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Memory functions of the human medial temporal lobe studied with fMRI

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
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Hukommelsesfunksjoner i den mediale temporallappen studert med funksjonell MR

Bakgrunn: Den *mediale temporallappen* (MTL) er et område i hjernen som er viktig for læring og hukommelse. Dette ble fastslått i 1957 da legene William Scoville og Brenda Milner beskrev pasienten H.M. H.M. fikk operert bort store deler av MTL som et ledd i behandlingen av epilepsi, men utviklet alvorlig amnesi (hukommelsesvansker) etter inngrepet. Siden den gang har MTL vært gjenstand for en betydelig forskningsaktivitet. I dag vet vi at MTL er viktig for *deklarativ hukommelse*, som omfatter evnen til bevisst gjenkalling av personlige opplevelser og faktakunnskap. Vi vet også at MTL består av ulike områder: hippocampus, entorhinal cortex, perirhinal cortex og parahippocampal cortex. Disse områdene har alle ulike anatomiske egenskaper og forbindelser med andre områder i resten av hjernen, noe som impliserer at de også har forskjellige funksjoner. Forskningen strides derimot om hva disse funksjonelle forskjellene innebærer.

Formål: Formålet med avhandlingen er å beskrive funksjonelle forskjeller mellom ulike områder i MTL relatert til hukommelse.

Metode: Fire eksperimentelle studier er gjennomført, alle basert på *funksjonell magnetisk resonans* bildedannelse (fMRI). FMRI er en teknikk som brukes til å avbilde aktiveringsmønstre i hjernen relatert til bestemte oppgaver som personen utfører under bildeopptakene. Alle studiene er gjennomført med friske, frivillige forsøkspersoner.

Hovedfunn: FMRI-studier av hukommelse har antydet at MTL er særlig aktiv når man *gjenkaller selvopplevde hendelser* fra det virkelige liv, sannsynligvis fordi slike hendelser har større detaljrikdom og personlig relevans enn den typen stimuli som vanligvis brukes i laboratorietester. I Studie 1 spurte vi om denne typen hukommelse aktiverer MTL sterkt nok til å kunne påvises i individuelle analyser. Individuelle analyser gjør det mulig å lokalisere aktiveringen mer nøyaktig enn i tradisjonelle gruppeanalyser, noe som er viktig for å kunne skille mellom de små områdene i MTL. I fMRI-eksperimentet ba vi forsøkspersonene huske hendelser fra en bursdagsfest de hadde vært med på to uker tidligere. Denne oppgaven ga sterk aktivering i hippocampus og parahippocampal cortex, og aktiveringen var meget signifikant på individnivå. De påfølgende studiene ble basert på gruppeanalyser for å bedre muligheten til generalisering av resultatene, men tok hensyn til fordelene med komplekse, naturlige stimuli.

Tidligere studier har antydet at hippocampus er særlig viktig for å assosiere informasjon i hukommelsen, men noen mener at også andre områder i MTL bidrar til dette. Vi undersøkte derfor om de ulike områdene i MTL former assosiasjoner av ulik art. I Studie 2 testet vi evnen til å *assosiere hendelser over tid*. Når man husker tidligere opplevelser kan man ofte se for seg en rekke hendelser som henger sammen og følger hverandre i tid. For å måle dette lot vi forsøkspersonene først se en film fra en TV-serie. Dagen etter deltok de i et fMRI-eksperiment hvor de fikk se bilder av ulike scener fra filmen og måtte plassere disse i riktig rekkefølge. Denne oppgaven aktiverte hippocampus, og jo flere riktige svar

en forsøksperson hadde, jo sterkere var aktiveringen. I Studie 3 testet vi evnen til å huske *assosiasjoner på tvers av sansemodaliteter.* Denne evnen er viktig for hukommelsen, fordi et minne ofte inneholder informasjon fra ulike modaliteter; f.eks. fargen, smaken og konsistensen på et eple. Vi lot forsøkspersonene først lære assosiasjoner mellom en rekke nye stimuli – visuelle (abstrakte bilder), auditive (lyder av musikk) og taktile (berøring av mønstret papir). I det påfølgende fMRI-eksperimentet fikk de presentert en auditiv eller taktil stimulus og ble bedt om å huske den tilhørende visuelle. Denne oppgaven aktiverte perirhinal cortex, og aktiveringen var sterkere enn når forsøkspersonenen husket assosiasjoner mellom stimuli fra samme modalitet.

De fleste studier av MTL har brukt visuelle stimuli som ord og bilder, og man vet derfor lite om hukommelse i andre modaliteter. I Studie 3 fant vi at hippocampus, entorhinal cortex og parahippocampal cortex viste sterkere responser til auditive enn taktile stimuli, men ikke perirhinal cortex. Dette kan skyldes at de førstnevnte områdene mottar mer auditiv enn taktil informasjon fra sensoriske områder i hjernen. I Studie 4 sammenlignet vi responser til *gjenkjenning av lukter og objekter*. Forsøkspersonene fikk først presentert forskjellige lukter og objekter. Dagen etter, i fMRI eksperimentet, fikk de se navn på gamle og nye lukter og objekter og måtte si hvilke de husket fra dagen før. Gjenkjenning av objekter aktiverte hippocampus, men gjenkjenning av lukter gjorde det ikke. Dette kan muligens skyldes en forskjell i strategi. Gjenkjenning av lukter var oftere basert på en ”magefølelse”, og denne typen hukommelse antas å ikke være avhengig av hippocampus.

Konklusjon: Våre funn viser at flere områder i MTL assosierer informasjon i hukommelsen, men assosiasjonene kan være av ulik art. Hippocampus knytter sammen hendelser over tid, slik at man i etterkant kan huske i hvilken rekkefølge de fant sted. Perirhinal cortex knytter sammen informasjon fra ulike sansemodaliteter til en helhetlig representasjon, slik at man senere kan relatere disse til hverandre. Våre funn viser også at områdene i MTL responderer ulikt på informasjon fra ulike sanser. Noen områder er mer sensitive til auditiv enn taktil informasjon, mens hippocampus aktiveres ved gjenkjenning av objekter, men ikke lukter. Til sammen gir disse funnene økt kunnskap om hvordan MTL bidrar til ulike aspekter av hukommelse.

