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Functional MRI Studies on Human Declarative Memory

Doctoral dissertation

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ABSTRACT

Declarative memory is defined as the conscious memory for facts and events. The medial temporal lobe (MTL) structures, *i.e.*, the hippocampus with the adjacent parahippocampal region, are considered to be critical for encoding of new events into long-term memory. The extent to which the MTL structures also participate in episodic retrieval or semantic memory is not clear. Knowledge about human declarative memory is largely based on the evidence of the behavioral studies in animals and neuropsychological studies on patients with MTL lesions or diseases such as Alzheimer's disease. Development of different functional imaging modalities, such as functional magnetic resonance imaging (fMRI), has in recent years provided tools with which to examine human memory *in vivo*.

The aim of this thesis was to establish fMRI methods suitable for investigating the functional differentiation of the MTL between and within the substructures. Three fMRI activation paradigms were created to cover various aspects of declarative memory. Verbal, visual, and visuospatial stimulus material was used to investigate memory encoding, retrieval, and recognition in a group of young control subjects. First, in the verbal fluency task, retrieval of semantically related words was challenged during listing of items belonging to a given category (Study I). Second, a visual paired-associates paradigm was used to study both episodic encoding and cued retrieval (Study II). Processing of object and spatial novelty were examined with the third activation paradigm (Studies III and IV). Functional imaging was performed using a Siemens Vision 1.5 T scanner and a T_2^*-weighted gradient echo echo-planar imaging sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast. The in-plane resolution of the functional images was 4 x 4 mm^2 and the thickness of the oblique axial slices 5 mm leading to a voxel-size of 0.08 cm^3. Based on the literature, the combined volume of the hippocampus and entorhinal, perirhinal and parahippocampal cortices of healthy control subjects is approximately 10 cm^3 indicating that the resolution of the raw images was adequate to investigate the MTL responses. The MTL data of the three paradigms were primarily analyzed at the level of individual study subjects using established anatomic criteria without spatial normalization or group-averaging, and the extent of spatial smoothing was minor. In addition, complementary data analysis was performed at the group-level.

This study showed that the MTL structures have specific functional roles in contributing to different elements of declarative memory. The anterior part of the hippocampus was involved in associative encoding of novel objects, whereas the more posterior parts of the hippocampus participated in memory retrieval and processing of the spatial relations of objects. The perirhinal cortex was activated during perception and encoding of pictures in comparison to both baseline and retrieval conditions, but no longer during cued retrieval of the missing member of the picture-pair. The parahippocampal cortex was involved in both memory encoding and retrieval. An anterior-posterior activation gradient for detection of novel objects *vs.* spatial relations among objects was observed not only inside the hippocampus but also in the parahippocampal cortex. Furthermore, the left hippocampus and parahippocampal cortex were activated during the semantic retrieval necessitated for performance of the category fluency task. In addition to the MTL responses, a wide network of cortical activation areas was observed during each of these activation paradigms.

fMRI has proved to be a valuable method for studying the contribution of the MTL structures to human memory, although the volume of the MTL is small and imaging artifacts are commonly reported. The most important new findings of this thesis concerned the functional differentiation of the hippocampus, and perirhinal and parahippocampal cortices in different aspects of declarative memory. These findings provide interesting insights into the nature of the episodic memory impairment in Alzheimer's disease, as those brain areas with the earliest neuropathological changes in the disease were activated during presentation of novel visual material and associative encoding. Advanced fMRI methods are promising tools for future investigation of the pathophysiology of memory impairment in neurodegenerative diseases.

National Library of Medicine Classification: WL 102, WL 307, WL 314, WL 705, WN 185, WT 155

Medical Subject Headings: Alzheimer disease; association learning; cerebral cortex; cognition; dementia; echo-planar imaging; hippocampus; magnetic resonance imaging; memory; memory disorders; mental recall; parahippocampal gyrus; recognition; temporal lobe; visual perception

To Jussi, Lilli and Ohto

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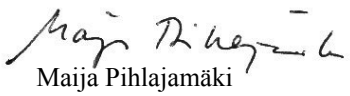

Maija Pihlajamäki

ABBREVIATIONS

AD	Alzheimer's disease
AG	angular gyrus
ANOVA	analysis of variance
B	baseline
BA	Brodmann area
BOLD	blood-oxygen-level-dependent
CA	cornu ammonis
CingG	cingulate gyrus
CingS	cingulate sulcus
circIS	circular insular sulcus
CS	collateral sulcus
DG	dentate gyrus
E	encoding
EEG	electroencephalography
EPI	echo-planar imaging
ErC	entorhinal cortex
ERP	event-related potentials
F	category fluency
FG	fusiform gyrus
fMRI	functional magnetic resonance imaging
FOV	field of view
FWHM	full width at half maximum
GE	gradient echo
GE-EPI	gradient echo echo-planar imaging
HC	hippocampus
HCa	anterior hippocampus
HCm	middle hippocampus
HCp	posterior hippocampus
IFG	inferior frontal gyrus
IFS	inferior frontal sulcus
IPL	inferior parietal lobule
IPS	intraparietal sulcus
IOG	inferior occipital gyrus
IOS	inferior occipital sulcus
IQ	intelligence quotient
ITS	inferior temporal sulcus
L	left
latOTS	lateral occipitotemporal sulcus
LG	lingual gyrus
longIG	long insular gyrus
MCI	mild cognitive impairment
MEG	magnetoencephalography
MFG	middle frontal gyrus
MP-RAGE	magnetization-prepared rapid acquisition gradient echo
MOG	middle occipital gyrus
MR	magnetic resonance
MRI	magnetic resonance imaging
MTG	middle temporal gyrus
MTL	medial temporal lobe
N	listing of numbers
CN	caudate nucleus
O	novel object
PET	positron emission tomography
PhC	parahippocampal cortex
PPA	parahippocampal place area
PrC	perirhinal cortex
preCG	precentral gyrus
preCS	precentral sulcus
preCun	precuneus
R	right; retrieval
resel	resolution element
RF	radio-frequency
ROI	region of interest
RS	retrosplenial region
S	spatial change
SD	standard deviation
SEM	standard error of mean
SFG	superior frontal gyrus
SFS	superior frontal sulcus
shortIG	short insular gyrus
SMA	supplementary motor area
SOG	superior occipital gyrus
SPECT	single photon emission computed tomography
SPL	superior parietal lobule
SPM	statistical parametric mapping
STS	superior temporal sulcus
subCG	subcentral gyrus
T_1	longitudinal (z-direction) magnetization recovery time constant
T_2	transverse (xy-direction) magnetization decay time constant
T_2^*	transverse decay time constant including magnetic field inhomogeneity effects
TE	time to echo (from the radio-frequency excitation pulse)
Th	thalamus
TI	inversion time
TR	time for repetition
WAIS-R	Wechsler adult intelligence scale, revised

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by the Roman numerals **I–IV**:

I **Pihlajamäki M**, Tanila H, Hänninen T, Könönen M, Laakso M, Partanen K, Soininen H, Aronen HJ. Verbal fluency activates the left medial temporal lobe: an fMRI study. **Annals of Neurology** 2000;47:470–6.

II **Pihlajamäki M**, Tanila H, Hänninen T, Könönen M, Mikkonen M, Jalkanen V, Partanen K, Aronen HJ, Soininen H. Encoding of novel picture pairs activates the perirhinal cortex: an fMRI study. **Hippocampus** 2003;13:67–80.

III **Pihlajamäki M**, Tanila H, Könönen M, Hänninen T, Hämäläinen A, Soininen H, Aronen HJ. Visual presentation of novel objects and new spatial arrangement of objects differentially activates the medial temporal lobe subareas in humans. **European Journal of Neuroscience** 2004;19:1939–49.

IV **Pihlajamäki M**, Tanila H, Könönen M, Hänninen T, Aronen HJ, Soininen H. Distinct and overlapping fMRI activation networks for processing of novel identities and locations of objects. Submitted for publication.

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1. INTRODUCTION

Declarative memory is what we commonly understand with the word "memory" – it is defined as the conscious memory for facts and events (Schacter and Tulving 1994, Milner et al. 1998). The brain structures of the medial temporal lobe (MTL) are considered as being necessary for learning and remembering new material. In particular, the hippocampal formation and the adjacent parahippocampal region are critical for successful encoding of new events into long-term memory (Squire and Zola-Morgan 1991, Eichenbaum 2000). Theories on the function of human declarative memory are largely based on the electrophysiological and lesion studies in rodents and monkeys (Suzuki 1999, Eichenbaum 2000, Brown and Aggleton 2001), although verbal and semantic memory functions are impossible to assess in animals which do not possess a language system equivalent to humans.

Valuable knowledge about the memory systems has been gained in neuropsychological studies on human patients with MTL lesions (Scoville and Milner 1957, Vargha-Khadem et al. 1997, Corkin 2002), although lesions that are surgically introduced or caused by variable disease states are rarely anatomically restricted to a specific brain structure. Observations in patients with early Alzheimer's disease (AD) typically presenting neuropathological changes in the MTL structures, also support a role for the hippocampal formation and parahippocampal region in consolidating new events into long-term memory (Braak and Braak 1996, Gomez-Isla et al. 1996, Kordower et al. 2001). The evidence of the memory processing that is gathered using neuropsychological testing is indirect, because the success of encoding, for example, is commonly assessed via testing of the delayed recall performance.

The development of different functional imaging modalities, such as positron emission tomography (PET), magnetoencephalography (MEG), or, most recently, functional magnetic resonance imaging (fMRI), has provided tools to examine human memory *in vivo*. Functional imaging, unlike animal studies, enables one to examine those features of memory processing that are unique to human beings. Also, unlike the neuropsychological studies, fMRI and other functional imaging modalities with carefully designed cognitive paradigms can directly investigate the separate steps involved in memory processing (Wagner et al. 1999).

There is convincing fMRI and event-related potentials (ERP) data from recent years suggesting that successful incidental or intentional memory encoding activates the parahippocampal region (Gabrieli et al. 1997, Brewer et al. 1998, Wagner et al. 1998) and also the hippocampal formation (Dolan and Fletcher 1999, Fernandez et al. 1999, Kirchhoff et al. 2000). In particular, visual presentation and encoding of scenes or other kinds of complex novel pictures, has consistently activated the MTL structures (Stern et al. 1996, Gabrieli et al. 1997, Rombouts et al. 1997, Kirchhoff et al. 2000). However, in terms of the participation of the hippocampal formation to episodic memory retrieval, the PET and fMRI findings have been controversial suggesting that there are both anterior and posterior MTL as well as hippocampal and

parahippocampal contributions to retrieval (Gabrieli et al. 1997, Lepage et al. 1998, Dolan and Fletcher 1999, Schacter and Wagner 1999). In most of the early fMRI studies on declarative memory, the parahippocampal region has been considered as one anatomic entity, and therefore, the possible role of the entorhinal and perirhinal cortices has remained unclear. Only a few fMRI studies have focused on the MTL during semantic memory paradigms and those few studies have yielded conflicting results with respect to the participation of the MTL (Schlösser et al. 1998, Daselaar et al. 2002, Maguire and Frith 2004). According to one prevailing view, well-learned semantic, or autobiographical, memories finally become independent of the MTL structures, and thus retrieval of semantic information from neocortical long-term memory storage is not necessarily thought to require the participation of the hippocampal formation or related MTL structures (Vargha-Khadem et al. 1997, Bayley et al. 2003, Manns et al. 2003b). There are also some suggestions that the involvement of MTL structures is not restricted to mnemonic processes but they also contribute to cognitive processing at the perceptual level (Murray and Richmond 2001). In general, animal studies have suggested that the individual MTL structures might have different cognitive functions (Suzuki 1996, Brown and Aggleton 2001, Eichenbaum 2001), but the evidence in humans is sparse.

In conclusion, the MTL structures are known to participate actively in declarative memory, but the precise roles of the hippocampus and the structures of the parahippocampal region in the service of human memory and, perhaps, also in other cognitive functions are currently unknown. The present series of studies was designed to establish fMRI methods — consisting of the development of activation paradigms, an imaging protocol, and data analysis — to allow the investigation of the function, and the intrinsic functional differentiation of the MTL both between and within the substructures in episodic and semantic declarative memory. One long-standing interest of our group is to investigate the neural basis of AD and therefore the activation paradigms were intended to target those anatomic structures and memory processes that are known to deteriorate during the earliest stages of AD (Hänninen et al. 1995, Juottonen et al. 1998, Laakso et al. 1998).

2. REVIEW OF THE LITERATURE

2.1. Anatomy of the medial temporal lobe (MTL)

2.1.1. The MTL structures

In macroscopic anatomic terms (Fig. 1), the MTL extends from the anterior part of the temporal pole posteriorly to the junction of the temporal and occipital lobes, where it interfaces with the retrosplenial region of the cingulate gyrus (Duvernoy 1988, Van Hoesen 1995, Duvernoy 1999). In the medio-lateral direction, the hippocampus and parahippocampal region have sometimes been viewed as the "fifth temporal gyrus" in addition to the superior, middle, and inferior temporal, and fusiform (or, occipitotemporal) gyri. The lateral boundary of the human parahippocampal region (Witter and Wouterlood 2002) lies in the collateral sulcus located between the parahippocampal and fusiform gyri. This sulcus is deep and approximately 12–15 cm long, but it is anatomically highly variable and has separate anterior and posterior parts in many individuals (Insausti et al. 1998, Pruessner et al. 2002). Functionally, the MTL structures were included into "Le grand lobe limbique" already over 125 years ago (Broca 1878). The vascular supply to the hippocampus and parahippocampal region is derived from the internal carotid artery branching to the middle cerebral and anterior choroidal arteries, and from the vertebrobasilar artery giving rise to the posterior cerebral artery (Duvernoy 1998, Huther et al. 1998). Leptomeningeal branches to MTL have also been described. The macroscopic anatomy of the MTL and related structures as visible in coronal T_1-weighted magnetic resonance (MR) images is presented in Figure 2.

The two major functional components of the MTL are the hippocampal formation and the parahippocampal region, both of which are composed of several anatomically distinct subdivisions (Suzuki and Amaral 1994b, Van Hoesen 1995, Witter et al. 2000). The subdivisions of the hippocampal formation include the hippocampus proper, the dentate gyrus, and the subiculum (Fig. 1). Hippocampus proper is further divided into three cornu ammonis (CA) fields, CA1–CA3 (Duvernoy 1988, Amaral and Insausti 1990). For simplicity, in the remainder of this thesis, the term "hippocampus" is usually used to refer to the "hippocampal formation". The parahippocampal region, in turn, consists of a set of neighboring cortical structures including the entorhinal (Brodmann area, BA, 28), perirhinal (BA 35 and 36), and parahippocampal cortices (BA 35 and 36), and the presubiculum and parasubiculum (Brodmann 1909, Witter and Wouterlood 2002, Suzuki and Amaral 2003). The lateral transitional zone between the entorhinal allocortex and the temporal isocortex that forms the medial part of the perirhinal cortex in magnetic resonance imaging (MRI) volumetric assessment methods (Insausti et al. 1998, Pruessner et al. 2002) is called the transentorhinal cortex by some investigators (Braak and Braak 1985), whereas some other authors consider the region clearly as a part of the perirhinal cortex (Van Hoesen et al. 1991).

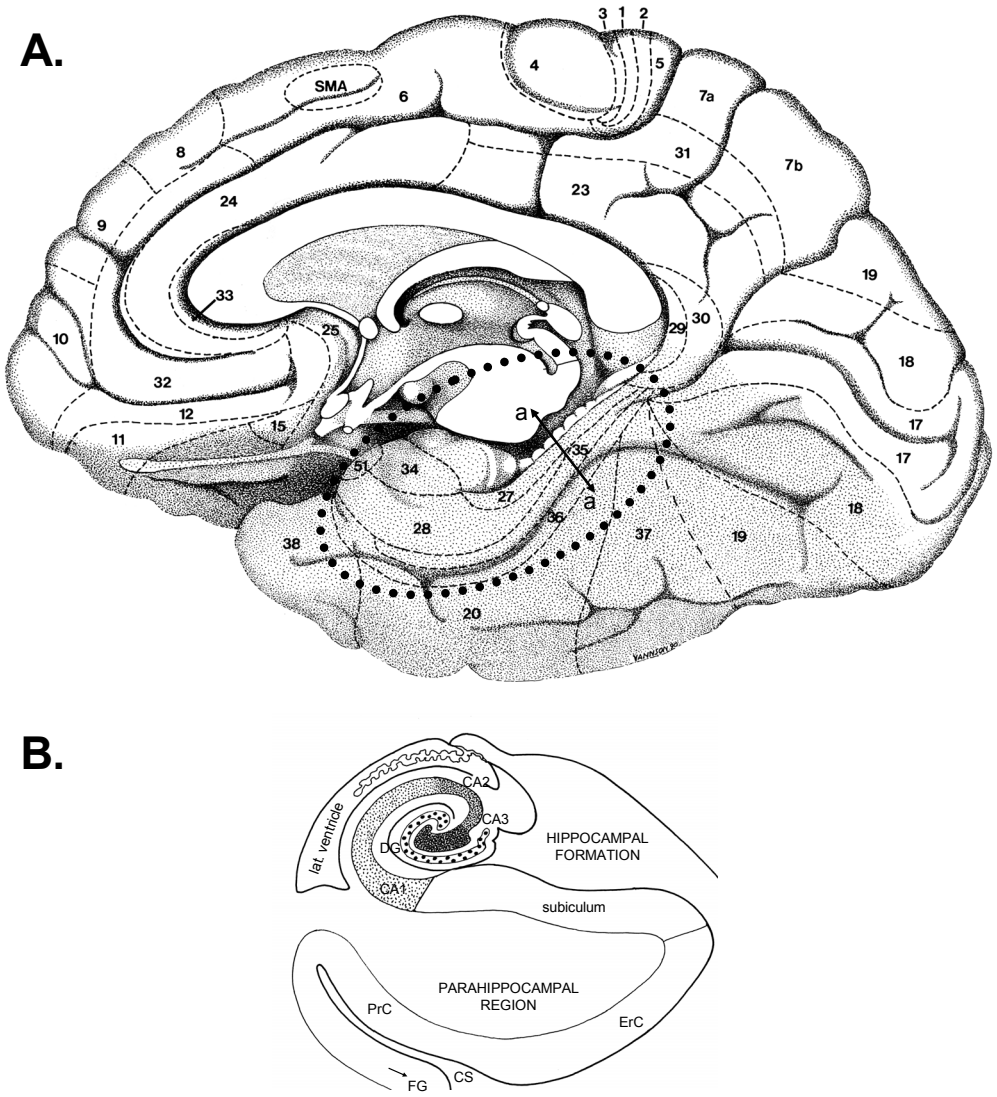


Figure 1. Inferomedial surface of the right hemisphere of the human brain with the cytoarchitectonic Brodmann areas (BA) and a transverse section through the medial temporal lobe (MTL), modified from Duvernoy 1999. The dotted line in Fig. 1A roughly delineates the main area of interest of this thesis, the MTL with its neighboring areas. The a–a line indicates the plane of the schematic transverse section through the hippocampal formation and parahippocampal region (Fig. 1B). The hippocampus is composed of two layers: the dentate gyrus (DG) and the cornu ammonis (CA) fields CA1–CA3. The parahippocampal region consists of entorhinal (ErC; BA 28) and perirhinal cortices (PrC; BA 35 and 36), and is located laterally to the subicular area of the hippocampal formation. Collateral sulcus (CS) is the landmark separating the parahippocampal gyrus from the fusiform gyrus (FG). Other BAs to mention (Fig. 1A) are BA 27 corresponding to the presubiculum, and the periamygdaloid cortex BA 34, which is considered as the most medial part of the ErC (Witter and Wouterlood 2002).

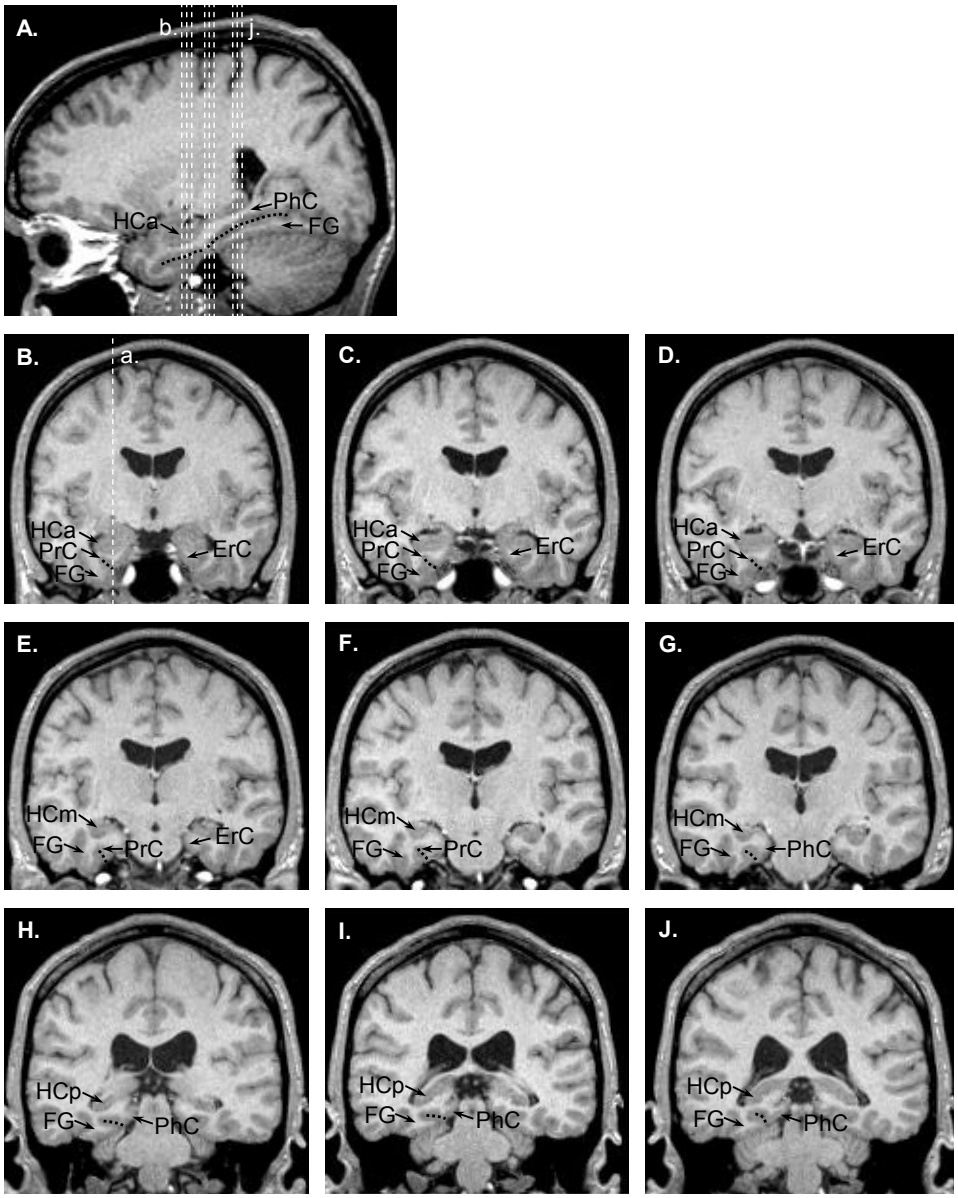


Figure 2. Macroscopic MRI-anatomy of the MTL. A T_1-weighted sagittal MR image (Fig. 2A) demonstrates the locations (lines b–j) of the corresponding coronal images B–J. The position of the sagittal image A is through line a in Fig. 2B. The coronal images are perpendicular to the intercommissural line. The head of the hippocampus (anterior hippocampus, HCa) can be seen in the most anterior coronal images B–D, and in the sagittal image A. The entorhinal cortex (ErC) is visible in images B–E, and the perirhinal cortex (PrC) in images A–F. The body of the hippocampus (the middle hippocampus, HCm) is shown in sections E–G. The tail, or the posterior hippocampus (HCp), and the parahippocampal cortex (PhC) posterior to the PrC are presented in images A and G–J, and the fusiform gyrus (FG) in images A–J. The collateral sulcus is marked with a dotted line (Duvernoy 1988, Insausti et al. 1998, Duvernoy 1999).

The parahippocampal cortex is further considered to correspond to areas TF and TH of the macaque monkey cerebral cortex (von Economo and Koskinas 1925, von Bonin and Bailey 1947, Witter et al. 1989a). Most of the human parahippocampal gyrus is occupied by the entorhinal cortex, which is surrounded by the perirhinal cortex in all but its most medial aspects (Suzuki 1996, Insausti et al. 1998). The parahippocampal cortex (proper), in turn, is situated posterior to the entorhinal and perirhinal cortices. There are no very clear-cut anatomic landmarks for distinguishing the exact borders of the perirhinal and parahippocampal, parahippocampal and lingual, or of the parahippocampal and fusiform cortices (Witter and Wouterlood 2002), but anatomic criteria that have been published for MRI volumetry of the MTL structures are used in this thesis whenever possible (Insausti et al. 1998, Pruessner et al. 2002).

2.1.2. Connectivity of the MTL

The sensory information that is initially processed in the uni- and polymodal neocortical areas is conveyed to the hippocampal formation via the parahippocampal, perirhinal, and entorhinal cortices. The largely reciprocal feedback connections of the MTL structures are then thought to project the resultant information back to the cortical areas for long-term storage (Squire and Zola-Morgan 1991, Suzuki and Amaral 1994a, 1994b, Lavenex and Amaral 2000, Witter et al. 2000, Lavenex et al. 2002). A schematic picture of the neocortical-hippocampal loop is presented in Figure 3.

The cortical input and output connections of the parahippocampal and perirhinal cortices are listed in Table 1. The most essential connections to the parahippocampal cortical area TF arise from the visual areas V4, and caudal parts of the areas TE and TEO (Suzuki and Amaral 1994a). The nomenclature of the temporal lobe subareas of the macaque monkey, such as areas TF, TH, TE and TEO, was originally proposed by von Economo and Koskinas (1925), later modified by von Bonin and Bailey (1947), and most recently by Suzuki and Amaral (2003). Other prominent afferent connections to the parahippocampal cortex are from the posterior parietal, cingulate and retrosplenial cortices (Morris et al. 1999). Further input projections to this area come from dorsal superior temporal sulcus, and from frontal, insular, and perirhinal cortices (Delatour and Witter 2002). The most intense connections to the parahippocampal area TH arise from its neighboring area TF, but interestingly TH receives almost no input from the visual areas TE and TEO. The parahippocampal connections are reciprocal to a large extent (Lavenex et al. 2002).

In contrast to the parahippocampal cortex, the perirhinal cortex has little or no connections with the posterior parietal and retrosplenial cortices. The main input connections to the perirhinal cortex arise from the unimodal visual areas TE and TEO (Suzuki and Amaral 1994a). The second most important source of input is the parahippocampal cortex, followed by the dorsal superior temporal sulcus, anterior cingulate cortex, orbitofrontal areas, and insular cortex. Interestingly, the perirhinal cortical projections are not as reciprocal as those of the parahippocampal cortex (Lavenex et al. 2002). The parahippocampal and perirhinal cortices constitute the most important sources and targets of the entorhinal cortical connections

in the monkey, although the entorhinal cortex has other direct connections as well (Suzuki and Amaral 1994b, Lavenex and Amaral 2000).

