and familiarity (blue). In order to directly compare MTL regions across studies, all Talairach&Tournoux coordinates were transformed into MNI space using the non-linear matlab function tal2mni authored by M. Brett. Note that these points demonstrate approximate locations. Some studies reported several peak voxels which are all represented by separate points. Data from: Cansino et al., 2002; Daselaar et al., 2006; Dobbins et al., 2003; Dolcos et al., 2005; Eldridge et al., 2000; Fenker et al., 2005; Gonsalves et al., 2005; Henson et al., 1999 & 2005; Kahn et al., 2004; Kirwan et al., 2004; Montaldi et al., 2006; Sharot et al., 2004; Vilberg et al., 2007; Weis et al., 2004; Wheeler et al., 2004; Woodruff et al., 2005; Yonelinas et al., 2005.

Daselaar et al. (2006) illustrate nicely that the posterior hippocampus follows a nonlinear function supporting recollection, i.e. only recollection is associated with activation within the posterior hippocampus whereas no activation for increasing confidence is shown (see Fig. 4A). In contrast, the posterior parahippocampal gyrus showed a continuous increase in activity with increasing confidence (see Fig. 4B). Hence, the posterior parahippocampal gyrus is associated with familiarity but also responds to recollection. In accordance to this, literature examining the role of the posterior parahippocampal gyrus in recollection revealed a less robust pattern than for the hippocampus (for a review see (Eichenbaum, Yonelinas et al. 2007). Unlike the hippocampus and posterior parahippocampal gyrus, perirhinal activation is rarely associated with recollection. Whereas during encoding, activity in the perirhinal cortex increases for items that are later familiar (see Sec. 1.3.2.1), during retrieval, activity in this area is decreased for familiar relative to forgotten or new items (see Fig. 4C), which is also supported by other studies (Yonelinas, Hopfinger et al. 2001; Daselaar, Veltman et al. 2003; Weis, Specht et al. 2004; Gonsalves, Kahn et al. 2005; Daselaar, Fleck et al. 2006; Montaldi, Spencer et al. 2006). Using intracranial recording in humans, Viskontas et al. (2006) found that perirhinal neurons show decreased activation for familiar in comparison to novel stimuli. These results support the functional anatomical model (see Sec. 1.3.1, Fig. 1) that activity patterns in the hippocampus and parahippocampal gyrus can be distinguished from those in the perirhinal area.

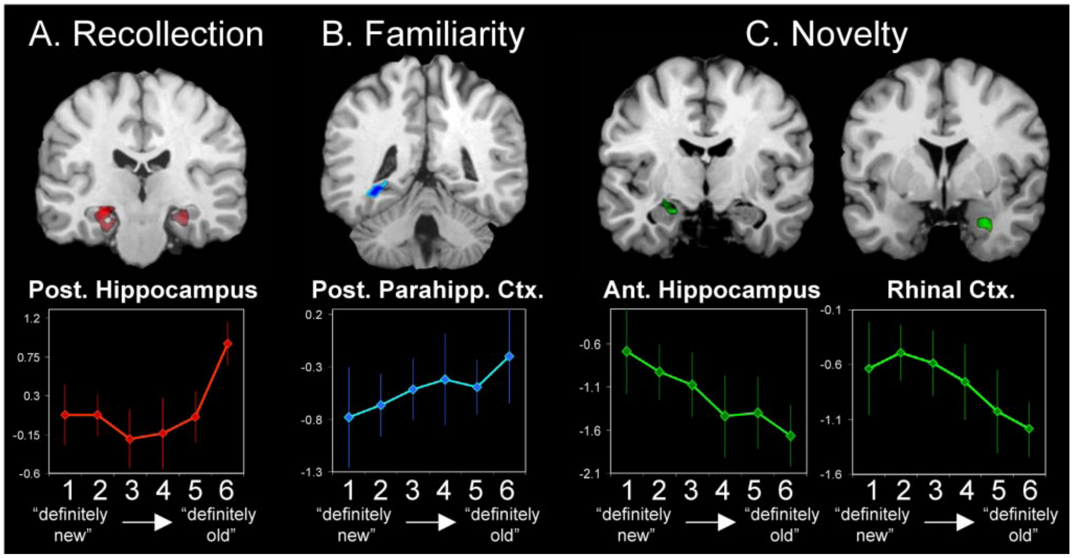

Figure 4: Triple dissociation within the MTL (adapted from Daselaar et al. 2006).

Using confidence ratings for previously studied words, the posterior hippocampus selectively responds to the highest confidence rating (confidence rating 6=recollection, A), whereas the posterior parahippocampal gyrus shows a linear increase with memory confidence (confidence ratings 2-5=familiarity, B). The anterior hippocampus and perirhinal cortex show a decrease in activation correlating to confidence ratings (confidence rating 1=novelty, C).

1.3.2.3 Comparison between Encoding and Retrieval

Only a few studies have compared encoding and retrieval of relational information directly (Cansino, Maquet et al. 2002; Kirwan and Stark 2004; Eldridge, Engel et al. 2005; Prince, Daselaar et al. 2005). In a study of object-location associations, Cansino and colleagues (2002) reported increased right hippocampal activation at retrieval when location was remembered versus forgotten but no differential MTL activation during encoding. In a study using face-name pairs, Kirwan and Stark (2004) reported extensive MTL activation including the right hippocampus that differentiated retrieval versus forgetting of associations at both encoding and recognition phases. They noted that the hippocampal activation was somewhat more anterior during encoding in comparison with retrieval. A similar pattern of results but lateralized to the left hippocampus was reported by Prince and colleagues (2005) who examined both semantic (word pairs) and perceptual (word-font pairings) associations. Finally, using a design similar to the present study, Eldridge and colleagues (2005) presented object/word pairs with items varying in color and position, and a 24-hour delay test using Remember/Know decisions. At retrieval, they found greater activation in the subiculum for items in which the context was retrieved; however, this pattern was not present at encoding. Rather, hippocampal activation was seen for episodic memory formation in general, but subsequent recollection and familiarity were not distinguishable. Further, there was actually an inverse pattern in the subiculum; subsequent familiarity was associated with greater activation within the subiculum than subsequent recollection. The binding processes at encoding were found instead in the parahippocampal and fusiform cortices. Thus, although there is substantial evidence regarding the engagement of the hippocampus in establishing and retrieving relational information, questions remain regarding the similarity of processes and precise anatomy.

1.3.3 Summary

Recollection and familiarity are two subjective experiences underlying recognition memory. Recollection refers to memory retrieval accompanied by the recovery of specific contextual details, whereas familiarity refers to the feeling that an event is old in the absence of confirmatory contextual information. Functional imaging studies suggest that the hippocampus selectively supports formation, binding and reintegration of relational memory but not of item memory. However, it is unknown whether relational memory processes and underlying neuronal networks involved in retrieval are the same as those involved in encoding. Only very few studies have examined within the same experiment the role of the hippocampus for relational memory during both, encoding and retrieval.

1.4 Face Memory

The following section will summarize the relevant literature of face memory. As described above, the relevant processes of episodic memory are processing, encoding and retrieval. Here, these processes for face memory will be described briefly. Afterwards, the literature on face recollection and familiarity will be discussed.

1.4.1 Face Processing, Encoding and Retrieval

The importance of face perception is reflected in our extraordinary ability to remember faces. In browsing through an old family book, we readily recognize the faces of people who were 30 years younger on the picture than they are today. Though people may have characteristic physiques and mannerisms, facial features provide the strongest distinctions of one person from another.

Given the importance of face perception, prosopagnosia is one of the most fascinating and debilitating disorders of object recognition. Prosopagnosia describes a deficit in the ability to recognize familiar or unfamiliar faces, leaving other forms of object recognition abilities intact (Bodamer 1947). As a result, face processing is thought to be independent of object and verbal processing (Moscovitch 1997; Farah, Wilson et al. 1998). Numerous ERP and imaging studies have confirmed engagement of the right fusiform gyrus (now known as fusiform face area, FFA) during a range of face perception tasks (Kanwisher, McDermott et al. 1997; Moscovitch 1997; Farah, Wilson et al. 1998; Epstein, Harris et al. 1999; Vuilleumier, Armony et al. 2001; Gauthier, Curran et al. 2003; Polyn, Natu et al. 2005; Kanwisher 2006).

Whereas the studies mentioned above examined the passive viewing of faces, it is also well established that face encoding is associated with activation within the MTL. Kelley et al. (1998) showed a hemispheric specific activation for face encoding within the right hippocampus. Especially during deep encoding tasks, the right hippocampus showed greater activation than the left (Kelley, Miezin et al. 1998). Besides the right MTL, prefrontal areas also show this effect (Haxby, Ungerleider et al. 1996; Frey and Petrides 2003).

The neuroanatomy underlying face recognition is controversial. Whereas some studies found greater activation in the hippocampus and surrounding areas (Iidaka, Terashima et al. 2003; Bernard, Bullmore et al. 2004; Coleshill, Binnie et al. 2004), other studies did not find any MTL activation during the retrieval of previously unfamiliar faces (Haxby, Ungerleider et al. 1996). This study revealed mostly prefrontal activation during face recognition.

Another group of studies examined patients with unilateral temporal lobe epilepsy (TLE) behaviourally in order to confirm the importance of the right MTL in face memory (Milner 1968; McGlone 1994; Barr 1997; Dade and Jones-Gotman 2001; Crane and Milner 2002; Moscovitch and McAndrews 2002; Chiaravalloti and Glosser 2004; Glogau, Ellgring et al. 2004; Testa, Schefft et al. 2004; Vaz 2004; Bengner, Fortmeier et al. 2006; Gillespie, Bowen et al. 2006). Although they found impairments in face memory only in patients with right TLE, these behavioural studies do not indicate the stage of processing in which face memory is disturbed.

1.4.2 Face Recollection and Familiarity

The majority of the current literature on recollection and familiarity used verbal test material. Faces are likely to produce feelings of familiarity without recollection because unfamiliar faces are completely novel whereas words, in most cases, are already known (Yovel and Paller 2004; MacKenzie and Donaldson 2007). Studies addressing recollection and familiarity for faces are rather controversial (Mantyla 1997; Moscovitch and McAndrews 2002; Sperling, Chua et al. 2003; Kirwan and Stark 2004; Dewhurst, Hay et al. 2005; Fenker, Schott et al. 2005; Cipolotti, Bird et al. 2006; Bird, Shallice et al. 2007; Chua, Schacter et al. 2007; Gruppuso, Lindsay et al. 2007; Taylor, Henson et al. 2007). Some suggest that recollection of faces is hippocampus-independent (Cipolotti, Bird et al. 2006; Bird, Shallice et al. 2007), whereas others suggest that recollection of faces is a hippocampus-dependent process (Moscovitch and McAndrews 2002; Kirwan and Stark 2004). fMRI studies revealed that during encoding there was greater bilateral activation of anterior hippocampus for recollected face-name pairs than for forgotten pairs (Sperling, Chua et al. 2003; Chua, Schacter et al. 2007). Another study found that at retrieval, the posterior hippocampus is involved in recollection of emotional faces (Fenker, Schott et al. 2005). These studies suggest a specific role for the hippocampus during encoding and retrieval of facial recollection. However, one can argue that face-name pairs may involve verbal recollection as well or that emotional faces are differently recollected than neutral ones. Indeed, some other studies do report intact recollection for unfamiliar neutral faces in patients with bilateral hippocampal damage (Cipolotti, Bird et al. 2006; Bird, Shallice et al. 2007; Taylor, Henson et al. 2007).

In a previous study, Moscovitch and McAndrews (2002) found that patients with right medial temporal lobe damage showed reduced recollection but intact familiarity during face recognition. In particular, they failed to show an advantage (increase in recollection) following encoding that encouraged the formation of rich, multifaceted representations (i.e., they were asked to make 'personality' decisions about target faces) relative to encoding based on a simple discrimination (gender). Moscovitch and McAndrews had argued that this impairment might reflect disruption of operations that enable binding various elements of an experience, although it was not possible to know whether this was at encoding or retrieval.

1.4.3 Summary

In summary, face memory is one of the most amazing human abilities. Prosopagnosia is known as the specific disability to recognise faces, while leaving object recognition intact and is thought to be a neurological defect of the fusiform face area. Further, the right MTL seems to be crucial in face memory but it is not fully resolved in which stage of the memory process, whether it is crucial at encoding, retrieval or both. Only few fMRI studies examined recollection of faces, yielding controversial results. None of those studies investigated recollection and familiarity for unfamiliar neutral faces during encoding and retrieval with fMRI. Further, examining face memory with fMRI could also lead to more clarity about the hemispheric lateralization of recollection and familiarity underlying encoding and retrieval.

2 AIM OF STUDY AND HYPOTHESES

2.1 Primary Hypotheses

Recollection is thought to be dependent on the hippocampus. Several studies showed that the hippocampus is more active during successful relational binding than non-successful relational binding (Davachi and Wagner 2002; Sperling, Chua et al. 2003; Kirwan and Stark 2004; Ranganath, Yonelinas et al. 2004; Prince, Daselaar et al. 2005; Uncapher and Rugg 2005; Kensinger and Schacter 2006; Chua, Schacter et al. 2007; Otten 2007) and successful retrieval of that context (Eldridge, Knowlton et al. 2000; Cansino, Maquet et al. 2002; Dobbins, Rice et al. 2003; Kahn, Davachi et al. 2004; Weis, Specht et al. 2004; Wheeler and Buckner 2004; Dolcos, LaBar et al. 2005; Woodruff, Johnson et al. 2005; Yonelinas, Otten et al. 2005; Daselaar, Fleck et al. 2006; Montaldi, Spencer et al. 2006; Vilberg and Rugg 2007). Whilst the hippocampus supports memory for relational information, however, it is unclear whether encoding and retrieval of this information engage the same circuitry. Only very few studies examined relational processing during encoding and retrieval within the same experiment (Cansino, Maquet et al. 2002; Kirwan and Stark 2004; Prince, Daselaar et al. 2005). Evidence from fMRI, behavioural and lesion studies indicate that face processing is mediated by the right hemisphere (Kanwisher, McDermott et al. 1997; Moscovitch 1997; Farah, Wilson et al. 1998; Epstein, Harris et al. 1999; Vuilleumier, Armony et al. 2001; Gauthier, Curran et al. 2003; Polyn, Natu et al. 2005; Bengner, Fortmeier et al. 2006; Kanwisher 2006). However, it is still unclear which processes of face memory rely on the right, left or both hemispheres. Further, some studies suggest that recollection of faces is hippocampal independent (Cipolotti, Bird et al. 2006; Bird, Shallice et al. 2007), whereas others suggest that recollection of faces is a hippocampal dependent process (Moscovitch and McAndrews 2002; Kirwan and Stark 2004). The current study therefore examines the role of the hippocampus during encoding and retrieval of relational face memory and whether there are lateralization effects.

Our primary hypotheses are:

1. During encoding, the hippocampus will be more activated during successful relational than non-successful relational encoding. This effect should be more prominent in the right hemisphere.
2. During retrieval, the hippocampus will be more activated during successful than non-successful retrieval of this context. This effect should be more prominent in the right hemisphere.