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LIST OF PAPERS

Paper 1 Lehn H, Steffenach H-A, Witter MP, Veltman DJ, Haraldseth O. A birthday to remember: Subject-specific activation in the medial temporal lobe. *Manuscript.*

Paper 2 Lehn H, Steffenach H-A, van Strien NM, Veltman DJ, Witter MP, Håberg AK (2009). A specific role of the human hippocampus in recall of temporal sequences. *J Neurosci 29:3475-3484.*

Paper 3 Van Strien NM, Lehn H, Gonlag AM, Ceritoglu C, Miller MI, Witter MP. Retrieval of learned crossmodal associations specifically involves the perirhinal cortex. *Submitted to Eur J Neurosci, April 23 2009.*

Paper 4 Lehn H, Kjønigsen LJ, Kjelvik G, Håberg AK. Distinct patterns of brain activity during episodic retrieval of odors and objects. *Submitted to Neuropsychologia, April 28 2009.*

ABBREVIATIONS

BOLD	blood oxygen level-dependent, contrast mechanism for fMRI
CA(1-3)	cornu ammonis (fields 1-3)
DG	dentate gyrus
EC	entorhinal cortex
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
HF	hippocampal formation, hippocampus
LEC	lateral entorhinal cortex
MEC	medial entorhinal cortex
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MTL	medial temporal lobe
PER	perirhinal cortex
PHG	parahippocampal gyrus
PHC	parahippocampal cortex
PET	positron-emission tomography
T	Tesla, unit of magnetic field strength
TE	area in the inferior temporal cortex in the macaque monkey
TR	repetition time, time required for acquisition of one fMRI volume
V4	area in the extrastriate visual cortex in the macaque monkey
VR	virtual reality

INTRODUCTION

ANATOMY OF THE MEDIAL TEMPORAL LOBE

The medial temporal lobe (MTL) of the human brain is located at the ventro-medial surface of the hemisphere. It comprises a network of several highly interconnected structures (*Fig 1*). The major components of the network are the hippocampal formation (HF), which is located on the floor of the lateral ventricle, and the adjacent parahippocampal gyrus (PHG). The PHG can be further divided into five cortical regions; the entorhinal cortex (EC), the perirhinal cortex (PER), the parahippocampal cortex (PHC), the presubiculum and the parasubiculum. Within the HF a number of cytoarchitectonically distinct subfields can be distinguished, including the cornu ammonis (CA) fields 1-3, the dentate gyrus (DG), and the subiculum. The pre- and parasubiculum are too small to be studied with the current resolution of fMRI and will therefore not be discussed further in this thesis.

Anatomical studies in rodents and monkeys have given insights into the connectivity among the above regions (*Fig 1*). The findings are broadly consistent across species and likely to apply in humans as well. The MTL forms a hierarchy of projections, with the HF situated at the top, and the prevailing model of the projection pathways is as follows (Burwell, 2000; Lavenex and Amaral, 2000; Witter et al., 2000a; Insausti and Amaral, 2004; Van Strien et al., 2009). The PER and the PHC receive cortical inputs from widespread unimodal and polymodal association areas, as well as several subcortical projections. The projections continue their path to the EC, which also receives direct projections, most notably from the piriform cortex and olfactory bulb. The EC mediates the main cortical input to the HF. Its major output projections are through the perforant path, which targets all subdivisions of the HF. The intrinsic wiring of the HF is largely unidirectional such that the DG projects to CA3 through the mossy fibers, and CA3 projects to CA1 through the Schaffer collaterals. CA1 projects mainly to the subiculum, and both CA1 and the subiculum project back to the EC. The EC communicates back to cortex, mainly through its connections with the PER and the PHC. As can be seen in *Fig 1*, there are direct reciprocal connections between the PER and the PHC. The HF is

also reciprocally connected via the fimbria-fornix with a number of subcortical regions, including the amygdala, thalamus, basal forebrain and basal ganglia.

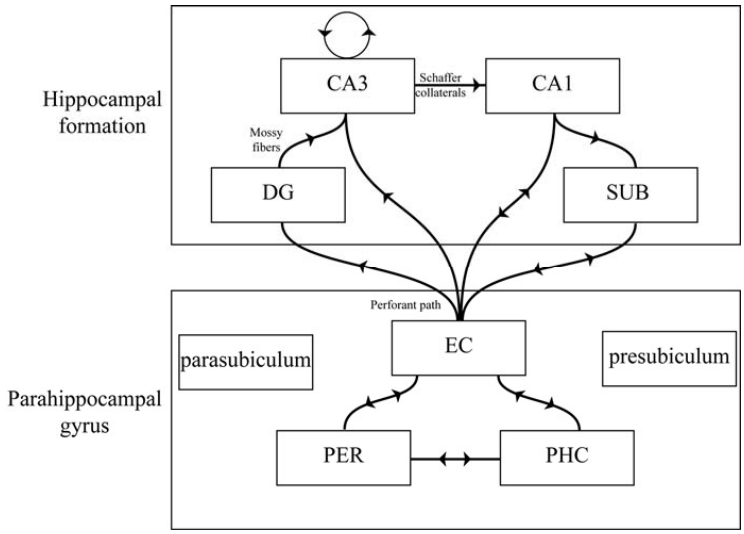


Figure 1. Diagram of the medial temporal lobe: subregions and major intrinsic connections. SUB = subiculum. For further abbreviations, see text.

Anatomy and function

The networks in the MTL are thought to be engaged in processes such as memory and spatial cognition, and their anatomical characteristics provide several clues as to how these functions are achieved. For example, the convergence of inputs suggests that the MTL is capable of integrating information from various sources to form complex and multimodal representations. However, there is also evidence for segregation of inputs. The PER receives visual input mainly from the adjacent inferotemporal cortex (area TE), which conveys representations of object features. In contrast, the PHC receives visual input mainly from area V4 and the posterior parietal cortex, conveying representations of spatial locations and motion. Furthermore, polymodal inputs to the PER originate mainly in anterior association areas (e.g., orbitofrontal cortex), while polymodal inputs to the PHC originate mainly in posterior association areas (e.g., retrosplenial cortex). This is similar in rats (Burwell and Amaral, 1998) and monkeys

(Suzkuki and Amaral, 1994). The divergence of object and spatial information can be seen as extensions of 'what' and 'where' processing in the ventral and dorsal visual stream, respectively (Ungerleider and Mishkin, 1982). Studies in rats suggest that the two types of information remain partially segregated also at subsequent levels of processing (Burwell, 2000; Witter et al., 2000b). The PER and the PHC project most strongly to the lateral EC (LEC) and the medial EC (MEC), respectively, which in turn project to distinct portions of CA1 and the subiculum. However, projections from the LEC and the MEC converge in the DG and CA3. This pattern of connections suggests that object and spatial information are processed in parallel streams through the MTL, but become fully integrated in the HF.