Table 1. The main cortical connections of the perirhinal and parahippocampal cortices. Strong connections are marked with "++" and other connections with "+" (Suzuki and Amaral 1994a, Lavenex et al. 2002).

	Perirhinal cortex		Parahippocampal cortex	
Cortical areas	Input	Output	Input	Output
TE, TEO	++	++	+	+
V4	+	+	++	++
Superior temporal	+	+	+	+
Prefrontal	+	+	+	+
Insular	+	+	+	+
Cingulate	+	+	++	+
Retrosplenial	–	–	++	+
Parietal	–	–	+	++

The cortical connections of the parahippocampal region have interesting functional implications. The perirhinal cortex is uniquely situated to fulfill its proposed function in high-level visual processing, such as object identification (Murray and Richmond 2001), whereas associational inputs to the parahippocampal cortex suggest a role in visual and visuospatial cognition (Bohbot et al. 2000). Since the perirhinal cortex does not have connections with parietal or retrosplenial cortices, it is not thought to have a significant role in visuospatial processing. In the diagram (Fig. 3), the perirhinal and parahippocampal cortices are at the same hierarchical level, *i.e.* the first stage on the neocortical-hippocampal system for memory consolidation. These cortical structures seem, however, to differ in terms of reciprocity of their cortical connections, although the functional significance of these differences is not known.

The final stage of the neocortical-hippocampal loop is the hippocampal formation. Connections within the parahippocampal, perirhinal, and entorhinal cortices first enable a significant integration of information that eventually reaches the hippocampus (Suzuki and Amaral 1994b, Witter et al. 2000). The strongest projection to the hippocampus, the perforant pathway, arises from layer II of the entorhinal cortex (Witter et al. 1989b, Lopes da Silva et al. 1990). In addition, the perirhinal and parahippocampal cortices have direct connections to the CA1 and subicular subfields of the hippocampal formation (Insausti and Munoz 2001). In view of its unique input of information, the hippocampal formation may contribute to the formation of new associations between novel stimuli and their spatial contexts thus forming new events, or associating facts with their semantic contexts thus forming new semantic concepts (Eichenbaum 2001, Manns et al. 2003b).

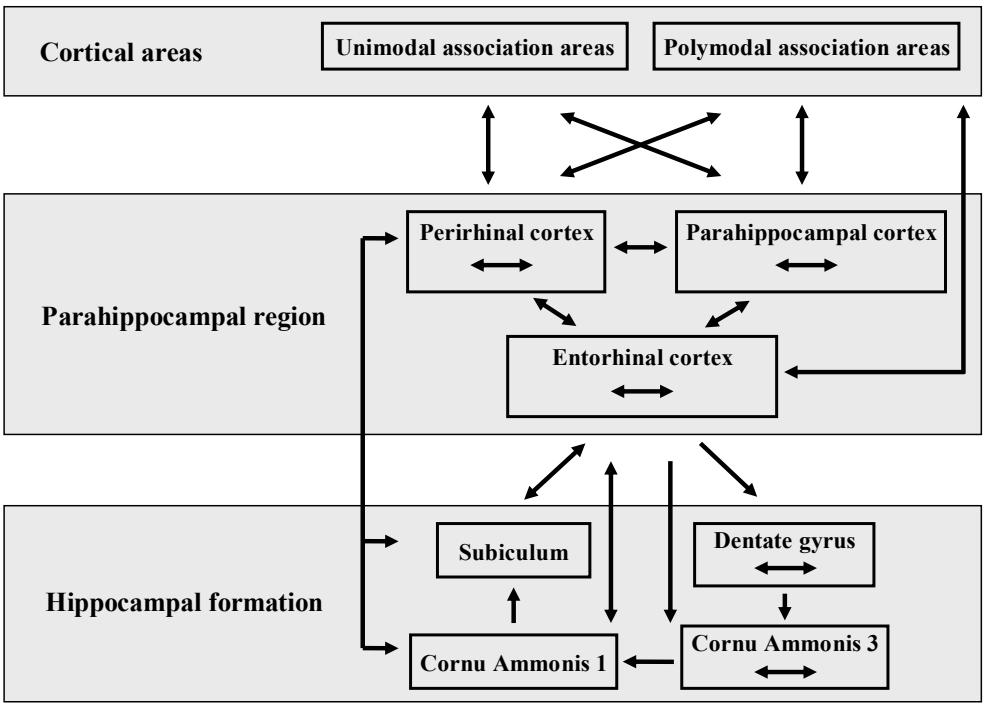


Figure 3. Cortical and intrinsic connections of the MTL in the monkey (adapted from Lavenex and Amaral 2000). The unimodal and polymodal neocortical areas send feedforward projections to the "supramodal" parahippocampal and perirhinal cortices, which present the first stage of integration of information in the neocortical-hippocampal loop. The main flow of information is further projected to the entorhinal cortex. Finally, the information reaches the hippocampal formation with its internal associational networks between the dentate gyrus, cornu ammonis -fields, and subiculum. The subiculum, via the entorhinal cortex, provides the major output route for the reciprocal connections towards long-term memory strorages supposedly located in the neocortical areas. There are important intrinsic connections in every step of this hierarchical system, for example, between and within the parahippocampal and perirhinal cortices. Direct projections from the perirhinal and parahippocampal cortices to the hippocampal formation also exist.

2.2. Declarative memory

2.2.1. Episodic and semantic memory

"Memory" refers to the mind's ability to retain and retrieve past experiences. The human brain is considered to support several different memory systems, which are thought to be supported by distinct neural networks (Baddeley and Hitch 1974, Squire and Zola-Morgan 1991, Schacter and Tulving 1994, Milner et al. 1998). The two main classes of long-term memory are declarative, or explicit, and non-declarative, or implicit, memory (Cohen and Squire 1980, Schacter and Tulving 1994, Squire and Zola 1996). Declarative memory is the kind of memory that we mean in everyday use of words such as

"memory" or "remembering". The concept of declarative memory refers to the capacity to consciously recollect facts and events. The different forms of non-declarative long-term memory abilities including habits, skills and simple classical conditioning are expressed through performance rather than via conscious remembering. The classical view on the organization of long-term memory systems and the responsible brain structures is presented in Figure 4 (Squire and Zola-Morgan 1991, Milner et al. 1998). The counterpart of the long-term memory is the short-term, or working, memory, which is largely supported by the fronto-parieto-cingulate network. The working memory system is considered to maintain and manipulate items in memory for a short while, until they are replaced by new information. The most widely accepted model of working memory divides it into three subsystems: a central executive, a visual storage system called the visuospatial sketchpad, and a verbal strorage system called the phonological loop (Baddeley and Hitch 1974, Suzuki 1999, Baddeley 2003).

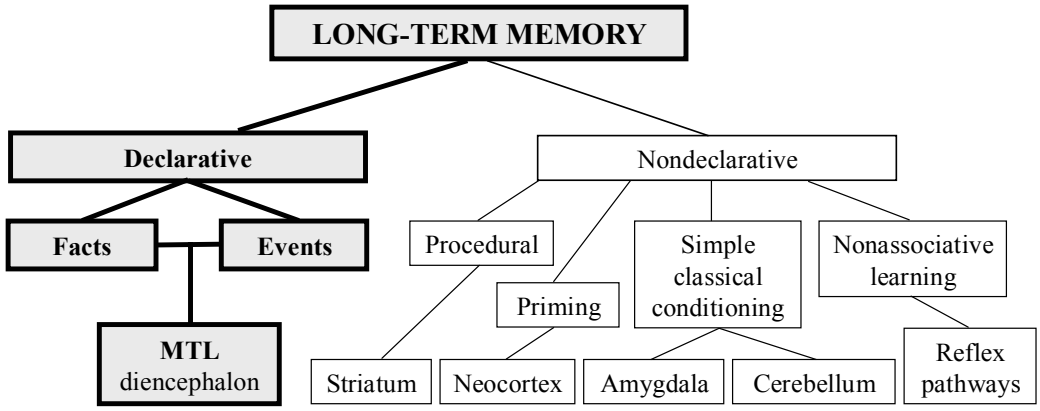


Figure 4. Classical view of the organization of the long-term memory systems (adapted from Milner et al. 1998). Different forms of long-term memory and the brain structures that are thought to support them are presented in this diagram. Declarative memory is further divided into episodic memory for events and semantic memory for facts. The role of the MTL structures, especially of the hippocampus, in episodic memory is well-established, whereas its role in semantic memory is intensively debated. Interestingly, recent fMRI studies have challenged this classical view by demonstrating hippocampal activation during implicit learning conditions (Schendan et al. 2003).

Declarative memory has been further subdivided into episodic and semantic memory components (Squire and Zola 1998, Tulving and Markowitsch 1998). Episodic memory deals with the conscious recall of specific past experiences, whereas semantic memory involves the storage and retrieval of general factual knowledge about the world. Episodic memory provides information about the "what", "when", and "where" unique personal events have happened, *i.e.* episodic memories are considered to have a specific spatio-temporal context. This is the distinguishing feature between the episodic and semantic memory, because the semantic knowledge of objects, facts and words is considered to become independent of the

original situation when it was acquired (Vargha-Khadem et al. 1997, Manns et al. 2003b). More specifically, episodic encoding refers to the initial information processing steps whereby a memory trace is created. The initial transformation of sensory input information into internal cognitive representations often engages also the memory retrieval processing of relevant, previously stored, associated knowledge. The final memory representation may thus include perceptual and conceptual components, as well as contextual details of that particular episodic event. The dichotomy of episodic and semantic memory is commonly used, although these two types of memory are often intertwined: facts are acquired in "episodic" situations at school, for example, and unique autobiographical events are understood within the reference-frame of general knowledge. In addition to episodic and semantic memory, recognition memory is a fundamental part of our ability to remember. This concept refers to the capacity for on-line identification of items together with judgment of the prior occurrence of the items that are being perceived and identified (Stark and Squire 2000a, Brown and Aggleton 2001, Murray and Richmond 2001, Manns et al. 2003a). A widely used recognition memory paradigm in animal studies is the "delayed matching-to-sample" task, in which presentation of a stimulus is followed by a delay, after which a choice is offered. In matching tasks, the originally presented stimulus must be chosen whereas in non-matching tasks a new stimulus must be identified and selected (Eichenbaum 2000).

2.2.2. The MTL in episodic and semantic memory

The MTL structures, including the hippocampus and the surrounding parahippocampal region, appear to be critical for the formation of long-term memories for facts and events (Squire and Zola-Morgan 1991, Milner et al. 1998, Eichenbaum 2000, Brown and Aggleton 2001). In early studies, the role of the hippocampus alone in declarative memory formation was emphasized (Scoville and Milner 1957, Zola-Morgan and Squire 1986), but more recent studies indicate that the surrounding cortical regions are also important for mnemonic processing (Suzuki 1996, Eichenbaum 2000, Brown and Aggleton 2001, Murray and Richmond 2001). The specific contribution of the individual MTL structures has remained elusive. Whereas many studies on patients and some studies in monkeys indicate that the severity of amnesia depends on the extent of MTL damage (Zola-Morgan et al. 1993, Rempel-Clower et al. 1996, Spiers et al. 2001), other studies point to qualitative differences between MTL subareas (Murray and Mishkin 1998, Steckler et al. 1998). It is not clear whether the MTL, or more specifically the hippocampus, has a selective role in episodic memory (Vargha-Khadem et al. 1997, Tulving and Markowitsch 1998), or whether it has a more general role in both episodic and semantic memory (Reed and Squire 1998, Squire and Zola 1998, Bayley et al. 2003, Manns et al. 2003b). These two views regarding the participation of the hippocampus in different forms of declarative memory are labeled the "episodic" and "declarative" theories of hippocampal or MTL function (Squire and Zola 1998, Tulving and Markowitsch 1998). The declarative theory of the MTL function in the consolidation of both episodic and semantic memories also includes the view that the

memories acquired a long time ago become independent of the function of the MTL structures (Bayley et al. 2003).

Behavioral and electrophysiological studies in rodents and monkeys have considerably influenced the theories about human memory. The necessity of the hippocampus and entorhinal, perirhinal, and parahippocampal cortices in declarative memory encoding and association formation is well established in lesion and electrophysiological studies in animals (Zola-Morgan et al. 1989, Sakai and Miyashita 1991, Suzuki et al. 1993, Higuchi and Miyashita 1996, Young et al. 1997, Wirth et al. 2003, Yanike et al. 2004). Specifically, the perirhinal cortex is considered to be an essential MTL structure for visual recognition memory (Suzuki 1996, Buffalo et al. 2000, Brown and Aggleton 2001, Naya et al. 2001), but it is not clear whether the importance of the perirhinal cortex in recognition memory is mainly due to its perceptual or mnemonic functions (Eacott et al. 1994, Buckley and Gaffan 1998).

Another distinction that has evolved from the animal studies is that the hippocampus supports spatial learning (Parkinson et al. 1988, Moser and Moser 1998), and the perirhinal cortex is involved in identification of objects (Murray and Mishkin 1998, Wan et al. 1999), although the findings regarding the participation of the hippocampus in object recognition are controversial (Zola et al. 2000). Animal studies have also found some differences in the functions of the anterior (or ventral, in the rat) *vs.* posterior (or dorsal) parts of the hippocampus. In rats, lesion and electrophysiological studies have suggested that the dorsal hippocampus is critical for spatial learning and memory (Jung et al. 1994, Moser and Moser 1998, Fyhn et al. 2004). Furthermore, single-unit recording studies in monkeys have more commonly detected spatial delay activity in the posterior than anterior hippocampus (Colombo et al. 1998).

The neuropsychological studies on patients with MTL lesions provide perhaps the most convincing evidence about the necessity of the MTL structures for human declarative memory (Cohen and Squire 1980), although the lesions seldom are anatomically specific. The best known amnesic patient of the neurological literature is the individual H.M., who suffers from anterograde amnesia after a neurosurgical operation to alleviate his severe epilepsy (Scoville and Milner 1957). The extent of the lesion in H.M.'s MTL structures has been verified using high-resolution anatomic MR imaging: it covered bilaterally the medial temporal polar cortex, most of the amygdaloid complex, entorhinal cortices, and anterior parts of the hippocampal formation, but portions of the perirhinal cortex and the parahippocampal areas TF and TH were spared. The caudal hippocampus was intact, although atrophic (Corkin et al. 1997, Corkin 2002). H.M. suffers from global and pervasive anterograde amnesia, which manifests as impaired acquisition of both episodic and semantic knowledge, but his short-term memory is intact. This suggests that the MTL structures are important for both episodic and semantic long-term memory, although H.M's episodic memory is essentially more impaired than his semantic learning abilities (O'Kane et al. 2004). H.M.'s language comprehension abilities are nearly normal, but, interestingly, he is impaired in verbal fluency (Schmolck et al. 2002). Surprisingly, H.M. can acquire new topographic memories (*i.e.*, a floor plan of his

home), which has been attributed to the presence of the posterior hippocampi and parahippocampal cortices. He is also able to recognize pictures based on familiarity judgements probably due to his spared parts of the perirhinal cortices (Corkin 2002).

Studies in patients with developmental amnesia caused by damage to the hippocampus early in life suggest that only the episodic long-term memory component is fully dependent on the hippocampus, because these patients can acquire factual knowledge (Vargha-Khadem et al. 1997, Tulving and Markowitsch 1998). Functional reorganization and alternative learning strategies are, however, probable to happen if the MTL damage is suffered in the early childhood. Some other authors have argued, however, that both episodic and semantic memory depend on the MTL function, since the MTL lesions seem to affect episodic as well as semantic memory (Reed and Squire 1998, Squire and Zola 1998, Bayley and Squire 2002). Recent evidence from a group of six patients with damage limited to the hippocampus bilaterally convincingly demonstrated that the hippocampus was necessary also for the acquisition of semantic knowledge (Manns et al. 2003b) and for recognition memory (Manns et al. 2003a). Additionally, these studies reported that the role of the hippocampus is time-limited such that the well-learned semantic knowledge gained long before (over 11-30 years) the onset of amnesia will remain intact.

The necessity of the MTL structures in memory encoding and association formation is established also in neuropsychological studies on other patients in addition to H.M. that have emphasized the mnemonic role of the perirhinal cortex in contrast to its purely perceptual role (Buffalo et al. 1998, Stark and Squire 2000b). Despite the strong emphasis on the involvement of the human hippocampus in episodic memory, its role in spatial processing has also been documented (Cave and Squire 1991, Bohbot et al. 1998, Astur et al. 2002), although there are also reports of subjects with hippocampal lesions that do not differ from controls in their abilities to perform spatial tasks (Spiers et al. 2001). Examination of unilateral MTL lesions has given rise to the view that right-sided lesions are associated with deficits in spatial memory or global visual processing (Doyon and Milner 1991, Bohbot et al. 2000), while left-sided lesions lead to impairment of verbal memory (von Cramon et al. 1988). There are no reports on selective anterior *vs.* posterior hippocampal lesions in monkeys or human patients, and the specific functional roles of the close connecting areas of the MTL, such as the cingulate cortex, in the service of declarative memory are not known.

2.3. Functional magnetic resonance imaging (fMRI)

2.3.1. Blood-oxygen-level-dependent (BOLD) contrast imaging

Functional neuroimaging provides non-invasive methods of mapping human brain functions *in vivo*. In these methods, electrical, metabolic or hemodynamic parameters reflecting the brain function are measured during rest and stimulation conditions, for example, and the brain areas that are more active

during stimulation are revealed by subtracting the control images from the activation images (Fox and Raichle 1986). Functional MRI is based on imaging of the endogenous blood-oxygen-level-dependent (BOLD) contrast (Ogawa et al. 1990) and is nowadays a widely used brain mapping method. The first human BOLD fMRI experiments were performed using visual and motor activation tasks and robust hemodynamic responses were observed in the primary visual and motor cortices, respectively (Kwong et al. 1992, Ogawa et al. 1992). In fact, already before the establishment of the actual BOLD fMRI method, regional changes in the blood volume of the calcarine cortex had been successfully recorded during visual stimulation using gadolinium as the intravascular contrast agent (Belliveau et al. 1991). The original idea of neurovascular coupling, which is the basic physiological feature behind the BOLD fMRI, was introduced as early as 1890 by Roy and Sherrington: "…the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with the local variations of functional activity" (Roy and Sherrington 1890).

The magnetic properties of the hemoglobin molecule in its different oxygenation states have been known since 1936; oxyhemoglobin is a "diamagnetic" agent which has little effect on its environment, whereas "paramagnetic" deoxyhemoglobin influences significantly its magnetic surroundings by introducing distortions and inhomogeneity (Pauling and Coryell 1936). Furthermore, the concept of "magnetic susceptibility" on which the BOLD contrast imaging is based was reported in 1988 (Villringer et al. 1988), although then it was achieved by using paramagnetic lanthanide chelates as the intravascular contrast medium. In the current BOLD fMRI method, the susceptibility effect of deoxyhemoglobin is the basis for the endogeneous contrast formation (Ogawa et al. 1990, Kwong et al. 1992, Ogawa et al. 1992). Despite these early reports of the basics of the BOLD fMRI, its underlying physiology is still not fully known (Sheth et al. 2004). The relation of fMRI and some other functional brain imaging methods to the stimulus-induced electrical neural activity and its metabolic and hemodynamic consequences is illustrated in Figure 5.

fMRI based on BOLD contrast imaging reflects the integrated synaptic activity of neurons indirectly via MR signal changes due to changes in blood flow, blood volume, and blood oxygen concentration in activated brain areas (Logothetis et al. 2001, Thompson et al. 2003, Sheth et al. 2004). These hemodynamic changes are commonly measured in fMRI experiments using T_2^*-weighted (*i.e.* gradient-echo) imaging sequences. In MR imaging in general, two commonly applied concepts are T_1 and T_2 relaxation times, which refer to the recovery of the longitudinal and decay of the transverse magnetization vectors, respectively, to their equilibrium values after the tilting effect of a radio-frequency pulse. The concept T_2^* relaxation further incorporates the dephasing effects of local magnetic field inhomogeneities into the concept of T_2 relaxation. Different normal or diseased tissues have different relaxation times thus creating typical tissue-specific contrasts in MR images.

During task activation, the electrical neural activity in a particular brain area causes an increase in local blood flow and a subsequent oversupply of oxyhemoglobin (Fox and Raichle 1986) thus resulting in a relative decrease of deoxygenated hemoglobin. In the presence of diamagnetic oxyhemoglobin, local field inhomogeneities are not created, the T_2^* relaxation is not enhanced, and therefore the recorded MR signal is higher during the activation than during the baseline condition (Thulborn et al. 1982, Ogawa et al. 1990, Kwong et al. 1992, Ogawa et al. 1992). Correspondingly, in the resting condition, the concentration of the paramagnetic deoxyhemoglobin is higher, which causes distortion of the magnetic field resulting in a rapid local T_2^* relaxation and further in lower signal intensities in T_2^*-weighted MR images. The positive BOLD fMRI signal during neuronal activation thus actually represents a decrease in the concentration of the paramagnetic deoxyhemoglobin.

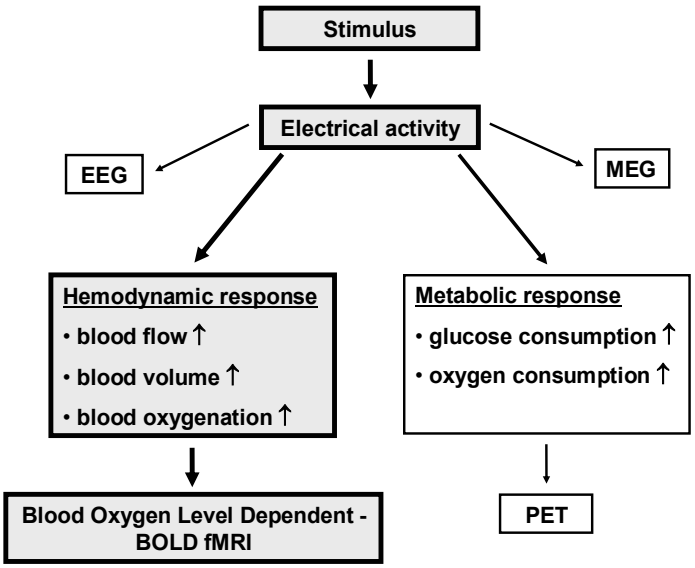


Figure 5. Metabolic and hemodynamic correlates of the brain's electrical activity. Electroencephalography (EEG) and magnetoencephalography (MEG) are methods to directly measure the electromagnetic activity of the brain, whereas positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) measure the metabolic or hemodynamic changes caused by the underlying, stimulus-induced electrical activity. In fMRI, electrical activity of neurons is considered to be translated into an increase in cerebral blood flow, which further produces an increase in blood volume and in capillary and venous oxygenation (Fox and Raichle 1986, Sheth et al. 2004).

The shape of the BOLD signal can be considered as tri-phasic with a small initial signal decrease, or "initial dip" (Ernst and Hennig 1994) followed by the main positive BOLD response, and then finally a slower post-stimulus undershoot before the normalization of the blood volume (Buxton et al. 1998, Mandeville et al. 1999, Heeger and Ress 2002, Sheth et al. 2004). The details of this hypothesized BOLD hemodynamic response function to a single stimulus are presented in Figure 6.

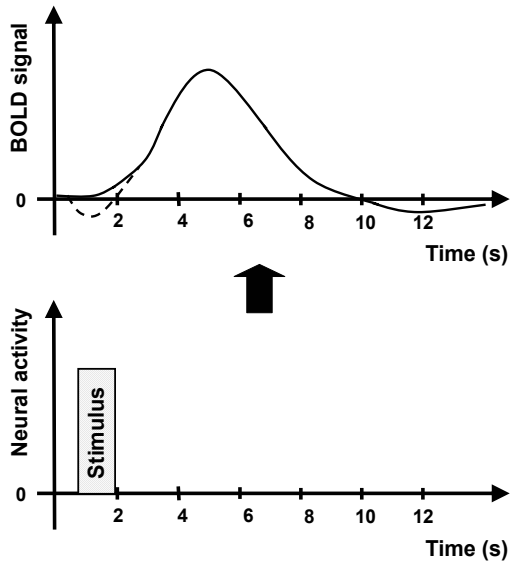


Figure 6. A blood-oxygen-level-dependent (BOLD) signal response to a single stimulus trial (Heeger and Ress 2002). The BOLD response is believed to consist of three phases. First, there is a (speculated) "initial dip" of the signal intensity below baseline level due to intravascular deoxygenation before the overcompensatory increase of cerebral blood flow. The initial dip is followed by the positive BOLD response due to oversupply of oxygenated blood and simultaneous decrease in the deoxyhemoglobin concentration of the capillary and venule beds of the activated brain area. This phase forms the main source of the BOLD fMRI signal. Finally, the slow post-stimulus undershoot is considered to be based on return of the normal blood flow but with a slow recovery of the blood volume leading again to an effective increase in deoxyhemoglobin.

2.3.2. Gradient echo echo-planar imaging

Like the common medical MR imaging, BOLD fMRI is based on the nuclear magnetic resonance phenomena (Bloch et al. 1946, Purcell et al. 1946), *i.e.* on imaging of protons of hydrogen nuclei that are abundant in water and fat of the human body (Lauterbur 1973). A little more than half of the proton spins naturally align parallel to the surrounding magnetic field (*z*-axis) creating a weak net magnetization. These lower-energy spins can be excited to a higher-energy state using radio-frequency pulses. Following this perturbating radio-frequency pulse, the spins are coherently rotating in phase and the net magnetization vector is at a given angle against the external magnetic field, thus creating a transverse (*x, y* plane) net magnetization vector. As mentioned in the previous chapter, loss of this transverse magnetization due to dephasing of spins under the influence of local magnetic field inhomogeneities is called T_2^* relaxation.

Accordingly, T_2^*-weighted imaging sequences are sensitive to the local inhomogeneities of the magnetic field created, for example, by different magnetic properties of oxy- and deoxyhemoglobin. Gradient echo (GE) sequences are suitable for T_2^*-weighted BOLD contrast imaging, because they do not

weaken the T_2^* relaxation effects. The other possibility for functional MR imaging are the spin echo sequences that may provide better localization accuracy but smaller activation-induced signal changes (Bandettini et al. 1994, Boxerman et al. 1995, van Zijl et al. 1998, Ugurbil et al. 2003). Echo-planar imaging (EPI), in turn, is a rapid functional imaging technique which is capable of forming complete sets of images after a single radio-frequency excitation pulse using a special spatial encoding method (Mansfield 1977, Stehling et al. 1991). A combination of these GE and EPI techniques, *i.e.* a gradient echo echo-planar imaging (GE-EPI) sequence is the most common sequence for BOLD fMRI purposes. A schematic picture of the GE-EPI sequence is shown in Figure 7.