We are further interested in neural correlates of familiarity-related processes during encoding and retrieval. However, MTL participation for familiarity-related processes might be rather a linear process whereas recollection clearly involves separate neuroanatomical structures (see Sec. 1.3.2.2, Fig. 4) (Daselaar, Fleck et al. 2006). We therefore come to the following hypotheses:

3. During encoding, there will be no greater hippocampal activation for non-successful relational than successful relational encoding.
4. During retrieval, there will be no greater hippocampal activation for non-successful than successful retrieval of this context.

2.2 Secondary Hypotheses

In a next step we would like to corroborate current findings from the literature on relational face memory.

2.2.1 Secondary Hypotheses at Encoding

During encoding, we are interested in the overall neuroanatomical structures which support subsequent successful memory. In accordance to the Multiple Trace Theory (MTT), any kind of encoding should activate the hippocampus, regardless of whether it will later be recollected or familiar (Nadel and Moscovitch 1997). Therefore, we predict that, in comparison to faces which are later forgotten, both subsequent recollection and subsequent familiarity responses should activate the hippocampus. Further, some studies show an increase of activation within the anterior parahippocampal gyrus (APHG) for familiarity-related processes at encoding (Davachi, Mitchell et al. 2003; Ranganath, Yonelinas et al. 2004).

Our hypotheses are:

1. At encoding, the hippocampus should be more activated during subsequent recollected than subsequent forgotten faces.
2. At encoding, the hippocampus should be more activated during subsequent familiar than subsequent forgotten faces. The APHG should also be more activated during subsequent familiar than subsequent forgotten faces.

Examining general face encoding, we expect that the usual neuroanatomical structures underlying face processing would be active, such as the fusiform gyrus and hippocampus (Haxby, Ungerleider et al. 1996; Kelley, Miezin et al. 1998). We therefore predict:

3. During encoding of faces, the fusiform gyrus and the hippocampus should be more activated than during baseline.

2.2.2 Secondary Hypotheses at Retrieval

The general overview of the retrieval-related data is very similar to the encoding process. We are interested in the overall neuroanatomical structures which support successful memory, regardless of whether it would be recollection or familiarity. In comparison to faces which are forgotten, recollection responses activate the hippocampus, whereas familiarity responses are not associated with hippocampal activity (Moscovitch 2008). In contrast to encoding, a decrease for familiarity-related processes was shown for the APHG at retrieval (Daselaar, Fleck et al. 2006; Viskontas, Knowlton et al. 2006).

Our hypotheses are as followed:

1. At retrieval, the hippocampus should be more activated during recollected than forgotten faces.
2. At retrieval, there should be no greater hippocampal activation of familiar than forgotten faces. In contrast, within the APGH, there should be greater activation for forgotten or new than familiar faces.

A few studies have illustrated that the hippocampus is involved in novelty detection (see also Sec. 1.3.2.2, Fig. 4C) (Kohler, Danckert et al. 2005; Daselaar, Fleck et al. 2006; Poppenk, Walia et al. 2008). Mostly, this was related to relational spatial memory (Kohler, Danckert et al. 2005). Here, we would like to test whether the hippocampus is more activated during correctly recognized new faces (correct rejections) than forgotten (old) faces. Accordingly to the novelty effect, we would predict:

3. The hippocampus should be more active during correct rejections than during forgotten faces.

In order to examine general face recognition, we expect that the neuroanatomical structures underlying face processing would be active, such as fusiform gyrus and hippocampus (Haxby, Ungerleider et al. 1996; Kelley, Miezin et al. 1998). We therefore predict:

4. The fusiform gyrus and hippocampus should be more activated when the participants are judging faces than during baseline.

3 METHODS

3.1 Participants

19 right-handed healthy participants with an average age of 26 years (3.4 SD; age ranges between 34 and 20) were scanned for the study. Due to technical problems during scanning four subjects were completely excluded, whereas for two subjects only the retrieval data were recorded. Another subject was excluded because she did not have any familiarity responses. The following study includes therefore 12 subjects (5 females; average age 25 ± 3.1, range 20-32) at encoding and 14 (6 females; average age 25 ± 3.1, range 20-32) at retrieval. The subjects were either employees of Toronto Western Hospital, relatives of the patients, or volunteers recruited from the University of Toronto subject pool. Every participant gave oral informed consent to the study. The study was approved by the University Health Network Research Ethics Board.

3.2 Stimuli and Experimental Procedure

We used E-Prime 1.1 (Psychology Software Tools Inc., Pittsburgh) to generate and present the experiment. 117 black and white photographs of faces (58 female; age ranges between 25 and 35 years) shown in a frontal view with hairs cropped from the images (see Fig. 5) were used in the experiment. Some studies show a gender interaction effect, i.e. women recognise female faces easier and men male faces (McKelvie 1981; Shapiro 1986; Lewin and Herlitz 2002; Wright and Sladden 2003; Fischer, Sandblom et al. 2004; Rehnman and Herlitz 2006). To control this effect we used an equal amount of male and female faces in every experimental set. The gender, emotionality, attractiveness of the faces and the quality of the images were rated by two independent persons. In cases where the gender of a face was rated differently by the two evaluators, it was excluded from the stimuli pool. The reliability between the results of both persons was sufficiently with r=0.84 (Friede 1981). In the experiment 60 faces (30 females) were used as targets and 32 as lures.

Prior to performing the test, subjects performed a practise test of 15 study faces and 15 +10 retrieval faces outside the scanner. In addition to verbal explanations, the following instructions were shown on the screen:

> "You are going to see some faces which you should try to remember for a later test. Try for each face to think about whether the person is a "homebody", "party-goer", "sporty-type" or "intellectual". When the face disappears, rise a finger to show in which category you would put the face:
> Forefinger = homebody
> Middle finger = party-goer
> Ring finger = sporty-type
> Little finger = intellectual
> Please try to fix the position of the cross for the whole experiment.
> Click either button to begin."

At retrieval of the practise test, the following instructions were shown:

> "Now we will test your memory for the faces you saw earlier. You will see faces again; some are the ones you saw earlier and some are new. For each face, you must make two decisions.
> First, is the face "old" (one from earlier) or "new" (not seen before). Press the left key for "old" and the right key for "new".
> Second, for "old" faces, do you "re-experience" the original study (what you thought about the personality of the person) or do you "know" the face was shown before without recalling the details of the original study experience? Hit the left key for "re-experience" and the right key for "know"
> If the face is "new", hit the right key here.
> Click either button to begin."

The participants were explicitly encouraged to make as many associations with a study face as possible. Although the participants were asked to assign each face to a personality category, they were also invited to create their own associations. This could be for example a big nose or a reminiscence of a relative. The real experiment only began when subjects could describe examples of remembering and knowing to the experimenter.

The experiment consisted of two subsequent encoding/retrieval blocks, both of which took place in the fMRI scanner. During the encoding block subjects saw 30 faces (15 females) for 5 seconds each. The inter stimulus intervals (ISI) were randomised between 6, 8 and 10 seconds (average of 8 sec) showing a black fixation cross on a white screen. These trials were incorporated to act as baseline trials. To enhance the depth of the encoding subjects were instructed to decide whether the face belongs to a person which is a "homebody", "party-goer", "sporty-type", or "intellectual". This procedure was adapted from an earlier study (Moscovitch and McAndrews 2002). Participants were asked to communicate their opinion by rising one finger for each category so that the experimenter in the MRI room could record their response. This procedure was used to encourage the participants to pay attention and create associations to the faces. However, their responses were not further examined.

After a short delay the recognition test began. The target faces and lures were shown for 3 sec each in a randomised order. After each face, the participants had to answer two questions. First, they were asked to report per mouse click whether they studied the face before (old) or not (new). In a second question they were asked to decide whether they "know" (Familiarity response, K) or "re-experience" (Recollection response, R) the face. A recollection response was only counted if the participant reported "old" at the first question and "re-experience" at the second question. In accordance, familiarity responses were counted if the participant reported “old” at the first and “know” at the second question. “Correct rejections” were counted, when the participants clicked “new” at the first and “know” at the second time. As a result, eprime recorded three different response patterns which were then compared to the true old and new faces. Ambiguous responses were rated as missing values and excluded from further analyses. There was a time limit of 3 seconds for each question. Before the next face appeared on the screen there was a fixation cross for 3 seconds. These trials were incorporated to act as baseline trials.

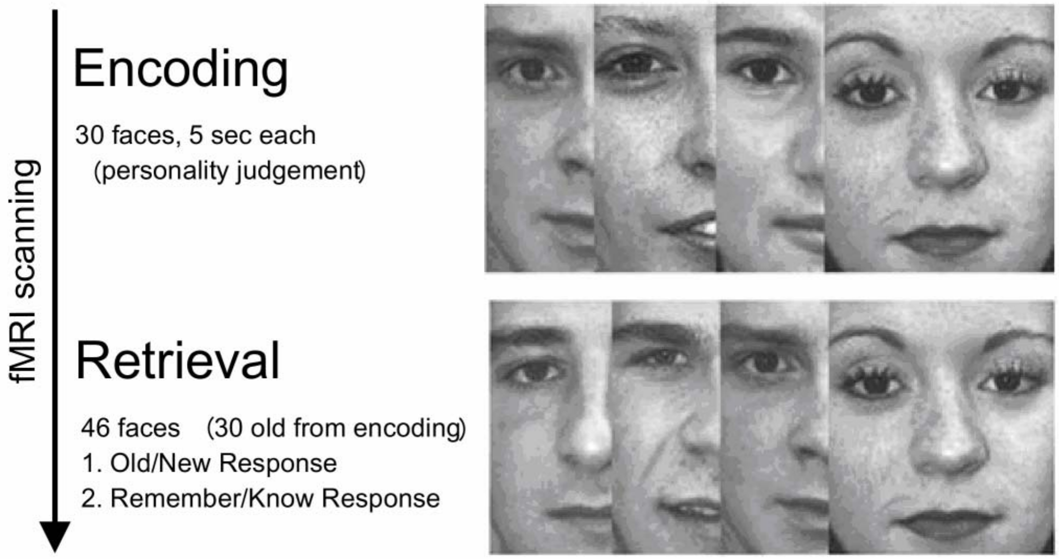

Figure 5: Experimental procedure.
Participants studied a sequence of 30 faces and were asked to judge the personalities of the faces. During recognition 30 old and 15 new faces were presented. Participants were asked to first indicate by mouse click whether they had studied the face before (Old/New response) and second, if they remembered any associations with the face (Remember response) or not (Familiarity response). To increase the number of responses, a second test set with different faces followed the first. Participants were scanned during both encoding and retrieval.

3.3 Behavioural Statistics

The accuracy was measured by calculating the corrected hit rate (CHR) for each subject:

CHR = (R+K+CR)/ (92-missing values)

The CHR was defined as faces correctly recognized as old or new divided by the amount of valid responses. Thus, scores falling around 0 reflect poor accuracy and scores around 1 indicate good accuracy.

All behavioural statistics were done with STATISTICA 7.0 for Windows (StatSoft, Hamburg, Germany). These included descriptive statistics of frequencies, means, standard deviations and standard errors. To analyze differences in accuracy and reaction time between response groups we used Student's t tests with the significance level set at 0.05.

We further conducted an item analyses to test for item-specific effects, using the Kolmogorov-Smirnoff test for Gaussian distributions.

3.4 Imaging Data Acquisition and Processing

Anatomical and functional data were aquired on a 3-T Sigma MR System (GE Medical Systems, Milwaukee WI, USA). The anatomical scans were taken first (T1-weighted sequence, 120 slices, 220 mm FOV, 256 x 256 matrix, resulting in a voxel size of 0.78 x 0.78 x 1.1mm). Functional data were acquired in an ascending order every 2 sec (25 slices, 440 mm FOV, 64 x 64 matrix, resulting in a voxel size of 3.75 x 3.75 x 4.4mm). For every encoding phase we acquired 199 frames and 302 frames for each recognition phase. The first three frames were dropped to allow signal equilibrium.

All pre-processing and analyses of imaging data were performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Imaging Neuroscience, London, UK), only the headers were created with SPM99. Data were co-registered to a structural image, time-sliced (Reference Slice=1, Bin=1), realigned and unwarped for motion, spatially normalized to the Montreal Neurological Institut (MNI) template and smoothed using a Gaussian kernel of 7.6 mm full-width half maximum. Each stimulus event was modelled by SPM2's canonical hrf. This was applied at the onset of the face stimulus as reaction time analyses (see Sec. 4.1) indicated that processing relevant to the Remember/Know decision was undertaken during the initial old/new recognition decision. Contrasts of interest for each subject's data were analyzed as a fixed-effects model, and the resulting contrast images were taken to the second level and analyzed as a random-effects model.

3.5 Image Analyses

3.5.1 Univariate Contrasts

We defined five conditions for the recognition data: (1) Recollection (R), (2) Know/Familiarity (K), (3) Correct Rejections (CR), (4) Forgotten/Misses (M) and (5) baseline (Fix). The behavioural measures of subsequent recognition responses were used to back-sort the fMRI encoding events into four conditions: 1) subsequent Recollection (sR), (2) subsequent Know/Familiarity (sK), (3) subsequent Forgotten/Misses (sM) and (4) baseline (Fix). According to the prior hypotheses the following contrasts were analyzed:

Encoding:

(1) Subsequent recollection: sR > sK and (2) Subsequent familiarity: sK > sR. For a general overview of the current data, we analyzed further: (3) Total recollection response: sR > sM; (4) Total familiarity response: sK > sM; and (5) Encoding of faces: sR+sK+sM > Fix.

Retrieval:

(1) Recollection: R > K and (2) Familiarity: K > R. Again, for a general overview of the retrieval data, we analyzed further: (3) Total recollection response: R > M; (4) Total familiarity response: M > K and CR > K; (5) Novelty response: CR > R+K; (6) Total correct rejection response: CR > M; and (7) Retrieval of faces: R+K > M.

To analyze the total recollection or familiarity response we used forgotten faces (sM) as the contrasts. This procedure was chosen because first, the participants saw faces during both conditions and second, there is evidence that CR may activate the MTL as well, known as "novelty effect" (Kohler, Crane et al. 2002; Gonsalves, Kahn et al. 2005; Kohler, Danckert et al. 2005; Strange, Hurlemann et al. 2005; Daselaar, Fleck et al. 2006). The contrast between R and CR could therefore eliminate MTL activation.

Regions of at least 5 contiguous voxels that exceeded a threshold of $p<0.001$, uncorrected for multiple comparisons, were considered significant. Furthermore, as we had an a priori prediction that the hippocampus would be activated during encoding and retrieval, a small volume correction (SVC) was applied to the activation map from this contrast, with the threshold set at $p<0.005$, uncorrected. Both hippocampal region of interest masks were created in Montreal Neurological Institute (MNI) space using MARINA (Bertram Walter Bender Institute of Neuroimaging, University of Giessen, Germany). Using MarsBar (http://marsbar.sourceforge.net), signal change was extracted from spherical ROIs (radius= 2mm) centred on the peak voxel of interest for each subject. Differences in the activation level were calculated with ANOVAs. For all voxel analyses, we used the SPM Anatomy Toolbox to localize regions of activation within the standard MNI space (http://www.fz-juelich.de/inb/inb-3//spm_anatomy_toolbox).