Computational models have described functional implications of specific network characteristics in the MTL. Several models of PHG subregions exist (e.g., Fuhs and Touretzky, 2006; McNaughton et al., 2006; Burgess et al., 2007), but most models focus on hippocampal subfields. A characteristic feature of CA3 is its extensive recurrent connections with associatively modifiable synapses. The recurrent connections are thought to allow autoassociation between related input signals, whereby a stored representation can be reactivated from a partial or degraded version of the original input ('pattern completion'; Marr, 1971; O'Reilly and McClelland, 1994; Treves and Rolls, 1994). In contrast, the DG is distinguished by granule cells that fire sparsely and have sparse but powerful connections to CA3. This may allow overlapping inputs to be orthogonalized ('pattern separation'; O'Reilly and McClelland, 1994; Treves and Rolls, 1994), which may reduce interference between similar experiences in memory. A given input will be treated either as similar to a stored pattern and initiate recall (pattern completion) or as different and encoded as a new experience (pattern separation) (O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2001). CA1 has been proposed to provide the required 'match/mismatch' signal (Lisman and Otmakhova, 2001) by comparing stored representations from CA3 with new input conveyed through the direct projections from the EC. CA1 may also recode input from CA3 into more compressed representations (Rolls, 1996) and support temporal processing of information (Rolls and Kesner, 2006). The functional relevance of the subiculum is still poorly understood (O'Mara, 2006).

Please note that the term 'hippocampus', as used in the remainder of this thesis, refers to the HF.

THEORIES OF THE MEDIAL TEMPORAL LOBE

In one of the first accounts of MTL function, the hippocampus and the PHG were described as part of the limbic system or 'Papez' circuit', a set of interrelated brain structures that were involved in the regulation of emotions (Papez, 1937). Later, this function was located more specifically to the amygdala, and other theories developed regarding the role of the MTL. Most of these theories describe a role in either memory or spatial cognition.

Memory

Declarative theory

Our current understanding of MTL function took shape with Scoville and Milner's (1957) description of the now famous patient H.M. He underwent bilateral medial temporal lobectomy at the age of 27 to reduce the severity of his epileptic seizures. Tissue was resected from the hippocampus and adjacent structures, mainly the temporopolar cortex, the amygdala and the EC (Corkin, 1997). The surgery successfully reduced the frequency of seizure attacks but caused H.M. to suffer from severe memory impairments. Although his intellectual and perceptual abilities remained intact, H.M. was unable to learn new information (anterograde amnesia) and had difficulties recalling events that occurred prior to his surgery (retrograde amnesia). These findings provided the first clear evidence that the MTL is critically involved in learning and memory, and initiated extensive research into the amnesic syndrome, both in human patients and animal models. This research formed the basis of the declarative theory of 'the medial temporal lobe memory system' (Squire, 1986; Squire and Zola-Morgan, 1991).

Three observations had particular influence on the formulation of the declarative theory. The first observation was that MTL damage affected some but not all types of memory. H.M. was severely impaired on tasks that required explicit (conscious) storage and recollection of information, such as free recall of word pairs, but not on tasks that relied on implicit (unconscious) learning, such as mirror drawing (Milner et al., 1968; Corkin, 1984). Also his short-term memory was intact. Based on these and similar observations in other amnesic patients, long-term memory was proposed to consist of two separate

types, declarative (explicit) and non-declarative (implicit) memory (see *Fig 2*). Only declarative memory was said to depend on the MTL (Squire and Zola-Morgan, 1996). Tulving (1972) made a further distinction between semantic and episodic memory; the former includes general, factual knowledge, and the latter unique events from one's personal past. However, the declarative theory claims that the MTL is equally important for both types (Squire and Zola, 1998).

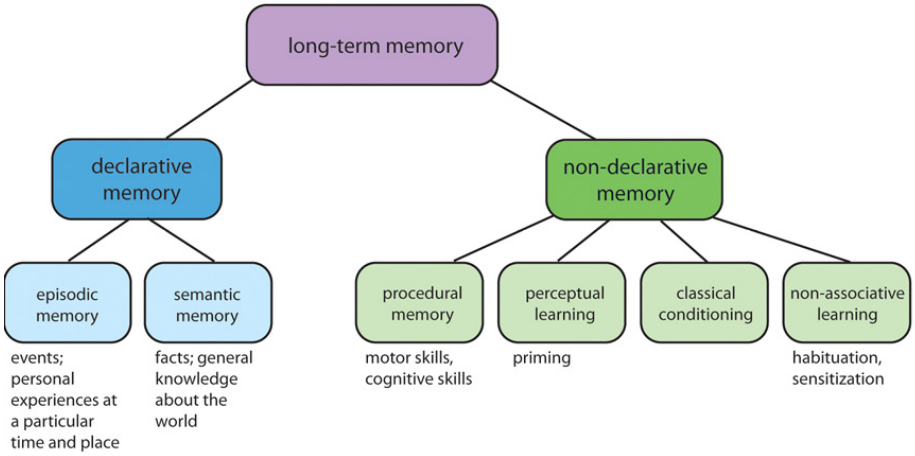


Figure 2. Classification of long-term memory. The medial temporal lobe is involved in declarative memory. Other brain regions, like the striatum, cerebellum and amygdala, support non-declarative memory. Declarative and non-declarative memory are sometimes referred to as explicit and implicit memory, respectively.

The second important observation was that the retrograde amnesia tended to be temporally graded, i.e., affect recent memories more than remote (Squire and Zola-Morgan, 1985; Zola-Morgan and Squire, 1990). According to the declarative theory, the MTL facilitates the encoding and storage of information in interaction with neocortical regions, where the permanent memory traces are stored. The MTL is said to establish connections between different cortical modules that represent the multiple features of an experience, and to keep an index that allows the complete representation to be reactivated at the time of retrieval (Teyler and DiScenna, 1986). However, repeated reactivation of a memory trace will gradually strengthen the direct connections between

the relevant cortical modules ('consolidation'), whereby retrieval becomes independent of the MTL over time (Alvarez and Squire, 1994; McClelland et al. 1995).