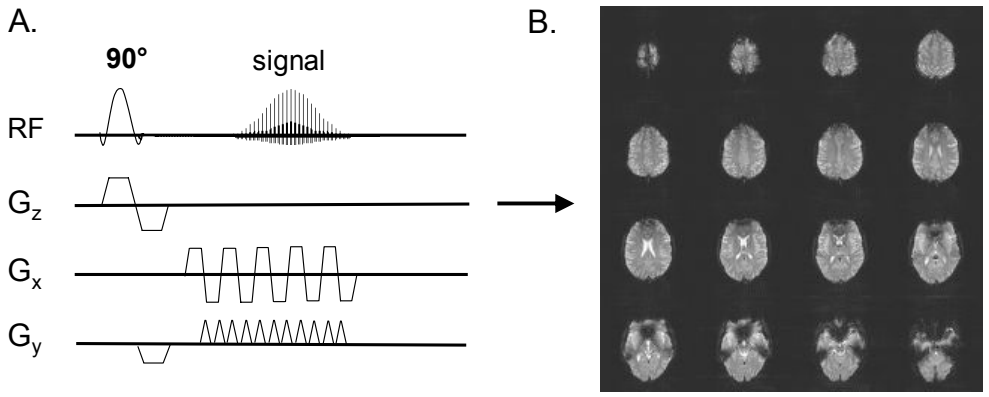


Figure 7. Gradient echo echo-planar imaging (GE-EPI) sequence. Echo-planar imaging possesses demands on the hardware of the MR scanner because it requires rapid switching of the read (G_x) and phase-encoding (G_y) gradients (A). Reversal of the applied field gradients (G_z) is used to generate the echo, hence the name gradient-echo. All the data can be collected after a single 90° radio-frequency (RF) excitation pulse. Typical resulting fMRI volume with 16 oblique axial slices is illustrated in panel B. The in-plane resolution of these functional images is 4 x 4 mm^2 and the slice thickness 5 mm.

2.3.3. Spatial and temporal resolution of fMRI

Functional MR imaging, PET, MEG and EEG are methods commonly used to assess human brain function, all of which can be exploited for both experimental and clinical purposes. They provide complementary information about the brain function in terms of their different spatial and temporal resolution properties (Tuunanen et al. 2003), although only the neuropsychological studies on patients with lesions offer convincing evidence regarding the necessity of specific brain structures for certain cognitive functions. The magneto-electrophysiological methods such as EEG or MEG can define the underlying neuronal activity in real-time, in a scale of 10–100 ms, but their spatial resolution in deep brain structures is not good (Hari et al. 2000). In contrast, high-field fMRI with optimized imaging parameters can offer a high spatial resolution in the order of 1 mm, or even less (Cheng et al. 2001), but the temporal resolution of

fMRI is in the range of seconds due to the sluggish nature of the hemodynamic response (Fig. 6). One recent study (Ogawa et al. 2000) reported, however, that evoked electrical responses could be followed by fMRI even at time scale down to milliseconds using high magnetic field strengths. Important aspects that affect the spatial resolution of the fMRI are the ability of study subjects to remain still during scanning and the overall spatial accuracy of the hemodynamic response. In the future, the spatial resolution of fMRI may be improved up to submillimeter (columnar) level using, for example, advanced perfusion-based fMRI methods or spin-echo BOLD imaging at high magnetic field strengths (Thompson et al. 2003, Ugurbil et al. 2003). An overview of the spatial and temporal resolution of different methods to study the human brain is shown in Figure 8 (Cohen and Bookheimer 1994).

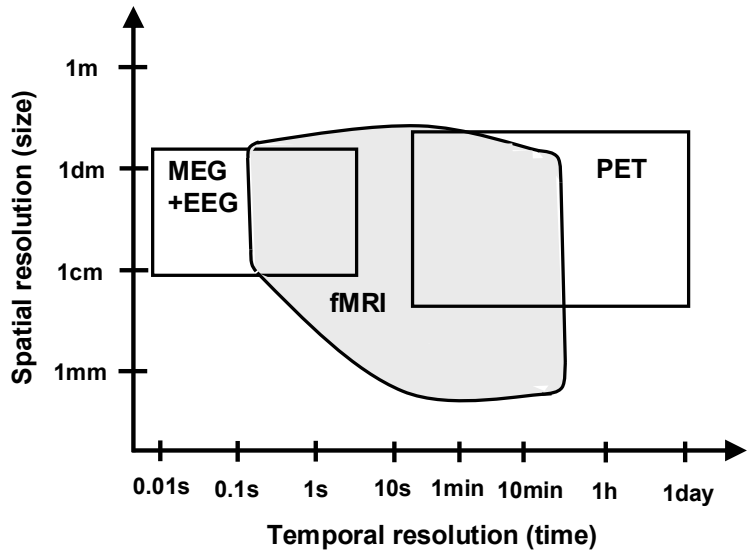


Figure 8. Spatial and temporal resolution of some functional brain mapping methods, modified from Cohen and Bookheimer 1994. Magnetoencephalography (MEG) and electroencephalography (EEG) provide excellent temporal resolution, whereas fMRI offers relatively high spatial resolution combined with a reasonable temporal resolution.

2.4. fMRI studies on declarative memory and the MTL

2.4.1. The MTL responses in episodic memory tasks

There are convincing fMRI and ERP data from recent years demonstrating that successful incidental or intentional memory encoding activates the parahippocampal region (Brewer et al. 1998, Wagner et al. 1998, Fernandez et al. 1999, Kirchhoff et al. 2000, Sperling et al. 2003a), and the hippocampal formation (Fernandez et al. 1998, Fernandez et al. 1999, Kirchhoff et al. 2000, Sperling et al. 2003a). In many of the previous fMRI studies reporting MTL activation areas, the encoding activity was located in the parahippocampal gyrus (Stern et al. 1996, Gabrieli et al. 1997, Brewer et al. 1998, Wagner et al. 1998,

Rombouts et al. 1999, Kirchhoff et al. 2000), but in several studies also in the hippocampus itself (Stern et al. 1996, Henke et al. 1997, Rombouts et al. 1997, Dolan and Fletcher 1999, Kirchhoff et al. 2000, Small et al. 2001, Sperling et al. 2001, Sperling et al. 2003a). The fMRI findings have been more controversial with respect to the participation of the hippocampal formation in episodic memory retrieval. In those earlier fMRI studies that reported MTL activations during retrieval, the area of activation was located mainly in the parahippocampal gyrus (Schacter and Wagner 1999), but recent studies have reported also hippocampal activity during retrieval. Hippocampal activations during retrieval processing have been detected, for example, during retrieval of old autobiographical events (Maguire et al. 2000), retrieval accompanied by a conscious recollection of the learning event (Eldridge et al. 2000), and during recall of face-name (Small et al. 2001) or face-house associations (Ranganath et al. 2004). In most of the early fMRI studies on declarative memory, the parahippocampal region has been considered as one single anatomic entity, and therefore, the possible specific role of the entorhinal or perirhinal cortices in memory encoding or retrieval has remained obscure. In those few functional imaging studies reporting rhinal cortical activation, the tasks have varied from successful word encoding (Fernandez et al. 1999) to incidental face encoding (Small et al. 1999).

Direct comparisons between the MTL responses to spatial and non-spatial processing have been rare. Processing of spatial information has been found to activate posterior MTL structures (Maguire et al. 1997, Epstein and Kanwisher 1998, Epstein et al. 1999, Mayes et al. 2004, Meulenbroek et al. 2004), and, in particular, a region in the posterior parahippocampal cortex that has accordingly been named as “the parahippocampal place area” or PPA (Epstein and Kanwisher 1998, Epstein et al. 1999, Ranganath et al. 2004). The parahippocampal responses during spatial processing have often been bilateral (Aguirre and D'Esposito 1997, Epstein et al. 1999, Shelton and Gabrieli 2002), but sometimes also right-sided unilateral responses have been reported (Johnsrude et al. 1999, Mayes et al. 2004).

Some previous functional imaging studies have pointed to functional differences along the long axis of the hippocampus based, for example, on the familiarity of the stimuli (Dolan and Fletcher 1999). Posterior hippocampal responses have been found to be related with increasing stimulus familiarity (Strange et al. 1999), whereas anterior hippocampal responses are suggested to occur during viewing of novel visual stimuli or novel associations (Stern et al. 1996, Rombouts et al. 1997, Sperling et al. 2001, Strange et al. 2002, Sperling et al. 2003a, Zeineh et al. 2003, Bernard et al. 2004), or during active maintenance of novel information (Ranganath and D'Esposito 2001, Stern et al. 2001). Interestingly, one recent PET study (Köhler et al. 2002) reported anterior hippocampal activation also when subjects viewed novel scenes. Overall, the findings of the contributions of the individual MTL structures for memory encoding, retrieval and recognition of different stimulus-modalities are not comprehensive, but are sometimes even conflicting.

2.4.2. The MTL responses in semantic memory tasks

There are few functional imaging studies that have addressed the participation of the MTL in semantic memory, and even those have described somewhat conflicting results. Some studies have reported MTL activation during semantic processing (Vandenberghe et al. 1996, Otten et al. 2001, Bernard et al. 2004) or classification (Daselaar et al. 2002) tasks, but many other studies investigating different aspects of semantic memory have not found any MTL activity (Mummery et al. 1999, Cabeza and Nyberg 2000, Martin and Chao 2001). This inconsistency may partly be explained by differences in the memory tasks, especially with regards to semantic retrieval or classification paradigms where encoding processes are often intertwined (Buckner et al. 2001). In contrast, several functional imaging studies lend support to the view that semantic memory performance is dependent on the function of the left prefrontal and anterior and lateral temporal cortices (Vandenberghe et al. 1996, Maguire et al. 2000, Wagner et al. 2001). One specific category of neuropsychological tasks that investigates semantic memory is verbal fluency tasks (Lezak 1995), which traditionally are considered to assess frontal lobe functions. This view is also supported by functional imaging studies demonstrating consistent activation in the left prefrontal cortex during verbal fluency tasks (Parks et al. 1988, Phelps et al. 1997, Schlösser et al. 1998, Gurd et al. 2002, Amunts et al. 2004), whereas the importance of the MTL structures for normal performance in fluency tests is unclear. Interestingly, patients with early AD are often impaired in verbal fluency tests (Hänninen et al. 1995), which indirectly suggests that successful performance in category fluency, for example, might require intact function of the MTL structures.

2.5. Clinical implications to Alzheimer's disease (AD)

2.5.1. Neuroimaging of the MTL in early AD

Clinical interest in the MTL and in the entorhinal and perirhinal cortices, in particular, is based on the fact that the earliest neuropathological changes (*i.e.* neuronal loss and neurofibrillary tangles) in AD are usually found in the transentorhinal cortex (Braak and Braak 1996, Gomez-Isla et al. 1996, Kordower et al. 2001). According to structural MRI studies, a remarkable loss of entorhinal and perirhinal cortical volumes is observable already in patients with early AD (Juottonen et al. 1998, Bobinski et al. 1999, Killiany et al. 2000) or even earlier in patients with mild cognitive impairment (MCI) (Korf et al. 2004, Pennanen et al. 2004). After the earliest neuropathological changes in the transentorhinal region, AD progresses to the hippocampus, and subsequently to the neocortical temporal lobe areas such as the fusiform gyrus (Braak and Braak 1996, Laakso et al. 1998, Convit et al. 2000, Visser et al. 2002). In contrast, the frontal lobes are considered to be relatively spared in the early stage of AD in terms of distribution of histopathological changes, volume loss, or perfusion deficits (Braak and Braak 1996, Lehtovirta et al. 1996, Sandson et al. 1996, Johnson and Albert 2000). The PET imaging findings in early AD or MCI describe the most

consistent pathological changes in the MTL projection areas such as the posterior cingulate, retrosplenial or parietal regions (Minoshima et al. 1997, Herholz et al. 2002, Nestor et al. 2003a). Recent fMRI studies, in which the MTL activation findings of the early AD patients have been compared with the findings of elderly normal subjects, have reported diminished entorhinal (Small et al. 1999), or hippocampal and parahippocampal (Rombouts et al. 2000, Machulda et al. 2003, Sperling et al. 2003b) BOLD responses, whereas one very recent study described a compensatory increase of the MTL activation in MCI subjects (Dickerson et al. 2004).

2.5.2. Neuropsychology of early AD

A progressive memory decline is the earliest sign of AD in most patients. In neuropsychological tests, the early stages of AD are typically accompanied by deficits in delayed recall performance (Moss et al. 1986, Albert 1996, Chen et al. 2000). In memory tests, the procedures that control for acquisition during the learning phase have consistently proved to be good discriminators between subjects with early AD and non-demented controls (Grober et al. 1988, Petersen et al. 1994, Welsh et al. 1994). Impairment in paired-associates learning was found to predict development of probable AD in cognitively normal individuals as early as 10 years before the disease (Elias et al. 2000). Recent evidence suggests that the memory deficit at this transentorhinal early stage of AD (Braak and Braak 1996), is due to impaired consolidation into long-term memory rather than accelerated forgetting (Carlesimo et al. 1995, Christensen et al. 1998). The neuropathological and neuropsychological changes in early AD thus further support a role for the hippocampal formation and parahippocampal region in the consolidation of new events into long-term memory. In addition to the episodic memory tests, the verbal fluency tests are among the best neuropsychological tests to diagnose and predict AD (Masur et al. 1994, Hänninen et al. 1995). A category fluency task is even incorporated in the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) protocol for diagnosing and staging AD (Monsch et al. 1992, Welsh et al. 1992). The cascade of progressing neuropathological changes (Braak and Braak 1996) is concomitantly followed with gradual deterioration of other neuropsychological functions such as visuospatial and executive functions and semantic memory (Kanne et al. 1998, Huang et al. 2003, Lambon Ralph et al. 2003).

3. AIMS OF THE STUDY

The general aim of this thesis was to establish fMRI methods — consisting of development of activation paradigms, an imaging protocol, and data analysis — suitable to investigate the normal function of the human MTL. These fMRI methods were used to examine functional differentiation of the hippocampus and parahippocampal region in different aspects of human declarative memory. Because of the long-standing interest of our group in investigating the neural basis of AD, the activation paradigms were aimed to target those elements of memory that are known to deteriorate during the earliest stages of AD.

The specific aims of studies I–IV were

1. To investigate whether the MTL participates in retrieval of semantically related words during a verbal fluency task (Study I).

2. To examine the neural correlates of visual associative encoding and retrieval during a paired-associates task (Study II).

3. To determine whether the human perirhinal cortex and hippocampus are differentially involved in processing of object and spatial novelty as has been reported in animals (Study III).

4. To reveal the whole-brain networks that support processing of object and spatial novelty (Study IV).

4. SUBJECTS AND METHODS

4.1. Subjects (Studies I–IV)

Fourteen young healthy subjects (7 males; age range 21–36 years) participated in Study I, and twelve of these in Studies II–IV (Table 2). The two subjects (Subjects S3 and S13 in Table 2) who were the first to be scanned in this series performed only the Category Fluency Task, because the other two tasks were not finished at that time.

Table 2. Details of the study subjects. Fourteen subjects participated in Study I, and twelve in Studies II–IV. Verbal, performance, and total intelligence quotients (IQ) were assessed in a separate neuropsychological testing session, as well as delayed recall of a word list learning test (Wechsler 1981). The behavioral results 1) for the Category Fluency task are given as the number of animal names produced per 60 s, 2) for the Paired-Associates Task as the number of correct choices (out of eight choices) in a forced choice recognition task, and 3) for the Object *vs*. Spatial Novelty Task as the number of correct answers (out of 75 choices).

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14
Subjects														
Study I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Studies II–IV	+	+	–	+	+	+	+	+	+	+	+	+	–	+
Age	21	23	23	25	27	27	27	27	28	25	24	29	36	22
Sex	M	F	F	F	F	M	M	M	F	F	F	M	M	M
Neuropsychology														
Verbal IQ	123	117	128	118	132	118	108	114	126	119	108	114	129	117
Performance IQ	100	107	125	106	116	112	123	106	115	112	116	103	130	126
Full scale IQ	114	114	129	114	127	117	116	111	123	117	112	110	132	123
Delayed recall %	100	80	100	100	100	78	70	100	100	90	100	88	90	89
Post-scan testing														
Categ. Fluency	20	21	24	25	24	22	26	27	28	24	23	26	27	28
Paired-Assoc. / 8	4	8	–	8	8	7	5	8	8	7	8	8	–	8
Obj. vs Spat. / 75	52	75	–	74	75	75	75	72	75	69	73	75	–	75

All subjects were right-handed, had no history of neurologic or psychiatric disease, and had normal vision. Subjects gave written informed consent to participate in the study after an explanation of the study protocol. The study was approved by the Ethics Committee of the Kuopio University Hospital (133/1998). The three fMRI paradigms, *i.e.* the Category Fluency Task (Study I), the Paired–Associates Task (Study II) and the Object *vs.* Spatial Novelty Task (Studies III–IV), were presented to the subjects during the same imaging session always in the same order (Fig. 9).

4.2. fMRI activation paradigms

4.2.1. The Category Fluency Task (Study I)

Verbal fluency tasks are widely-used neuropsychological tests that measure the number of words produced within a given time frame and within a restricted category (Lezak 1995). The most common forms of verbal fluency tests are category fluency and letter fluency, in which, correspondingly, the essential component is either retrieval of semantically- or lexically-associated words from long-term memory storages. The verbal fluency performance is impaired in AD (Monsch et al. 1992, Masur et al. 1994), and therefore we were interested to develop an fMRI modification of the category fluency task (Morris et al. 1989, Welsh et al. 1992). In the task design, the category fluency was contrasted with orderly listing of numbers, which represents an easier retrieval process that requires no associative component. The Category Fluency paradigm (Fig. 9A) consisted of two different conditions: 1) during the category fluency condition, subjects had to covertly retrieve as many words as possible belonging to the category defined in the preceding instruction slide. Categories were of both living and non-living items (clothes, animals, furniture, plants, and food); 2) during the baseline block, the subjects were instructed to covertly list numbers, starting from the number one. A black cross-hair was present on the screen for fixation during both of the task blocks. Task performance was further controlled after the imaging session with the 60-second animal naming task (Morris et al. 1989) in order to estimate the behavioral performance of the subjects during scanning (Table 2).

4.2.2. The Paired-Associates Task (Study II)

The Paired-Associates Task (Fig. 9B) was developed to examine the neural correlates of intentional visual associative encoding and retrieval. During the baseline condition, two familiar, randomly alternating picture-pairs were presented. During the encoding condition, eight novel picture-pairs consisting of complex colorful pictures were shown to the subjects, whereas during the subsequent retrieval condition, either the right- or left-sided picture was replaced with a question mark and the other member of the pair was given as a cue. The order of picture-pairs was mixed during retrieval, and the right-left location of the question mark was balanced. A delay period, consisting of the familiar baseline picture-pairs, separated the encoding and retrieval conditions. The instructions for the task were presented immediately before the task: For the encoding and retrieval conditions, the subjects were instructed to try to "memorize the novel picture-pairs" and to "remember the other member of the pair when seeing the cue picture", correspondingly. For the baseline condition, they were instructed to "only follow the familiar picture-pairs". After, the imaging session, the task performance was further controlled with a forced–choice recognition test (Table 2).

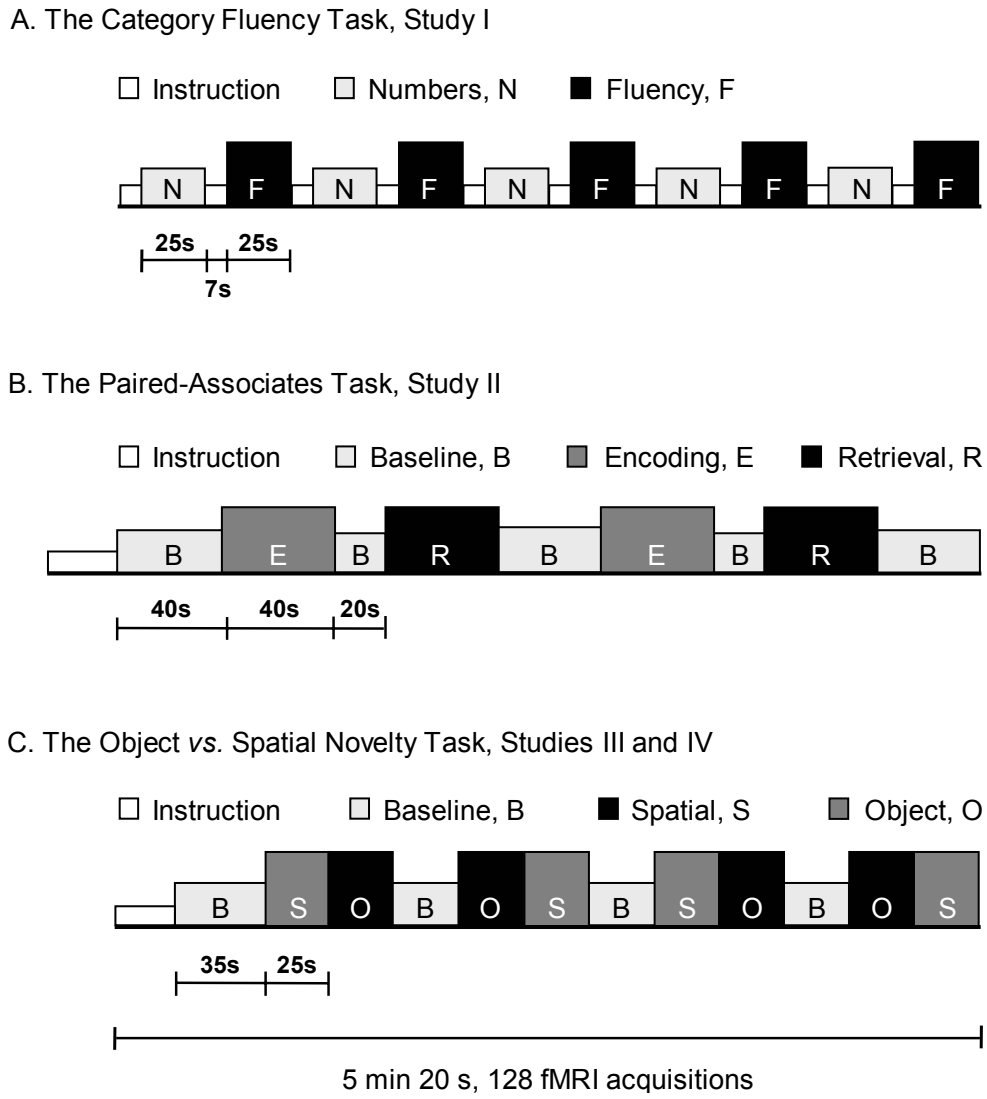


Figure 9. Overview of the three activation paradigms. In the Category Fluency Task (Fig. 9A), the duration of the category fluency (F) and baseline conditions with orderly listing of numbers (N) was 25 s. The instruction slides for the next category, or alternatively, for listing of numbers, were shown for 7 s. The Paired-Associates Task (Fig. 9B) consisted of three different conditions: baseline (B), encoding (E), and retrieval (R). The duration of the encoding, retrieval and baseline conditions was 40 s, except the shorter 20 s- baselines that served as delay periods before the next retrieval condition. In the Object *vs.* Spatial Novelty Task (Fig. 9C), the first baseline (B) period was longer (35 s), whereas the other baselines as well as the novel object (O) and spatial change (S) conditions were 25 s. Total functional scanning time was 5 min 20 s per task corresponding to 128 fMRI acquisitions with time for repetition (TR) of 2.5 s. One set of 128 fMRI acquisitions was collected per task and the order of the tasks was always the same.

4.2.3. The Object *vs.* Spatial Novelty Task (Studies III–IV)

The Object *vs.* Spatial Novelty Task (Fig. 9C) was designed in order to study whether the MTL structures and the whole-brain networks along the ventral and dorsal visual streams, and prefrontal, cingulate and temporal neocortical areas are differentially engaged in processing of novel identities and locations of objects. The visual stimuli consisted of gray-white 3 x 3 background grids containing five colorful pictures of concrete verbalizeable objects. The actual stimuli were always followed by a fixation stimulus consisting of empty grids with a small fixation cross in the middle square. The task consisted of three different conditions: a baseline condition with five familiar objects always in the same spatial order; a spatial change condition (S) with the five familiar objects in new spatial arrangements; and a novel object condition (O) with same spatial arrangement but a novel object among the four familiar objects. Within each spatial change and novel object block, 4 of the 6 single trials were altered S or O patterns, and two of the six were familiar B patterns. The presentation order of the single patterns was pseudorandom and the order of the blocks counterbalanced. This variant of blocked-type activation task was used to prevent the strong expectation of the stimulus type. Before the task, an instruction slide was presented, where the subjects were instructed to "carefully look at the pictures of objects and their arrangement, and to maintain gaze fixation in the center of the grid". Task performance was controlled with an identical visuospatial task after scanning; *i.e.*, further 12 blocks of six stimuli were readministered to the subjects, and the subjects were asked to indicated whether they recognized the S/O changes in the patterns (Table 2).

4.3. fMRI data acquisition

Functional MR imaging was performed during December 1998 and January 1999 on a Siemens Vision 1.5 T scanner (Erlangen, Germany) equipped with an EPI capability. A circular-polarized head-coil was used and the head was stabilized with foam rubber pads to minimize head movement. Functional images were collected using a T_2^*-weighted GE-EPI sequence sensitive to BOLD contrast [time for repetition (TR) = 2550 ms in Study I; TR = 2500 ms in Studies II–IV; time to echo (TE) = 70 ms, flip angle = 90°]. During the fMRI session, 128 sets of 16 oblique axial slices were acquired parallel to the intercommissural line [slice thickness = 5 mm; interslice gap = 1 mm; in-plane resolution = 4 × 4 mm^2]. The volume of the voxels of the raw data was 0.08 cm^3. The combined volume of the hippocampus and entorhinal, perirhinal and parahippocampal cortices of healthy subjects is approximately 10 cm^3 indicating that our imaging resolution was sufficient to investigate the MTL responses. The relatively large voxel-size was expected to provide a reasonable signal-to-noise ratio. High-resolution anatomic images were acquired as a set of 180 contiguous sagittal slices using a T_1- weighted magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence [TR = 9.7 ms; TE = 4.0 ms; inversion time (TI) = 20 ms; flip angle = 10°; in-plane resolution = 1 x 1 mm^2]. The visual stimuli were generated using a laptop computer located

outside the scanning room (Fig. 10). The timing of the stimuli in relation to the functional MR imaging was manually synchronized. The stimuli were projected to the subjects by a video projector (Lite Pro 620, In Focus Systems Inc, Wisconville, OR). Behavioral responses were not collected during functional MR imaging. The duration of one set of 128 fMRI acquisitions was 5 min 20 s (Fig. 9). The total duration of the fMRI session was approximately 30 min consisting of acquiring of the localizer images, anatomic images (6 min 51 s), three sets of functional images (3 x 5 min 20 s) and time to adjust the MR scanner between the functional acquisition sets.