3.5.2 Lateralization Index

We calculated a lateralization index to investigate whether the left or right hippocampus is more involved in encoding or recognizing faces. The same hippocampal masks as described above were used. These were then applied to map t-scores corresponding to each contrast using the imcalc function in SPM2, thus creating images containing only those t-scores within the left or right hippocampus. Counts of voxels whoses t-scores exceeded the relevant threshold ($p<0.005$) were extracted using the Anatomy Toolbox of SPM2. These counts were then used to calculate a lateralization index (LI) using the formula:

$$LI = (L-R)/(L+R)$$

L indicates the number of voxels within the left hippocampus exceeding significance threshold and R the number of voxels within the right hippocampus exceeding significance threshold. Thus, scores falling around zero indicate little asymmetry in hippocampal activity; a negative score reflects more activation in the right hippocampus relative to the left and a positive score indicates more activation in the left hippocampus relative to the right.

4 RESULTS

4.1 Behavioural Results

The following section will describe the behavioural results, including accuracy, reaction time and an item analysis.

Accuracy: The mean corrected hit rate (CHR) was 0.81 ± 0.06 (mean ± SD). On average, every subject responded with 23 ± 7 R (range 11-32), 21 ± 5 K (range 10-26), 26 ± 4 CR (range 16-30), 12 ± 5 M (range 4-22) and 5 ± 3 FP (range 0-12) responses. Table 3 shows the summarized behavioural results over both test blocks. Of all 72 FP, 12 were "false R" and 60 "false K" responses. There was no difference between the first and second test for the amount of responses in each category (see Tab. 4 and Fig. 6). Therefore, we collapsed both test blocks into one further analysis.

Reaction Times (RT): The following R- and K-RT were measured during the first (Old/New) distinction, i.e. R and K responses were back-sorted to the Old/New decision. On average, subjects responded within 780 ± 266 msec for R, 1028 ± 280 msec for K, 917 ± 184 msec for CR, 1041 ± 338 msec for M and 1110 ± 407 msec for FP responses. See table 4 and figure 7 for an overview of reaction times for each category for both test blocks individually. There was no difference within each category (e.g. R1 and R2) between both test blocks. Over both test blocks, however, R responses were made faster than K, M and FP responses (t-tests, dF=24, p's < 0.04). There was no difference in the RT at the second (R/K) distinction.

Table 3: Behavioural results

	Recognition judgments					
Accuracy	Remember	Know	CR	Misses	FP	CHR
Mean proportion	23.38	21.15	25.64	12.00	4.79	0.81
SD	7.04	4.77	4.18	5.45	3.49	0.06
Total	304	275	343	163	72	
Reaction time (ms)						
Mean	780.91	1028.48	917.20	1041.06	1109.93	
SD	266.12	279.68	184.30	338.07	407.49	

Table 4: Behavioural results for both individual test blocks

Test Block 1

	Recognition judgments					
Accuracy	Remember	Know	CR	Misses	FP	CHR
Mean proportion	12.05	11.08	13.85	6.85	2.23	0.80
SD	4.27	2.78	1.63	3.13	2.17	0.06
Total	151	131	180	89	29	
Reaction time						
Mean	798.31	1043.13	894.68	1066.04	1194.25	
SD	330.12	322.30	263.05	285.66	635.30	

Test Block 2

	Recognition judgments					
Accuracy	Remember	Know	CR	Misses	FP	CHR
Mean proportion	12.50	12.60	12.79	5.64	3.14	0.83
SD	3.96	2.32	2.42	2.53	2.48	0.08
Total	153	144	163	74	43	
Reaction time						
Mean	666.09	911.43	782.13	934.96	935.10	
SD	234.24	278.77	170.87	438.05	315.27	

Mean accuracy, standard deviations (SD) and total numbers for different recognition judgments over both test blocks (Tab. 3) and for both test blocks individually (Tab. 4). CR=correct rejection; FP=false positives; CHR=(Remember +Know+CR)/all judged faces.

Mean reaction time and SD for different recognition judgments over both tests (Tab. 3) and for both test blocks individually (Tab. 4). Remember and Know reaction times are counted at the first step (Old/New decision); CR, Misses and FP at the second step (R/K/N decision).

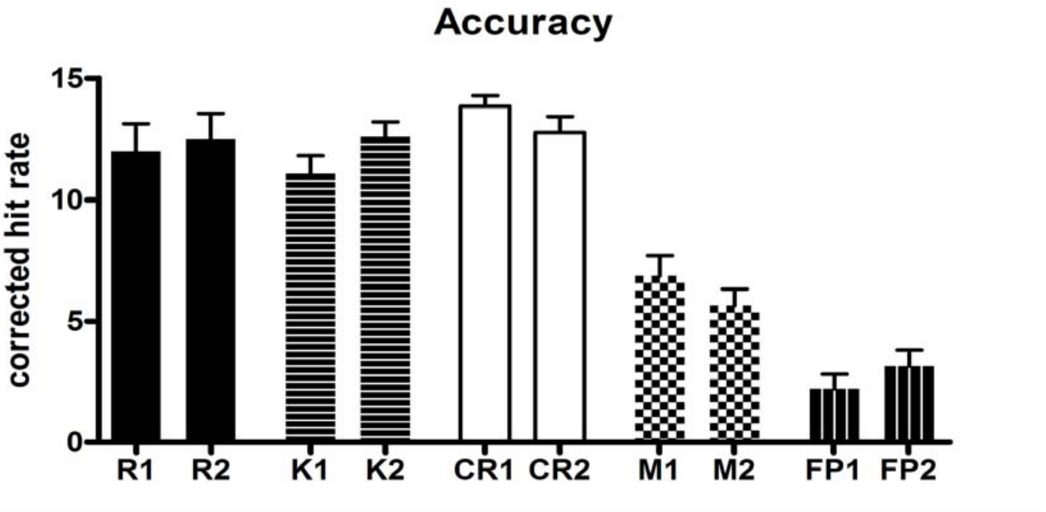

Figure 6: Accuracy.

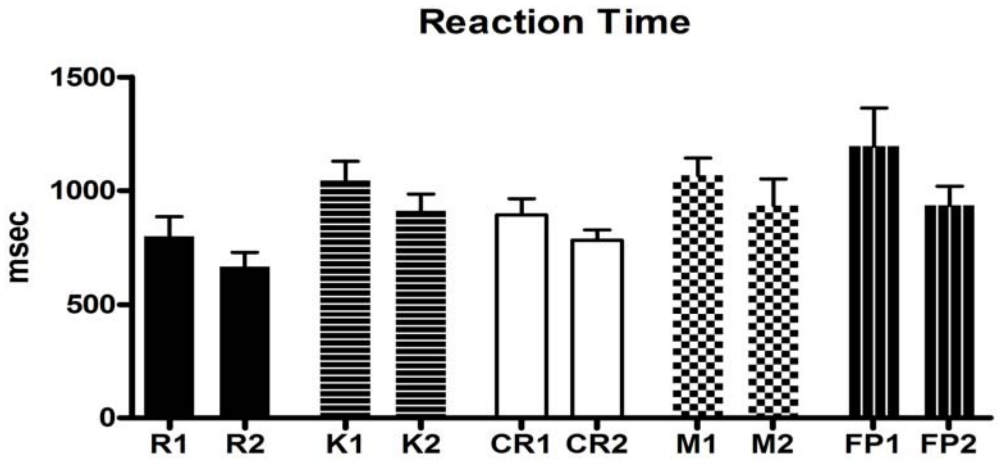

Figure 7: Reaction time.

Mean proportions for both test blocks individually (Fig. 6) and reaction time in msec for each category of both test blocks individually (Fig. 7). The whiskers indicate standard deviations.

R1=Remember responses of test block 1; R2= Remember responses of test block 2; K1= Know responses of test block 1; K2 = Know responses of test block 2; CR1 = Correct rejection responses of test block 1; CR2 = Correct rejection responses of test block 2; M1 = Misses of test block 1; M2 = Misses of test block 2; FP1 = False positive responses of test block 1; FP2 = False positive responses of test block 2. There is no statistical significance within each category between both test blocks for accuracy or reaction time. R(1+2) are made faster than K(1+2), M(1+2) and FP(1+2).

Item analyses: To test for item-specific effects, we conducted an item analysis. On average each face were 5.5 (SD=2.6) times recollected (range 2-13) and 4.7 (SD= 1.9) times familiar (range 1-9). CR responses ranged from 5 to 14 (mean= 11.8; SD=1.9); Misses from 1 to 6 (mean= 3.0; SD= 1.6) and FP responses ranged from 1 to 9 (mean= 2.3; SD= 1.8). The distribution of recollection and familiarity responses did not differ significantly from the Gaussian distribution (Kolmogorov-Smirnoff p>.01), indicating that there was no subset of faces which were recognized more often.

4.2 FMRI Results

The following section will describe the fMRI results. First, the encoding results and then the retrieval results will be illustrated. For encoding and retrieval, the main findings and then the results for the corroborating and explorative results will be displayed. All coordinates correspond to MNI space.

4.2.1 Encoding

4.2.1.1 Subsequent Recollection

We conducted random effects one sided t-tests, comparing the blood oxygenation level-dependent (BOLD) signal associated with subsequently recollected versus subsequently familiar faces (sR>sK) (see Fig. 8). In the overall brain analysis both posterior hippocampi showed greater activation for sR than sK (L: -22 -30 -10; R; 26 -24 -16). The lateralization index (LI) of 0.87 indicates that the left hippocampus is much stronger activated than the right hippocampus. The activation on the left side extended into the left parahippocampal gyrus (-24 -38 -10). Further, we found greater activation for sR than sK in the left inferior frontal gyrus and left amygdala (see Tab. 5).

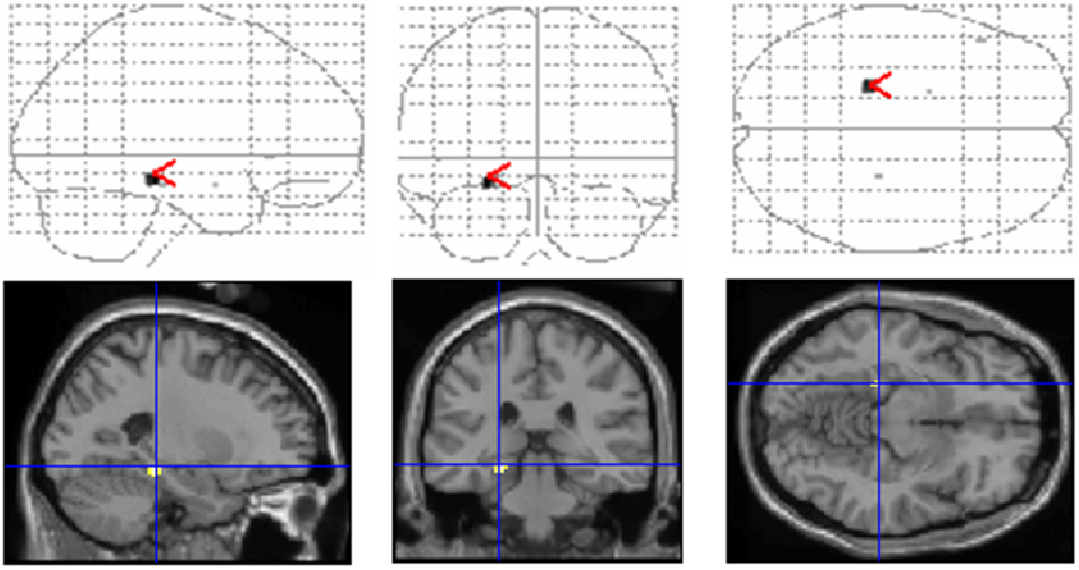

Figure 8: fMRI results for sR>sK.
Hippocampal activation for subsequently recollected versus familiar faces during encoding. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM Template; p<.001. Crosshair at global peak voxel (-22 -30 -10).

Table 5: fMRI results for sR>sK

Recollection (sR>sK) **Region**	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Hippocampus	left	-22	-30	-10	28	5.5
Hippocampus	right	26	-24	-16	28	4.1
Parahippocampal gyrus	left	-24	-38	-10	36	4.05
Inferior frontal gyrus	left	-48	26	0	45	4.04
Amygdala	left	-20	0	-16	34	3.96

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

We conducted a one-way ANOVA to examine differences in signal intensity magnitudes (Beta values) for sR, sK and sM of each subject in the left (Beta values: sR 2.20 ±0.25, sK 0.84 ±0.17, sM -1.12 ±0.38) and right (Beta values: sR 1.43 ±0.15, sK 0.73 ±0.15, sM -0.52 ±0.29) posterior hippocampus (see Fig. 9). For the left posterior hippocampus, the analysis revealed a main effect, F(2,33)

=34.9, p<0.0001. Post-hoc Bonferroni's Multiple Comparison test (BF) found greater activation for sR than sK, t =3.41, p<0.01, but also greater activation for sK than sM, t =4.91, p<0.001. For the right hippocampus, the analysis revealed a similiar pattern, F(2,33) =21.66, p<0.0001. Activation was greater for sR than sK, BF, t =2.32, p<0.05 and sK than sM, BF, t =4.18, p<0.001.

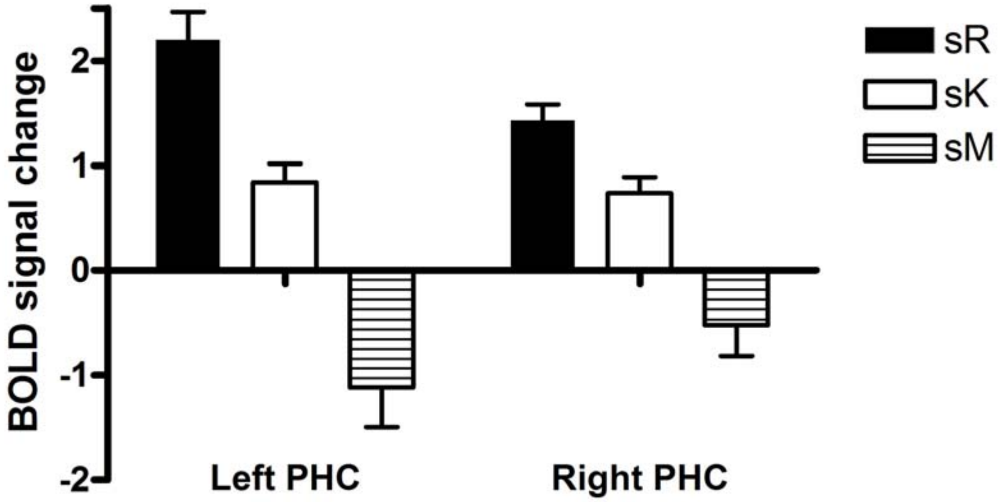

Figure 9: BOLD signal change for sR>sK within the posterior hippocampi. The hemodynamic responses for each condition are modeled from an ROI (sphere, radius=2mm) around the peak voxel within the posterior hippocampus (PHC) for each subject using MarsBar. The whiskers indicate standard errors. sR activation is greater than sK and sM in both PHC.