The third observation that shaped the declarative theory was that the severity of amnesia depended on the location and extent of MTL damage. Whereas H.M. suffered from extensive MTL lesions, another patient (R.B.) with selective damage to CA1 was shown to have similar, though somewhat less severe, memory deficits (Zola-Morgan et al., 1986). The hippocampus was therefore assigned a central function within the MTL memory system. However, other studies demonstrated that both hippocampal and parahippocampal structures are important for memory (Zola-Morgan et al., 1989), and that the severity of amnesia increased with size of the lesion (Zola-Morgan et al., 1994). Therefore, although the declarative theory accepts that different subregions of the MTL may have different functional properties, it stresses that they operate in a highly cooperative manner and that each one is required for intact memory performance.

The declarative theory remains one of the most influential theories of MTL function to date. It receives continuing support from studies of amnesic patients and animals with experimental lesions, and more recently also from functional neuroimaging studies of healthy human subjects (for review, see Squire et al., 2004).

Dual-process theories

Early research on amnesia suggested that different subregions of the MTL do not operate in a unitary manner but make distinct contributions to memory. For example, recognition of visual objects was found to be impaired in monkeys with selective lesions to the parahippocampal region (Zola-Morgan et al., 1989; Meunier et al., 1993), but intact in monkeys with hippocampal lesions (Murray and Mishkin, 1998). In particular the PER/EC seemed to be important for object recognition (Meunier et al., 1993; 1996), and electrophysiological recordings in monkeys indicated that cells in this region respond to item familiarity (Miller et al., 1993). Other tasks appeared more sensitive to hippocampal function. For example, rats with hippocampal damage were found to be impaired on tasks that required learning of stimulus relationships or implementation of past learning in novel situations (e.g., Morris et al., 1982; Eichenbaum et al., 1988; 1989).

To account for these findings, a dual-process theory (sometimes referred to as the 'relational theory' of hippocampal function; Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994) was proposed. Here, the existence of two separate but complementary forms of memory processes within the MTL was hypothesized. Parahippocampal regions were considered to represent individual items in memory and support passive retention of specific sensory features. In contrast, the hippocampus was suggested to represent relationships between multiple items, and to connect current inputs with previously stored knowledge in order to enable flexible expressions of memory. This theory agrees that the MTL supports encoding and storage of long-term declarative memories, both episodic and semantic, but claims that the hippocampus is only required for associative operations. A related dual-process account was proposed by Aggleton and Brown (1999). In line with others (Tulving, 1985; Yonelinas et al., 2001), Aggleton and Brown distinguish between recognition based on recollection (retrieval of contextual details associated with the previous encounter of an item) and recognition based on familiarity (a subjective feeling that a specific item has appeared before). They claim that the hippocampus preferentially supports recollection, whereas parahippocampal regions, and in particular the PER, support item familiarity.

The dual-process theories described above have similarities with several other views of MTL function. For example, one view holds that the hippocampus is only necessary for episodic memory, since this requires associations between a past experience and its unique spatio-temporal context, and that parahippocampal structures mediate semantic memory, considered to be 'context-free' (Tulving and Markowitsch, 1998). This view was inspired by the report of three patients with selective hippocampal lesions who were are unable to recall events from their personal past, but had intact factual knowledge (Vargha-Khadem et al., 1997). Others have emphasized the associative capacities of the hippocampus but been less explicit about the role of parahippocampal structures. The 'multiple-trace theory' (Nadel and Moscovitch, 1997; Moscovitch et al., 2005) asserts that the hippocampus is crucial for 'detail binding' and hence required for contextually rich, i.e., episodic and spatial memory, but not semantic memory. This theory claims that the hippocampus has a permanent role in retrieval of contextually rich memories, as demonstrated by a patient who was unable to recall detailed spatial memories from his remote past (Rosenbaum et al., 2000). Yet others have suggested that the hippocampus represents stimulus conjunctions ('configural association theory';

Sutherland and Rudy, 1989), associates temporally discontinuous events (Rawlins, 1985), or represents the spatial relationships between landmarks in the environment ('cognitive map theory'; O'Keefe and Nadel, 1978; see below).

The view that MTL subregions are functionally heterogeneous is increasingly acknowledged in the literature, and several lines of evidence support a distinction between associative and item-based processing (for reviews, see Brown and Aggleton, 2001; Eichenbaum et al., 2007). More recently, a 'three-component model' has been proposed as an extension of the dual-process accounts (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007). This model claims that the PER supports memory for single objects (items), whereas the PHC supports memory for spatial locations (context). The hippocampus is said to be responsible for binding of information across these domains (item-in-context), and as such to represent the most generic level of processing.

Spatial cognition

Cognitive map theory

In 1971, O'Keefe and Dostrovsky reported electrophysiological data recorded from hippocampal cells in freely moving rats. Of particular interest were their descriptions of cells that increased their firing rate whenever the rat entered a specific location in the environment, the so-called 'place cells'. Based on the discovery of place cells, O'Keefe and Nadel (1978) proposed the 'cognitive map theory' of hippocampal function. The theory states that the hippocampus represents the spatial geometry of the local environment as a cognitive map (Tolman, 1948), i.e. an allocentric (viewpoint independent) representation of the spatial relationships between landmarks in the environment and of one's own position relative to those landmarks. Further investigations into the properties of place cells largely confirmed this view (Muller et al., 1996). Place cells were observed also in humans (Ekstrom et al., 2003), suggesting homology across species.

The cognitive map theory is primarily a theory about memory, but strictly confined to the spatial domain (Nadel, 1991). The hippocampus is said to both create and store spatial maps, and to use these to support navigation and other forms of adaptive

behavior. Consistent with this view, hippocampal lesions were found to disrupt spatial learning in rats (Morris et al., 1982), and patients with MTL damage were reported to have impairments in recall of spatial locations (Smith and Milner, 1981). Additional lesion and functional neuroimaging studies confirmed that the human hippocampus supports spatial memory and navigation (for review, see Burgess et al., 2002).