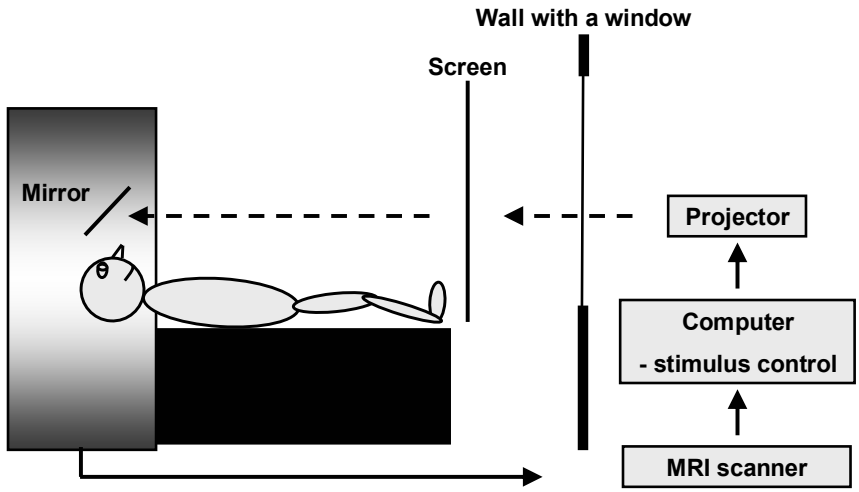


Figure 10. Experimental setup in an fMRI session. The visual stimuli were generated using a laptop computer located outside the scanning room, and projected to the subjects by a video projector via a semitransparent screen. The stimuli were presented in central vision (horizontal visual angle 9.4° and vertical 7.6°) and viewed by the subjects through a mirror positioned on the head coil.

4.4. fMRI data analysis

Image processing was performed using MEDx software (Sensor Systems Inc., Sterling, VA). The amount of head motion during scanning was studied using the "motion detection by center of intensity" method, which produces a plot of the estimated motion relative to the first functional volume in mensurated space (mm) in *x*, *y*, and *z* directions. Overall, the amount of motion was minor (< 0.4 mm, corresponding to < 10 % of the voxel size) in this group of young healthy subjects. Nevertheless, motion correction was performed for all functional scans by registering all the scans in the analysis to one reference scan which was taken from the middle of the fMRI time series. Images were spatially filtered using an 8-mm isotropic Gaussian 3 x 3 kernel in order to reduce noise in the images (Xiong et al. 1996). Eight fMRI volumes were omitted from the beginning of each session to allow the MR signal to reach an equilibrium state.

Additionally, one (Studies I, III and IV) or two (Study II) functional volumes were omitted from the beginning of each block in order to allow hemodynamic responses to stabilize. The scans obtained during instruction slides were not included in analysis. Thereafter, the remaining functional volumes were classified as the baseline and activation conditions using the paradigm editor that was specifically created for each of the three activation paradigms in the Studies I–IV. Furthermore, a linear detrending method was used to remove low frequency signal intensity drifts. In the case of fMRI time-series, the signal at each voxel may "drift" during a long imaging session, which may cause artifactual linear trends that contaminate the time-series and may affect the resulting statistical maps. Finally, statistical parametric maps comparing different task conditions were generated voxel-by-voxel from the functional time series using a standard unpaired Student's *t*-test (Xiong et al. 1996).

Voxel-by-voxel statistical testing leads to the possibility of false positive significance of single voxels because of the large number of voxels in one functional volume. Therefore, the choice of the statistical threshold for determining the significantly activated voxels or brain areas is an important step in the analysis. The thresholds for statistical significance were different in Studies I–IV. In Studies I and II, *i.e.* the Category Fluency and the Paired-Associates Task, we used a relatively conservative statistical threshold concerning voxels having *Z*-values ≥ 4.32 as being statistically significant. This *Z*-score threshold corresponds to an uncorrected $p < 0.00001$ or, in other words, $p < 0.01$ after correction for multiple comparisons using resolvable elements, *i.e.* resels (Worsley et al. 1992). The resel correction takes into account the effective resolution of the statistical images using an estimate of the spatial smoothness which is considered to reduce the amount of independent statistical tests (Worsley et al. 1992). In Study II, the MTL activation areas in each individual subject were additionally examined using a low statistical threshold $Z \geq 1.64$ corresponding to an uncorrected $p < 0.05$. The logic behind this selection of a low threshold was to try to ensure that the MTL subareas that were not activated when using the conservative threshold are also not activated when using a liberal threshold. In particular, we wanted to confirm the finding that the anterior hippocampus and perirhinal cortex were not activated during retrieval, but only during the encoding condition. Subthreshold, very weak activations ($Z < 1.64$) still remain, however, a possibility. In Study III *(i.e.* the Object *vs.* Spatial Novelty Task), we focused the data analysis on the MTL region of interest (ROI) and decided to use a single statistical threshold, *i.e.* different from in Study II. Therefore, voxels exceeding $Z \geq 3.08$, corresponding to an uncorrected $p < 0.001$, were considered as significantly activated.

The resulting thresholded *Z*-maps were co-registered with the three-dimensional anatomic images. This was done by using location and orientation information available in the image file headers and using nearest neighbor interpolation. Both the individual statistical maps and anatomic images were further transformed into Talairach standard coordinates (Talairach and Tournoux 1988). In Study IV examining

the whole-brain activation network during the Object *vs.* Spatial Novelty Task, a second-level analysis was performed using a one-sample *t*-test to investigate the mean group effect of the four first-level statistical comparisons, and thereafter a cluster detection method was used for assessing the final statistical significance of activations (Friston et al. 1994). The *Z*-score threshold for significant activation clusters was $Z \geq 3.59$ (corresponding to a resel corrected $p < 0.05$ of the gray matter), and the probability threshold $p < 0.05$. For the purpose of this thesis, also the data of Studies I and II were analyzed using a similar within-group second-level analysis (one-sample *t*-test, $Z \geq 3.59$) as in Study IV (see Figures 11 and 12, unpublished observations).

In Studies I–III, brain activation areas were assessed at the level of individual study subjects. The anatomic location of the activated brain areas for each individual was defined from the high-resolution images using anatomic atlases (Damasio 1995, Duvernoy 1999). Regarding the MTL structures, the anatomic landmarks for the location of the MTL activations were assessed according to previous MRI volumetric criteria (Insausti et al. 1998). In practical terms, these criteria were needed for defining the posterior limit of the perirhinal cortex *vs.* the anterior parahippocampal cortex. As in the method developed by Insausti et al. (1998), the gyrus intralimbicus was used as a landmark and on the coronal MP-RAGE-images with 1.0 mm slice thickness, the perirhinal cortex was considered to continue four slices posterior to the gyrus intralimbicus. In Study III, the hippocampal formation was further divided into head (or anterior part), body (or middle part), and tail (or posterior part) (Duvernoy 1988). The corresponding Talairach coordinates of the center of brain activation areas were determined, and the mean values of the center coordinates of individuals were calculated. The approximate Talairach coronal levels for the anterior hippocampus were slices from $y = -8$ to $y = -16$, for the middle hippocampus from $y = -20$ to $y = -32$, and for the posterior hippocampus from $y = -35$ to $y = -40$. The thresholded and Talairach-transformed *Z*-maps were also averaged across subjects for the visualization purposes in Studies II and III.

In Studies II and III, the voxel-based statistical analysis at the individual level was supplemented with an ROI analysis at the group level. For this ROI analysis, time-series of the voxel intensities of the MTL structures were examined in the raw *Z*-maps. The relative signal intensity changes were submitted to analysis of variance (ANOVA) with repeated measures to evaluate whether the activation of the MTL structures was differentially modulated by different cognitive conditions. In Study III, the statistical comparisons over the four regions within the same cognitive condition were performed using the non-parametric Friedman test, and the paired testing between ROI areas using Wilcoxon tests. Non-parametric tests were used for this purpose because they do not require assumptions about the shape of the underlying distribution. Furthermore, in Study III, the differences of localization of the hippocampal and parahippocampal activation areas along the Talairach *x*-, *y*-, and *z*-axis were tested between the novel object and spatial change conditions using paired samples *t*-test.

In Study IV, besides examining the distinct activation areas for perception of the Object *vs.* Spatial Novelty in the direct novel object (O) *vs.* spatial change (S) and S *vs.* O statistical comparisons, the brain responses common for both conditions were determined. Therefore, conjunction maps combining the information of the within-group O *vs.* baseline (B) and S *vs.* B statistics were generated. First, the cluster detection algorithm was performed to the O *vs.* B and S *vs.* B *Z*-statistical maps resulting from the one-sample *t*-tests. All voxels that did not belong to any cluster were set to zero, and all voxels in the masks of significant clusters to number one. These binary masks were used to generate a conjunction mask that included only those voxels that were activated in both O and S conditions. This conjunction mask was then further used to restrict the activation areas common for both O *vs.* B and S *vs.* B conditions. Additionally, to demonstrate the possible fMRI deactivation responses behind the statistical significance of brain activation areas in direct O *vs.* S and S *vs.* O contrasts, the mean percentage signal intensity changes in the O *vs.* B and S *vs.* B were investigated.

When analyzing the neuropsychological data, the non-parametric Mann-Whitney test was used for between-group comparisons. Statistical analysis of the data was performed using SPSS 10.0 software. The results were expressed as mean ± standard deviation (SD). A *p*-level of less than 0.05 was considered statistically significant.

5. RESULTS

5.1 Neuropsychology and behavioral responses

Since there is some earlier evidence that performance on verbal fluency tests may be affected by gender (Lezak 1995) and we found some minor differences in fMRI activation areas between male and female subjects during performance of the Category Fluency Task (see appendix, Study I), the neuropsychological data was assessed separately for male and female subjects in Study I. According to the WAIS-R subtests, the difference in the verbal IQ between the male (117.6 ± 6.8, mean ± SD) and female (121.1 ± 8.1) subjects was, however, not significant (unpaired t-test, $p = 0.39$) in this group of fourteen subjects who participated in Study I.

In the group of the twelve study subjects in Studies II–IV, the average total IQ was 116.5 ± 5.3, performance IQ, 111.8 ± 7.9, and the verbal IQ, 117.8 ± 6.9. There were also no significant differences between female and male groups in these tests (total IQ, $p < 0.42$; performance IQ, $p < 0.63$; verbal IQ, $p < 0.23$; recognition $p < 0.18$). The neuropsychological and behavioral details of the individual subjects are presented in Table 2.

Regarding the verbal fluency performance that was tested after the imaging session in Study I, all subjects produced over 20 words in the 60 s time. In the post-scan forced-choice recognition testing of Study II, the percentage of correctly recognized pictures was 90.6 ± 17.0. In Studies III and IV, the mean percentage of correct post-scan recognition responses was 92 ± 26% for novel objects, 92 ± 19% for new spatial arrangements of objects, and 96 ± 10% for total recognition performance. The difference in correct behavioral responses between men and women was not significant; the percentage of correct recognition responses was 94 ± 13 % in men and 99 ± 1 % in women ($p = 0.39$).

5.2. fMRI responses during retrieval of semantically related words (Study I)

In the Category Fluency Task, listing of items belonging to a given category was contrasted with orderly listing of numbers. This contrast resulted in activation of areas (Table 3, Fig. 11) both in the anterior and ventral part (BA 45 / 47) of left inferior frontal gyrus (IFG), and in the posterior and dorsal extent of the IFG (BA 44), extending further up to the bordering precentral gyrus (preCG). The medial part of the left superior frontal gyrus (SFG), corresponding to the supplementary motor area (SMA), was also activated on the left side. In the right frontal lobe, activation was detected only in the inferior part of the IFG (BA 47). A left-sided activation was observed in the superior parietal lobule (SPL), and bilateral, but left-dominant activation in the retrosplenial region (RS). In the temporo-occipital areas, left-sided activation areas were found in the middle part of the hippocampus (HC; mean Talairach coordinate $y = -24$), and in the parahippocampal cortex (PhC) and adjacent fusiform gyrus (FG).

Table 3. fMRI activation areas ($Z \geq 4.32$; $p < 0.00001$, uncorrected) during the Category Fluency Task *vs.* listing of numbers.

Brain region	BA[a]	Mean (*x, y, z*)[b]
Frontal		
L SFG	6	–6, 6, 56
L preCG	6	–40, 4, 32
R IFG	47	32, 16, 14
L IFG	44/45/47	–38, 24, 6
Parietal		
L SPL	7	–26, –68, 40
L RS	29/30	–10, –54, 8
Temporo-occipital		
L FG	37	–30, –46, –12
Medial temporal		
L HC	–	–24, –24, –10
L PhC	35/36	–20, –36, –8

[a]The corresponding Brodmann area (BA). [b]Talairach coordinates (*x, y, z*) of the mean location. Abbreviations. L, left; R, right; SFG, superior frontal gyrus; preCG, precentral gyrus; IFG, inferior frontal gyrus; SPL, superior parietal lobule; RS, retrosplenial region; FG, fusiform gyrus; HC, hippocampus; PhC, parahippocampal cortex.

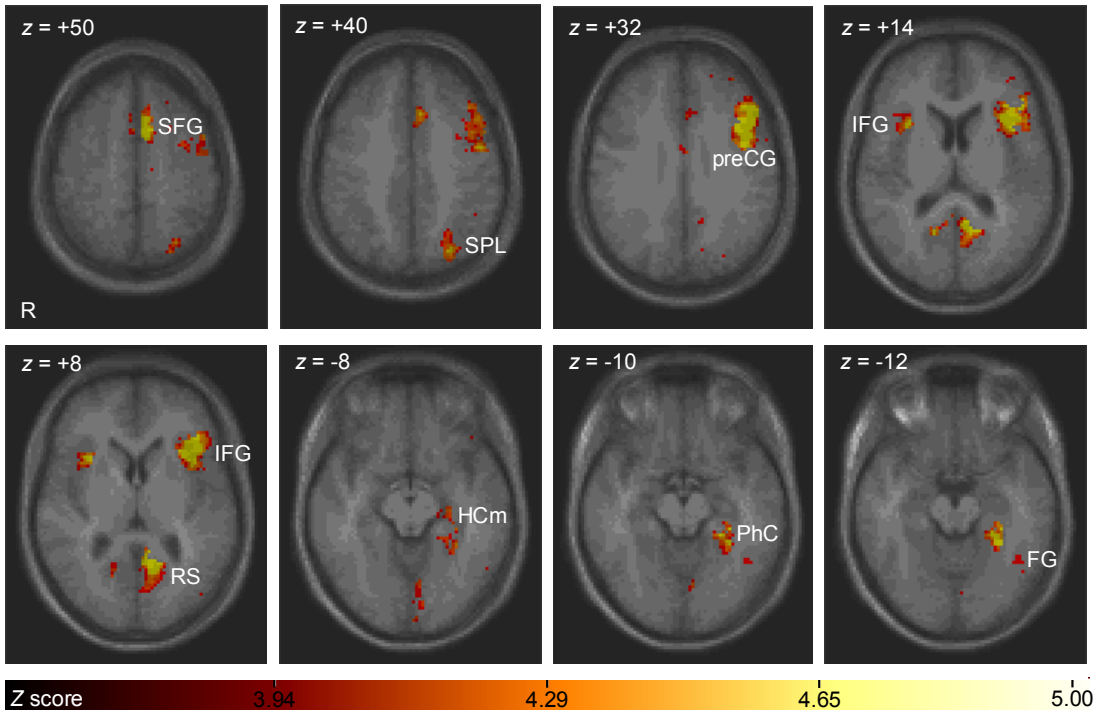


Figure 11. fMRI activation areas during the Category Fluency Task *vs.* listing of numbers (second-level analysis, one-sample *t*-test, $Z \geq 3.59$, $p < 0.05$ corrected). The brain activation areas of Table 3 are shown in these functional MR images in the following order: superior frontal gyrus (SFG; $z = +50$), superior parietal lobule (SPL; $z = +40$), precentral gyrus (preCG; $z = +32$), right inferior frontal gyrus (IFG; $z = +14$), left IFG and retrosplenial region (RS; $z = +8$), left middle hippocampus (HCm; $z = -8$), parahippocampal cortex (PhC; $z = -10$), and fusiform gyrus (FG; $z = -12$). Activations are visualized on the axial slices of the averaged structural MRI scan of the subjects, and the corresponding Talairach *z*-coordinate is shown in the upper left corner. The right (R) side of the images corresponds to the left side of the brain. The color bar indicates the *Z*-score values of the brain activation areas.

5.3. fMRI responses during encoding and retrieval of picture-pairs (Study II)

In Study II, the encoding condition of the Paired-Associates Task was contrasted to the baseline and retrieval conditions, and similarly, the retrieval condition to both the baseline and encoding conditions. In the original publication (see appendix, Study II, Table 3), the MTL responses were examined at the level of the individual study subjects using two statistical thresholds, *i.e.* a conservative threshold of $Z \geq 4.32$ ($p < 0.00001$, uncorrected), and a liberal threshold $Z \geq 1.64$ ($p < 0.05$, uncorrected). A summary of the MTL responses during the Paired-Associates Task using the conservative threshold $p < 0.00001$, uncorrected, is presented in Table 4 of this thesis, whereas the results of the liberal threshold are only presented in the appendix. The anterior–middle HC, the perirhinal cortex (PrC) and PhC were activated during encoding of

novel picture-pairs irrespective of whether they were contrasted to the baseline or retrieval (Table 4, Fig. 12A). The mean Talairach coordinates of the HC activation were $y = –20$ and $y = –10$ in the encoding *vs.* baseline, and encoding *vs.* retrieval comparisons, correspondingly. The location of the PrC activation area was in the medial bank of the collateral sulcus, in the posterior part of the PrC (Insausti et al. 1998). During the retrieval condition, activations were observed in the middle HC, and in the PhC in comparisons both to the baseline and encoding, but the PrC was not activated (Table 4, Fig. 12B). The mean Talairach coordinate of the middle HC activation was $y = –23$ in both the retrieval *vs.* baseline, and retrieval *vs.* encoding comparisons. The neighboring fusiform gyrus, located in the inferior part of the temporal lobe, was also activated (Table 5, Figure 12A). At the group level, a repeated-measures ANOVA revealed a significant interaction between the cognitive condition and the anatomic areas HC and PrC ($F(2,14) = 10.340$, $p = 0.002$). Further, paired *t*-tests on the cognitive condition / anatomic area differences were significant in 5 of the 6 contrasts. In the HC, in all of the three cognitive comparisons the difference was statistically significant (encoding – baseline, $p < 0.0001$; retrieval – baseline, $p = 0.05$; encoding – retrieval, $p < 0.0001$. In the PrC, the statistical comparisons in the encoding – baseline ($p = 0.024$) and in the encoding – retrieval ($p = 0.024$) were significant, but the retrieval – baseline comparison ($p = 0.318$) was not.

Table 4. fMRI activation areas of the MTL structures ($Z \geq 4.32$; $p < 0.00001$, uncorrected) in the encoding (E) *vs.* baseline (B), E *vs.* retrieval (R), R *vs.* B, and R *vs.* E comparisons.

		E *vs.* B	E *vs.* R	R *vs.* B	R *vs.* E
Brain region	BA[a]	Mean (*x, y, z*)[b]	Mean (*x, y, z*)[b]	Mean (*x, y, z*)[b]	Mean (*x, y, z*)[b]
Medial temporal					
R HC	–	22,–16,–16	25,–10,–16	26,–23,–11	26,–22,–12
L HC	–	–22, –24, –11	–27, –10, –18	–27, –22, –12	–28, –24, –13
R PrC	35/36	28,–16,–19	29,–13,–22	–	–
L PrC	35/36	–30, –20, –19	–31, –15, –21	–	–
R PhC	35/36	22,–26,–16	25,–32,–12	26,–29,–11	27,–24,–17
L PhC	35/36	–24, –34, –14	–25, –32, –12	–24, –30, –12	–21, –30, –12

[a]The corresponding Brodmann area (BA). [b]Talairach coordinates (*x, y, z*) of the mean location. Abbreviations. PrC, perirhinal cortex; other abbreviations as in Table 3.

The whole-brain responses during encoding and retrieval conditions when contrasted to the baseline are presented in detail in Table 5 ($p < 0.00001$, uncorrected). During encoding, small activation areas were detected in the right preCG, IFG, and circular insular sulcus (circIS), whereas the wide left frontal activation area extended from the IFG and circIS to the preCG and precentral sulcus (preCS). The medial part of the left SFG was also activated. Both the right and left SPL including the intraparietal sulcus (IPS)

were activated. The inferior temporo-occipital regions along the ventral visual stream were strongly activated on both sides (Fig. 12A). Also during the retrieval condition, the frontal activation was left-dominant. In the right frontal lobe, activation areas were located in the IFG, insular areas, and in the medial SFG. The wide left frontal activation consisted of areas in the lateral premotor cortex (Broca's area) and in the prefrontal association areas. This activation area extended from the IFG, inferior frontal sulcus (IFS) and insular regions superiorly to the precentral region. A small right-sided parietal activation was located in the IPS, whereas the wide left parietal activation area covered both the SPL and IPS. In both the frontal and parietal lobes, the brain activation areas were more widespread on the left covering several anatomic structures and Brodmann areas compared with the corresponding activation areas on the right side. In the temporo-occipital regions, there were small activation areas along the ventral visual stream.

Table 5. fMRI whole-brain activation areas ($Z \geq 4.32$; $p < 0.00001$, uncorrected) in the encoding (E) *vs.* baseline (B) and retrieval (R) *vs.* B comparisons.

E *vs.* B			R *vs.* B		
Brain region	BA[a]	Mean (*x, y, z*)[b]	Brain region	BA[a]	Mean (*x, y, z*)[b]
Frontal			*Frontal*		
L SFG	6	–6, 6, 54	R SFG	6	4, 14, 52
R preCG	4/6	36, –2, 36	L SFG	6/8	–6, 12, 55
L preCG, preCS	4/6	–45, –3, 40	L preCG, preCS	4/6	–44, 2, –40
R IFG, circIS	44/45	35, 16, 16	R IFG, circIS, shortIG	44/45	34, 14, 14
L IFG, circIS	44/45	–40, 23, 15	L IFG, circIS, shortIG	44/45/47	–34, 14, 10
Parietal			*Parietal*		
R SPL, IPS	7	24, –64, 48	R IPS	7	22, –78, 42
L SPL, IPS	7	–9, –63, 45	L SPL, IPS	7/39/40	–34, –54, 40
Temporo-occipital			*Temporo-occipital*		
R CS, FG	19/37	30, –47, –13	R LG	18	8, –80, –6
L CS, FG	37	–34, –38, –20	R MOG	18/19	32, –86, 8
R FG, IOG, IOS	19	32, –68, –12	L FG, IOS, MOG	19/37	–39, –49, –12
L latOTS	19/37	–40, –62, –8			
R IOG, MOG, SOG	19	33, –74, 7			
L IOG, MOG, SOG	18/19	–25, –87, 9			

[a]The corresponding Brodmann area (BA). [b]Talairach coordinates (*x, y, z*) of the mean location. Abbreviations. circIS, circular insular sulcus; shortIG, short insular gyrus; preCS, precentral sulcus; IPS, intraparietal sulcus; CS, collateral sulcus; IOG, inferior occipital gyrus; IOS, inferior occipital sulcus; latOTS, lateral occipitotemporal sulcus; MOG, middle occipital gyrus; SOG, superior occipital gyrus; LG, lingual gyrus; other abbreviations as in Tables 3 and 4.

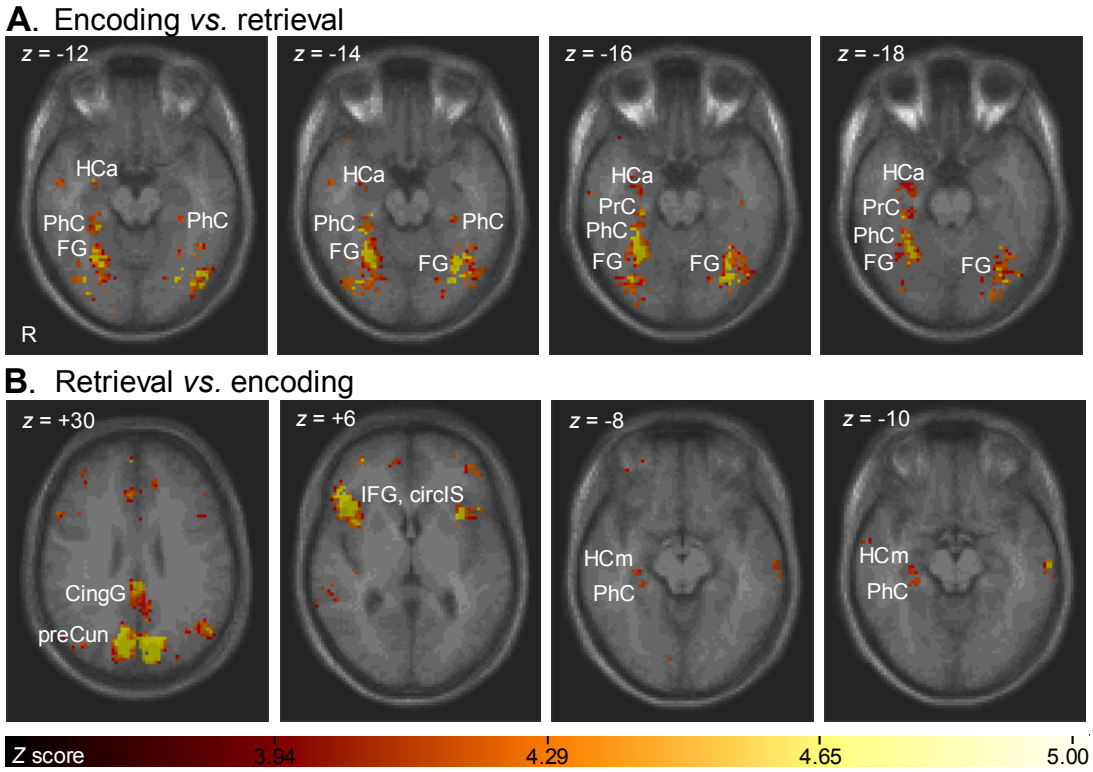


Figure 12. fMRI activation areas during the Paired-Associates Task in the direct encoding *vs.* retrieval (Fig. 12A) and retrieval *vs*. encoding (Fig. 12B) comparisons (second level analysis, one-sample t-test, $Z \geq 3.59$, $p < 0.05$ corrected). The anterior hippocampal (HCa), parahippocampal cortical (PhC), and fusiform gyral (FG) activation areas during encoding of picture-pairs are shown on axial slices $z = -12$, $z = -14$, $z = -16$, and $z = -18$. The activation of the right perirhinal cortex (PrC) is visible in slices $z = -16$ and $z = -18$. Additionally, the direct encoding *vs.* retrieval comparison activated inferior and middle occipital areas. During retrieval (Fig. 12B), the MTL activation areas were located in the middle hippocampus (HCm), and in the PhC ($z = -8$ and $z = -10$). Prominent activation responses were also observed in the posterior cingulate gyrus (CingG; $z = +30$), precuneus (preCun; $z = +30$), and bilaterally in the inferior frontal gyrus (IFG; $z = +6$), and insular regions (circular insular sulcus, circIS; $z = +6$). The right (R) side of the images corresponds to the left side of the brain; other details as in Fig. 11.

5.4. fMRI responses of the MTL during processing of object and spatial novelty (Study III)

In the Object *vs.* Spatial Novelty Task, the aim was to investigate the possible functional dissociation between the PrC and HC in processing of object and spatial novelty that is reported in animals. Therefore, the condition with novel objects was contrasted to the baseline and spatial change conditions, and the spatial change condition was compared with both baseline and object novelty conditions. The significant MTL activation areas ($Z \geq 3.08$; $p < 0.001$, uncorrected) are presented in Table 6 and Figure 13. The areas that were consistently activated during presentation of novel objects in both statistical

comparisons were the anterior HC, PrC and anterior PhC. Also the middle parts of the HC were activated during encoding, although less frequently (appendix, Study III, Table 1). The mean Talairach coordinate for the anterior HC activation was $y = -13$, for the middle HC $y = -25$, and for the PhC $y = -30$. During processing of spatial changes, significant activation areas were detected in the posterior HC (mean $y = -35$) and PhC (mean $y = -37$).