Although neither anterior hippocampi demonstrated a significant recollection effect (sR>sK) in the whole brain analysis or using small volume correction, we explored this region further given the existing literature demonstrating anterior hippocampal engagement during associative encoding. Therefore, we examined the beta values for each individual (see Fig. 10), based on the non-significant peak voxel for each subject within this area (left AHC: sR=0.93 ±0.6, sK=0.31 ±0.8, sM=-0.32 ±1.7; right AHC: sR=0.82 ±1.2, sK=0.36 ±1.3, sM=-0.68 ±1.7). Within the left anterior hippocampus, the analysis revealed a main effect, F(2,33) =3.59, p<0.05. Although sR and sK did not differ from each other, sR was greater than sM t =2.68, p<0.05). The right anterior hippocampus showed a similar pattern, F(2,33) =3.55, p<0.05. Again, sR and sK did not differ significantly, but sR was greater than sM (t =2.59, p<0.05).

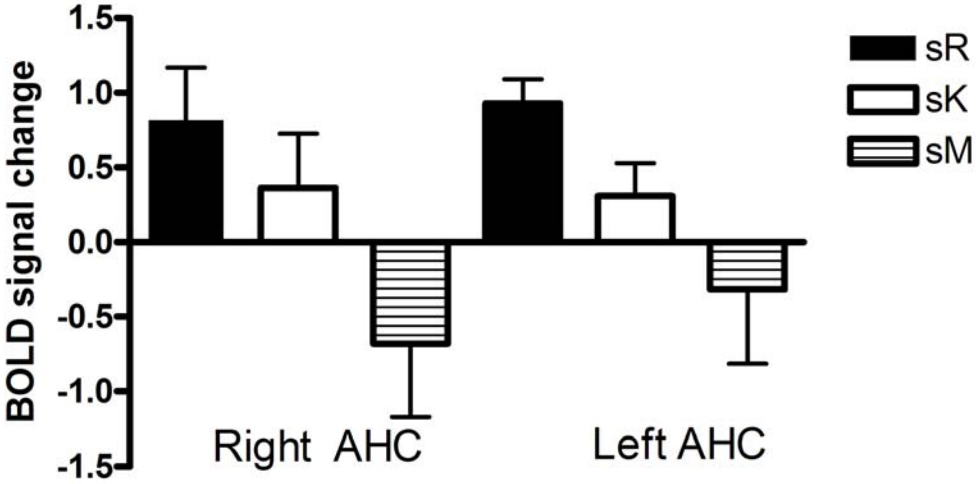

Figure 10: BOLD signal change for sR>sK within the anterior hippocampi. The hemodynamic responses for each condition are modeled from an ROI (sphere, radius=2mm) around the peak voxel within the anterior hippocampus (AHC) for each subject using MarsBar. The whiskers indicate standard errors. In both AHC, sR and sK did not differ, however, sR showed greater activation than sM.

4.2.1.2 Subsequent Familiarity

There was no brain activation greater for sK than sR, even after lowering the threshold to p<0.02.

4.2.1.3 Other relevant findings

The following contrasts were analyzed to corroborate the current literature on face encoding.

4.2.1.3.1 Total Subsequent Recollection Response

Here, we examined the contrast sR versus sM in order to analyze the total subsequent recollection response (see Fig. 11, Tab. 6). During subsequent recollection responses (sR) bilateral hippocampal activation was greater than for subsequent forgotten responses (sM). The lateralization index of 0.38 indicates that the left hippocampus is slightly stronger activated than the right hippocampus.

We found several other brain regions which show greater activation during subsequent recollection responses (sR) than during subsequent forgotten responses (sM). These regions include parahippocampal gyri, fusiform gyri, both amygdalae and precunei. Further, we found greater activation for sR than sM within frontal, parietal and occipital regions.

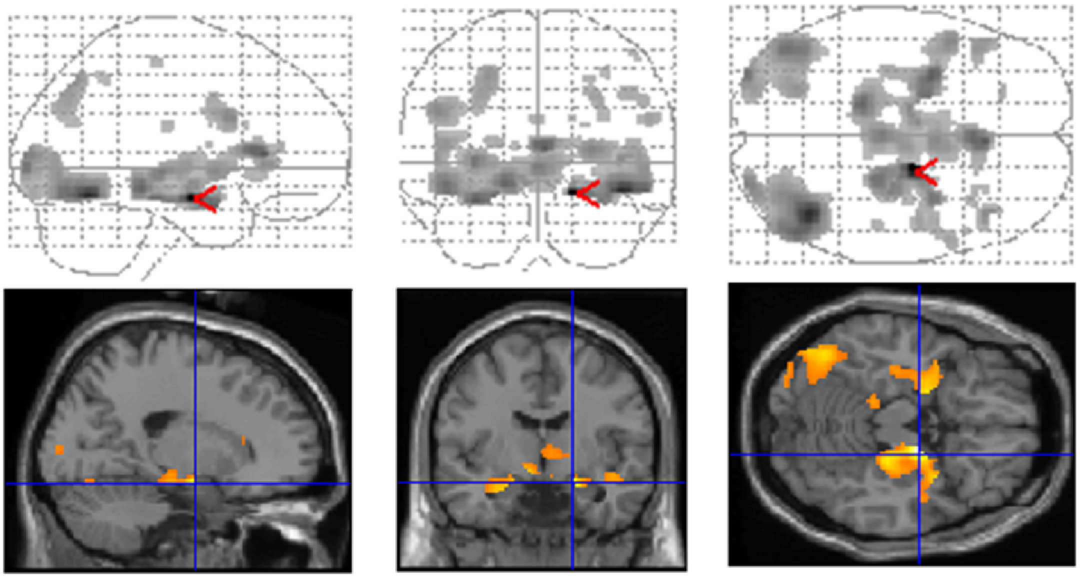

Figure 11: fMRI results for sR>sM.

Hippocampal activation for subsequent recollected versus forgotten faces during encoding. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM Template; p<.001. Crosshair at global peak voxel (18 -6 -16).

Table 6: fMRI results for sR>sM

Recollection (sR>sM) **Region**	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Amygdala	Right	18	-6	-16	28	9.16
Fusiform Gyrus	Right	42	-60	-14	37	7.67
Amygdala	Left	-30	2	-20	34	6.33
Hippocampus	Left	-34	-20	-16		6.26
Inferior Occipital Gyrus	Right	52	-66	-14	37	6.25
Parahippocampal Gyrus	Left	-16	-34	-10	35	6.12
Fusiform Gyrus	Left	-46	-72	-12	19	5.88
Parahippocampal Gyrus	Right	24	-26	-16	35	5.83
Middle Occipital Gyrus	Left	-32	-92	2	18	5.7
Hippocampus	Right	28	-18	-18	2	5.31
Inferior Frontal Gyrus (p. Opercularis)	Left	-48	10	28	9	5.28
Inferior Frontal Gyrus (p. Triangularis)	Right	42	28	2	13	5.14
Superior Parietal Lobule, Precuneus	Left	-24	-68	46	7	4.96
Middle Occipital Gyrus	Right	50	-78	4	18	4.83
Lingual Gyrus	Left	-24	-90	-14	1	4.75
Caudate Nucleus	Right	6	10	-2		4.62
Superior Occipital Gyrus, Precuneus	Right	28	-74	36	31	4.62
Inferior Frontal Gyrus (p. Opercularis)	Right	56	10	24	9	4.59
Superior Temporal Gyrus	Right	44	-6	-12	13	4.39
Precentral Gyrus	Right	46	2	36	6	4.39
Insula Lobe	Right	34	22	-4		4.15
Postcentral Gyrus	Right	48	-26	58	40	4.15
Inferior Frontal Gyrus (p. Orbitalis)	Right	30	24	-6		4.14
Inferior Parietal Lobule	Right	34	-52	48	7	4.02

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

4.2.1.3.2 Total Subsequent Familiarity Response

We conducted the contrast sK versus sM in order to analyze the total subsequent familiarity response (see Fig. 12, Tab. 7). Both hippocampi are more activated during sK than sM. The lateralization index of 0.09 indicates that the left hippocampus is only marginal more activated than the right hippocampus. Additionally, we found several other brain regions which show greater activation for sK than sM. These regions include bilateral parahippocampal gyri, fusiform gyri, and some occipital, frontal and temporal areas.

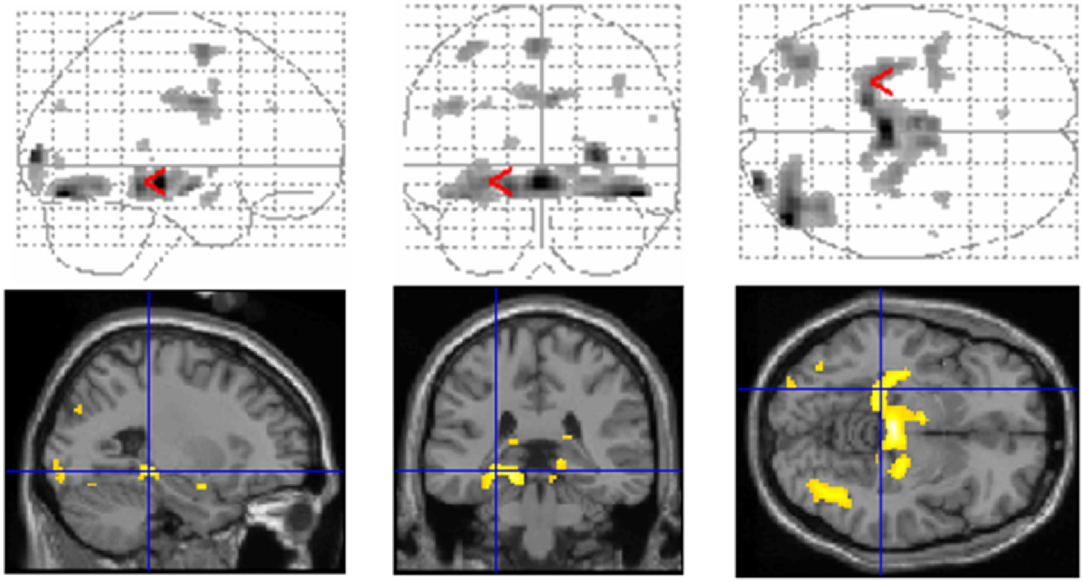

Figure 12: fMRI results for sK>sM.
Whole brain activation for subsequent familiar versus forgotten faces during encoding. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM Template; p<.001. Crosshair at the peak voxel within the left hippocampus (-30 -30 -10).

Table 7: fMRI results for sK>sM

Familiarity sK>sM **Region**	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Inferior Occipital Gyrus	Right	48	-76	-14		6.73
Middle Occipital Gyrus	Right	26	-92	6	18	5.9
Fusiform Gyrus	Right	38	-74	-14	19	5.82
Linual Gyrus	Right	14	-36	-2		5.67
Parahippocampal Gyrus	Left	-20	-36	-12	27	5.6
Middle Cingulate Cortex	Right	6	-4	34	24	5
Inferior Temporal Gyrus	Right	40	-58	-10		4.97
SMA	Left	-4	-2	62	6	4.97
Inferior Occipital Gyrus	Left	-44	-76	-14		4.7
Precentral Gyrus	Left	-44	-2	30	6	4.62
Fusiform Gyrus	Left	-32	-34	-18	19	4.49
Middle Cingulate Cortex	Left	-6	-18	36	23	4.49
Middle Occipital Gyrus	Left	-30	-92	-2	18	4.34
Amygdala	Left	-28	0	-18	2	4.34
Middle Frontal Gyrus	Right	38	4	44	6	4.21
Hippocampus	Left	-30	-30	-10		4.14
Parahippocampal Gyrus	Right	32	-27	-18	27	4.13
Inferior Occipital Gyrus	Left	-26	-90	-12	36	4.13
Hippocampus	Right	27	-30	-6		3.65

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

Although the overall SPM analysis as well as using the small volume correction did not reveal significant activation for sK versus sM within the anterior parahippocampal gyrus (APHG), we examined this region further, given the existing literature demonstrating APGH engagement during associative encoding. Therefore, we extracted beta values for sK and sM, based on the highest non-significant voxel of each subject (Left APHG: sK= 0.26 ±1.2, sM=-0.59 ±1.2; Right APHG: sK=0.41 ±1.5, sM=-0.42 ±0.9). The analyses revealed a trend in the left (t(22)=1.50, p=0.07) as well as in the right (t(22)=1.57, p=0.07) APHG, showing greater activation for sK than sM (see Fig. 13).

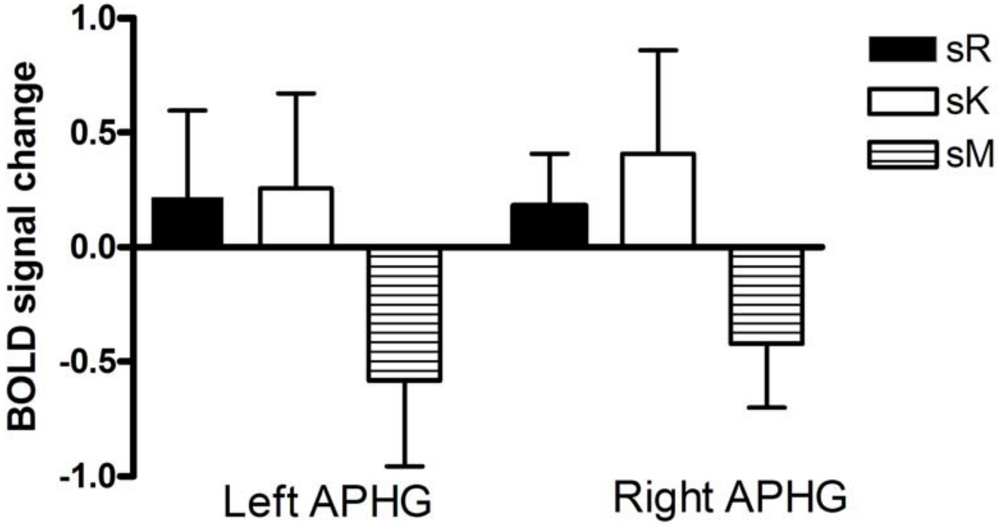

Figure 13. BOLD signal change for sK>sM within the anterior parahippocampal gyri

The hemodynamic responses for each condition are modeled from an ROI (sphere, radius=2mm) around the peak voxel within the anterior parahippocampal gyrus (APHG) for each subject using MarsBar. The whiskers indicate standard errors. There is a trend in both APHG for sK>sM.

4.2.1.3.3 Encoding of Faces

In order to examine the effect of encoding faces, we conducted the contrast sR, sK, sM versus baseline (fix) (see Fig. 14, Tab. 8).

Bilateral hippocampal activation was greater for encoding faces than fix. The lateralization index of -0.84 indicated that face encoding is predominantly dependent on the right MTL. Further, the analysis revealed greater activation of the right fusiform gyrus for face encoding than for fix.

There were several other regions involved in face processing, such as bilateral frontal, occipital and parietal areas.