Recent work has necessitated some modifications of the above theory. Electrophysiological recordings in rats have demonstrated that hippocampal neurons are not only sensitive to spatial location, but also have non-spatial firing correlates. For example, hippocampal neurons have been shown to respond selectively to specific odors regardless of spatial location, or to certain odor-place combinations (Wood et al., 1999). Place cells may code for both spatial position and non-spatial cues in the environment, by modifications in firing location and firing rate, respectively (Leutgeb et al., 2005). Place cells also express temporal coding, such as 'phase precession' (tendency of place cells to fire at progressively earlier phases of the theta cycle; O'Keefe and Recce, 1993) and 'replay' (reactivation of a previous firing sequence; Skaggs and McNaughton, 1996). Furthermore, the MEC was recently shown to contain so-called grid cells, i.e., cells that fire preferentially at multiple locations across the whole environment in a repetitive, triangular pattern (Hafting et al., 2005). Cells in this region may also be sensitive to head direction (Sargolini et al., 2006) and geometrical borders (Solstad et al., 2008).

According to a contemporary view of 'the brain's spatial representation system' (Moser et al., 2008), the hippocampus integrates spatial and non-spatial cues to represent one's current location in the environment, as well as the temporal sequence of past and future locations. The EC may provide a metric representation of space and operate as a 'path integrator', i.e., integrate self-motion cues like direction and speed to keep track of one's changing position (Hafting et al., 2005).

Relevance for memory

The capacity to form conjunctive representations and represent temporal sequences can be seen to support both spatial cognition and memory, perhaps in particular episodic memory. Episodic memory depends on the ability to combine information about 'what' happened 'where' and 'when', and to organize past experiences as temporal sequences

of related events (Tulving, 1983; Tulving, 2002; Eichenbaum, 2004). The cognitive map theory recognizes that at least the human hippocampus may have evolved to support not only spatial but also verbal and episodic memory (O'Keefe and Nadel, 1978; Nadel, 1991; see also Burgess et al., 2002). Others have argued that also the rat hippocampus supports 'episodic-like' memory, such as one-trial learning of flavor-place associations (Day et al., 2003; Tse et al., 2007), and recall of temporal order based on a combination of spatial and olfactory cues (Ergorul and Eichenbaum, 2004).

It can be argued that the MTL is best described in terms of the representations and computations it performs, rather than as a system dedicated to a specific cognitive function. As described above, computational models suggest that the hippocampus performs 'pattern completion', 'pattern separation' and 'mismatch detection'. Experimental work in rodents has made considerable progress in describing how these computations affect spatial processing in the hippocampus. For example, place cells are said to reflect pattern completion when the location of firing remains stable after some characteristics of the environment have been changed, which occurs most clearly in CA3 (Lee et al., 2004). Pattern separation is apparent when place cells fire in distinct locations or at different rates in two highly similar environments, and this has been shown to occur in the DG and CA3 (Leutgeb et al., 2007). Mismatch detection can be measured when rats respond to alterations in a previously learned sequence of stimuli, i.e., by orienting toward the unexpected stimulus. Honey et al. (1998) found that hippocampal lesions disrupt this type of response, but the lesions were not confined to a specific hippocampal subfield. Although mismatch detection is proposed to occur in CA1 (Lisman and Otmakhova, 2001), one study suggests that also CA3 contributes (Lee et al., 2005; but see Hasselmo, 2005).

It is often argued that the above described computations also contribute to memory performance in humans (e.g., Eichenbaum, 2004; Knierim et al., 2006; Bird and Burgess, 2008; Moser et al., 2008; Kumaran and Maguire, 2009). Empirical support for this view is now emerging, and some examples of this will be described later.

FUNCTIONAL NEUROIMAGING STUDIES OF THE MEDIAL TEMPORAL LOBE

Functional magnetic resonance imaging (fMRI), based on the blood oxygen level-dependent (BOLD) contrast (see Boxes 1 and 2), is becoming increasingly important as a tool to study MTL functions in healthy human subjects. There are several other neuroimaging methods available, such as positron-emission tomography (PET), magnetoencephalography (MEG), quantitative electroencephalography (EEG), and fMRI depending on other contrast that than BOLD. Since all studies in the present thesis are based on BOLD fMRI, the focus here will be on results obtained with this method.

In a pioneering study, Stern et al. (1996) showed increased activation in the hippocampus and the PHG during presentation of novel, as compared to repeated, pictures. Based on the assumption that novel stimuli induce more encoding-related activation than repeated stimuli (Tulving and Kroll, 1995), this was the first fMRI study to demonstrate involvement of the MTL in memory. Later, Brewer et al. (1998) used an event-related paradigm to locate the effects of successful encoding. They compared encoding of pictures that were recognized on a subsequent memory test to encoding of pictures that were later forgotten, and observed increased PHG activation in the former condition ('subsequent memory effect'; Sanquist et al., 1980). Additional work soon confirmed the involvement of MTL structures in both encoding and retrieval of declarative memories (Schacter and Wagner, 1999).

Ongoing research in the field has several focuses. Among these is the attempt to determine what type of memory the MTL is sensitive to, and whether different subregions make different functional contributions in this regard. Functional differentiation among subregions of the MTL is the main focus of this thesis, and fMRI studies that are relevant to this issue will be reviewed in further detail below. Before proceeding, it should be noted that imaging MTL subregions is technically challenging, due to their small size and convoluted structure. Separating activation in the hippocampus from activation in parahippocampal structures is just about possible with conventional fMRI methods, i.e., with a voxel size of 3x3x3 mm, spatial filter of 5-8 mm, and transformation of images to a group template or standard brain. The accuracy of localization may also be hampered by signal loss and geometric distortions caused by

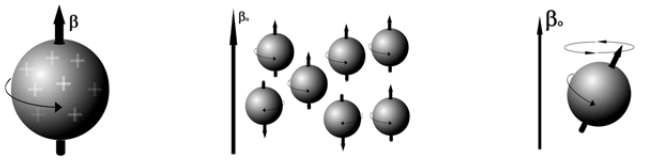
magnetic field inhomogeneities that are particularly prominent in ventromedial parts of the brain (Ojemann et al., 1997). Despite these difficulties, continuing improvements in fMRI methodology allow MTL functions to be studied with increasing anatomical specificity. Several studies have now applied high-resolution techniques (e.g., 1.5x1.5x1.5 mm) in combination with improved methods for cross-participant image alignment, and report activation within hippocampal subfields (e.g., Zeineh et al., 2003; Eldridge et al., 2005; Bakker et al., 2008). Below, relevant studies are discussed regardless of spatial resolution and activations are therefore described at varying levels of anatomical specificity.