The analysis of the MTL activation areas of individual study subjects was supplemented with the analysis of ROI time-series at the group level, and therefore, time-series of the anterior and posterior HC, as well as PrC and PhC voxel intensities were extracted. The repeated-measures ANOVA of the percent intensity changes in these four areas revealed a significant main effect of the cognitive condition (spatial change *vs.* novel object) [$F(1,11) = 5.6$, $p = 0.037$] but no effect of the anatomic area alone [$F(3,33) = 1.5$, $p = 0.25$] or right-left lateralization of the brain activation [$F(1,11) = 1.0$, $p = 0.34$]. There was a significant interaction between the cognitive condition and the anatomic area [$F(3,33) = 6.0$, $p = 0.03$]. BOLD responses in the anterior HC and PrC were significantly stronger in the novel object condition than in the spatial change condition. Conversely, in the posterior HC, spatial changes evoked significantly stronger responses than novel objects. The magnitude of PhC responses did not differ between the two activation conditions, although the locations of the PhC activation areas in the anterior-posterior direction (*y*-coordinates in Table 6) were different. To quantify the differential localization of fMRI responses to object and spatial novelty inside the HC and PhC, the Talairach-coordinates of significant activation areas along the *x*-, *y*-, and *z*-axes were contrasted. The *y*-coordinates of the HC ($T = 12.9$, $p < 0.001$) and PhC ($T = 5.7$, $p < 0.001$) activation areas indicated a more anterior location of the responses to novel objects as compared with spatial changes.

Table 6. fMRI activation areas of the MTL structures ($Z > 3.08$; $p < 0.001$, uncorrected) in the novel object (O) *vs.* baseline (B), O *vs.* spatial change (S), S *vs.* B, and S *vs. O* comparisons.

		O *vs.* B	O *vs.* S	S *vs.* B	S *vs.* O
Brain region	BA[a]	Mean (*x, y, z*)[b]	Mean (*x, y, z*)[b]	Mean (*x, y, z*)[b]	Mean (*x, y, z*)[b]
Medial temporal					
R HCa	–	23, –12, –16	25, –12, –15	–	–
L HCa	–	–28, –14, –15	–25, –14, –15	–	–
R HCm	–	27, –25, –10	28, –24, –12	26, –25, –13	24, –27, –10
L HCm	–	–28, –27, –9	–26, –25, –12	–25, –24, –11	–24, –27, –9
R HCp	–	18, –36, –2*	–	22, –34, –4	23, –36, –5
L HCp	–	–24, –36, –4*	–	–25, –34, –5	–20, –36, –4
R PrC	35/36	30, –20, –18	31, –17, –20	–	–
L PrC	35/36	–30, –20, –18	–31, –17, –19	–	–
R PhC	35/36	24, –32, –11	27, –28, –15	21, –35, –8	20, –36, –8
L PhC	35/36	–25, –30, –12	–26, –30, –14	–22, –37, –9	–22, –40, –8

[a]The corresponding Brodmann area (BA). [b]Talairach coordinates (*x, y, z*) of the mean location. *During the object novelty condition, posterior hippocampal activity was detected in only one subject. Abbreviations. HCa, anterior hippocampus; HCm, middle hippocampus; HCp, posterior hippocampus; other abbreviations as in Tables 3–5.

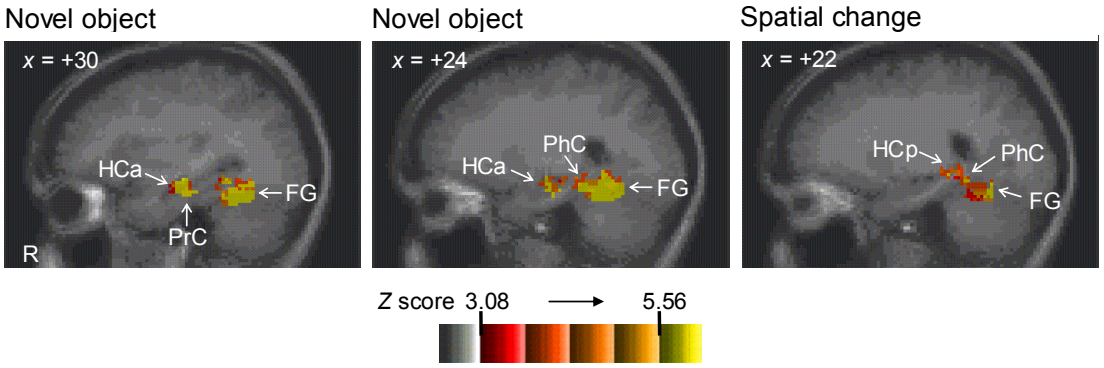


Figure 13. The MTL activation areas during the Object *vs.* Spatial Novelty Task when compared with baseline (unpaired *t*–test, $Z \geq 3.08$, $p < 0.001$ uncorrected). Sagittal images $x = +30$ and $x = +24$ demonstrate the anterior hippocampal (HCa), perirhinal (PrC), and parahippocampal cortical (PhC) responses during processing of novel objects, and the sagittal image $x = +22$ the posterior hippocampal (HCp) and PhC responses during viewing of new spatial configurations. Activations are visualized on right (R) sagittal slices of the averaged structural MRI scan of the subjects, and the corresponding Talairach *x*-coordinate is shown in the upper left corner. The color bar indicates the *Z*-score values of the brain activation areas.

5.5. fMRI responses of the MTL connection areas during processing of object and spatial novelty (Study IV)

Introduction of novel objects into the array of objects, when contrasted to spatial changes in the arrangement of familiar objects, activated a wide network of frontal and temporo-occipital cortical areas, but no parietal areas (Table 7, Fig. 14A). The prefrontal and insular activation areas are presented in detail in Table 7. Interestingly, the left anterior cingulate gyrus (CingG) was more active in the novel object than in the spatial change condition. Another characteristic finding during the object novelty condition was the bilateral, but left-dominant, activation of the anterior temporo-occipital structures. In the right temporal lobe, separate activation areas were found in the superior temporal sulcus (STS) and in the middle temporal gyrus (MTG), whereas on the left side, the activation of the anterior STS, MTG, and inferior temporal sulcus (ITS) formed a confluent cluster. The anterior FG was activated on the right, and on the left, where the activation also extended to the lateral occipitotemporal sulcus (latOTS). A small activation area was detected in the head of the left caudate nucleus (CN). Investigation of the mean relative signal intensity changes in the novel object *vs.* baseline and spatial change *vs.* baseline comparisons revealed that all the object-areas that are reported in Table 7 showed positive percentage signal intensity changes also when contrasted to the baseline, except for the right long insular gyrus (longIG) and the CN. A clear fMRI deactivation response during processing of spatial changes was found in the anterior CingG, where the positive activation response in the novel object *vs.* baseline contrast was very small.

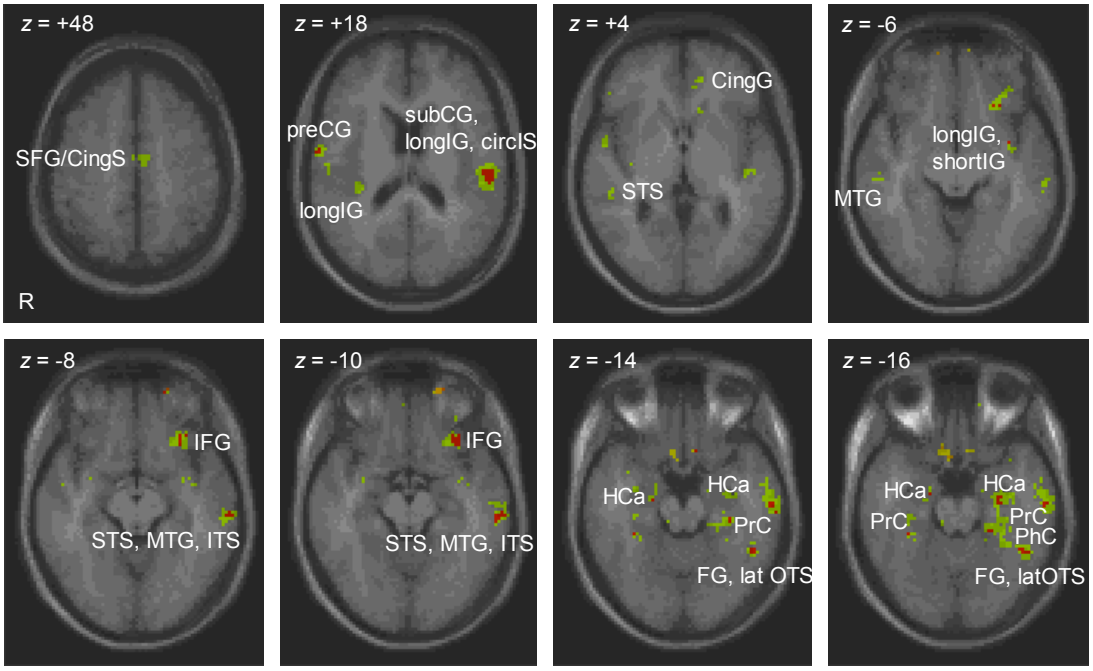
When the presentation of spatial changes was contrasted to novel objects, the most prominent activation areas were observed in the parietal cortices, and in the right retrosplenial and posterior cingulate regions (Table 7, Fig. 14B). The prefrontal activation areas are presented in Table 7. The parietal activation areas were widespread on both sides. On the preponderant right side, the activation covered parts of the SPL, IPS, inferior parietal lobule (IPL), angular gyrus (AG), and precuneus (preCun). The SPL, IPS, and IPL were activated also on the left side, but not the AG and preCun. A large right-sided activation cluster covered the right RS and posterior CingG, and extended via a few connecting voxels bilaterally to the posterior parts of the thalamus, and to the right posterior HC and PhC. The mean location of this activation area in the cingulate gyrus and retrosplenial region was very posterior (y = –46) compared with the activation of the anterior cingulate gyrus during processing of novel objects (y = +40).

Table 7. fMRI whole-brain activation areas ($Z \geq 3.59$; $p < 0.05$ corrected) in the novel object (O) *vs.* spatial change (S), and S *vs. O* comparisons.

O *vs.* S			S *vs.* O		
Brain region	BA[a]	Mean (*x,y,z*)[b]	Brain region	BA[a]	Mean (*x,y,z*)[b]
Frontal			*Frontal*		
L SFG, CingS	6/24	–6, –10, 48	R SFG, SFS, MFG	6/8	32, 8, 52
R preCG	4/6	58, –6, 18	L SFG, SFS, MFG	6/8	–42, 8, 46
L IFG	47	–28, 28, –8	L SFG, SFS	6	–20, –8, 58
R longIG	43	32, –28, 16	R MFG	10/46	24, 48, 10
L subCG, longIG, circIS	43	–50, –20, 16	L MFG	10/46	–38, 46, 12
L longIG, shortIG	45	–40, –8, –4	R IFG	44	48, 10, 22
L CingG	24/32	–8, 40, 4	R IFG, circIS	45/47	28, 20, 12
			L IFG, circIS	45/47	–34, 18, 18
			R preCG	4	8, –33, 68
			Parietal		
			R SPL, IPS, IPL, AG, preCun	7/39/40	32, –52, 42
			L SPL, IPS, preCun	7/40	–26, –56, 44
			R RS, CingG	29/30	6, –46, 10
Temporo-occipital			*Temporo-occipital*		
R STS	21/22	46, –30, 4	L STS	21/22	–44, –58, 18
R MTG	21	52, –26, –10	L MTG	37	–44, –68, 8
L STS, MTG, ITS	21/22	–58, –24, –8	L FG	19	–20, –68, –8
R FG	20/37	32, –36, –16	R LG	18	6, –84, –2
L FG, latOTS	37	–44,–46, –14	R Cuneus	18	12, –92, 4
			L Cuneus	18	–14, –96, 4

[a]The corresponding Brodmann area (BA). [b]Talairach coordinates (*x, y, z*) of the mean location. Abbreviations. SFS, superior frontal sulcus; MFG; middle frontal gyrus; CingG, cingulate gyrus; CingS, cingulate sulcus; longIG, long insular gyrus; subCG, subcentral gyrus; IPL, inferior parietal lobule; AG, angular gyrus; preCun, precuneus; STS, superior temporal sulcus; MTG, middle temporal gyrus; ITS, inferior temporal sulcus; other abbreviations as in Tables 3–6.

A. Novel object *vs.* spatial change



B. Spatial change *vs.* novel object

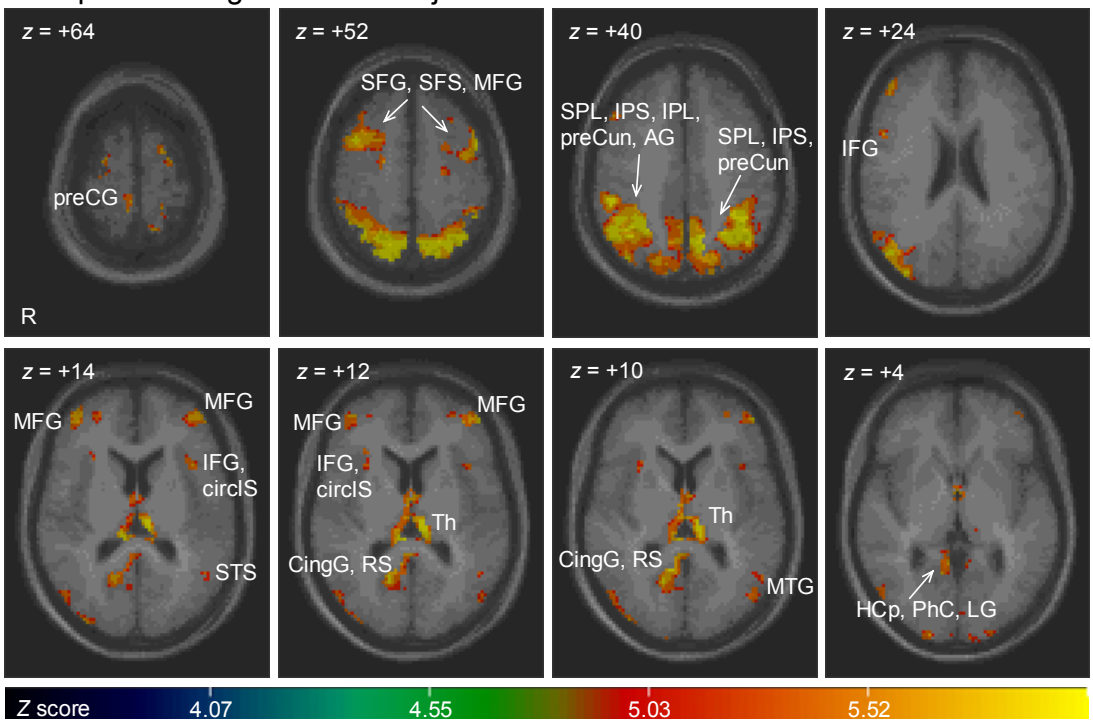


Figure14 (on the previous page)**.** fMRI whole-brain activation areas during the Object *vs.* Spatial Novelty Task in the direct novel object (O) *vs.* spatial change (S) and S *vs*. O comparisons (one-sample *t*-test, $Z \geq 3.59$, $p < 0.05$ corrected). Following areas were activated during processing of novel objects (Fig. 14A): the left superior frontal gyrus (SFG) and dorsal cingulate sulcus (CingS; $z = +48$); the right precentral (preCG) and long insular (longIG) gyri, and left subcentral (subCG) gyrus, longIG, and circular insular sulcus (circIS; $z = +18$); the right superior temporal sulcus (STS) and left anterior cingulate gyrus (CingG; $z = +4$); the right middle temporal gyrus (MTG) and left longIG and short insular gyrus (shortIG; $z = –6$); the left inferior frontal gyrus (IFG) and STS, MTG, and inferior temporal sulcus (ITS; $z = –8$ and $z = –10$); bilaterally the anterior hippocampi (HCa) and perirhinal cortices (PrC), and the left parahippocampal cortex (PhC), fusiform gyrus (FG) and lateral occipitotemporal sulcus (latOTS; $z = –14$ and $z = –16$). In contrast, processing of new spatial arrangements activated following areas (Fig. 14B): the right preCG ($z = +64$); bilaterally SFG, superior frontal sulcus (SFS), and middle frontal gyrus (MFG; $z = +52$); bilaterally the superior parietal lobule (SPL), intraparietal sulcus (IPS), and precuneus (preCun), and on the right side the inferior parietal lobule (IPL) and angular gyrus (AG; $z = +40$); the right IFG ($z = +24$); bilaterally the MFG ($z = +14$ and $z = +12$), and the left IFG, circIS, and posterior STS ($z = +14$); the right IFG and circIS ($z = +12$), posterior CingG and retrosplenial region (RS), and bilaterally the thalamus (Th; $z = +12$ and $z = +10$); the left posterior MTG ($z = +10$); left posterior hippocampus (HCp), PhC and lingual gyrus (LG; $z = +4$). The right (R) side of the images corresponds to the left side of the brain; other details as in Fig. 11.

Also in the temporo-occipital areas, new spatial arrangements activated more posterior areas than novel objects. Activation clusters were found in the left STS ($y = –58$), and MTG ($y = –68$). Left posterior FG ($y = –68$), right posterior end of LG ($y = –84$), and the cuneus bilaterally also responded to spatial changes. When one considers the anterior-posterior locations of the temporal neocortical activation areas during object *vs.* spatial changes, the locations of activations in the STS and MTG were clearly different. During processing of novel objects, the *y*-coordinates were –30 and –24 for the right and left STS, and –26 and –24 for the right and left MTG, whereas during processing of spatial changes, the corresponding coordinates were –58 for the STS and –68 for the MTG. This result suggests an approximately 4 cm more posterior location of the STS / MTG activation areas during the conditions with spatial changes. The same finding regarding the anterior-posterior distinction of activation was also found inside the FG: coordinates for the novel objects were $y = –36$ and –46 (right and left FG), and for the spatial changes $y = –68$ (left FG). Finally, an additional activation area was detected in the midline cerebellar structures (vermis). The results of investigating the mean signal intensity changes demonstrated that all of the brain activation areas that were significantly activated in the direct spatial change *vs.* novel object comparison also showed positive percentual signal intensity changes in the spatial change *vs.* baseline comparison. The positive fMRI responses during processing of spatial changes were generally clearly larger than the object-responses.

5.6. Summary of the MTL responses of the three activation paradigms (Studies I–III)

In Study I, the middle part of the left HC and the left PhC were activated during retrieval of semantically related words in the category fluency task. In Study II, the anterior parts of the HC, and the PrC and PhC were activated during encoding of picture-pairs, whereas the middle HC and the PhC were activated during retrieval of the other member of the pair. In Study III, activation of the anterior and middle HC as well as of the PrC and PhC was observed during processing of novel objects, whereas the new spatial relations of familiar objects activated the posterior HC and PhC. These results are summarized in Table 9.

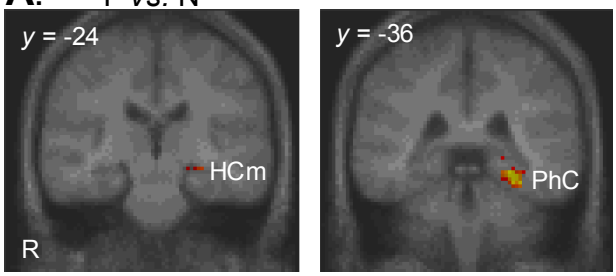
Table 9. The MTL activation areas and their anterior-posterior locations as expressed by the Talairach *y*-coordinates. In Study I, category fluency (F) was contrasted to listing of numbers (N); in Study II encoding (E) of picture-pairs was compared with retrieval (R) and *vice versa*. In Study III, direct statistical contrasts were created between novel object (O) and spatial change (S) conditions.

	Study I: F *vs.* N	Study II: E *vs.* R	Study II: R *vs.* E	Study III: O *vs.* S	Study III: S *vs.* O
Brain region	Mean *y*[a]	Mean *y*[a]	Mean *y*[a]	Mean *y*[a]	Mean *y*[a]
Medial temporal					
R / L HCa	–	–10	–	–13	–
R / L HCm	–24	–	–23	–25	–27
R / L HCp	–	–	–	–	–36
R / L PrC	–	–14	–	–17	–
R / L PhC	–36	–32	–27	–29	–38

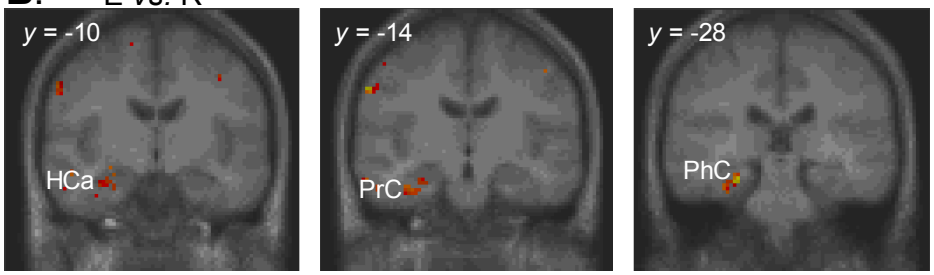
[a]Mean Talairach *y*-coordinate of the activation area. Abbreviations as in the Tables 3–8.

Figure 15 (on the next page)**.** The MTL activation areas in the category fluency *vs.* listing of numbers (Fig. 15A; *Z* score ≥ 3.59), encoding *vs.* retrieval of picture-pairs (B) and retrieval *vs.* encoding of picture-pairs (C; *Z* score ≥ 3.59) as well as novel objects *vs.* spatial changes (D) and spatial changes *vs.* novel objects (E; *Z* score ≥ 3.08) comparisons. The anterior hippocampus (HCa) was activated during encoding of picture-pairs (B; $y = -10$) and processing of novel objects (D; $y = -12$), the middle hippocampus (HCm) during retrieval of semantically related words (A; $y = -24$) and picture-pairs (C; $y = -22$), and the posterior hippocampus (HCp) during processing of spatial changes (E; $y = -34$). Activation of the perirhinal cortex (PrC) was observed during encoding of picture-pairs (B; $y = -14$) and processing of novel objects (D; $y = -20$). The parahippocampal cortex (PhC) was activated in all of these statistical comparisons, but during processing of novel objects (D; $y = -30$) the PhC activation area was slightly more anterior than during processing of spatial changes (E; $y = -38$). Abbreviations. R, right; F, category fluency; N, listing of numbers; E, encoding; R, retrieval; O, novel object; S, spatial change.

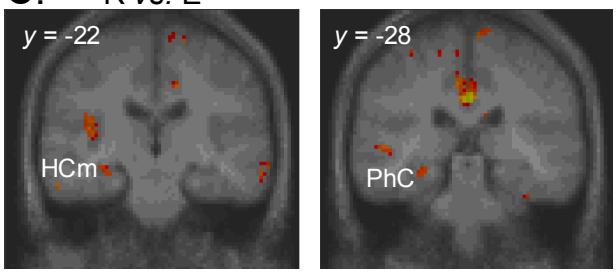
A. F *vs.* N



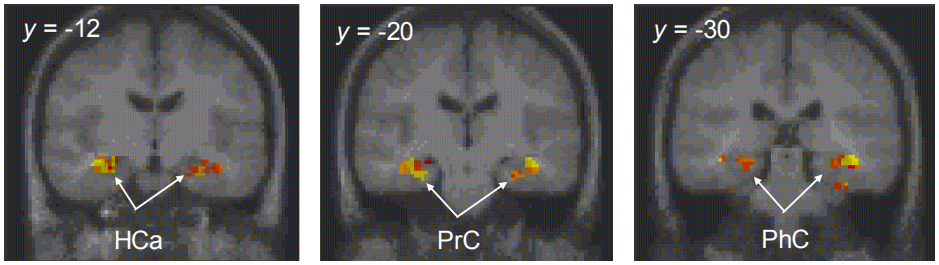
B. E *vs.* R



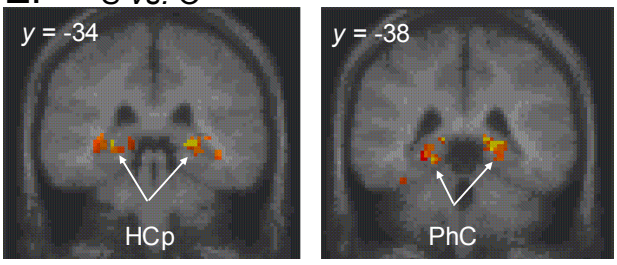
C. R *vs.* E



D. O *vs.* S



E. S *vs.* O



6. DISCUSSION

6.1. Study subjects

The study group comprised of 14 young, healthy, and co-operative control subjects. They performed well in both the neuropsychological and post-scan testing, and the amount of motion was minor during imaging. The results of Studies I–IV can be compared with each others, because the same subjects participated in all studies except for the presence of the two additional subjects in Study I. In Studies I–III, the fMRI data were primarily analyzed at the level of the individual study subjects. In order to summarize the results of the separate Studies I–III in this thesis, new tables of averaged fMRI responses of the individuals (Tables 3–9) were prepared. New figures (Figures 10–12 and 14) were also made to present the results of separate studies using a similar second level analysis and statistical threshold to enable direct comparisons between Studies I–IV. These new tables and figures present the results at the group level thus supplementing the results at the individual level that are given in detail in the original publications in the appendix of this thesis (Studies I–III).

The interindividual variability of fMRI responses was not investigated in detail in this series of studies. However, it will be discussed here, because it is certainly an interesting feature of fMRI data and an important point to clarify when planning to introduce BOLD fMRI methods into clinical research of neurodegenerative disorders, for example, or to evaluate if it is a possible diagnostic tool at the level of individual patients. The interindividual variability of the location, size and intensity of the brain activation areas was remarkable even in this homogeneous group of young subjects. A recent study addressed the issue of interindividual variability of the MTL responses during a simple face encoding task in a group of 29 elderly men (Vandenbroucke et al. 2004). When their data were analyzed at the individual level, eighteen of the 29 subjects demonstrated activation in the MTL structures, but a considerable variability was observed in location and size of the MTL activation areas. Importantly, if one registered the data to the Talairach standard space and averaged across the group, then no single MTL region was significantly activated. It has to be concluded that there is functional, as well as structural, variability between individual subjects. Therefore, fMRI data analysis using group averaging in standard stereotaxic space may not always be the most appropriate method for studies targeting the MTL, instead the analysis at the individual level is recommended. These problems may well be more pronounced in elderly subjects and memory-impaired patients but the observations regarding the interindividual variability described by Vandenbroucke et al. also concur with our findings in young control subjects, although in the present series of studies the MTL findings were also observed at the group level.

In addition to the interindividual variability, the effect of gender on brain activations during the Category Fluency Task was assessed and these results are reported in the appendix (Study I). It was found that the male group had somewhat stronger activations in the precentral, superior frontal, and retrosplenial

regions during the Category Fluency Task. A recent PET study examined the differences between men and women in naming concrete entities in one or more conceptual categories and found a greater modulation of activity (in terms of both activation and deactivation effects) in men (Grabowski et al. 2003). Another recent study found no significant sex differences in fMRI responses during letter fluency (Weiss et al. 2003). Overall, as in the present study, the gender effects seem to be much smaller than the task effects (Grabowski et al. 2003), although not totally negligible.