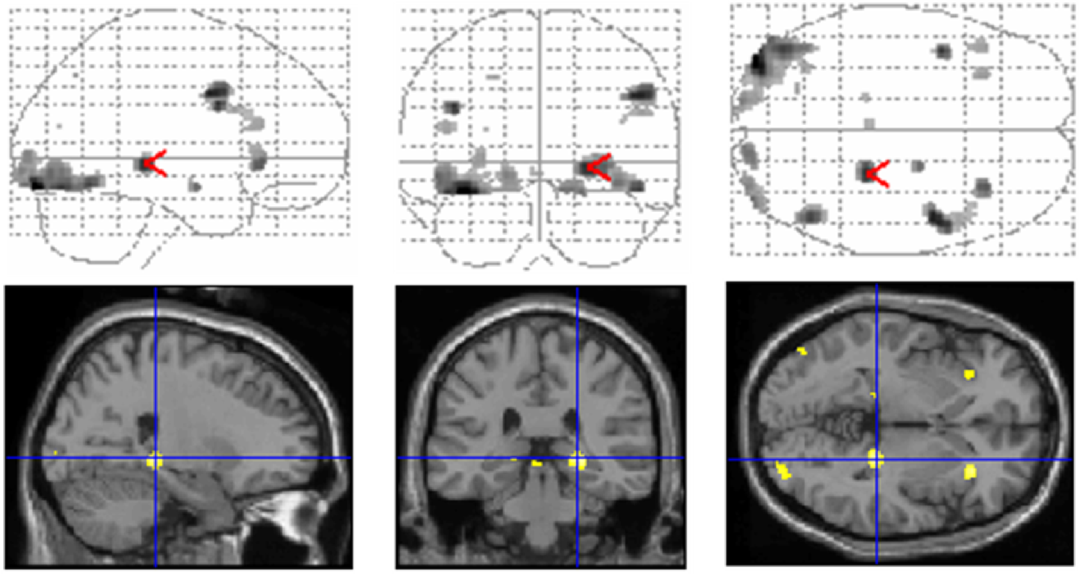

Figure 14: fMRI results for sR+sK+sM > Fix.

Whole brain activation for face encoding versus fix. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM Template; p<.001. Crosshair at the peak voxel within the right hippocampus (24 -32 -2).

Table 8: fMRI results for sR+sK+sM > Fix

Encoding of faces (sR+sK+sM > Fix) **Region**	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Linual Gyrus	Left	-36	-88	-16		5.85
Precentral Gyrus	Right	48	2	36	6	5.41
Hippocampus	Right	24	-32	-2		5.3
Precentral Gyrus	Left	-42	6	30	6	5.16
Inferior Occipital Gyrus	Left	-44	-74	-16		5.12
Fusiform Gyrus	Right	48	-60	-14	37	5.02
Inferior Occipital Gyrus	Right	38	-90	-10	18	4.57
Middle Occipital Gyrus	Right	30	-92	0		4.42
Insula Lobe	Left	-28	26	4		4.17
Fusiform Gyrus	Left	-34	-62	-16	19	4.14
Inferior Frontal Gyrus (p. Triangularis)	Left	-46	28	18	46	4.14
Inferior Frontal Gyrus (p. Opercularis)	Right	50	14	28	9	4.11
Inferior Occipital Gyrus	Left	-26	-94	-8	18	4.09
Superior Parietal Lobule	Left	-22	-68	46	7	4.09
Inferior Frontal Gyrus (p. Triangularis)	Right	40	22	22	9	3.93
Hippocampus	Left	-18	-32	-2		3.92
Calcarine Gyrus	Left	-16	-96	-6	17	3.86
Superior Parietal Lobule, Precuneus	Right	9	-66	52	7	3.56

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

4.2.2 Retrieval

4.2.2.1 Recollection

To identify brain regions associated with recollection within the MTL, we analysed the contrast R versus K (see Fig. 15, Tab. 9). The overall brain analysis revealed greater activation for R than K in the left posterior parahippocampal gyrus (-26 -36 -16). Other corresponding regions included the left anterior cingulate cortex, left inferior frontal gyrus, left cuneus, left middle occipital gyrus and left inferior parietal lobule. Furthermore, as we had an a priori prediction that the hippocampus would be more activated during recollection than familiarity, we conducted a SVC (small volume correction) for both hippocampi. R was associated with greater activity in the left posterior hippocampus (-24 -32 -6).

As described, face processing is often associated with the right MTL, whereas our results revealed that at retrieval, only the left hippocampus showed greater activation for successful versus unsuccessful association processes. Therefore, we decided to examine the right MTL at a lower threshold. Lowering the threshold to p<0.007 revealed a greater activation within the right posterior parahippocampal gyrus as well. After lowering the significance level of the SVC, the right posterior parahippocampal gyrus (p<.007) and the right posterior hippocampus (p<0.015; (22 -30 -6)) showed the pattern of greater activation for R than K.

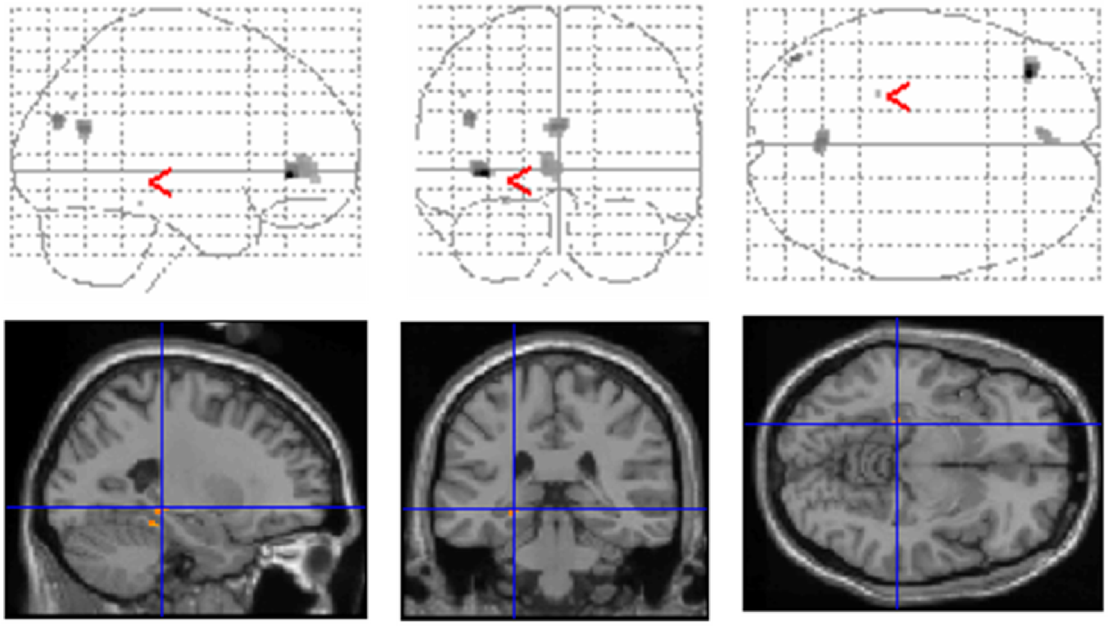

Figure 15: fMRI results for R>K.
Hippocampal activation for recollection versus familiarity during retrieval. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM Template. Crosshair at the peak voxel within the left hippocampus using small volume correction (-24 -32 -6).

Table 9: fMRI results for R>K

Recollection (R>K) **Region**	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Inferior frontal gyrus	Left	-36	38	-2	46	7.19
Middle occipital gyrus	Left	-42	-78	26	19	5.02
Cuneus	left	-2	-64	22	23	4.97
Anterior cingulate gyrus	left	-6	44	2	32	4.55
Angular gyrus	left	-46	-70	38	39	4
Parahippocampus	left	-26	-36	-16	36	3.87
Hippocampus	left	-24	-32	-6	27	3.53**

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster
**p<0.002 SVC

Comparison of Beta values for R, K, CR and M (Beta values, R 1.61 ±0.46, K -0.45 ±0.36, CR 0.47±0.36, M 0.22 ±0.46) in the left hippocampus revealed a main effect of response type F(3,52) =4.50, p<0.01 (see Fig. 16). The activation for R was greater than K (BF, t =3.57, p<0.01), whereas no other significant results were detected. Although the right posterior hippocampus did not reach statistical significance in the SPM analysis, we examined this region further, given the existing literature demonstrating right hippocampal engagement during face recognition. We calculated the beta values for R, K, CR and M based on the peak voxels for each participant within this area (Beta values, R 0.89 ±0.71, K -0.10 ±1.17 CR -0.12 ±0.93, M -0.16 ±0.99). This analysis revealed a main effect of response type F(3,52) =3.95, p<0.05. Although R did not differ from K, the activation for R was still greater than M (BF, t =2.90, p<0.05) and R was greater than CR (BF, t =2.79, p<0.05).

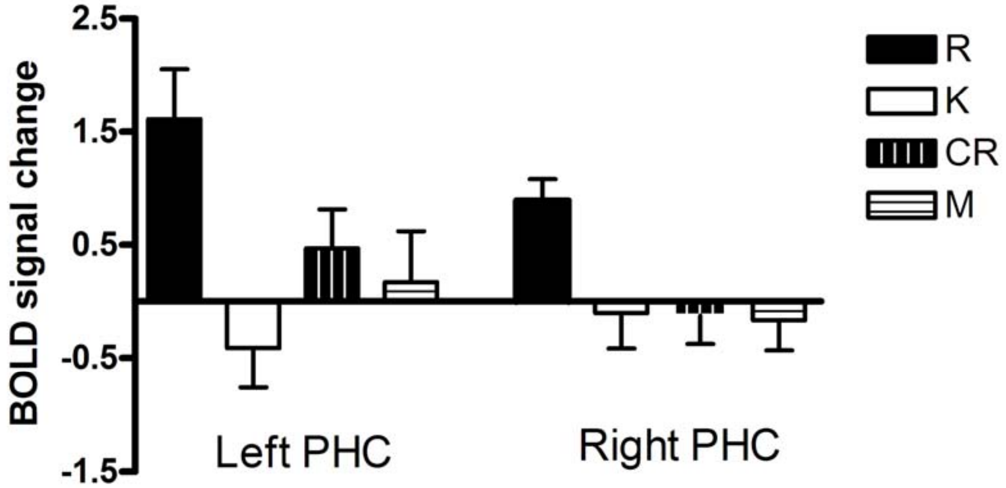

Figure 16: BOLD signal change for R>K within the posterior hippocampi.
The hemodynamic responses for each condition are modeled from an ROI (sphere, radius=2mm) around the peak voxel within the posterior hippocampus (PHC) for each subject using MarsBar. The whiskers indicate standard errors. Within the left PHC, R showed greater activation than K. Within the right PHC, R did not differ from K, but activation for R was greater than for K and M.

4.2.2.2 Familiarity

We did not find any brain region showing the opposite pattern (K>R) at p<0.001. Further, there was no MTL activation showing a greater activation for familiarity than recollection, even after lowering the threshold to p<0.02.

4.2.2.3 Other relevant findings

The following contrasts were conducted to corroborate the current literature on face memory.

4.2.2.3.1 Total Recollection Response

We conducted the contrast R versus M in order to examine the total recollection response (see Fig. 17, Tab. 10). The left hippocampus was more activated during R than M.

Other activated brain regions included the left caudate nucleus, amygdala and the right inferior frontal gyrus.

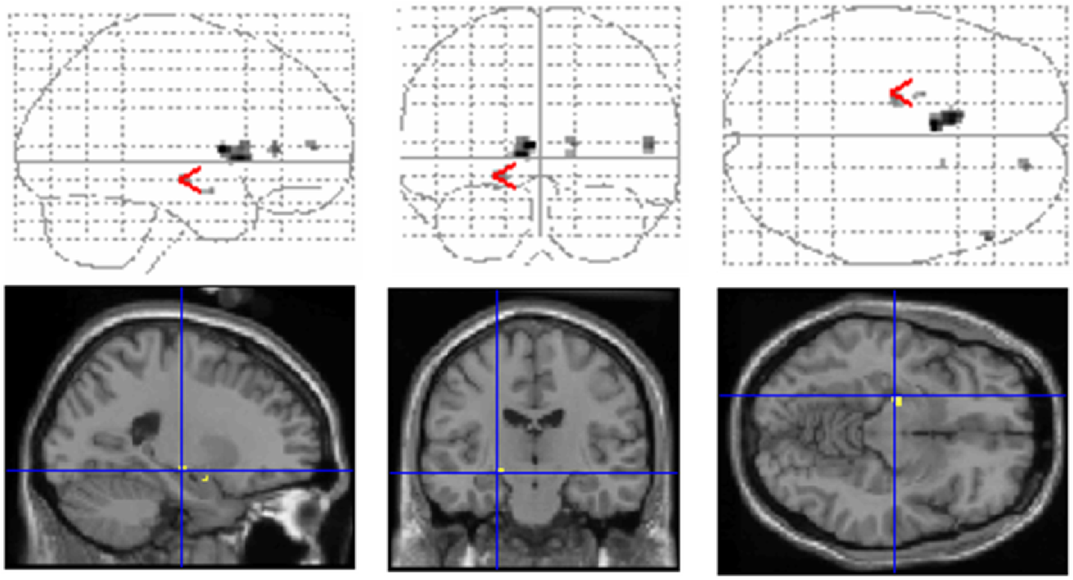

Figure 17: fMRI results for R>M.
Whole brain activation pattern for recollected versus forgotten faces during retrieval. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM template brain. P<.001, uncorrected. Crosshair at the peak voxel within the left hippocampus (-20 -14 -10).

Table 10: fMRI results for R>M

Recollection (R>M)						
Region	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Caudate Nucleus	Left	-8	14	2		5.15
Inferior Frontal Gyrus	Right	54	32	6	46	4.58
Superior Medial Gyrus	Right	16	52	8	10	4.44
Hippocampus	Left	-20	-14	-10		4.37
Amygdala	Left	-20	-4	-16	34	4.17

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

4.2.2.3.2 Total Familiarity Response

We did not find any hippocampal activation for the contrast K>M. Within the anterior parahippocampal gyrus (APHG), we did not find greater activation for CR or M than K. However, given the existing literature demonstrating greater activity for CR and M than K within the APGH, we examined this region further. At the time of retrieval, we extracted beta values for R, K, CR and M (see Fig. 18), based on the highest non-significant voxel of each subject (left APHG: K=0.91 ±0.6, CR=1.41, M±0.8, 1.5 ±1.1; right APHG: K=0.7 ±0.9, CR=1.19 ±0.9, M=1.34 ±1.1). Although these analyses did not reveal any significant effects within the right APHG (F(2,39) =1.69, p>0.05) or the left APHG (F(2,39) =2.01, p>0.05), there was a trend within the left APHG, showing greater activation for CR than K (t=1.62, p=0.06) and M greater than K (t=1.82, p=0.06).