Box 1: Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a technique that is used to visualize internal organs of the body, developed mainly for clinical purposes. MRI is based on signals from hydrogen nuclei which are abundant in fat and water and therefore also in the human body. A hydrogen nucleus consists of a single proton that spins around its own axis. This spinning induces a magnetic field with a certain direction and size, called magnetic moment (*Fig. 1A*), which induces the type of signal that is detected by MRI scanners.

When placed inside an MRI scanner, the majority of the hydrogen nuclei in the body align parallel with the external magnetic field (B_0), in order to maintain a low energy state (*Fig. 1B*). The sum of their magnetic moments is called the net magnetization vector (NMV). The magnetic moments spin around the external magnetic field, a process called precession (*Fig. 1C*). Nuclei precess with a certain frequency defined by the Larmor equation: [$\omega_0 = B_0 * \gamma$] where B_0 is the strength of external magnetic field expressed in Tesla, and γ is the precessional frequency of a specific nucleus at 1T.

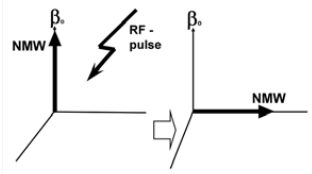
Fig. 1: Nuclear effects



A: Magnetic moment B: Nuclei align with B_0 C: Precession

During image acquisition, a radiofrequency (RF) pulse is applied at for instance 90 degrees to B_0 (*Fig. 2*). This has two effects: 1) The energy of the RF pulse is absorbed by the hydrogen nuclei, and NMV is flipped into the transverse plane, i.e., 90 degrees to B_0. 2) The magnetic moments of the hydrogen nuclei move into phase with each other, whereby NMV precesses in the transverse plane. The nuclei emit the absorbed energy and produce an electrical signal that is measured with a receiver coil in the transverse plane.

Fig. 2. Application of the RF pulse



When the RF pulse is turned off, the magnetic moments start to move out of phase and return to their low energy state. The loss of phase coherence results in decreased transverse magnetization. Several relaxation processes occur (e.g., T1 recovery, T2 decay) and at different rates in different types of tissue. This provides MR images with the contrast that display anatomy or function. Functional MRI is based on a relaxation process called T2* dephasing. This is the decrease in signal from NMV in the transverse plane, which occurs exponentially at a time constant called T2*.

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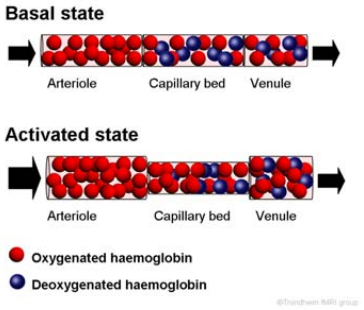
Box 2: Functional MRI

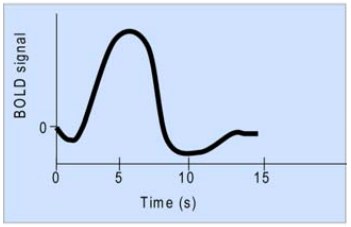
Functional magnetic resonance imaging (fMRI) is an MRI application that is used to image brain function, based on hemodynamic responses to neural activity. In 1990, Ogawa et al. demonstrated that gradient echo (i.e., T2*-weighted) MRI signals are sensitive to the level of blood oxygenation in the brain. They called this phenomenon 'blood oxygen level-dependent' (BOLD) contrast, which today is the most commonly used contrast mechanism in fMRI.

The BOLD contrast is based on the different magnetic properties of oxygenated and deoxygenated hemoglobin in the blood. Oxygenated hemoglobin is diamagnetic, which means it has no effect on the local magnetic field, whereas deoxygenated haemoglobin is paramagnetic and disturbs the magnetic field. This implies that T2* dephasing is accelerated, and that the MR signal decays faster, in the presence of deoxygenated haemoglobin. When a population of neurons becomes increasingly active, there is a local increase in cerebral blood flow, blood volume and blood oxygenation. Because the blood flow increases more than the metabolic rate of oxygen, the combined result of these changes is a decrease in deoxygenated hemoglobin in the capillary and venous blood volume. The BOLD signal is therefore enhanced in areas of increased neural activation. See *Fig. 1*.

Fig. 1: The BOLD effect



Fig, 2: The BOLD signal curve



Since the BOLD signal is measured in arbitrary units, only relative changes in activation can be inferred. *Fig. 2* shows the prototypical BOLD signal curve in response to a transient stimulus (e.g., a flickering light) relative to a baseline condition (e.g., blank screen). The response is delayed by ~2 s compared to the onset of neural activity. It peaks after 5-8 seconds, and returns to baseline approximately 10 s later. A transient decrease in BOLD signal intensity is sometimes observed before the onset of the standard increase. This 'initial dip' is thought to reflect a rapid increase in oxygen consumption that precedes the increase in cerebral blood flow[1,2]. A more prolonged signal decrease can occur in the final stage of the BOLD response ('post-stimulus undershoot'). This may be caused by a continuation of oxygen consumption in the absence of flow changes[3], or by a slow return of venous blood volume[4]. There are still many controversies regarding the relationship between the hemodynamic responses and the underlying neural activity[5]. However, the BOLD signal has been found to correlate well with neural activity, and in particular with local field potentials, i.e., local synaptic processing[6,7].

fMRI is typically used to measure changes in brain activity during performance of a cognitive or behavioral task. Rapid image acquisition techniques like echo-planar imaging (EPI[8]) allow the whole brain to be imaged approximately every 2 s and with a spatial resolution of 1-3 mm. Compared to other functional neuroimaging techniques like positron-emission tomography (PET) and magnetoencephalography (MEG), fMRI has the advantage of being both non-invasive with a superior spatial resolution, and is more available than PET and MEG. For these reasons, fMRI has become a valuable tool for studying brain functions in healthy human subjects.

(continues on next page)

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Encoding *vs.* retrieval

One of the earliest fMRI studies of memory (Gabrieli et al., 1997) suggested that encoding and retrieval are supported by posterior and anterior parts of the MTL, respectively. Encoding of novel pictures yielded posterior activation that was focused in the PHC, whereas cued recall of line drawings yielded anterior activation that was focused in the subiculum. Other fMRI studies (see Schacter and Wagner, 1999) also reported activation primarily in the posterior MTL during encoding. However, more recent studies often find the opposite pattern of activation and suggest that anterior regions respond preferentially to stimulus novelty or encoding, and posterior regions to familiarity or retrieval (Dolan and Fletcher, 1999; Saykin et al., 1999; Prince et al., 2005; Strange et al., 2005; Daselaar et al., 2006). These latter findings are consistent with the Hippocampal Encoding/Retrieval (HIPER) model that describes an anterior-posterior gradient in encoding and retrieval processes, based on a meta-analysis of 52 PET studies (Lepage et al., 1998).