6.2. Methodological considerations

6.2.1. Activation paradigms

All the three paradigms were short and simple block-designed paradigms that were imaged using the 64x64 mosaic sequence with 128 whole-brain fMRI acquisitions per one cognitive task. No behavioral responses were collected during scanning, but the subjects were prepared and trained before and tested after the functional MR imaging session. The reason to use these kinds of short and easily feasible paradigms was that the tasks were designed for later imaging of patients with MCI and early AD, who may not necessarily be able to use response buttons under the fMRI experimental conditions. The advantage of the block-designed paradigms is a good detection power, which is a measure of the ability to detect brain activation areas, whereas the ability of block-paradigms to estimate the shape of the hemodynamic response is poor (Liu et al. 2001). A recently introduced "semirandom" paradigm design may provide both good detection power and temporal estimation efficiency, but the length of the imaging experiment is somewhat increased, which is not desirable when planning to image elderly patients. In these mixed blocked / event-related designs, single trials are presented during activation blocks at varying time intervals thus providing information about both sustained and transient changes of activity (Visscher et al. 2003).

In Study I, the goal of the Category Fluency Task design was to image the retrieval of semantically related words (Morris et al. 1989, Lezak 1995). To this end, neuronal mechanisms responsible for sensory and motor functions were excluded by contrasting the activation condition, *i.e.* production of words by category name, to rote production of an overlearned word list in the baseline block. Thus, the resulting main difference between activation and baseline conditions was considered to be the retrieval of semantically associated words. The fluency performance during the scanning was not controlled for, because of the scanner noise and the risk that overt word production would cause a serious head motion artifact. According to the post-scanning verbal fluency test there were no uniform differences in the strategy that could explain the interindividual differences (see appendix, Study I, Table), or especially the failure to detect MTL activations in some of the subjects. Similar block-designed approach with a task instruction to covert word production has been used in other fMRI studies on verbal fluency (Gurd et al.

2002, Adcock et al. 2003, Weiss et al. 2003), although methods to image overt word production have recently also been developed (Abrahams et al. 2003).

In the Paired-Associates Task (Study II), novel and colorful picture-pairs were presented during encoding, whereas during retrieval the other member of the pair was presented together with a question mark. Thus, the pictures were no longer novel during retrieval, when they were shown for the second time. The baseline condition for comparison to both of these conditions consisted of highly familiar picture-pairs that alternated randomly to suppress the monotony and the predictability of the baseline in order to reduce habituation and anticipation effects (Stark and Squire 2000a, Liu et al. 2001). The baseline familiar picture-pairs were always two of the same objects and active encoding of the baseline picture-pairs was not required but the baseline rather served as a control for visual stimulation. During the encoding and retrieval conditions, the perceptual and attentional demands were relatively similar, but this kind of task design cannot determine whether the activation responses during the encoding condition are due to the stimulus novelty effect or the intentional encoding process itself. The mean delay from the moment of encoding to retrieval was 56.0 s (ranging from 21.0 – 91.0 s) that is consistent with the studies reporting delay-dependent impairment in recognition memory in patients with damage to the perirhinal cortex (Buffalo et al. 1998). The short 20-s baseline conditions that were placed as delay-periods between the encoding and retrieval conditions were not used in the data analysis, because rehearsal of the encoded picture-pairs is likely to occur during the delay before retrieval. Associative encoding and retrieval have been investigated not only using picture-pairs (Henke et al. 1997, Rombouts et al. 1997, Poldrack et al. 2001), but also using word-picture-pairs (Sperling et al. 2001, Sperling et al. 2003a, Zeineh et al. 2003) and word-pairs with or without semantic tasks (Henke et al. 1999, Jackson and Schacter 2004). These studies report — in concordance with the present Study II — that the anterior and middle parts of the hippocampus and entorhinal / perirhinal and parahippocampal cortices become activated during presentation of novel, complex material.

Studies III and IV employed the Object *vs.* Spatial Novelty Task that made a distinction between the presentation of a single new object and the rearrangement of the five familiar objects. It is likely that our task with new spatial arrangements encouraged the subjects to pay attention to the mutual relation of the objects rather than encoding each scene as a whole. First, each array consisted of only five distinct pictorial items that became highly familiar during the practice session. Second, 16 different new arrangements of the objects were presented in a random order alternating with the familiar standard arrangement, making it unlikely that the subject would remember any of the new arrangements as a particular configuration. This stimulus was a passive viewing task without overt behavioral responses during scanning. The advantage of a passive task is that the possible confounding activation effects of the response selection, planning, and actual motor responses do not affect the network of activated brain regions (Downar et al. 2000). It was recently demonstrated that the MTL structures may be activated even during simple explicit and implicit

reaction time tasks with no obvious memory component or conscious awareness of the repeating sequence pattern (Schendan et al. 2003). However, such a perceptual task without behavioral responses is not able to reveal, whether the observed activations are directly dependent on memory processing such as incidental encoding or rather are based on perceptual processing (Bussey et al. 2003). The baseline condition was a spatial array of five objects, whereas the object condition exchanges one of the five familiar objects for a novel object. It can be argued that the novel object condition thus consists of the appearance of both a novel object and a novel arrangement. In contrast, the spatial condition moves objects to new spatial locations rather than using the same five locations but arranging the five familiar stimuli in a different order. Thus this condition involves both an appearance at a novel position and a novel arrangement, although both of these aspects are spatial and may thus be expected to activate hippocampal areas. In the present study, eye movements were not recorded during the task performance. It is, however, quite likely that eye movements were more pronounced during the spatial change than during the object novelty condition. This may partly contribute to the more widespread right-dominant parietal activation areas during visual monitoring of the new spatial arrangements (Konen et al. 2004). In the baseline (B) condition, all stimuli were highly familiar, whereas novel object (O) and spatial change (S) conditions introduced some kind of novelty. This may results in different levels of expectation in the subjects between the baseline and test conditions, but, importantly, not between O and S conditions that were statistically directly compared with each other. An approximately similar question about the participation of the MTL in processing of new identities and locations has been recently addressed by other investigators using stimuli such as combinations of faces and tools (Düzel et al. 2003) or objects and scenes (Köhler et al. 2002). There are, however, differences in the stimulus design; the stimulus array of five colorful objects in our study was visually more complex than the gray-scale pictures in the study of Düzel et al., placing thus more demand on the perceptual processing. Additionally, in their study the “new configurations” were new only with respect to establishment of novel associations but the faces and tools as such were highly familiar to the subjects. The instruction to intentionally encode and maintain the stimuli in memory (Düzel et al. 2003) may also affect the results.

6.2.2. fMRI data acquisition and analysis

A common clinically used 1.5 T MRI scanner equipped with GE-EPI capabilities appears to be sufficient to detect MTL activations. The use of spin-echo sequences and / or 4–7 T high magnetic field strengths may, however, accentuate microvasculature contributions to the BOLD signal and thus improve the ability of fMRI to more exactly localize neuronal activity (Cheng et al. 2001, Duong et al. 2003, Ugurbil et al. 2003). A recent study assessed the effect of the number of fMRI acquisition to be averaged on the spatial extent of activation areas, and the activation volume was found to be increased with increasing number of the acquisitions up to 22 scans (Saad et al. 2003). Expansions in the spatial extent of

activation were not random, but centered about the activation loci that appeared already with little or no averaging. Based on these findings, it seems that even the short acquisition periods such as the 128 fMRI acquisitions per paradigm in the present studies, may have enough detection power to pinpoint the true positive activation areas, but not the voxels with very low signal-to-noise ratios. The substantial interindividual variability of fMRI responses that was observed in the present study may, however, be partly due to the limited amount of data collected per task per subject. We did not find separate entorhinal cortical activations which may be due to the susceptibility artifacts in the anterior and medial parts of the MTL (Greicius et al. 2003). Undistortion methods have recently been developed for echo-planar images to improve the anatomic localization of activation and to increase the statistical power particularly in those brain areas where differences in magnetic properties of the tissue, bone, and air commonly distort the images (Cusack et al. 2003). In contrast to the entorhinal cortex, the perirhinal cortex is to a large extent located in the depth of the collateral sulcus (Insausti et al. 1998) that is not as prone to artifacts. In the present series of studies, the in-plane resolution of the functional MR images was 4 x 4 mm^2, and the slice thickness 5 mm, which is a commonly used resolution in fMRI studies. According to a recent review, the signal-to-noise ratio of this voxel-size is relatively good and the BOLD signal can be considered to reasonably reflect the underlying neuronal activity (Ugurbil et al. 2003). The mean volumes of the MTL structures of healthy subjects are 1600 mm^3 for the entorhinal cortex (corresponding to approximately 17 voxels in the functional images of the present study), 2500 mm^3 for the perirhinal cortex (26 voxels), 2600 mm^3 for the parahippocampal cortex (27 voxels), and 3250 mm^3 for the hippocampus (34 voxels) indicating that the resolution of the functional images used in the present study is, however, sufficient for examining the MTL structures (Laakso et al. 1997, Insausti et al. 1998, Pruessner et al. 2002).

According to our experience and also others (Vandenbroucke et al. 2004), data analysis at the individual level might be preferred for assessing the MTL activation areas, because in the case of small focal activation areas, a slight change in the location inside the same structure may result in a failure to detect the activations at the group level. In order to use published anatomic criteria for the borders of the MTL structures (Insausti et al. 1998, Pruessner et al. 2002), it is a good practice to use the functional images overlayed on the high-resolution anatomic images without spatial normalization to Talairach space. The practical disadvantage of the data analysis at the individual level is that it is very time-consuming. In addition to the data analysis at the individual level, we analyzed the data of Studies II and III at the group level using repeated measures ANOVA on the fMRI time-series of the MTL regions, and, for the present thesis, also using a second-level analysis (a one-sample *t*-tests). The results of these studies were essentially the same irrespective of the methods of analysis, *i.e.* whether observing the mean responses of the individual study subjects, the results of the repeated measures ANOVA of the time-series, or the second-level analysis.

Standard unpaired Student's *t*-test was used to generate statistical images (*Z*-maps) resulting from the contrast between two groups of images. MedX software offers three alternative statistical tests for this between groups statistical testing: paired t-test, unpaired t-test, and Kolmogorov-Smirnov test. Our decision to use the unpaired t-test was originally based on a publication (Xiong et al. 1996), which reported that the unpaired *t*-test (together with the cross-correlation coefficient) was the most powerful test because it maximized the true-positive rate while controlling the false-positive rate. The authors further argued that there is, in fact, no intrinsic pairing of data points in the activation and resting conditions, and therefore, fMRI data could be treated as uncorrelated samples. The statistical methods were maintained as stable as possible throughout these studies in order to enhance the comparability across Studies I–IV. In Study I, we used a relatively conservative statistical threshold for the significance of brain activation areas. In Studies II–III, we also used more liberal thresholds given the *a priori* expectations of MTL activations in those studies. However, we did not use an actual small volume correction that would lead to even lower statistical thresholds than, for example the threshold of $Z \geq 3.08$ in Study III. Overall, the signal changes of the MTL structures are small, but the range of 0.4–1.0 % signal intensity changes that were reported in Study III are very much in line with other studies (Davachi and Wagner 2002, Davachi et al. 2003, Sperling et al. 2003a, Zeineh et al. 2003, Jackson and Schacter 2004, Ranganath et al. 2004). In Study III, the differences of localization of the hippocampal and parahippocampal activation areas along the Talairach *x*-, *y*-, and *z*-axis were tested using parametric paired samples *t*-test. Instead, non-parametric tests were used for the statistical comparison over the four ROIs within the same condition, and the paired testing between ROI areas. Non-parametric tests were used for this purpose because they do not require assumptions about the shape of the underlying distribution. Paired statistical testing between ROI areas was also performed using a parametric paired samples t-test, which yielded essentially the same result. However, the distribution of the relative intensity changes in the perirhinal cortex during the novel object conditions was not normally distributed (one-sample Kolmogorov-Smirnov, $p = 0.03$), and therefore non–parametric tests were used for final data analysis.

6.3. The MTL activation areas

Study I In the Category Fluency Task, fMRI was used to study brain activation areas during retrieval of semantically-associated words relative to listing of numbers. This comparison resulted in activation of the left MTL structures, the hippocampus and parahippocampal cortex. Activation of the left MTL during a verbal fluency task is a novel finding. In the earlier functional imaging studies during performance of a verbal fluency task, the MTL was not imaged or analyzed or the data reported, probably because those studies rather focused on the fronto-parietal areas (Schlösser et al. 1998). To date, the fMRI studies using category fluency task are still few (Gurd et al. 2002, Perani et al. 2003), whereas letter

fluency has been used more frequently, although with contradictory results regarding the MTL (Curtis et al. 2001, Fu et al. 2002, Weiss et al. 2003). One recent fMRI study reported right hippocampal and parahippocampal activations during a covert block-designed letter fluency task in which the volunteers were asked to generate words beginning with letters B, A, F and S and this was compared to a relaxed resting condition (Weiss et al. 2003). Another recent study found hippocampal and parahippocampal activation areas during word production from the "hard" (A, E, F, G, I, N, O) but not "easy" (B, C, L, P, R, S, T) letters (Fu et al. 2002). Additionally, one study found hippocampal responses during letter fluency in patients with bipolar disorder but not in schizophrenic patients (Curtis et al. 2001). Although the fMRI studies on category fluency are few, evidence for the importance of the hippocampus in fluency performance has been obtained from studies on patients with temporal-lobe epilepsy with either hippocampal or non-hippocampal damage. In these studies, the patients with damage to hippocampal structures performed worse in the semantic fluency task (Gleissner and Elger 2001). Furthermore, the patient H.M. is impaired in verbal fluency (Schmolck et al. 2002), although he has some remaining semantic learning abilities (O'Kane et al. 2004).

A more common fMRI approach to the interface of episodic and semantic memory is to investigate word encoding during shallow and deep semantic processing tasks (Wagner et al. 1998, Otten et al. 2001), in which the incidental or intentional encoding is intertwined with the semantic retrieval of the knowledge about, for example, concrete and abstract or living and non-living categories. Interestingly, using this approach, one recent study demonstrated left hippocampal ($y = -16$) activation in young volunteers, and anterior hippocampal ($y = -9$) activations in young *vs.* elderly subjects in the deep (living or non-living decision) *vs.* shallow (lowercase or uppercase font) encoding contrast (Daselaar et al. 2003a). Retrieval of semantic knowledge related to spoken words was also recently investigated, and activations were found along the longitudinal axis of the hippocampus and parahippocampal gyrus as well as in the fusiform and lingual gyri (Bartha et al. 2003). Other studies have described posterior hippocampal responses during elaborative verbal rehearsal (Davachi and Wagner 2002), variable MTL activations during retrieval of semantic information related to faces (Henke et al. 2003), and, again, posterior hippocampal activation during successful retrieval of old semantic information (Bernard et al. 2004). Taken together, the functional imaging findings of associative semantic retrieval are insufficient to allow firm conclusions, but possibly the hippocampus and parahippocampal region act together for associative retrieval of items regardless of the more episodic or semantic nature of information. In the study by Manns et al. (2003), the crucial role of the hippocampus for learning and remembering facts was convincingly documented and the patients also demonstrated retrograde amnesia for factual information for even 30 years preceding the MTL damage. They concluded that the hippocampal region supports not only episodic but also semantic memory and that its role in the storage of semantic knowledge may be time limited (Manns et al. 2003b).

Study II The main MTL activation finding during the Paired-Associates Task was the activation of the perirhinal cortex during encoding of novel picture-pairs. This result is in line with experimental data from animal studies (Suzuki 1996, 1999, Brown and Aggleton 2001), especially because lesions confined to the rhinal cortex induce a severe deficit in visual paired-associate learning (Bunsey and Eichenbaum 1993, Murray et al. 1993, Higuchi and Miyashita 1996, Buckley and Gaffan 1998). It has been also documented in animals that some of the perirhinal neurons respond best to complex and colored stimuli, whereas the memory-related perirhinal neurons can be modulated by stimulus novelty so that the selective responses of these neurons rapidly decline as the stimuli become familiar (Fahy et al. 1993, Suzuki 1996). Our finding of perirhinal activation during the encoding of novel picture-pairs when compared either with baseline or retrieval conditions could be explained by a similar rapid decline in the responses of a large number of perirhinal neurons (Henson et al. 2003, Stark and Okado 2003, Jackson and Schacter 2004). It has been suggested that the perirhinal cortex, together with the parahippocampal cortex proper, plays a crucial role in object identification by integrating information from different sensory systems into complex polymodal feature conjunctions (Bar and Aminoff 2003, Bar 2004, Tyler et al. 2004). This view is supported by a recent fMRI study demonstrating that object processing always activated the fusiform gyrus irrespective of the task, whereas the perirhinal cortex was activated only when the task involved detailed discriminations, and also naming and probably incidental encoding, of objects (Tyler et al. 2004).

Experimental and clinical evidence points to a role of the perirhinal cortex not only in perceptual processes but in memory formation as well (Fernandez et al. 1999, Fernandez et al. 2002, Strange et al. 2002). In monkeys with rhinal cortical lesions, the impaired paired-associates learning has been attributed to a memory deficit because the responses of the perceptual inferotemporal neurons to items to be remembered were unaffected (Higuchi and Miyashita 1996). Furthermore, a dissociation between lesions of the perirhinal and inferotemporal cortices has been reported, such that the perirhinal cortex lesion did not affect visual discrimination but severely impaired learning and recognition memory (Buckley et al. 1997). One study of amnesic patients with perirhinal cortical damage reported a delay-dependent impairment of recognition memory (Buffalo et al. 1998). The mnemonic, in contrast to visual perceptual, role of the perirhinal cortex was also emphasized in another recent study in patients with total damage to the perirhinal cortex (Stark and Squire 2000b). Our findings in Studies II and III are consistent with the most recent results in monkeys with perirhinal cortical lesions that support the 'perceptual-mnemonic' role for the perirhinal cortex: the perirhinal cortex seems to be involved in both perception and memory rather than only in declarative memory having little or no role in perception (Bussey et al. 2003).

In addition to the perirhinal cortex, the anterior parts of the hippocampus and parahippocampal cortex were activated during associative encoding of novel pictures. Corresponding findings of anterior hippocampal and parahippocampal activations have been reported during successful learning of visuospatial paired-associates (Gould et al. 2003). Two other recent studies observed both anterior

hippocampal and rhinal cortical activations during successful encoding of word-pairs further promoting the concept that the anterior MTL supports the successful binding of information in memory (Henke et al. 1999, Jackson and Schacter 2004). Consistent with our findings in Studies II and III, an activation of the anterior and middle hippocampal, and perirhinal and parahippocampal cortical areas was observed during encoding of novel visual material irrespective whether the encoding was incidental or intentional (Rombouts et al. 2001, Stark and Okado 2003). On the other hand, several excellent studies have demonstrated posterior parahippocampal (Gabrieli et al. 1997, Brewer et al. 1998) and also hippocampal (Stern et al. 1996, Kirchhoff et al. 2000) activation areas during encoding. These studies have utilized complex, color photographs of indoor and outdoor scenes as the pictorial material to be encoded. The visuospatial nature of the scenic stimuli may be one factor that favours activation of the predominantly posterior parts of the MTL (Aguirre et al. 1996, Gabrieli et al. 1997, Epstein and Kanwisher 1998, Epstein et al. 1999, Köhler et al. 2002). In these studies, the task performance did not necessitate the formation of new associations as was the case in many studies reporting anterior MTL activation areas (Henke et al. 1997, Rombouts et al. 1997, Sperling et al. 2001, Sperling et al. 2003b, Zeineh et al. 2003, Jackson and Schacter 2004) as well as in Studies II and III of the present thesis. As Stern et al. (1996) discuss in their pioneering fMRI study during novel picture encoding, the functional roles of the anterior and posterior parts of the hippocampal formation are most probably qualitatively different, but all the factors that lead to this anterior-posterior distinction are to date not exactly known. In Study II, the hippocampus and parahippocampal cortex were also activated during retrieval, which is a consistent finding with other studies (Gabrieli et al. 1997, Eldridge et al. 2000, Davachi et al. 2003). One recent study concluded that the activation of the perirhinal cortex correlates with later successful item recognition, whereas the hippocampal and parahippocampal activation occurring during memory formation correlates with later source recollection, suggesting that the MTL subregions subserve distinct, but complementary, learning mechanisms (Davachi et al. 2003).

Study III Differential activation of the MTL areas in processing of novel objects and spatial configurations were observed during the Object *vs.* Spatial Novelty Task, such that the anterior MTL structures including the hippocampus and perirhinal cortex process object novelty, and the posterior MTL structures are involved in assessing the spatial relations of familiar objects. Imaging studies have reported anterior hippocampal responses during viewing of novel visual stimuli (Rombouts et al. 2001, Düzel et al. 2003, Bernard et al. 2004) and during active maintenance of novel information (Ranganath and D'Esposito 2001, Stern et al. 2001, Ranganath et al. 2004). As was discussed in the previous paragraph several studies have found posterior MTL activations during encoding of novel scenes (Stern et al. 1996, Gabrieli et al. 1997, Brewer et al. 1998, Kirchhoff et al. 2000). Pictures of complex scenes may encourage the subject to assess the relations among different items inside the scenes (Goel et al. 2004) as most probably is the case during observation of the novel spatial arrangements of the familiar items in Study III. Thus, the finding of

posterior hippocampal activations in all of these studies is not surprising. In Study III the presentation of one single novel item during the novel object condition may, in turn, incidentally lead to formation of new associations between the novel item and the rest of the layout which may partly impact on the anterior location of the hippocampal activation (Düzel et al. 2003, Zeineh et al. 2003, Jackson and Schacter 2004). Additionally in the present study, maintenance of novel object information is a possible cause for the observed anterior hippocampal response, but maintenance of novel configurational information does not seem to drive the anterior hippocampal region. The PET study by Köhler et al. (2002) reported anterior hippocampal activation during viewing novel scenes but not during searching for small changes inside familiar scenes, whereas in the study of Düzel et al. (2003) the right hippocampus responded to spatial associations, and the anterior hippocampus reacted bilaterally to recognition of new *vs.* old configurations (Düzel et al. 2003).

The lesion and electrophysiological studies in rats have indicated that the dorsal two thirds of the hippocampus are critical for spatial learning and memory (Jung et al. 1994, Moser and Moser 1998), and single-unit recording studies in monkeys have revealed that spatial delay activity is more common in the posterior hippocampus (Colombo et al. 1998). Additionally, studies in patients with anterior temporal lobectomies have found some remaining spatial learning abilities despite otherwise profound anterograde amnesia (Scoville and Milner 1957, Corkin 2002). There has also been a long ongoing debate as to whether the hippocampus is involved in recognition memory in monkeys (Murray and Mishkin 1998, Zola et al. 2000) and in humans (Manns et al. 2003a). The present results offer one possible resolution suggesting an important role of the anterior but not posterior hippocampus in processing of novel objects, and of the posterior hippocampus in spatial memory.

Functional distinction between the two parts of the parahippocampal region, the perirhinal and parahippocampal cortices, fits with the known anatomic connections in primates. Strong inputs from visual areas and outputs to the entorhinal cortex and hippocampus suggest a role for the perirhinal cortex in visual perception and memory (von Bonin and Bailey 1947, Suzuki and Amaral 1994a). Recent lesion and electrophysiological data also point to a 'perceptual-mnemonic' function of the perirhinal cortex in higher order visual processing as a final site of the ventral visual stream (Murray and Richmond 2001, Bussey et al. 2003). In contrast to the perirhinal cortex, the parahippocampal cortex receives projections also from the visuospatial areas, *i.e.* from the retrosplenial cortex and posterior parietal lobe (Suzuki and Amaral 1994a). Based on the anatomic connections, a dual role of the parahippocampal cortex in both object and spatially oriented memory processing is well possible (Suzuki and Amaral 1994a). In the present study, the finding of a distinction between the anterior parahippocampal activation associated with object novelty and the partly overlapping posterior activation associated with spatial rearrangements might reflect the presence of a human homologue of parahippocampal areas TF and TH. The parahippocampal zone that was activated

by the new spatial arrangements overlaps with the previously reported parahippocampal place area (Epstein and Kanwisher 1998, Epstein et al. 1999).

The proposed functions of the parahippocampal cortex such as memory encoding (Stern et al. 1996, Rombouts et al. 1997, Brewer et al. 1998, Wagner et al. 1998, Rombouts et al. 1999, Strange et al. 2002), visuospatial attention or perceptual matching of scenes (Burgess et al. 2002) may have contributed to the bilateral parahippocampal activation during the activation conditions when compared with baseline. However, the direct statistical comparison between the novel object and new arrangement conditions also revealed anatomically distinct bilateral parahippocampal activation zones, although the perceptual, attentional, and mnemonic requirements remained the same, indicating that the nature of the stimulus (novel object *vs*. new spatial arrangement) determined the location of the parahippocampal activation. Both bilateral (Aguirre and D'Esposito 1997, Epstein et al. 1999, Shelton and Gabrieli 2002) and right-sided unilateral (Johnsrude et al. 1999) posterior parahippocampal responses to processing of spatial scenes have previously been reported. In our study, most objects were easily nameable which is likely to influence the bilateral activation findings during spatial novelty processing.

Studies I–III In the present study, the anterior parts of the hippocampus were activated during processing and encoding of novel pictures, the middle parts of the hippocampus during episodic and semantic retrieval, and the posterior hippocampus during processing of visuospatial changes. Differences in hippocampal activation patterns along the long axis have been addressed in some previous studies (Small et al. 2001). Anterior hippocampus has been found to be activated during successful encoding of novel material irrespective whether the task instructions encouraged the participants to use incidental or intentional encoding (Rombouts et al. 1997, Sperling et al. 2003a, Stark and Okado 2003, Zeineh et al. 2003). Additionally, anterior hippocampal responses have been documented during novelty processing, and especially for initially remembered words in a list thus demonstrating a primacy effect (Strange et al. 1999, Strange et al. 2002, Bernard et al. 2004). The anterior hippocampal responses have also been suggested to decrease, and correspondingly, the posterior hippocampal responses to increase, with increasing stimulus familiarity (Strange et al. 1999, Yanike et al. 2004). Furthermore, there is evidence that the anterior hippocampus is sensitive to the "novelty of novelty" of oddball stimuli suggesting that one function of the anterior hippocampus is to register mismatches between expectation and experience (Strange and Dolan 2001). In one recent study, the mnemonic properties of different subregions of the hippocampus were assessed during learning of face-name associations. It was claimed that the CA fields 2 and 3 and the dentate gyrus of the anterior hippocampus were active during encoding but not during retrieval, and this activity decreased as associations were learned. In contrast, activity of the posterior subiculum was observed primarily during retrieval and to a lesser extent during encoding (Zeineh et al. 2003). These results suggest, in concordance with our results, that subdivisions within the hippocampus make distinct contributions to memory formation.