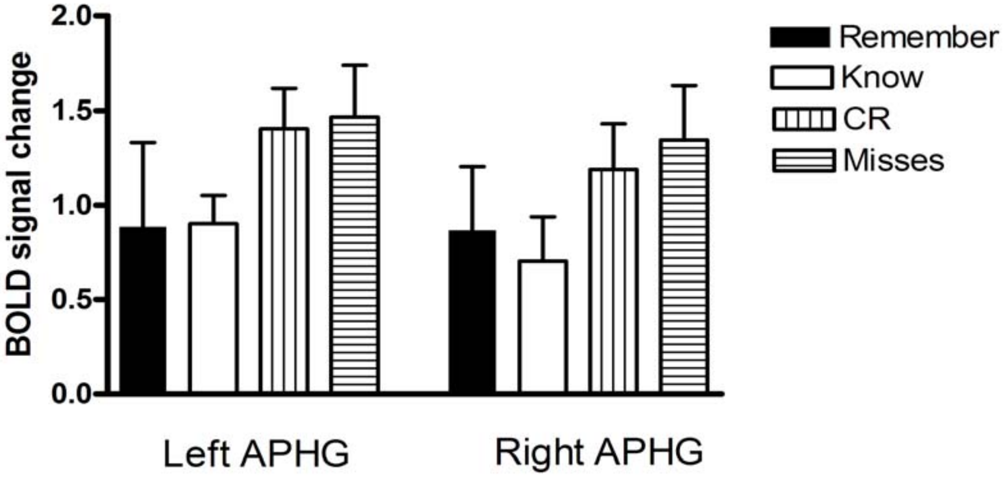

Figure 18: BOLD signal change for CR>K within the anterior parahippocampal gyri.
The hemodynamic responses for each condition are modeled from an ROI (sphere, radius=2mm) around the peak voxel within the anterior parahippocampal gyri (APHG) for each subject using MarsBar. The whiskers indicate standard errors. Within the left APHG, there was a trend showing greater activation for CR and M than K.

4.2.2.3.3 Novelty Effect

The novelty effect is described as higher hippocampal activation for new in contrast to old items. In order to examine this effect, we conducted the contrast CR versus M (see Fig. 19, Tab. 11). There was no greater hippocampal activation for new than old faces. However, there were a few regions which were more activated for CR than M. These regions include bilateral superior temporal, supramarginal gyri and the right postcentral gyrus.

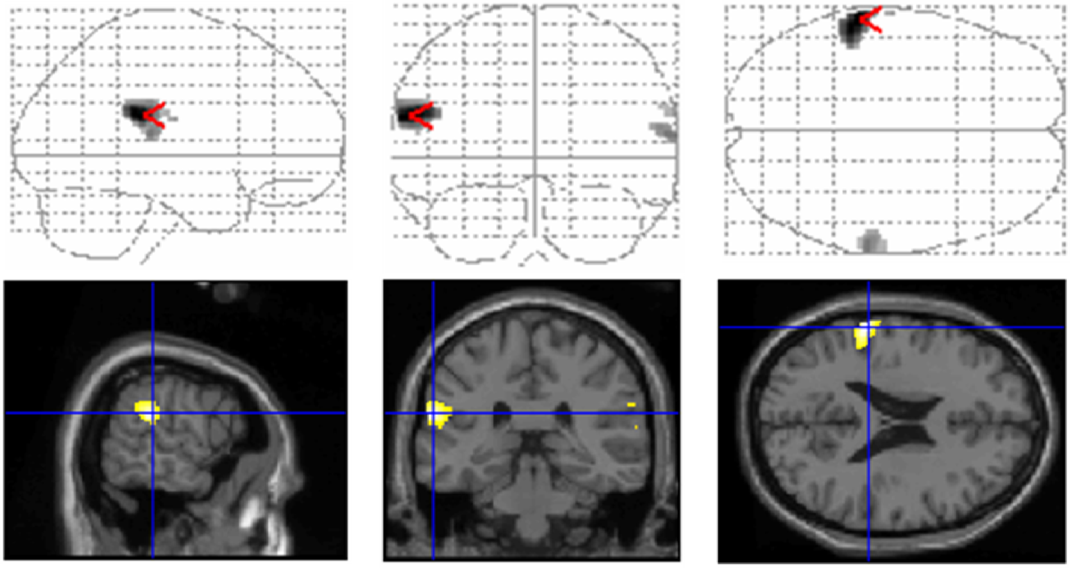

Figure 19: fMRI results for CR>M.
Whole brain activation pattern for new versus old faces during retrieval. Top panel shows acitvaion overlaid on the glass brain; bottom panel shows acitvaion overlaid on SPM template brain. P<.001, uncorrected. Crosshair at global peak voxel (-60 -32 22).

Table 11: fMRI results for CR>M

Novelty (CR>M)						
Region	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Superior Temporal Gyrus	Left	-60	-32	22	13	6.19
Superior Temporal Gyrus	Right	64	-28	12	42	4.66
Postcentral Gyrus	Left	-64	-16	20	40	4.17
SupraMarginal Gyrus	Right	64	-22	24	40	3.97
SupraMarginal Gyrus	Left	-56	-36	24	13	3.88

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

4.2.2.3.4 Retrieval of Faces

In order to examine the effect of retrieving faces, we conducted the contrast R, K, CR, M versus baseline (see Fig. 20, Tab.12).

The left hippocampus was greater activated for retrieving faces than seeing the fixation cross. In contrast to encoding of faces (see Sec. 4.2.1.3.3), during retrieval the left fusiform gyrus was more activated and there was no BOLD signal change in the right fusiform gyrus. Additionally to these MTL regions, we found elevated activation within bilateral SMA, frontal and occipital areas. Further, the left amygdala showed greater activation for retrieving faces than baseline.

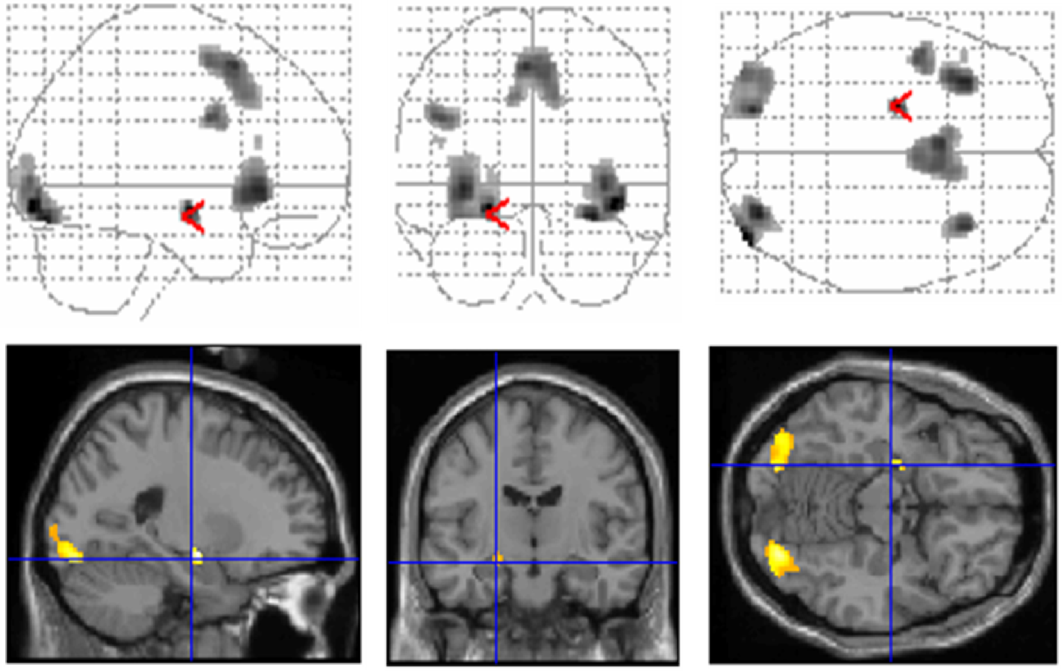

Figure 20: fMRI results for R+K+CR+M > Fix.
Whole brain activation pattern for faces versus baseline during retrieval. Top panel shows activation overlaid on the glass brain; bottom panel shows activation overlaid on SPM template brain. P<.001, uncorrected. Crosshair at the peak voxel within the left hippocampus (-20 -12 -23).

Table 12: fMRI results for R+K+CR+M > Fix

Retrieval of faces (R+K+CR+M > Fix) **Region**	**Side**	**X**	**Y**	**Z**	**BA**	**T-Value**
Inferior Occipital Gryus	Right	42	-88	-8		7.66
Amygdala	Left	-22	-8	-12		7.46
Inferior Frontal Gyrus (p. Triangularis)	Left	-34	26	-2	45	6.72
Fusiform Gyrus	Left	-20	-84	-12		6.57
SMA	Left	-4	14	54	6	6.45
Insula Lobe	Right	36	26	0	13	6.39
Hippocampus	Left	-20	-12	-23		6.32
Precentral Gyrus	Left	-46	2	30		5.92
SMA	Right	6	12	52	6	5.91
Middle Occipital Gyrus	Left	-38	-88	-6		5.59
Middle Occipital Gyrus	Right	38	-90	2		4.23

Locations (x,y,z) correspond to MNI space; BA, nearest corresponding Brodmann's areas; T-values correspond to the peak voxel within the cluster

5 DISCUSSION

The focus of the current study was to examine the role of the medial temporal lobe during encoding and retrieval of relational face memory. At the beginning of this chapter the main findings of this study will be summarized.

Then, the behavioural results will be discussed in order to analyze the reliability and validity of this data. Afterwards, the main findings of the fMRI data will be discussed separately for encoding and retrieval. One of the central advantages of the current study is that participants were scanned during both encoding and retrieval. Therefore, the main findings of encoding and retrieval of relational face memory will then be compared. At the end of this chapter, the main limitations of this study as well as future directions of research will be discussed.

Behavioural results

(1) On average 81% of the faces were recognized correctly, either as new or old. There was no difference in the accuracy for recollection and familiarity. The reaction times for recollection responses were faster than for familiarity, misses and FP responses but not for CRs.

fMRI results at the time of encoding

Subsequent recollection and familiarity:

(2) Bilateral hippocampal activation predicted whether a face was subsequently remembered or familiar. There was no MTL activation greater for sK than sR.

Other relevant findings:

(3) Bilateral hippocampal activation predicted whether a face was subsequently recollected or forgotten. However, bilateral hippocampal activation also predicted whether a face was later familiar or forgotten.

fMRI results at the time of retrieval

Recollection and familiarity:

(4) Left posterior hippocampal activation was associated with recollection, but not with familiarity. There was no MTL activation greater for familiar than recollected faces.

Other relevant findings:

(5) Left hippocampal activation was greater for recollected than forgotten faces. In contrast to encoding, there was no hippocampal activation greater for K than M or K than CR.

5.1 Behavioural Results

The overall accuracy of the participants with 81% for faces was very high. As expected there was no difference between the first and second test block (see Sec. 4.1, Fig. 6). In contrast to other methodological approaches to separate recollection and familiarity (see Sec. 1.3), we were dependent on subjective reports of the participants for recollection and familiarity responses. The major drawback of this technique is that sometimes participants might say “remember”, not because they recall any context but because the stimulus felt familiar, which might lead to a poor reliability. In the current study, we accurately trained the participants before scanning, until they understood the difference between R and K and were able to give examples for both conditions. Further, although it is not the only aspect, the level of confidence is seen as a strong predictor of recollection (Ranganath, Yonelinas et al. 2004; Daselaar, Fleck et al. 2006; Skinner and Fernandes 2007). According to this, 84% of all FPs of the current study were “false know” responses suggesting a poorer level of confidence for familiarity than recollection responses. Despite the subjectivity of our data, objective measurements can be even more inaccurate. For example, source memory paradigms only regard items as recollection on the basis of one specific aspect, i.e. whether the source is correct or incorrect. However, if the participant fails to recollect the source, this item is not regarded as recollection, even if the participant recalls other details of this item.

The reaction times (RT) for recollection responses were faster than for familiarity, misses and FP responses but not for CRs (see Sec. 4.1, Fig.7). This finding is in line with others who also report that R responses are made faster than K responses (Wheeler and Buckner 2004; Woodruff, Johnson et al. 2005; Yonelinas, Otten et al. 2005; Daselaar, Fleck et al. 2006; Dewhurst, Holmes et al. 2006; Vilberg and Rugg 2007). In contrast to these findings, neuroanatomical models propose that familiarity is supported by regions earlier in the processing stream than those supporting recollection and is therefore mediated faster than recollection responses (Yonelinas 2002), which was also shown in ERP studies (MacKenzie and Donaldson 2007; Otten 2007). The discrepancy between behavioural and neuroanatomical models remains unclear. However, in contrast to behavioural output, ERP recordings obtain a very high temporal resolution. Therefore, on the processing level, familiarity may be faster, but the confidence of an occurring recollection response may lead to a faster behavioural response than familiarity.

In the current study, we used the same set of faces for encoding and retrieval for each participant. Therefore, it might be possible that some faces were somehow different than others, so that the results could have been polluted with item-specific effects. Before including a face in this experiment, two independent persons rated a total set of 662 faces for their gender, emotionality, attractiveness, gaze direction and quality of the image. The 117 finally included faces showed mild or neutral emotionality, average attractiveness, straight gaze and good image quality. Half of the faces were females. Nevertheless, to control item specific effects we showed that the frequency of R or K responses of our stimuli followed the Gaussian distribution. This indicates that no subset of faces was rated as R or K at a higher frequency that another subset.

In summary, our behavioural results are generally in line with the current literature on recollection and familiarity.

5.2 FMRI Results

5.2.1 Encoding

The next section will discuss the results of the encoding phase of this study. First, the main findings will be illustrated and afterwards other relevant findings will be described.

5.2.1.1 Subsequent Recollection and Familiarity for Faces

The present study examined the role of the hippocampus during encoding and retrieval of successful versus unsuccessful relational memory processing. Participants were scanned while creating associations with unfamiliar faces, and later during retrieval of the faces and their associations. Based on the responses of the participants we were able to determine the faces for which they had built successful associations and for which they had a memory but no recollected associations. Accordingly to our hypothesis (see Sec. 2.1, hypothesis 1), there was greater activity in both posterior hippocampi for successful relational processing (sR) than for unsuccessful relational processing (sK). The task for every face at encoding was the same: build as many associations with the face as you can. However, already at this early stage of learning the hippocampus showed more activation for associations which were subsequently recalled than for associations which were not recalled. Our findings are in line with the current literature on associative encoding of verbal and non-verbal stimuli (see Fig. 21) (Davachi, Mitchell et al. 2003; Ranganath, Yonelinas et al. 2004; Uncapher and Rugg 2005; Kensinger and Schacter 2006; Chua, Schacter et al. 2007; Otten 2007; Uncapher and Rugg 2008). The peak voxels of our study within the posterior hippocampi for successful relational processing [(L: -22 -30 -10 and R: 26 -24 -16)] are close to other reports [(R: 26 -30 -4) (Ranganath, Yonelinas et al. 2004) and (L: -33 -21 -21 and R: 30 -9 -24) (Davachi, Mitchell et al. 2003)].