Some fMRI studies have found no difference in MTL activation during encoding and retrieval (Greicius et al., 2003; Daselaar et al., 2004), and rather suggest that that the same network is engaged in reactivation of a stored pattern as in the initial encoding hereof (Small et al., 2001). Zeineh et al. (2003) examined the distribution of activation across hippocampal subfields in the transversal plane during encoding and retrieval of face-name associations. They found that a region that comprised the CA2, CA3 and DG was only activated during learning, whereas the subiculum was more active during retrieval. Also in a more recent study, encoding and retrieval were associated with activation in the CA2/CA3/DG and subiculum, respectively (Eldridge et al., 2005). However, subicular activation has also been associated with successful encoding of faces and scenes (Preston et al., 2009).

Clearly, no consensus has yet emerged regarding a segregation of encoding and retrieval processes within the MTL. At the behavioral level, the two processes may be difficult to separate, as incidental encoding may occur during retrieval (Stark and Okado, 2003). There is also no anatomical (Insausti and Amaral, 2004) nor electrophysiological (Suzuki and Eichenbaum, 2000) evidence to suggest that encoding and retrieval occur in distinct subregions. Based on research in animals, differences along the anterior-posterior axis of the hippocampus seem more likely to reflect other functional specializations. For example, in rats, spatial memory has been shown to depend in particular on the dorsal two third of the hippocampus (Moser and Moser, 1998), which corresponds to the posterior hippocampus in humans. The ventral hippocampus (anterior in humans) seems less sensitive to spatial variables (Kjelstrup et al., 2008) and may serve a specific function in fear-related behavior (Kjelstrup et al., 2002). These findings are consistent with fMRI data that show greater activation in the anterior hippocampus during successful encoding of emotional versus neutral pictures (Dolcos et al., 2004). Among subregions in the transversal plane of the hippocampus, functional differences may not portray either encoding or retrieval but rather reflect more specific network capacities, like pattern completion and pattern separation (see below).

Episodic *vs.* semantic memory

Although most fMRI studies have focused on the role of MTL in episodic memory, a few studies have also explored its contribution to semantic memory. Activation in the

hippocampus and the PHG has been observed during recognition of famous faces (Bernard et al., 2004; Elfgren et al., 2006) and famous names (Douville et al., 2005), and activation in the hippocampus during acquisition of new factual knowledge (Maguire and Frith, 2004).

The multiple trace theory (Nadel and Moscovitch, 1997) and related accounts of MTL function (Tulving and Markowitsch, 1998) predict that the hippocampus is preferentially involved in episodic memory. Ryan et al. (2008) tested this prediction by comparing episodic retrieval (recall of category exemplars presented 24h earlier) to semantic retrieval (generation of category exemplars) but found similar levels of hippocampal and PHG activation in both conditions. In a later study, Ryan et al. (2009) tested retrieval of episodic and semantic associations among previously studied objects, and found increased activation in the hippocampus and the PHG during episodic retrieval. Recall of autobiographical events has more consistently been associated with increased hippocampal activation when compared to semantic retrieval, e.g., recall of public events (Maguire and Frith, 2003), retrieval of factual knowledge (Mayes et al., 2004; Svoboda and Levine, 2009) and category generation (Greenberg et al., 2005). In two of these studies, additional activation was observed in the PHC (Mayes et al., 2004) and the PHG (Greenberg et al., 2005).

The hippocampus may be more sensitive to recall of autobiographical events than to traditional laboratory tasks of episodic memory, because autobiographical events are personally more relevant and embedded in a rich context of temporal, spatial and perceptual details (Cabeza and St. Jacques, 2007). Cabeza et al. (2004) found support for this view when testing scene recognition with a 'novel photo paradigm'. Participants were shown their own pictures of various campus locations (autobiographical condition), similar pictures taken by other participants (laboratory condition), and new pictures (control condition). Activation in the hippocampus and the PHG increased when subjects recognized pictures in the autobiographical condition, compared to in the laboratory condition.

Although MTL regions appear particularly sensitive to recall of autobiographical events, direct comparisons with semantic retrieval are complicated by several factors. First, autobiographical memories are difficult to standardize or control in terms of encoding conditions, retrieval accuracy, and content (Cabeza and St. Jacques, 2007),

and this may introduce possible confounds in comparisons with semantic memory. Prospective paradigms can be useful in this regard. For example, Svoboda and Levine (2009) showed that increased activation during autobiographical retrieval was not due to more frequent repetitions and hence better consolidation of the semantic memories. In their study, all stimuli were collected prospectively and subject to multiple (1-8) repetitions. The hippocampus was more active during autobiographical retrieval, regardless of the number of repetitions. Second, autobiographical memories are tightly bound to semantic knowledge about one's personal past (Conway and Pleydell-Pearce, 2000), and episodic and semantic processes may therefore interact during retrieval. However, Addis et al. (2004a) found that that the hippocampus was equally involved in retrieval of unique autobiographical events and 'facts', and that hippocampal involvement was mainly determined by recollective qualities like number of details, emotional intensity and personal significance.

Item *vs.* associative memory

Among the most debated issues in research on the MTL is whether its subregions are differentially involved in memory for items and associations. One line of research is rooted in dual-process theories of recognition and has adopted the *'Remember/Know'* procedure (Tulving, 1985) to separate recognition based on recollection of the study context ('Remember') from recognition based on feelings of familiarity ('Know'). Subjects first encode a list of items, typically words or pictures. On a subsequent recognition test, they are asked to discriminate old from new items, and for items judged as old, to indicate whether they 'Remember' or 'Know' they have seen it before. FMRI studies that have used this type of test show increased activation in the hippocampus (Wheeler and Buckner, 2004), the PHC (Sharot et al., 2004), or both (Eldridge et al., 2000; Dolcos et al., 2005; Woodruff et al., 2005) on Remember as opposed to Know trials. During encoding, hippocampal activation has been shown to predict subsequent recollection, whereas activation in the PHG predicts subsequent familiarity (Uncapher and Rugg, 2005).