In summary, the hippocampus seems to be activated, whenever novel complex material is presented and this activity is probably futher strengthened when establishment of new associations is needed (Studies II and III). Hippocampus also participated in declarative memory retrieval irrespective of whether the nature of the retrieval processing was more semantic (Study I) or episodic (Study II). The parahippocampal region was activated during all tasks in Studies I–III. In addition to its function in supporting declarative memory formation, the activity of the parahippocampal region may be affected by visual perceptual, attentional and novelty-related effects. It perhaps also integrates semantic knowledge to the visually presented information (Eichenbaum 2000, Ranganath and Rainer 2003, Bar 2004).

6.4. The network of cortical activation areas

The whole-brain fMRI data during the Category Fluency, Paired-Associates and Object *vs.* Spatial Novelty Tasks that were presented in Tables 3, 5 and 7 as well as in Figures 10, 11 and 13 is discussed in the three following paragraphs.

Study I Similarly to the prefrontal activation areas detected during the Category Fluency Task in our study, earlier functional imaging studies have suggested that the left anterior inferior frontal gyrus (BA 47) is associated with semantic processing, whereas the more posterior part (BA 44 / 45) might be responsible for the phonologic processing (Fiez 1997, Gurd et al. 2002, Amunts et al. 2004). The same Brodmann areas are thought to be a part of the semantic executive system that contributes to immediate access to stored semantic knowledge and response selection (Demb et al. 1995, Thompson-Schill et al. 1998). In addition to these attentional and executive functions, it is likely that the large left frontal activation observed in the present study reflects the verbal working memory component required for the verbal fluency (Gabrieli et al. 1998, Smith et al. 1998, Wagner 1999, Veltman et al. 2003). An active inhibition in working memory is needed in the verbal fluency task to prevent the re-naming of items, and this might explain the activation observed in the right prefrontal region (Konishi et al. 1998). The retrosplenial region mediates major neural connections between the prefrontal cortex and the hippocampus (Suzuki and Amaral 1994a). Previous functional imaging studies have reported retrosplenial activations during language tasks (Binder et al. 1997, Daselaar et al. 2003b) and encoding of semantically associated word-pairs (Shallice et al. 1994). Additionally, the left fusiform gyrus has been described to be active during naming of concrete entities (Grabowski et al. 2003) and the superior parietal regions during performance of a semantic fluency task (Gurd et al. 2002).

Study II The whole-brain activation pattern in the encoding-baseline comparison of the Paired-Associates Task demonstrating activation areas in the temporo-occipital, and mainly left frontal and parietal regions is consistent with previous fMRI reports regarding the lateralization of activations according to the stimulus material, *i.e.* easily verbalizeable pictures (Kelley et al. 1998). The whole-brain neural correlates of memory retrieval suggesting left-dominant activation in the frontal and parietal regions

are somewhat contradictory to the early proposals of the hemispheric encoding/retrieval asymmetry (HERA) model for right-sided prefrontal activation during retrieval processing (Tulving et al. 1994), but consistent with more recent studies in which left prefrontal activation was detected during effortful (Buckner et al. 1998) and easily verbally coded information retrieval (Opitz et al. 2000). Notably, despite the pictorial nature of the stimuli, most subjects later reported using verbalization as the strategy to enhance memory encoding and retrieval. The fusiform gyrus is an interesting area that has been activated in several fMRI studies, in which visually presented material has been used in the memory tasks (Stern et al. 1996, Rombouts et al. 1997, Brewer et al. 1998, Sperling et al. 2001). There is evidence that the right fusiform gyrus is more involved in visual processing of objects, whereas the left fusiform is also involved in semantic processing (Simons et al. 2003), and that the activity of the fusiform gyrus is diminished during pharmacologically induced memory impairment (Sperling et al. 2002).

Study IV The presence of two functionally specialized visual pathways (Ungerleider and Mishkin 1982, Ungerleider and Haxby 1994, Vaina 1994, Aguirre and D'Esposito 1997), the ventral stream for identification of novel objects, and the dorsal stream for assessing new locations of familiar objects was verified in Study IV. We found evidence for the different roles of the ventrolateral and dorsolateral prefrontal cortices in processing of visual and visuospatial novelty (Wilson et al. 1993), but also for a common left middle prefrontal area for both conditions. The main new result of this study was that the cingulate / retrosplenial, and lateral temporal cortical regions show different functional roles and intrinsic specialization in processing of novel identities and locations of objects. The anterior parts of both the cingulate gyrus and superior and middle temporal regions were more activated by novel objects, whereas the posterior cingulate gyrus, retrosplenial region, and posterior parts of the lateral temporal neocortex were active during viewing of new spatial relations. This is in accordance with the findings regarding the anterior-posterior distinction among the MTL structures in Study III that are densely connected with the lateral temporal and mid-line cortical structures. Activation of the posterior cingulate gyrus during a visuospatial task is reported in some previous studies (Belger et al. 1998, Hopfinger et al. 2000). The neighboring retrosplenial region is an interesting area situated in an anatomically strategic gateway position. In the monkey, the retrosplenial region has connections with the dorsolateral prefrontal, posterior parahippocampal, superior temporal, and precuneal areas, and subcortically with the anterior and lateral thalamic nuclei (Morris et al. 1999). All areas of this retrosplenial network were activated during processing of new spatial locations. Anatomically, the retrosplenial region is in a position to act as an interface between the working memory functions of the mid-dorsolateral prefrontal areas and the long-term memory encoding of the MTL, whereas the posterior cingulate cortex is thought to be more involved in visuospatial attentional functions (Morris et al. 1999, Kobayashi and Amaral 2003). In functional terms, the retrosplenial region seems to have a role in processing of various aspects of spatial information and memory (Maguire 2001, Bar and Aminoff 2003, Meulenbroek et al. 2004). Patients with retrosplenial

lesions suffer loss of memory for spatial relationships (Takahashi et al. 1997), but have preserved abilities for discriminating and identifying buildings and landscapes. Damage to the right retrosplenial cortex has caused impaired learning of new routes, and defective navigation even in familiar environments (Maguire 2001).

6.5. Relevance of fMRI findings to AD

On the basis of common neuropathological and psychological findings in early AD, it can be hypothesized that MTL function is necessary for the retrieval of semantically-associated words that is required in a category fluency task. Our results indicate that the left MTL is engaged in the retrieval process during a category fluency task. This finding might explain why patients with early AD, presenting mainly with MTL pathology, are often impaired in verbal fluency tasks (Henry et al. 2004). In early AD, neuronal loss in the hippocampal formation is commonly observed in the subicular region, CA1 area, and in the entorhinal cortex (West et al. 1994, Gomez-Isla et al. 1996, Gomez-Isla et al. 1997, Killiany et al. 2000). Of these areas, the subicular complex was most consistently activated hippocampal area during the category fluency. Additionally, the parahippocampal and fusiform gyri are among the first affected cortical regions in AD (Braak and Braak 1996, Convit et al. 2000). Therefore, activation of these brain areas gives support to the neuropsychological observation that the category fluency is one of the most sensitive tests for detection of early stages of AD (Meulen et al. 2004). Recently, fMRI was used to compare cortical activation during a letter fluency task between two groups of cognitively normal women differing in their risk for developing AD with respect to family history of AD and apolipoprotein E allele status. The high-risk group showed increased activation in the left parietal region despite identical fluency performance (Smith et al. 2002), but, unfortunately, the MTL responses were not reported. In accordance with earlier studies, category fluency was recently described to be good in discriminating the MCI from AD patients (Chen et al. 2000, De Jager et al. 2003), but there are so far no published functional imaging studies on AD patients during performance of a category fluency task.

Detection of perirhinal cortical activations during visual perception and encoding of novel pictures is consistent with observations in AD. The earliest pathological neurofibrillary changes are observed in the transentorhinal cortex (Braak and Braak 1985, 1996), and at this preclinical stage of the disease, subjects might demonstrate difficulties in neuropsychological tests of episodic memory (Albert 1996). Furthermore, the volume of the hippocampal formation has been found to correlate with paired-associates learning in probable AD (Deweer et al. 1995). On the other hand, temporoparietal hypometabolism in PET studies has been predictive for AD in patients with memory impairment (Minoshima et al. 1997, Berent et al. 1999). Regional hypometabolism similar to that reported in AD patients was reported in monkeys with bilateral lesions in the rhinal cortex (Meguro et al. 2001). Interestingly, in Study II, both the rhinal cortex and its

projection areas in the temporoparietal association cortices were activated during the Paired-Associates Task.

The typical neuropsychological impairment in early AD is the failure to encode novel material (Carlesimo et al. 1995, Christensen et al. 1998), whereas deteriorations of executive functions, attention, or visuospatial skills do not belong to the most commonly reported initial neuropsychological deficits. Accordingly, one might expect that it would be the network for processing of novel objects rather than that for spatial changes which would correspond to the pathologically affected brain areas in early AD. With respect to the activation findings of the perirhinal, parahippocampal, fusiform and superior temporal cortical areas, this seems to be true, because neuropathological and structural MRI studies have detected neurofibrillary tangles, amyloid accumulation, and structural atrophy in these regions (Gomez-Isla et al. 1996, Convit et al. 2000, Killiany et al. 2000, Scheltens et al. 2002). The findings concerning the atrophy or hypometabolism of anterior cingulate cortex in early AD are discrepant, but in a very recent study both the mean SPECT activity, and the MRI volume of anterior cingulate cortex were decreased already in patients with prodromal AD (El Fakhri et al. 2003). There is also evidence for hypofunction of areas that were involved in detection of spatial changes in early AD patients; PET studies in patients with early AD or mild MCI have consistently demonstrated a characteristic pattern of hypometabolism in the posterior cingulate, temporoparietal, and frontal multimodal association cortices (Herholz et al. 2002, Chetelat et al. 2003, Nestor et al. 2003b). The posterior cingulate / retrosplenial region was extensively activated for the new spatial relations of objects, which could indirectly suggest that MCI and AD patients with PET hypometabolism in this region also would be impaired in performance of visuospatial or visuoconstructive tasks. Interestingly, there are very recent data reporting that the impairment may not always be restricted to episodic memory even the patients with MCI, but also extends to visuospatial and more general cognitive functions (Huang et al. 2003, Lambon Ralph et al. 2003). There is also a fascinating recent observation that the medial parietal and posterior cingulate regions reveal differences between young adults, older adults and patients with AD, such that the posterior cingulate responses are initially activated in all of these three groups, but in young adults the positive BOLD response quickly reverses to a deactivation, whereas the AD patients maintain the activation throughout the task (Lustig et al. 2003). In conclusion, fMRI has proved to be a valuable tool not only in cognitive neuroscience research into normal human memory but also in clinical research into the pathobiology of memory disorders (DeKosky and Marek 2003).

7. CONCLUSIONS

1. The present series of studies developed fMRI methods — consisting of activation paradigms, an imaging protocol, and data analysis — which are applicable to investigate both the normal and pathological function of the human MTL, as well as revealed specific functional roles of the MTL structures in certain declarative memory processes.
2. The left-sided MTL structures, *i.e.* the hippocampus and parahippocampal cortex participated in retrieval of semantically related words during the Category Fluency Task (Study I).
3. The hippocampus and parahippocampal cortex were activated during both encoding and retrieval of picture-pairs, but perirhinal cortical activation was observed only during encoding of novel visual paired-associates (Study II).
4. A partial functional dissociation was found between the perirhinal cortex and hippocampus in processing of object and spatial novelty, although the hippocampus also participated in processing of novel objects (Study III).
5. A corresponding distinction according to the object *vs.* spatial novelty processing was found along the ventral and dorsal visual streams, and prefrontal, cingulate and temporal neocortical areas (Study IV).
6. The anterior hippocampus was activated during associative encoding of picture-pairs and single novel objects (Studies II and III), the middle hippocampus during retrieval of semantically related words and picture-pairs (Studies I and II), and the very posterior hippocampus during processing of spatial relations (Study III).
7. Activation of the perirhinal cortex was observed during processing of novel pictures of objects (Studies II and III), whereas the parahippocampal cortex was activated during all of the three paradigms. During presentation of novel objects, the parahippocampal cortical activation area was, however, located more anteriorly than during presentation of new spatial configurations (Study III).
8. fMRI has proved to be a valuable tool in the basic neuroscience research of human memory. In addition, these findings provide interesting insights into the nature of the memory impairment in early AD, a disease where the earliest neuropathological changes occur in the MTL structures. Advanced fMRI methods are a promising instrument for future investigations of the pathophysiology of memory impairment in neurodegenerative diseases.

8. REFERENCES

Abrahams S, Goldstein LH, Simmons A, Brammer MJ, Williams SC, Giampietro VP, Andrew CM, Leigh PN. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. Hum Brain Mapp 2003;20:29-40.

Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage 2003;18:423-38.

Aguirre GK, D'Esposito M. Environmental knowledge is subserved by separable dorsal/ventral neural areas. J Neurosci 1997;17:2512-8.

Aguirre GK, Detre JA, Alsop DC, D'Esposito M. The parahippocampus subserves topographical learning in man. Cereb Cortex 1996;6:823-9.

Albert MS. Cognitive and neurobiologic markers of early Alzheimer disease. Proc Natl Acad Sci U S A 1996;93:13547-51.

Amaral DG, Insausti R. The hippocampal formation. In: Paxinos G, editor. The human nervous system. San Diego: Academic Press; 1990. p. 711-755.

Amunts K, Weiss PH, Mohlberg H, Pieperhoff P, Eickhoff S, Gurd JM, Marshall JC, Shah NJ, Fink GR, Zilles K. Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space--the roles of Brodmann areas 44 and 45. Neuroimage 2004;22:42-56.

Astur RS, Taylor LB, Mamelak AN, Philpott L, Sutherland RJ. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. Behav Brain Res 2002;132:77-84.

Baddeley A. Working memory: looking back and looking forward. Nat Rev Neurosci 2003;4:829-39.

Baddeley AD, Hitch GJ. Working memory. In: Bower GA, editor. The psychology of learning and motivation. New York: Academic Press; 1974. p. 47-89.

Bandettini PA, Wong EC, Jesmanowicz A, Hinks RS, Hyde JS. Spin-echo and gradient-echo EPI of human brain activation using BOLD contrast: a comparative study at 1.5 T. NMR Biomed 1994;7:12-20.

Bar M. Visual objects in context. Nat Rev Neurosci 2004;5:617-29.

Bar M, Aminoff E. Cortical analysis of visual context. Neuron 2003;38:347-58.

Bartha L, Brenneis C, Schocke M, Trinka E, Koylu B, Trieb T, Kremser C, Jaschke W, Bauer G, Poewe W, Benke T. Medial temporal lobe activation during semantic language processing: fMRI findings in healthy left- and right-handers. Brain Res Cogn Brain Res 2003;17:339-46.

Bayley PJ, Hopkins RO, Squire LR. Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. Neuron 2003;38:135-44.

Bayley PJ, Squire LR. Medial temporal lobe amnesia: Gradual acquisition of factual information by nondeclarative memory. J Neurosci 2002;22:5741-8.

Belger A, Puce A, Krystal JH, Gore JC, Goldman-Rakic P, McCarthy G. Dissociation of mnemonic and perceptual processes during spatial and nonspatial working memory using fMRI. Hum Brain Mapp 1998;6:14-32.

Belliveau JW, Kennedy DN, Jr., McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR. Functional mapping of the human visual cortex by magnetic resonance imaging. Science 1991;254:716-9.

Berent S, Giordani B, Foster N, Minoshima S, Lajiness-O'Neill R, Koeppe R, Kuhl DE. Neuropsychological function and cerebral glucose utilization in isolated memory impairment and Alzheimer's disease. J Psychiatr Res 1999;33:7-16.

Bernard FA, Bullmore ET, Graham KS, Thompson SA, Hodges JR, Fletcher PC. The hippocampal region is involved in successful recognition of both remote and recent famous faces. Neuroimage 2004;22:1704-14.

Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 1997;17:353-62.

Bloch F, Hansen WW, Packard M. The nuclear induction experiment. Physiol Rev 1946;70:474-85.

Bobinski M, de Leon MJ, Convit A, De Santi S, Wegiel J, Tarshish CY, Saint Louis LA, Wisniewski HM. MRI of entorhinal cortex in mild Alzheimer's disease. Lancet 1999;353:38-40.

Bohbot VD, Allen JJ, Nadel L. Memory deficits characterized by patterns of lesions to the hippocampus and parahippocampal cortex. Ann N Y Acad Sci 2000;911:355-68.

Bohbot VD, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 1998;36:1217-38.

Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. Magn Reson Med 1995;34:555-66.

Braak H, Braak E. On areas of transition between entorhinal allocortex and temporal isocortex in the human brain. Normal morphology and lamina-specific pathology in Alzheimer's disease. Acta Neuropathol (Berl) 1985;68:325-32.

Braak H, Braak E. Evolution of the neuropathology of Alzheimer's disease. Acta Neurol Scand Suppl 1996;165:3-12.

Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD. Making memories: brain activity that predicts how well visual experience will be remembered. Science 1998;281:1185-7.

Broca P. Anatomie comparée des circonvolutions cerebrales. Le grand lobe limbique et la scissure dans la série des mammifères. In: Rev Anthropol; 1878. p. 285-498.

Brodmann K. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: J. A. Barth; 1909.

Brown MW, Aggleton JP. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2001;2:51-61.

Buckley MJ, Gaffan D. Perirhinal cortex ablation impairs visual object identification. J Neurosci 1998;18:2268-75.

Buckley MJ, Gaffan D, Murray EA. Functional double dissociation between two inferior temporal cortical areas: perirhinal cortex versus middle temporal gyrus. J Neurophysiol 1997;77:587-98.

Buckner RL, Koutstaal W, Schacter DL, Wagner AD, Rosen BR. Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. Neuroimage 1998;7:151-62.

Buckner RL, Wheeler ME, Sheridan MA. Encoding processes during retrieval tasks. J Cogn Neurosci 2001;13:406-15.

Buffalo EA, Ramus SJ, Squire LR, Zola SM. Perception and recognition memory in monkeys following lesions of area TE and perirhinal cortex. Learn Mem 2000;7:375-82.

Buffalo EA, Reber PJ, Squire LR. The human perirhinal cortex and recognition memory. Hippocampus 1998;8:330-9.

Bunsey M, Eichenbaum H. Critical role of the parahippocampal region for paired-associate learning in rats. Behav Neurosci 1993;107:740-7.

Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. Neuron 2002;35:625-41.

Bussey TJ, Saksida LM, Murray EA. Impairments in visual discrimination after perirhinal cortex lesions: testing 'declarative' vs. 'perceptual-mnemonic' views of perirhinal cortex function. Eur J Neurosci 2003;17:649-60.

Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn Reson Med 1998;39:855-64.

Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000;12:1-47.

Carlesimo GA, Sabbadini M, Fadda L, Caltagirone C. Different components in word-list forgetting of pure amnesics, degenerative demented and healthy subjects. Cortex 1995;31:735-45.

Cave CB, Squire LR. Equivalent impairment of spatial and nonspatial memory following damage to the human hippocampus. Hippocampus 1991;1:329-40.

Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. Neurology 2000;55:1847-53.

Cheng K, Waggoner RA, Tanaka K. Human ocular dominance columns as revealed by high-field functional magnetic resonance imaging. Neuron 2001;32:359-74.

Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 2003;60:1374-7.

Christensen H, Kopelman MD, Stanhope N, Lorentz L, Owen P. Rates of forgetting in Alzheimer dementia. Neuropsychologia 1998;36:547-57.

Cohen MS, Bookheimer SY. Localization of brain function using magnetic resonance imaging. Trends Neurosci 1994;17:268-77.

Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science 1980;210:207-10.

Colombo M, Fernandez T, Nakamura K, Gross CG. Functional differentiation along the anterior-posterior axis of the hippocampus in monkeys. J Neurophysiol 1998;80:1002-5.

Convit A, de Asis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. Neurobiol Aging 2000;21:19-26.

Corkin S. What's new with the amnesic patient H.M.? Nat Rev Neurosci 2002;3:153-60.

Corkin S, Amaral DG, Gonzalez RG, Johnson KA, Hyman BT. H. M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. J Neurosci 1997;17:3964-79.

Curtis VA, Dixon TA, Morris RG, Bullmore ET, Brammer MJ, Williams SC, Sharma T, Murray RM, McGuire PK. Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. J Affect Disord 2001;66:111-21.

Cusack R, Brett M, Osswald K. An evaluation of the use of magnetic field maps to undistort echo-planar images. Neuroimage 2003;18:127-42.

Damasio H. Human brain anatomy in computerized images. New York: Oxford University Press; 1995.

Daselaar SM, Veltman DJ, Rombouts SA, Raaijmakers JG, Jonker C. Deep processing activates the medial temporal lobe in young but not in old adults. Neurobiol Aging 2003a;24:1005-11.

Daselaar SM, Veltman DJ, Rombouts SA, Raaijmakers JG, Jonker C. Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain 2003b;126:43-56.

Daselaar SM, Veltman DJ, Rombouts SA, Raaijmakers JG, Lazeron RH, Jonker C. Medial temporal lobe activity during semantic classification using a flexible fMRI design. Behav Brain Res 2002;136:399-404.

Davachi L, Mitchell JP, Wagner AD. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc Natl Acad Sci U S A 2003;100:2157-62.

Davachi L, Wagner AD. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. J Neurophysiol 2002;88:982-90.

De Jager CA, Hogervorst E, Combrinck M, Budge MM. Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. Psychol Med 2003;33:1039-50.

DeKosky ST, Marek K. Looking backward to move forward: early detection of neurodegenerative disorders. Science 2003;302:830-4.

Delatour B, Witter MP. Projections from the parahippocampal region to the prefrontal cortex in the rat: evidence of multiple pathways. Eur J Neurosci 2002;15:1400-7.

Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J Neurosci 1995;15:5870-8.

Deweer B, Lehericy S, Pillon B, Baulac M, Chiras J, Marsault C, Agid Y, Dubois B. Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. J Neurol Neurosurg Psychiatry 1995;58:590-7.

Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, Dale AM, Stern CE, Blacker D, Albert MS, Sperling RA. Medial temporal lobe function and structure in mild cognitive impairment. Ann Neurol 2004;56:27-35.

Dolan RJ, Fletcher PF. Encoding and retrieval in human medial temporal lobes: an empirical investigation using functional magnetic resonance imaging (fMRI). Hippocampus 1999;9:25-34.

Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 2000;3:277-83.

Doyon J, Milner B. Right temporal-lobe contribution to global visual processing. Neuropsychologia 1991;29:343-60.

Duong TQ, Yacoub E, Adriany G, Hu X, Ugurbil K, Kim SG. Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. Magn Reson Med 2003;49:1019-27.

Duvernoy H. The human parahippocampus: functional anatomy, vascularization and serial sections with MRI. Berlin: Springer; 1998.

Duvernoy H. The human brain: surface, three-dimensional sectional anatomy with MRI, and blood supply. second ed. Vienna: Springer-Verlag; 1999.

Duvernoy HM. The human hippocampus. An atlas of applied anatomy. Munich: Bergmann; 1988.

Düzel E, Habib R, Rotte M, Guderian S, Tulving E, Heinze HJ. Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. J Neurosci 2003;23:9439-44.

Eacott MJ, Gaffan D, Murray EA. Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. Eur J Neurosci 1994;6:1466-78.

Eichenbaum H. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 2000;1:41-50.

Eichenbaum H. The hippocampus and declarative memory: cognitive mechanisms and neural codes. Behav Brain Res 2001;127:199-207.

El Fakhri G, Kijewski MF, Johnson KA, Syrkin G, Killiany RJ, Becker JA, Zimmerman RE, Albert MS. MRI-guided SPECT perfusion measures and volumetric MRI in prodromal Alzheimer disease. Arch Neurol 2003;60:1066-72.

Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA. Remembering episodes: a selective role for the hippocampus during retrieval. Nat Neurosci 2000;3:1149-52.

Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of Alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol 2000;57:808-13.

Epstein R, Harris A, Stanley D, Kanwisher N. The parahippocampal place area: recognition, navigation, or encoding? Neuron 1999;23:115-25.

Epstein R, Kanwisher N. A cortical representation of the local visual environment. Nature 1998;392:598-601.

Ernst T, Hennig J. Observation of a fast response in functional MR. Magn Reson Med 1994;32:146-9.

Fahy FL, Riches IP, Brown MW. Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. Exp Brain Res 1993;96:457-72.

Fernandez G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dumpelmann M, Van Roost D, Elger CE. Real-time tracking of memory formation in the human rhinal cortex and hippocampus. Science 1999;285:1582-5.

Fernandez G, Klaver P, Fell J, Grunwald T, Elger CE. Human declarative memory formation: segregating rhinal and hippocampal contributions. Hippocampus 2002;12:514-9.

Fernandez G, Weyerts H, Schrader-Bolsche M, Tendolkar I, Smid HG, Tempelmann C, Hinrichs H, Scheich H, Elger CE, Mangun GR, Heinze HJ. Successful verbal encoding into episodic memory engages the posterior hippocampus: a parametrically analyzed functional magnetic resonance imaging study. J Neurosci 1998;18:1841-7.

Fiez JA. Phonology, semantics, and the role of the left inferior prefrontal cortex. Hum Brain Mapp 1997;5:79-83.

Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci U S A 1986;83:1140-4.

Friston KJ, Worsley KJ, Frackowiak RS, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. Human Brain Mapping 1994;1:210-220.

Fu CH, Morgan K, Suckling J, Williams SC, Andrew C, Vythelingum GN, McGuire PK. A functional magnetic resonance imaging study of overt letter verbal fluency using a clustered acquisition sequence: greater anterior cingulate activation with increased task demand. Neuroimage 2002;17:871-9.

Fyhn M, Molden S, Witter MP, I. ME, Moser MB. Spatial representation in the entorhinal cortex. Science 2004;305:1258-64.

Gabrieli JD, Brewer JB, Desmond JE, Glover GH. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 1997;276:264-6.

Gabrieli JD, Poldrack RA, Desmond JE. The role of left prefrontal cortex in language and memory. Proc Natl Acad Sci U S A 1998;95:906-13.

Gleissner U, Elger CE. The hippocampal contribution to verbal fluency in patients with temporal lobe epilepsy. Cortex 2001;37:55-63.

Goel V, Makale M, Grafman J. The hippocampal system mediates logical reasoning about familiar spatial environments. J Cogn Neurosci 2004;16:654-64.

Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann Neurol 1997;41:17-24.

Gomez-Isla T, Price JL, McKeel DW, Jr., Morris JC, Growdon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci 1996;16:4491-500.

Gould RL, Brown RG, Owen AM, ffytche DH, Howard RJ. fMRI BOLD response to increasing task difficulty during successful paired associates learning. Neuroimage 2003;20:1006-19.

Grabowski TJ, Damasio H, Eichhorn GR, Tranel D. Effects of gender on blood flow correlates of naming concrete entities. Neuroimage 2003;20:940-54.

Greicius MD, Krasnow B, Boyett-Anderson JM, Eliez S, Schatzberg AF, Reiss AL, Menon V. Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. Hippocampus 2003;13:164-74.

Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988;38:900-3.

Gurd JM, Amunts K, Weiss PH, Zafiris O, Zilles K, Marshall JC, Fink GR. Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: an fMRI study with clinical implications. Brain 2002;125:1024-38.

Hari R, Levänen S, Raij T. Timing of human cortical functions during cognition: role of MEG. Trends Cogn Sci 2000;4:455-462.