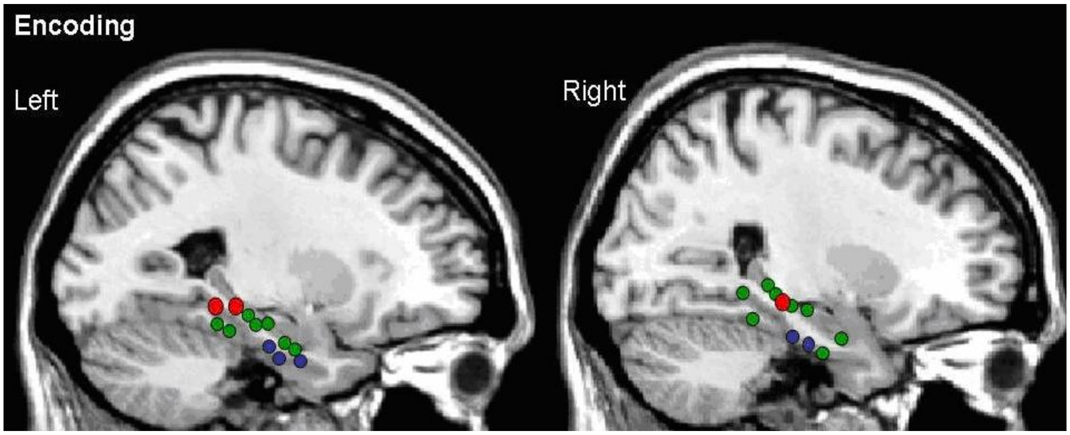

Figure 21: Comparison of relational processing in the literature and our data for encoding.
Summary of studies during encoding for subsequent recollection (green), subsequent familiarity (blue) and our encoding data (red). In order to directly compare MTL regions across studies, all Talairach&Tournoux coordinates were transformed into MNI space using the non-linear matlab function tal2mni authored by M. Brett. Note that these points demonstrate approximate locations. Some studies reported several peak voxels which are all represented by separate points. Data from: Chua et al., 2007; Davachi et al., 2002; Kensinger et al., 2006; Kirwan et al., 2004; Ranganath et al., 2003; Sperling et al., 2003.

Interestingly, the lateralization index of 0.73 indicates that the left hippocampus is more involved in sR than the right hippocampus. Based on literature of face encoding we predicted that the right MTL would be more involved than the left MTL (Haxby, Ungerleider et al. 1996; Kelley, Miezin et al. 1998). However, these studies did not examine subsequent face recollection which might make a difference. Further, in the current study, the participants were asked to build personality associations to the face. This might also involve verbal structures which are thought to be more left hemispherical (Kelley, Miezin et al. 1998; Lee, Yip et al. 2002). A recent study suggests that verbal mnemonic strategies can significantly affect the magnitude of hemispheric asymmetries of a non-verbal task (Clapp, Kirk et al. 2007). Further research will be necessary in order to distinguish between right and left hemispheric contributions to pure relational face memory.

Some studies suggest that the anterior hippocampus supports associative encoding rather than the posterior hippocampus (Sperling, Chua et al. 2003; Erk, Martin et al. 2005; Chua, Schacter et al. 2007). It might be that in our data only the posterior part of the hippocampus reached statistical significance, whereas the anterior part may show the same pattern but due to statistical power did not reach a significant level of activation. For both anterior hippocampi, we found a trend showing greater activation for successful versus unsuccessful relational encoding but clearly this was not as robust as the activation in the posterior hippocampus (see Sec. 4.2.1.1 Fig. 10).

It is of interest that during encoding, we found greater hippocampal activity for sR>sK but also sK>sM (see Sec. 4.2.1.1 Fig. 9). A few studies suggest that hippocampal activity reflects the relational load of the encoding task, i.e. the more associations are created during encoding, the more the engagement of the hippocampus increases (Henke, Weber et al. 1999; Davachi and Wagner 2002;

Addis and McAndrews 2006). Although we did not assess relational load of the created associations at encoding, it might be possible that the graded hippocampal activation reflects these processes.

Our main focus was to examine the role of the *hippocampus* during encoding and retrieval of successful versus unsuccessful relational memory processing. However, the overall brain analysis revealed other brain regions showing greater activation for successful versus unsuccessful relational processing of unfamiliar faces. Especially, the left inferior frontal gyrus is of great significance (Encoding: -48, 26, 0). Several studies showed the same effect in a similar area at the time of encoding (Ranganath, Yonelinas et al. 2004; Uncapher and Rugg 2005; Chua, Schacter et al. 2007; Otten 2007; Uncapher and Rugg 2008). Interestingly, an earlier study using effective connectivity analysis described the central role of the left inferior frontal gyrus in generating associations, a task which was also crucial in the present study (Addis and McAndrews 2006). At encoding, apart from the inferior frontal gyrus, hippocampal and parahippocampal regions, only the left amygdala was more activated during successful versus unsuccessful associative processing. This might be due to the mild emotional context of faces ((Erk, Kiefer et al. 2003; Kirwan and Stark 2004; Fenker, Schott et al. 2005), but see (Kensinger and Schacter 2006).

The contrast sK versus sR did not reveal any significant activation. Although subsequent recollection is associated with greater hippocampal activation, subsequent familiarity also activates the hippocampus (see Sec. 4.2.1.3.2). Some studies suggest that the parahippocampal areas are associated with increasing familiarity (Eichenbaum, Yonelinas et al. 2007). In some paradigms, recollection is described as the very end of the scale of increasing familiarity which then shows a linear increase for familiarity and recollection (see Sec. 1.3.2.2, Fig. 4B). As a result, by contrasting the highly familiar items with the recollected items, it would be difficult to detect a difference in parahippocampal activation. In the current study, we did not test relational load or the level of familiarity. This might be one explanation why we did not show any significant results for the contrast sK versus sR.

5.2.1.2 Other relevant findings

5.2.1.2.1 Total Subsequent Recollection

Both, sR and sK might rely on different anatomical structures, however, they are both involved in a very similar behaviour. In both cases the face was identified as being studied before. Therefore, several brain regions might be involved in both processes which cannot be identified with the contrast sR>sK. To identify the total subsequent recollection response, we analyzed the contrast sR versus sM (see Sec. 4.2.1.3.1).

As predicted (see Sec. 2.2.1, hypothesis 1), we revealed bilateral hippocampal activation. The lateralization index of 0.38 indicates that the left hippocampus is slightly more activated than the right hippocampus. This underlines the results described above, sR versus sK, however, here the lateralization index is smaller and indicates a more bilateral process.

Additionally, we found bilateral parahippocampal activation in the precunei, temporal, parietal and prefrontal areas. As briefly described in the introduction (see Sec. 1.3.2), all these regions are almost always associated with the recollection network (Cansino, Maquet et al. 2002; Kirwan and Stark 2004; Prince, Daselaar et al. 2005).

5.2.1.2.2 Total Subsequent Familiarity

As predicted (see Sec. 2.2.1, hypothesis 2), we revealed bilateral hippocampal activation for subsequently familiar faces in comparison to later forgotten faces. This finding also speaks to the importance of the hippocampus for general encoding. In accordance to the Multiple Trace Theory (MTT), any kind of encoding should activate the hippocampus, regardless of whether it will later be recollected or familiar (Nadel and Moscovitch 1997).

However, some studies observed that activity in the anterior parahippocampal gyrus (APHG) is specifically associated with familiarity at encoding (Ranganath, Yonelinas et al. 2004; Kensinger and Schacter 2006). Within the overall SPM analysis, we did not find APHG activation which was greater for unsuccessful binding (sK>sR) or total subsequent familiarity (sK>sM). However, by examining the signal change intensity for sK and sM within the APHG, our data suggest greater activation for sK versus sM. The discrepancy between the literature and our findings might be due to the very low number of participants, in addition to a lower signal intensity of the functional images within the APHG.

5.2.1.2.3 Encoding of Faces

To our knowledge, no other study examined recollection and familiarity for unfamiliar neutral faces during encoding as well as retrieval with fMRI. Therefore, a great advantage of the current study is that it allows the observer to “follow” the faces through different stages of memory, such as encoding and retrieval of face memory. As described in the introduction (see Sec. 1.4.1), face processing is thought to be dependent on the fusiform face area (FFA) (Kanwisher, McDermott et al. 1997; Kelley, Miezin et al. 1998) and face encoding on the right MTL (Haxby, Ungerleider et al. 1996; Kelley, Miezin et al.

1998). Here, we conducted the contrast sR, sK and sM versus baseline in order to examine the BOLD signal change when our participants encoded the faces.

As predicted (see Sec. 2.2.1, hypothesis 3) the FFA revealed greater activation for faces than baseline (see Sec. 4.2.1.3.3). Further, we found bilateral hippocampal activation for this contrast. Of interest, the LI of -0.84 indicates that the right hippocampus is much more involved in this process than the left hippocampus. This supports the idea that face encoding is predominantly dependent on the right MTL. On the other hand, the contrasts sR>sK, as well as sR>sM and sK>sM revealed that the left hippocampus is more engaged than the right hippocampus. The reasons for this controversy remain unclear. However, one reason might be the verbal load that comes along with more associations (Clapp, Kirk et al. 2007). Indeed, we specifically asked the participants to create verbal associations.

5.2.1.2.4 Summary

As predicted, at the time of encoding subsequently successful relational memory was to a greater extend dependent on the hippocampus than subsequently unsuccessful relational memory. We found a gradient function for this effect (sR>sK>sM) which supports the Multiple Trace Theory that the hippocampus is crucial for the formation of episodic memory.

Additionally, total sR as well as sK revealed bilateral hippocampal engagement. However, during general face encoding, we found greater right than left hippocampal engagement. This finding supports the importance of the right MTL for face encoding. However, sR and sK showed bilateral, or even more left MTL engagement. This might either be due to the verbal influence of the created associations or to a material-independent recollection network. Future research should address these questions systematically.

5.2.2 Retrieval

5.2.2.1 Recollection and Familiarity for Faces

At the time of retrieval, we found that the left posterior hippocampus was more activated when the participant reported successful retrieval of associations (R) than when the participant reported to know the face (K, i.e. without associations). Again, these findings are in line with the idea that the posterior hippocampus supports recollective or associative aspects of declarative memory at retrieval (Eldridge, Knowlton et al. 2000; Cansino, Maquet et al. 2002; Dobbins, Rice et al. 2003; Kahn, Davachi et al. 2004; Kirwan and Stark 2004; Sharot, Delgado et al. 2004; Weis, Specht et al. 2004; Wheeler and Buckner 2004; Dolcos, LaBar et al. 2005; Fenker, Schott et al. 2005; Woodruff, Johnson et al. 2005; Yonelinas, Otten et al. 2005; Daselaar, Fleck et al. 2006; Montaldi, Spencer et al. 2006; Vilberg and Rugg 2007). Our peak voxel is within the same area as other studies using words (-26 -26 -11) (Daselaar, Fleck et al. 2006), scenes (-12 -33 -3) (Montaldi, Spencer et al. 2006) and emotional faces (-33 -27 -15) (Fenker, Schott et al. 2005) (see Fig.22).

Interestingly and in contrast to our encoding results, during retrieval we found greater left posterior hippocampal activity for R>K but no difference between K>CR or K>M (see Sec. 4.2.2, Fig. 16). These findings suggest that the hippocampus is crucial for associative retrieval processes but provide no evidence that it is necessary for non-successful associative retrieval. This selective role for hippocampus in association-based retrieval is supported by a number of studies (Eldridge, Knowlton et al. 2000; Weis, Specht et al. 2004; Daselaar, Fleck et al. 2006). This finding supports the dual process theory (see Sec. 1.3) by stating different neuroanatomical areas associated with recollection and familiarity.

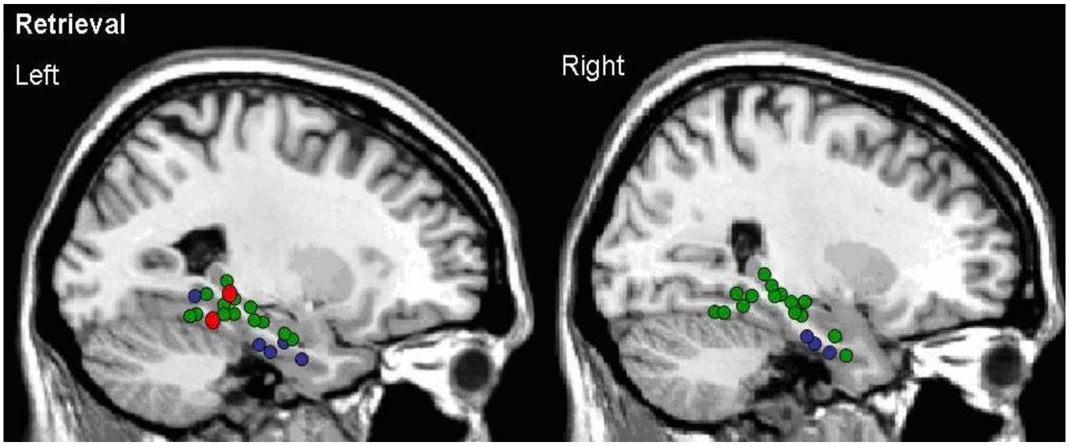

Figure 22: Comparison of relational processing in the literature and our data for retrieval.
Summary of studies during retrieval for recollection (green), familiarity (blue) and our data (red). In order to directly compare MTL regions across studies, all Talairach&Tournoux coordinates were transformed into MNI space using the non-linear matlab function tal2mni authored by M. Brett. Note that these points demonstrate approximate locations. Some studies reported several peak voxels which are all represented by separate points. Data from: Cansino et al., 2002; Daselaar et al., 2006; Dobbins et al., 2003; Dolcos et al., 2005; Eldridge et al., 2000; Fenker et al., 2005; Gonsalves et al., 2005; Kahn et al., 2004; Kirwan et al., 2004; Montaldi et al., 2006; Sharot et al., 2004; Vilberg et al., 2007; Weis et al., 2004; Wheeler et al., 2004; Woodruff et al., 2005; Yonelinas et al., 2005.

Further, in contrast to our encoding results, only the left hippocampus showed greater activation for recollection than familiarity. However, within the right posterior hippocampus, activation for R was still above activation for M (see Sec. 4.2.2, Fig. 16). These results may reflect a left-lateralization effect of recollection which occurs material nonspecifically (Denkova, Botzung et al. 2006; Denkova, Botzung et al. 2006). However, another reason could be the verbal load of associations which activates the left hippocampus more than the right (Clapp, Kirk et al. 2007).

The focus of the current study was to examine the role of the hippocampus during encoding and retrieval of relational memory. However, the overall brain analyses revealed a few other brain areas that are known to be involved in recollection. Successful relational retrieval activated the inferior frontal gyrus (Eldridge, Knowlton et al. 2000; Dobbins, Rice et al. 2003; Fenker, Schott et al. 2005; Montaldi, Spencer et al. 2006),anterior cingulate (Eldridge, Knowlton et al. 2000; Kahn, Davachi et al. 2004; Yonelinas, Otten et al. 2005; Daselaar, Fleck et al. 2006), cuneus (Dobbins, Rice et al. 2003; Fenker, Schott et al. 2005; Daselaar, Fleck et al. 2006), inferior parietal lobule (Eldridge, Knowlton et al. 2000; Wheeler and Buckner 2004; Montaldi, Spencer et al. 2006) and middle occipital gyrus (Daselaar, Fleck et al. 2006) more than unsuccessful associative retrieval.