Heeger DJ, Ress D. What does fMRI tell us about neuronal activity? Nat Rev Neurosci 2002;3:142-51.

Henke K, Buck A, Weber B, Wieser HG. Human hippocampus establishes associations in memory. Hippocampus 1997;7:249-56.

Henke K, Mondadori CR, Treyer V, Nitsch RM, Buck A, Hock C. Nonconscious formation and reactivation of semantic associations by way of the medial temporal lobe. Neuropsychologia 2003;41:863-76.

Henke K, Weber B, Kneifel S, Wieser HG, Buck A. Human hippocampus associates information in memory. Proc Natl Acad Sci U S A 1999;96:5884-9.

Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia 2004;42:1212-22.

Henson RN, Cansino S, Herron JE, Robb WG, Rugg MD. A familiarity signal in human anterior medial temporal cortex? Hippocampus 2003;13:301-4.

Herholz K, Salmon E, Perani D, Baron JC, Holthoff V, Frolich L, Schonknecht P, Ito K, Mielke R, Kalbe E, Zundorf G, Delbeuck X, Pelati O, Anchisi D, Fazio F, Kerrouche N, Desgranges B, Eustache F, Beuthien-Baumann B, Menzel C, Schroder J, Kato T, Arahata Y, Henze M, Heiss WD. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 2002;17:302-16.

Higuchi S, Miyashita Y. Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions. Proc Natl Acad Sci U S A 1996;93:739-43.

Hopfinger JB, Buonocore MH, Mangun GR. The neural mechanisms of top-down attentional control. Nat Neurosci 2000;3:284-91.

Huang C, Wahlund LO, Almkvist O, Elehu D, Svensson L, Jonsson T, Winblad B, Julin P. Voxel- and VOI-based analysis of SPECT CBF in relation to clinical and psychological heterogeneity of mild cognitive impairment. Neuroimage 2003;19:1137-44.

Huther G, Dorfl J, Van der Loos H, Jeanmonod D. Microanatomic and vascular aspects of the temporomesial region. Neurosurgery 1998;43:1118-36.

Hänninen T, Hallikainen M, Koivisto K, Helkala EL, Reinikainen KJ, Soininen H, Mykkänen L, Laakso M, Pyorälä K, Riekkinen PJ, Sr. A follow-up study of age-associated memory impairment: neuropsychological predictors of dementia. J Am Geriatr Soc 1995;43:1007-15.

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkänen A. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 1998;19:659-71.

Insausti R, Munoz M. Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (Macaca fascicularis). Eur J Neurosci 2001;14:435-51.

Jackson O, 3rd, Schacter DL. Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. Neuroimage 2004;21:456-62.

Johnson KA, Albert MS. Perfusion abnormalities in prodromal AD. Neurobiol Aging 2000;21:289-92.

Johnsrude IS, Owen AM, Crane J, Milner B, Evans AC. A cognitive activation study of memory for spatial relationships. Neuropsychologia 1999;37:829-41.

Jung MW, Wiener SI, McNaughton BL. Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. J Neurosci 1994;14:7347-56.

Juottonen K, Laakso MP, Insausti R, Lehtovirta M, Pitkänen A, Partanen K, Soininen H. Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. Neurobiol Aging 1998;19:15-22.

Kanne SM, Balota DA, Storandt M, McKeel DW, Jr., Morris JC. Relating anatomy to function in Alzheimer's disease: neuropsychological profiles predict regional neuropathology 5 years later. Neurology 1998;50:979-85.

Kelley WM, Miezin FM, McDermott KB, Buckner RL, Raichle ME, Cohen NJ, Ollinger JM, Akbudak E, Conturo TE, Snyder AZ, Petersen SE. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron 1998;20:927-36.

Killiany RJ, Gomez-Isla T, Moss M, Kikinis R, Sandor T, Jolesz F, Tanzi R, Jones K, Hyman BT, Albert MS. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 2000;47:430-9.

Kirchhoff BA, Wagner AD, Maril A, Stern CE. Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci 2000;20:6173-80.

Kobayashi Y, Amaral DG. Macaque monkey retrosplenial cortex: II. Cortical afferents. J Comp Neurol 2003;466:48-79.

Konen CS, Kleiser R, Wittsack HJ, Bremmer F, Seitz RJ. The encoding of saccadic eye movements within human posterior parietal cortex. Neuroimage 2004;22:304-14.

Konishi S, Nakajima K, Uchida I, Kameyama M, Nakahara K, Sekihara K, Miyashita Y. Transient activation of inferior prefrontal cortex during cognitive set shifting. Nat Neurosci 1998;1:80-4.

Kordower JH, Chu Y, Stebbins GT, DeKosky ST, Cochran EJ, Bennett D, Mufson EJ. Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. Ann Neurol 2001;49:202-13.

Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology 2004;63:94-100.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A 1992;89:5675-9.

Köhler S, Crane J, Milner B. Differential contributions of the parahippocampal place area and the anterior hippocampus to human memory for scenes. Hippocampus 2002;12:718-23.

Laakso MP, Juottonen K, Partanen K, Vainio P, Soininen H. MRI volumetry of the hippocampus: the effect of slice thickness on volume formation. Magn Reson Imaging 1997;15:263-5.

Laakso MP, Soininen H, Partanen K, Lehtovirta M, Hallikainen M, Hänninen T, Helkala EL, Vainio P, Riekkinen PJ, Sr. MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. Neurobiol Aging 1998;19:23-31.

Lambon Ralph MA, Patterson K, Graham N, Dawson K, Hodges JR. Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer's disease: a cross-sectional and longitudinal study of 55 cases. Brain 2003;126:2350-62.

Lauterbur PC. Image formation by induced local interactions: examples employing nuclear magnetic resonance. Nature 1973;242:190-1.

Lavenex P, Amaral DG. Hippocampal-neocortical interaction: a hierarchy of associativity. Hippocampus 2000;10:420-30.

Lavenex P, Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. J Comp Neurol 2002;447:394-420.

Lehtovirta M, Soininen H, Laakso MP, Partanen K, Helisalmi S, Mannermaa A, Ryynänen M, Kuikka J, Hartikainen P, Riekkinen PJ, Sr. SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E epsilon 4 allele. J Neurol Neurosurg Psychiatry 1996;60:644-9.

Lepage M, Habib R, Tulving E. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus 1998;8:313-22.

Lezak MD. Neuropsychological assessment. New York: Oxford University Press; 1995.

Liu TT, Frank LR, Wong EC, Buxton RB. Detection power, estimation efficiency, and predictability in event-related fMRI. Neuroimage 2001;13:759-73.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001;412:150-7.

Lopes da Silva FH, Witter MP, Boeijinga PH, Lohman AH. Anatomic organization and physiology of the limbic cortex. Physiol Rev 1990;70:453-511.

Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL. Functional deactivations: change with age and dementia of the Alzheimer type. Proc Natl Acad Sci U S A 2003;100:14504-9.

Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, Petersen RC, Boeve BF, Knopman D, Tang-Wai DF, Ivnik RJ, Smith GE, Tangalos EG, Jack CR, Jr. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology 2003;61:500-6.

Maguire EA. The retrosplenial contribution to human navigation: A review of lesion and neuroimaging findings. Scand J Psychol 2001;42:225-238.

Maguire EA, Frackowiak RS, Frith CD. Recalling routes around London: activation of the right hippocampus in taxi drivers. J Neurosci 1997;17:7103-10.

Maguire EA, Frith CD. The brain network associated with acquiring semantic knowledge. Neuroimage 2004;22:171-8.

Maguire EA, Mummery CJ, Buchel C. Patterns of hippocampal-cortical interaction dissociate temporal lobe memory subsystems. Hippocampus 2000;10:475-82.

Mandeville JB, Marota JJ, Ayata C, Moskowitz MA, Weisskoff RM, Rosen BR. MRI measurement of the temporal evolution of relative CMRO(2) during rat forepaw stimulation. Magn Reson Med 1999;42:944-51.

Manns JR, Hopkins RO, Reed JM, Kitchener EG, Squire LR. Recognition memory and the human hippocampus. Neuron 2003a;37:171-80.

Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. Neuron 2003b;38:127-33.

Mansfield P. Multi-planar image formation using NMR spin echoes. J Physiol Chem 1977;10:L55-8.

Martin A, Chao LL. Semantic memory and the brain: structure and processes. Curr Opin Neurobiol 2001;11:194-201.

Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. Neurology 1994;44:1427-32.

Mayes AR, Montaldi D, Spencer TJ, Roberts N. Recalling spatial information as a component of recently and remotely acquired episodic or semantic memories: an FMRI study. Neuropsychology 2004;18:426-41.

Meguro K, LeMestric C, Landeau B, Desgranges B, Eustache F, Baron JC. Relations between hypometabolism in the posterior association neocortex and hippocampal atrophy in Alzheimer's disease: a PET/MRI correlative study. J Neurol Neurosurg Psychiatry 2001;71:315-21.

Meulen EF, Schmand B, Van Campen JP, De Koning SJ, Ponds RW, Scheltens P, Verhey FR. The seven minute screen: a neurocognitive screening test highly sensitive to various types of dementia. J Neurol Neurosurg Psychiatry 2004;75:700-705.

Meulenbroek O, Petersson KM, Voermans N, Weber B, Fernandez G. Age differences in neural correlates of route encoding and route recognition. Neuroimage 2004;22:1503-14.

Milner B, Squire LR, Kandel ER. Cognitive neuroscience and the study of memory. Neuron 1998;20:445-68.

Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 1997;42:85-94.

Monsch AU, Bondi MW, Butters N, Salmon DP, Katzman R, Thal LJ. Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer type. Arch Neurol 1992;49:1253-8.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, Clark C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159-65.

Morris R, Petrides M, Pandya DN. Architecture and connections of retrosplenial area 30 in the rhesus monkey (Macaca mulatta). Eur J Neurosci 1999;11:2506-18.

Moser MB, Moser EI. Functional differentiation in the hippocampus. Hippocampus 1998;8:608-19.

Moss MB, Albert MS, Butters N, Payne M. Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. Arch Neurol 1986;43:239-46.

Mummery CJ, Patterson K, Wise RJ, Vandenbergh R, Price CJ, Hodges JR. Disrupted temporal lobe connections in semantic dementia. Brain 1999;122 (Pt 1):61-73.

Murray EA, Gaffan D, Mishkin M. Neural substrates of visual stimulus-stimulus association in rhesus monkeys. J Neurosci 1993;13:4549-61.

Murray EA, Mishkin M. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 1998;18:6568-82.

Murray EA, Richmond BJ. Role of perirhinal cortex in object perception, memory, and associations. Curr Opin Neurobiol 2001;11:188-93.

Naya Y, Yoshida M, Miyashita Y. Backward spreading of memory-retrieval signal in the primate temporal cortex. Science 2001;291:661-4.

Nestor PJ, Fryer TD, Ikeda M, Hodges JR. Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). Eur J Neurosci 2003a;18:2663-7.

Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. Ann Neurol 2003b;54:343-51.

Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 1990;87:9868-72.

Ogawa S, Lee TM, Stepnoski R, Chen W, Zhu XH, Ugurbil K. An approach to probe some neural systems interaction by functional MRI at neural time scale down to milliseconds. Proc Natl Acad Sci U S A 2000;97:11026-31.

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A 1992;89:5951-5.

O'Kane G, Kensinger EA, Corkin S. Evidence for semantic learning in profound amnesia: an investigation with patient H.M. Hippocampus 2004;14:417-25.

Opitz B, Mecklinger A, Friederici AD. Functional asymmetry of human prefrontal cortex: encoding and retrieval of verbally and nonverbally coded information. Learn Mem 2000;7:85-96.

Otten LJ, Henson RN, Rugg MD. Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain 2001;124:399-412.

Parkinson JK, Murray EA, Mishkin M. A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. J Neurosci 1988;8:4159-67.

Parks RW, Loewenstein DA, Dodrill KL, Barker WW, Yoshii F, Chang JY, Emran A, Apicella A, Sheramata WA, Duara R. Cerebral metabolic effects of a verbal fluency test: a PET scan study. J Clin Exp Neuropsychol 1988;10:565-75.

Pauling L, Coryell C. The magnetic properties and structure of hemoglobin, oxyhemoglobin, and carbon monoxyhemoglobin. Proc Natl Acad Sci U S A 1936;22:210-6.

Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hanninen T, Laakso MP, Hallikainen M, Vanhanen M, Nissinen A, Helkala EL, Vainio P, Vanninen R, Partanen K, Soininen H. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol Aging 2004;25:303-10.

Perani D, Cappa SF, Tettamanti M, Rosa M, Scifo P, Miozzo A, Basso A, Fazio F. A fMRI study of word retrieval in aphasia. Brain Lang 2003;85:357-68.

Petersen RC, Smith GE, Ivnik RJ, Kokmen E, Tangalos EG. Memory function in very early Alzheimer's disease. Neurology 1994;44:867-72.

Phelps EA, Hyder F, Blamire AM, Shulman RG. FMRI of the prefrontal cortex during overt verbal fluency. Neuroreport 1997;8:561-5.

Poldrack RA, Clark J, Pare-Blagoev EJ, Shohamy D, Creso Moyano J, Myers C, Gluck MA. Interactive memory systems in the human brain. Nature 2001;414:546-50.

Pruessner JC, Kohler S, Crane J, Pruessner M, Lord C, Byrne A, Kabani N, Collins DL, Evans AC. Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. Cereb Cortex 2002;12:1342-53.

Purcell EM, Torrey HC, Pound RV. Resonance absorbtion by nuclear magnetic moments in a solid. Physical Rev 1946;69:37-8.

Ranganath C, Cohen MX, Dam C, D'Esposito M. Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. J Neurosci 2004;24:3917-25.

Ranganath C, D'Esposito M. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 2001;31:865-73.

Ranganath C, Rainer G. Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 2003;4:193-202.

Reed JM, Squire LR. Retrograde amnesia for facts and events: findings from four new cases. J Neurosci 1998;18:3943-54.

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 1996;16:5233-55.

Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA, Lazeron RH, Valk J, Scheltens P. Functional MR imaging in Alzheimer's disease during memory encoding. AJNR Am J Neuroradiol 2000;21:1869-75.

Rombouts SA, Barkhof F, Witter MP, Machielsen WC, Scheltens P. Anterior medial temporal lobe activation during attempted retrieval of encoded visuospatial scenes: an event-related fMRI study. Neuroimage 2001;14:67-76.

Rombouts SA, Machielsen WC, Witter MP, Barkhof F, Lindeboom J, Scheltens P. Visual association encoding activates the medial temporal lobe: a functional magnetic resonance imaging study. Hippocampus 1997;7:594-601.

Rombouts SA, Scheltens P, Machielson WC, Barkhof F, Hoogenraad FG, Veltman DJ, Valk J, Witter MP. Parametric fMRI analysis of visual encoding in the human medial temporal lobe. Hippocampus 1999;9:637-43.

Roy CS, Sherrington CS. On the regulation of the blood supply of the brain. J Physiol 1890;11:85-108.

Saad ZS, Ropella KM, DeYoe EA, Bandettini PA. The spatial extent of the BOLD response. Neuroimage 2003;19:132-44.

Sakai K, Miyashita Y. Neural organization for the long-term memory of paired associates. Nature 1991;354:152-5.

Sandson TA, O'Connor M, Sperling RA, Edelman RR, Warach S. Noninvasive perfusion MRI in Alzheimer's disease: a preliminary report. Neurology 1996;47:1339-42.

Schacter DL, Tulving E. Memory systems. Cambridge: The MIT Press; 1994.

Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 1999;9:7-24.

Scheltens P, Fox N, Barkhof F, De Carli C. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. Lancet Neurol 2002;1:13-21.

Schendan HE, Searl MM, Melrose RJ, Stern CE. An FMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. Neuron 2003;37:1013-25.

Schlösser R, Hutchinson M, Joseffer S, Rusinek H, Saarimäki A, Stevenson J, Dewey SL, Brodie JD. Functional magnetic resonance imaging of human brain activity in a verbal fluency task. J Neurol Neurosurg Psychiatry 1998;64:492-8.

Schmolck H, Kensinger EA, Corkin S, Squire LR. Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. Hippocampus 2002;12:520-33.

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurochem 1957;20:11-21.

Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RS, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature 1994;368:633-5.

Shelton AL, Gabrieli JD. Neural correlates of encoding space from route and survey perspectives. J Neurosci 2002;22:2711-7.

Sheth SA, Nemoto M, Guiou M, Walker M, Pouratian N, Toga AW. Linear and Nonlinear Relationships between Neuronal Activity, Oxygen Metabolism, and Hemodynamic Responses. Neuron 2004;42:347-55.

Simons JS, Koutstaal W, Prince S, Wagner AD, Schacter DL. Neural mechanisms of visual object priming: evidence for perceptual and semantic distinctions in fusiform cortex. Neuroimage 2003;19:613-26.

Small SA, Nava AS, Perera GM, DeLaPaz R, Mayeux R, Stern Y. Circuit mechanisms underlying memory encoding and retrieval in the long axis of the hippocampal formation. Nat Neurosci 2001;4:442-9.

Small SA, Perera GM, DeLaPaz R, Mayeux R, Stern Y. Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. Ann Neurol 1999;45:466-72.

Smith CD, Andersen AH, Kryscio RJ, Schmitt FA, Kindy MS, Blonder LX, Avison MJ. Women at risk for AD show increased parietal activation during a fluency task. Neurology 2002;58:1197-202.

Smith EE, Jonides J, Marshuetz C, Koeppe RA. Components of verbal working memory: evidence from neuroimaging. Proc Natl Acad Sci U S A 1998;95:876-82.

Sperling R, Chua E, Cocchiarella A, Rand-Giovannetti E, Poldrack R, Schacter DL, Albert M. Putting names to faces: successful encoding of associative memories activates the anterior hippocampal formation. Neuroimage 2003a;20:1400-10.

Sperling R, Greve D, Dale A, Killiany R, Holmes J, Rosas HD, Cocchiarella A, Firth P, Rosen B, Lake S, Lange N, Routledge C, Albert M. Functional MRI detection of pharmacologically induced memory impairment. Proc Natl Acad Sci U S A 2002;99:455-60.

Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, Schacter DL, Albert MS. fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003b;74:44-50.

Sperling RA, Bates JF, Cocchiarella AJ, Schacter DL, Rosen BR, Albert MS. Encoding novel face-name associations: a functional MRI study. Hum Brain Mapp 2001;14:129-39.

Spiers HJ, Maguire EA, Burgess N. Hippocampal amnesia. Neurocase 2001;7:357-82.

Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A 1996;93:13515-22.

Squire LR, Zola SM. Episodic memory, semantic memory, and amnesia. Hippocampus 1998;8:205-11.

Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991;253:1380-6.

Stark CE, Okado Y. Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. J Neurosci 2003;23:6748-53.

Stark CE, Squire LR. Functional magnetic resonance imaging (fMRI) activity in the hippocampal region during recognition memory. J Neurosci 2000a;20:7776-81.

Stark CE, Squire LR. Intact visual perceptual discrimination in humans in the absence of perirhinal cortex. Learn Mem 2000b;7:273-8.

Steckler T, Drinkenburg WH, Sahgal A, Aggleton JP. Recognition memory in rats--II. Neuroanatomical substrates. Prog Neurobiol 1998;54:313-32.

Stehling MK, Turner R, Mansfield P. Echo-planar imaging: magnetic resonance imaging in a fraction of a second. Science 1991;254:43-50.

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A 1996;93:8660-5.

Stern CE, Sherman SJ, Kirchhoff BA, Hasselmo ME. Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. Hippocampus 2001;11:337-46.

Strange BA, Dolan RJ. Adaptive anterior hippocampal responses to oddball stimuli. Hippocampus 2001;11:690-8.

Strange BA, Fletcher PC, Henson RN, Friston KJ, Dolan RJ. Segregating the functions of human hippocampus. Proc Natl Acad Sci U S A 1999;96:4034-9.

Strange BA, Otten LJ, Josephs O, Rugg MD, Dolan RJ. Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. J Neurosci 2002;22:523-8.

Suzuki WA. The anatomy, physiology and functions of the perirhinal cortex. Curr Opin Neurobiol 1996;6:179-86.

Suzuki WA. The long and the short of it: memory signals in the medial temporal lobe. Neuron 1999;24:295-8.

Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J Comp Neurol 1994a;350:497-533.

Suzuki WA, Amaral DG. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. J Neurosci 1994b;14:1856-77.

Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cytoarchitectonic and chemoarchitectonic organization. J Comp Neurol 2003;463:67-91.

Suzuki WA, Zola-Morgan S, Squire LR, Amaral DG. Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. J Neurosci 1993;13:2430-51.

Takahashi N, Kawamura M, Shiota J, Kasahata N, Hirayama K. Pure topographic disorientation due to right retrosplenial lesion. Neurology 1997;49:464-9.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York: Thieme; 1988.

Thompson JK, Peterson MR, Freeman RD. Single-neuron activity and tissue oxygenation in the cerebral cortex. Science 2003;299:1070-2.

Thompson-Schill SL, Swick D, Farah MJ, D'Esposito M, Kan IP, Knight RT. Verb generation in patients with focal frontal lesions: a neuropsychological test of neuroimaging findings. Proc Natl Acad Sci U S A 1998;95:15855-60.

Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 1982;714:265-70.

Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Natl Acad Sci U S A 1994;91:2016-20.

Tulving E, Markowitsch HJ. Episodic and declarative memory: role of the hippocampus. Hippocampus 1998;8:198-204.

Tuunanen PI, Kavec M, Jousmäki V, Usenius JP, Hari R, Salmelin R, Kauppinen RA. Comparison of BOLD fMRI and MEG characteristics to vibrotactile stimulation. Neuroimage 2003;19:1778-86.

Tyler LK, Stamatakis EA, Bright P, Acres K, Abdallah S, Rodd JM, Moss HE. Processing objects at different levels of specificity. J Cogn Neurosci 2004;16:351-62.

Ugurbil K, Toth L, Kim DS. How accurate is magnetic resonance imaging of brain function? Trends Neurosci 2003;26:108-14.

Ungerleider LG, Haxby JV. 'What' and 'where' in the human brain. Curr Opin Neurobiol 1994;4:157-65.

Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. Analysis of visual behavior. Cambridge, MA: MTI Press; 1982. p. 549-86.

Vaina LM. Functional segregation of color and motion processing in the human visual cortex: clinical evidence. Cereb Cortex 1994;4:555-72.

Van Hoesen GW. Anatomy of the medial temporal lobe. Magn Reson Imaging 1995;13:1047-55.

Van Hoesen GW, Hyman BT, Damasio AR. Entorhinal cortex pathology in Alzheimer's disease. Hippocampus 1991;1:1-8.

van Zijl PC, Eleff SM, Ulatowski JA, Oja JM, Ulug AM, Traystman RJ, Kauppinen RA. Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging. Nat Med 1998;4:159-67.

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS. Functional anatomy of a common semantic system for words and pictures. Nature 1996;383:254-6.

Vandenbroucke MW, Goekoop R, Duschek EJ, Netelenbos JC, Kuijer JP, Barkhof F, Scheltens P, Rombouts SA. Interindividual differences of medial temporal lobe activation during encoding in an elderly population studied by fMRI. Neuroimage 2004;21:173-80.

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 1997;277:376-80.

Veltman DJ, Rombouts SA, Dolan RJ. Maintenance versus manipulation in verbal working memory revisited: an fMRI study. Neuroimage 2003;18:247-56.

Villringer A, Rosen BR, Belliveau JW, Ackerman JL, Lauffer RB, Buxton RB, Chao YS, Wedeen VJ, Brady TJ. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. Magn Reson Med 1988;6:164-74.

Visscher KM, Miezin FM, Kelly JE, Buckner RL, Donaldson DI, McAvoy MP, Bhalodia VM, Petersen SE. Mixed blocked/event-related designs separate transient and sustained activity in fMRI. Neuroimage 2003;19:1694-708.

Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. J Neurol Neurosurg Psychiatry 2002;72:491-7.

von Bonin G, Bailey P. The neocortex of *Macaca mulatta*. Urbana, IL: University of Illinois Press; 1947.

von Cramon DY, Hebel N, Schuri U. Verbal memory and learning in unilateral posterior cerebral infarction. A report on 30 cases. Brain 1988;111 (Pt 5):1061-77.

von Economo C, Koskinas GN. Die Cytoarchitectonik der Grosshirnrinde des erwachsenen Menschen. Berlin: Springer; 1925.

Wagner AD. Working memory contributions to human learning and remembering. Neuron 1999;22:19-22.

Wagner AD, Koutstaal W, Schacter DL. When encoding yields remembering: insights from event-related neuroimaging. Philos Trans R Soc Lond B Biol Sci 1999;354:1307-24.

Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. Neuron 2001;31:329-38.

Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 1998;281:1188-91.

Wan H, Aggleton JP, Brown MW. Different contributions of the hippocampus and perirhinal cortex to recognition memory. J Neurosci 1999;19:1142-8.

Wechsler D. WAIS-R manual. New York: Psychological Corporation; 1981.

Weiss EM, Siedentopf C, Hofer A, Deisenhammer EA, Hoptman MJ, Kremser C, Golaszewski S, Felber S, Fleischhacker WW, Delazer M. Brain activation pattern during a verbal fluency test in healthy male and female volunteers: a functional magnetic resonance imaging study. Neurosci Lett 2003;352:191-4.

Welsh KA, Butters N, Hughes JP, Mohs RC, Heyman A. Detection and staging of dementia in Alzheimer's disease. Use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. Arch Neurol 1992;49:448-52.

Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994;44:609-14.

West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. Lancet 1994;344:769-72.

Wilson FA, Scalaidhe SP, Goldman-Rakic PS. Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 1993;260:1955-8.

Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, Suzuki WA. Single neurons in the monkey hippocampus and learning of new associations. Science 2003;300:1578-81.

Witter MP, Groenewegen HJ, Lopes da Silva FH, Lohman AH. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog Neurobiol 1989a;33:161-253.

Witter MP, Van Hoesen GW, Amaral DG. Topographical organization of the entorhinal projection to the dentate gyrus of the monkey. J Neurosci 1989b;9:216-28.

Witter MP, Wouterlood F. The parahippocampal region. New York: Oxford University Press; 2002.

Witter MP, Wouterlood FG, Naber PA, Van Haeften T. Anatomical organization of the parahippocampal-hippocampal network. Ann N Y Acad Sci 2000;911:1-24.

Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 1992;12:900-18.

Xiong J, Gao J, Lancaster J, Fox P. Assessment and optimization of functional MRI analyses. Hum Brain Mapp 1996;4:153-167.

Yanike M, Wirth S, Suzuki WA. Representation of well-learned information in the monkey hippocampus. Neuron 2004;42:477-87.

Young BJ, Otto T, Fox GD, Eichenbaum H. Memory representation within the parahippocampal region. J Neurosci 1997;17:5183-95.

Zeineh MM, Engel SA, Thompson PM, Bookheimer SY. Dynamics of the hippocampus during encoding and retrieval of face-name pairs. Science 2003;299:577-80.

Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, Clark RE. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J Neurosci 2000;20:451-63.

Zola-Morgan S, Squire LR. Memory impairment in monkeys following lesions limited to the hippocampus. Behav Neurosci 1986;100:155-60.

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 1989;9:4355-70.

Zola-Morgan S, Squire LR, Clower RP, Rempel NL. Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation. J Neurosci 1993;13:251-65.