5.2.2.2 Other relevant findings

5.2.2.2.1 Total Recollection

In order to examine the total recollection response, we analyzed the contrast R versus M (see Sec. 4.2.2.3.1, Fig. 17, Tab. 10).

As predicted, we found greater hippocampal activation for recollection than misses. Here again, it is surprising that only the left hippocampus showed this effect and leads to the assumption that recollection might be a material-nonspecific memory process (Denkova, Botzung et al. 2006; Denkova, Botzung et al. 2006).

5.2.2.2.2 Novelty Effect

The novelty effect is described as the MTL involvement of new versus old stimuli (Kohler, Crane et al. 2002; Gonsalves, Kahn et al. 2005; Kohler, Danckert et al. 2005; Daselaar, Fleck et al. 2006; Poppenk, Walia et al. 2008). These studies have illustrated that the anterior hippocampus and rhinal cortex is involved in novelty detection, whereas other surrounding cortical areas do not respond to novel items. This clear dissociation is also found in electrophysiology studies (Elger, Grunwald et al. 1997; Fell, Dietl et al. 2004). Furthermore, an fMRI study indicated a direct relation between decreased activity in the rhinal cortex and the level of perceived familiarity (Gonsalves, Kahn et al. 2005). Therefore, we conducted the contrast CR versus M in order to examine a novelty response in our data. However, we did not find any MTL activation that was greater for CR than M (see Sec. 4.2.2.3.3). The reason for this controversy remains unclear. One study showed that one region within the right hippocampus responded to the novelty of spatial and non-spatial relationships but not to the novelty of individual objects (Kohler, Danckert et al. 2005). In this sense, only the relationship between two items showed this novelty effect. In our study, however, we did not control the relationship or the associations between faces. Our results only give information about the processing of an item as new versus old. This might be one reason why we did not see any hippocampal or rhinal activation for new versus old items.

5.2.2.2.3 Retrieval of Faces

As described in the introduction, it is still controversial whether face recognition is mediated right or left hemispheric (see Sec. 1.4.1). Whereas some studies found greater activation bilaterally or in the right hippocampus and surrounding areas (Iidaka, Terashima et al. 2003; Bernard, Bullmore et al. 2004; Coleshill, Binnie et al. 2004), one study did not find any MTL activation during the retrieval of previously unfamiliar faces (Haxby, Ungerleider et al. 1996). This latter study revealed mostly prefrontal activation during face recognition.

In the current study, we found left hippocampal activation for face recognition, as well as left fusiform activity. These findings indicate that retrieval of faces, in contrast to encoding of faces, are more left lateralized. Other brain regions showing engagement in face recognition include left amygdala, bilateral SMA, occipital regions and the left inferior frontal gyrus. In our study, retrieval of faces seems to be more dependent on the left than the right hemisphere. Kavcic et al. (2003) examined the material-specific effect of encoding and retrieval of the frontal lobe and revealed that retrieval might be more bilateral or left lateralized than encoding. However, these interpretations should be taken with caution as it is not clear to which degree verbal associations might have been recalled as well.

5.2.2.2.4 Summary

At the time of retrieval, recollection was associated with greater left posterior hippocampal activation than familiarity. This finding is in line with the literature on recollection memory. Further, during retrieval we found greater hippocampal activity for R>K but no difference between K>CR or K>M. This finding suggests that the hippocampus is crucial for associative retrieval processes but provides no evidence that it is necessary for non-successful associative retrieval. In contrast to the encoding results, only the left hippocampus showed R>K. This finding may lead to the assumption that either the recollected associations were mainly verbal or that recollection is predominantly a left-hemispherical process.

5.2.3 Comparison between Encoding and Retrieval

One of the main advantages of the current study is that participants were scanned during encoding and retrieval of the face memory paradigm. The next paragraph will therefore compare the main findings from encoding and retrieval.

One of the central tenets of episodic memory theory is that of ‘encoding specificity’ (Tulving 1973) or transfer-appropriate processing (Morris 1977), which reflects the typical memory advantage shown when retrieval conditions and processes recapitulate those present during encoding. Our finding that the same region in the left posterior hippocampus is activated for successful binding (sR>sK) and subsequent retrieval (R>K) of contextual information in our face memory paradigm is consistent with that hypothesis. Thus, encoding and retrieval of episodic memory should not be viewed as two separate memory stages than can be investigated in isolation from one another (Rugg, Johnson et al. 2008).

Further, our current findings revealed that at retrieval, only the left hippocampus showed greater activation for successful versus unsuccessful relational memory. However, within the right posterior hippocampus, activation for R was still above activation for M (see Sec. 4.2.2, Fig. 16). Furthermore, we note that the right hippocampus was identified as differentially activated for successful relational encoding (sR>sK). It may be that while our encoding task (the ‘personality’ designation) engages both left and right medial temporal regions, initial binding of elements is more dependent on the right hippocampus and thus this step is undermined selectively by right medial temporal damage. Nonetheless, the scant literature on face associative memory in patients with medial temporal damage is mixed with respect to laterality (Cipolotti, Bird et al. 2006; Bird, Shallice et al. 2007; Bengner and Malina 2008) and prevalence of deficits (Moscovitch and McAndrews 2002) and so it does not permit firm conclusions.

5.3 Limitations and further directions

Even though we used a 3T MRI scanner which provides very high spatial resolution and preprocessed the MRI data, individual parameters such as head movements during scanning and anatomical differences lead to a reduced spatial resolution of the SPM activation map. Especially, small structures within the MTL, such as anterior versus posterior parts of the hippocampus, cannot be identified without some remaining doubts. In addition, due to the close anatomical relationship of air filled cavities, signal intensity of MRI data within the anterior MTL can be very low. Within the current study, we failed to show any significant signal changes within these areas (see Sec. 4.2.1.3.2 and 4.2.2.3.2). The low number of participants aggravates this problem. In order to analyze further questions about the functional involvement of these structures, it will be necessary to use methods with even higher spatial resolution. One example would be single unit recording (SUR) which allows recording and stimulation of single neurons within the hippocampus (O'Keefe and Burgess 1996; Georges-Francois, Rolls et al. 1999). In a single unit recording study, Ekstrom et al (2003) recorded single hippocampal cells responding to specific spatial locations while participants explored and navigated through a virtual town. As a result, single unit recordings will allow examining specified types of neurons within a small area.

Another drawback of fMRI studies is the low temporal resolution. In the current study, stimuli were presented for 5 sec during encoding and 3 sec during retrieval. During this period, it is not possible to exactly identify when the participants recognized a face or decided between recollection and familiarity. By using reaction times, we identified the time point where the majority of decisions were made and then placed the hrf at the beginning of each stimulus. However, high temporal resolution methods, such as EEG or

MEG will be necessary to identify temporal differences in recollection and familiarity (Guderian and Duzel 2005; Neufang, Heinze et al. 2006).

The study design of the current study was separated into two consecutive encoding-retrieval blocks. Although we did not find any statistical differences between those test blocks, there might have been learning mechanisms in respect to the task. Especially, because the recollection/familiarity response was completely subjective, it might be that attentional or learning mechanisms changed the behavioural response of the participants within the experiment. We did not control for those changes.

In the current study, there was no pre-neuropsychological testing. Therefore, there might be differences in IQ and attentional characteristics. Further, we did not quantify strength of right-handedness which might have led to lateralization differences between participants. This might have be one reason why we could not corroborate findings about strict right-hemispheric face memory. Another reason for this missing lateralization could be the verbal load of the personal associations which is associated with left hemispheric processes (see Sec. 5.2.1.1). It will be necessary to study verbal and facial memory within the same experimental setting in order to identify dissociating and overlapping structures.

The current study leads to further questions concerning the nature of recollection and familiarity and episodic memory in general. Here, we found nearly the same brain areas being activated during encoding and retrieval for relational memory processes which has been confirmed by other fMRI studies (see Sec. 1.3.2.1 and 1.3.2.2). However, it still remains unclear how the circuitry differs from encoding to retrieval. Functional connectivity analyses like partial least squares (McIntosh 1999), structural equation modeling (Buchel and Friston 1997) or dynamic causal modeling (Friston, Harrison et al. 2003) will be required to further analyze similarities and differences in hippocampal contribution to encoding and retrieval of relational episodic memory (Addis, McIntosh et al. 2004; Poppenk, Walia et al. 2008). Research on functional connectivity will be immensely important in order to understand cognitive functions in general. In contrast to univariate analyses approaches, as the current study used, multivariate analyses are designed to investigate complex spatial and temporal networks, such as encoding and retrieval of relational memory. Therefore, and especially because the pattern of regional activation is similar between both memory forms, multivariate analysis is required in order to assess the causal relationship between activated areas.

Studying human episodic memory has major implications for diagnostics and treatment in a huge variety of neurological and psychiatric diseases, such as medial temporal lobe epilepsy, dementia and schizophrenia. Especially neuroimaging, such as fMRI or PET will play a major role in future research on neuropsychiartic diseases (Takahashi, Kato et al. 2007; Simons, Henson et al. 2008; Esslinger, Walter et al. 2009). Particularly fascinating, in this sense, is the combination of PET and fMRI as a way to image neuromodulatory and functional neuroanatomical aspects of the same participant. Future research will be necessary in order to examine differences and similarities between healthy controls and patients with memory disorders by using multimodal imaging techniques.

6 CONCLUSION

Our results corroborate the theory of ‘encoding specificity’ (Tulving 1973) or transfer-appropriate processing (Morris 1977), which reflects the typical memory advantage shown when retrieval conditions and processes reinstate those present during encoding. Here, we illustrate that the posterior hippocampus was more activated during successful than unsuccessful relational processing during both encoding and retrieval. Of note, the anatomic peaks were nearly identical for the two contrasts but the magnitude of the effect was somewhat different, with a step-wise function characterizing encoding effects for recollection and familiarity relative to missed items and a binary pattern for recollection versus familiarity at recognition.

In conclusion, the present study supports the hypothesis that the hippocampus is selectively engaged in relational processing during encoding and retrieval. Furthermore, our study design enables us to assert that the posterior hippocampus in particular mediates both the binding and the reintegration of elements of an experience. In this manner, recollection, versus familiarity, can be viewed as a consequence of reinstating such operations.

ZUSAMMENFASSUNG

Der mediale Temporallappen spielt eine zentrale Rolle bei der Enkodierung und dem Abruf des episodischen Gedächtnisses, also dem Erinnerungsvermögen für Episoden/Personen aus dem eigenen Leben. Das episodische Gedächtnis umfasst zwei Arten des erfolgreichen Abrufs von Erinnerungen, Recollection (R; die bewusste Erinnerung an kontextspezifische Informationen eines vorher gelernten Inhalts, z. B. das Gesicht eines nahen Verwandten) und Familiarity/ Know (K; das Gefühl der Bekanntheit eines Inhalts, ohne dass kontext-spezifische Informationen erinnert werden, z.B. das Erkennen eines Gesichtes, ohne zu wissen, woher die Bekanntschaft kommt). Bildgebende Verfahren, wie die funktionelle Magnetresonanz Tomographie (fMRT) konnten zeigen, dass R im Gegensatz zu K von hippokampaler Aktivität abhängig ist. Bislang ist unklar, inwiefern sich diese neuronalen Areale bei der Enkodierung und Rekognition unterscheiden. Die vorliegende Studie untersucht diese Frage für das Gesichtergedächtnis.

fMRT Daten von 14 gesunden Probanden sind in dieser Studie evaluiert worden. Während der Enkodierung sollten die Probanden 2x30 Gesichter studieren und zu jedem Gesicht ein Persönlichkeitsurteil abgeben, welches insbesondere die multimodale Kontextbildung anregen sollte. Während der Rekognition (2x 30 alte, 16 neue Gesichter) sollten die Probanden angeben, ob sie sich an kontextspezifische Informationen erinnern (R) oder nicht (K).

Sowohl bei der Enkodierung als auch bei der Rekognition war der linke posteriore Hippokampus stärker für kontextreiche (R) als für kontextarme Prozesse (K) aktiviert. Der rechte Hippokampus zeigte während der Enkodierung ebenfalls dieses Aktivierungsmuster. Diese Ergebnisse deuten daraufhin, dass die gleiche hippokampale Region sowohl die Bindung, als auch die Wiederherstellung einer kontextspezifischen Erinnerung unterstützt.

ABSTRACT

The medial temporal lobe plays a central role during encoding and retrieval of episodic memory, which contains autobiographical memories. There are two different processes underlying episodic memory; Recollection (R; context specific retrieval of a previously encountered item, e.g. the face of a close relative) and Familiarity/Know (K; the feeling of knowing an item without retrieving any additional context, e.g. you know the face but you cannot remember where from). Functional magnet resonance imaging (fMRI) studies have illustrated that R is dependent on hippocampal activation, whereas K is not. However, it is still unclear, if the neuronal circuitry for R is the same for encoding and retrieval. The current study examines this question using a face memory paradigm.

Here, we used event-related fMRI data of 14 healthy right-handed participants. At study, participants assigned a ‘personality type’ (e.g. “sporty-type”) to each face to encourage formation of a multidimensional context. At recognition (two sets of 30 old, 16 new faces), R versus K decisions identified whether subjects could recall the encoding context or could recognize the face as familiar in the absence of any recollection of that context.

One region in the left posterior hippocampus showed increased activation during retrieval of context for recognized faces and during successful encoding of that context versus unsuccessful relational processing. At encoding, right posterior hippocampal activation showed the same pattern. These results suggest that the same region of the hippocampus supports initial binding and retrieval/reintegration of elements of an experience.

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ACKNOWLEDGMENT

I would like to thank Dr. Morris Moscovitch and Dr. Mary Pat McAndrews for the wonderful supervision and all the time they put into this work. I always found open doors in their institutes, when I traveled back and forth between Germany and Canada. In Hamburg, I would like to thank Dr. Christian Huber and Prof. Dr. med. Dieter Naber for the great supervision and help. Without this cooperation, this thesis would not have been possible.

Furthermore, I would like to thank the research group in Toronto. Especially, I would like to thank two persons. First, Monica Shaw who showed me how to use SPM2 and a lot of other very useful little hints and tricks. And second, Adrian Crawley who was always there if I needed technical support. Thank you, Adrian, especially for your close eye on the SPM analyses!

I would also like to thank my parents, Anne Marie and Hubert Fortmeier, for their terrific support. At some point, this way was not easy but they were always there for me. It is fantastic to have parents like you both! My lovely Canadian husband, Patrick McCormick: I would like to thank you for your support and super good English skills! And thanks to Britta Galling, a superb friend throughout the whole study of medicine.

Last but not least, I would like to thank the Friedrich-Ebert-Foundation who supported my studies since 2003. I always felt in very good hands there and I believe, without this support – ideally and financially – I would not have been able to be at this point of my career now!

Without so much help from so many different people, countries and languages, this project would not have been possible.

Thank you very much!

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