Advocates of the declarative theory have claimed that findings like those just described are confounded by *memory strength.* It is argued that remembering and knowing are not qualitatively different but instead represent endpoints of a continuum from weak

(‘Know”) to strong (‘Remember’) memories (Wixted, 2007), and that both hippocampal and parahippocampal activations vary as a function of memory strength (Squire et al., 2007). In support of this view, a positive linear relationship has been found between the level of hippocampal and PER activation during encoding and the strength (confidence rating) of subsequent item recognition (Shrager et al., 2008; Kirwan et al., 2008). However, there is also evidence for non-linear responses in the hippocampus during retrieval, i.e. preferential activation during item recognition accompanied by the highest level of confidence (Daselaar et al., 2006) or recollection (Yonelinas et al., 2005; Montaldi et al., 2006). Moreover, several studies have observed a negative correlation between item recognition confidence and level of activation, frequently in the PER (Gonsalves et al., 2005; Daselaar et al., 2006; Montaldi et al., 2006). This may reflect a form of repetition suppression that signals stimulus familiarity or novelty (Fernández and Tendolkar, 2006; Grill-Spector et al., 2006), and is consistent with several other studies that report PER involvement in successful item encoding (Davachi et al., 2003; Uncapher et al., 2006) and recognition (Tendolkar et al., 2008).

In contrast to the Remember/Know procedure, other tasks provide more objective measures of associative memory. One example is tests of *source memory,* the ability to retrieve both an item (e.g., word, object) and the form or context in which it was presented during encoding (e.g., color, position). When comparing trials where subjects remember both the item and its source to trials where they remember only the item, increased activation has been found in the hippocampus (Weis et al., 2004; but see Wais et al., 2009), the PHC (Kahn et al., 2004) or both (Cansino et al., 2002). During encoding, successful source retrieval can be predicted by the level of activation in the hippocampus and the PHC (Davachi et al., 2003; Ranganath et al., 2004; but see Gold et al., 2006). FMRI studies have also tested retrieval of *temporal order,* i.e., the relative recency of previously presented items. Several studies do not find increased activation in the MTL during retrieval of temporal order compared to item recognition (e.g., Suzuki et al., 2002; Ekstrom and Bookheimer, 2007). However, PHC activation was shown to increase with the demands for recollection (Konishi et al., 2002; St. Jacques et al., 2008), and hippocampal activation was shown to increase when subjects had explicitly encoded the temporal relationships between items (Konishi et al., 2006). Finally, associative memory has been tested with encoding and retrieval of *stimulus pairs.* Kirwan and Stark (2004) asked subjects to learn face-name associations and in a

subsequent recognition test presented these in either intact or recombined form. Increased activation was observed in the hippocampus, PHC, PER and EC on trials where the face-name associations were correctly recognized (intact pair called 'intact'), relative to trials where the associations were forgotten (intact pairs called 'recombined'). During encoding, activation in the hippocampus and the PHC predicted whether the association was later remembered or forgotten. Another study found subsequent memory effects in the hippocampus and the PER/EC during encoding of word pairs (Jackson and Schacter, 2004).

Overall, the majority of relevant studies show that the hippocampus is preferentially involved in associative memory, consistent with dual-process theories of MTL function. However, there is also evidence for involvement of parahippocampal structures. This suggests that hippocampal and parahippocampal functions cannot be separated by a simple item-associative dichotomy, as emphasized in the declarative theory. In particular the PHC is frequently active in associative memory tasks, and several authors have therefore suggested that this region supports associative binding similarly to the hippocampus. Others have attempted to further differentiate their contributions. Tendolkar et al. (2008) recently showed that hippocampal activation increased during source relative to item retrieval, whereas PHC activation increased linearly with the amount of contextual details retrieved. Similarly to Daselaar et al. (2006), who found a positive correlation between PHC activation and recognition confidence, this result suggests that the hippocampus and the PHC support associative retrieval based on recollection and memory strength, respectively. Another view is that the PHC is selectively involved in memory for spatial context, which is discussed in further detail below.

Although most evidence favors a role for the PER in item memory, PER activation is often seen in studies that involve encoding or retrieval of stimulus pairs (see Eichenbaum et al., 2007). It has been suggested that the PER creates unitized or 'configural' object representations in memory (Bussey et al., 2005) and supports memory for intra-item or within-domain associations (e.g., an object's color and shape) (Mayes et al., 2007). Consistent with this view, Haskins et al., (2008) found increased PER activation during encoding of word pairs and preferentially on trials where words were treated as a single compound rather than as separate units. Similarly, Staresina and Davachi (2008) showed that PER activation predicts subsequent memory for both items

and item-related features, but only hippocampal activity predicted subsequent memory for item-context associations. Another view is that the hippocampus has a unique role in tasks that require flexible use of learned representations, which is confirmed by fMRI studies of transitive inference (Heckers et al., 2004; Preston et al., 2004).

Spatial *vs.* non-spatial memory

FMRI studies have demonstrated involvement of MTL regions in a variety of spatial tasks, such as free exploration (Aguirre et al., 1996) and wayfinding (Hartley et al., 2003) in virtual reality (VR) environments, and mental navigation through familiar towns (Rosenbaum et al., 2004). A recent study reported patterns of MTL activity that resemble the spatial coding expressed by hippocampal neurons in rats (Hassabis et al., 2009). Activation maps were obtained while subjects were positioned in two different rooms (VR). Pattern classification analyses revealed that activity within the hippocampus accurately predicted the subject's position within each room, whereas activity in the PHC predicted in which of the two rooms the subject was placed.

Several studies have tested whether MTL activation is greater in spatial compared to non-spatial memory tasks, as predicted by the cognitive map theory. For example, Pihlajamäki et al. (2004) showed that the posterior hippocampus and the posterior PHC responded more to novel spatial arrangements of objects than to novel objects as such, whereas the anterior hippocampus, the anterior PHC and the PER showed the opposite effect. A potential confound in this type of study is that the spatial condition requires associative memory but the non-spatial condition does not, hence the activations may reflect a difference in associative rather than spatial processing. Studies that manipulated the novelty of both spatial and non-spatial stimulus configurations found that the hippocampus responds to both (Köhler et al., 2005; Kumaran and Maguire, 2007).

Studies have also compared retrieval of spatial and non-spatial associations. Ryan et al. (2009) found that both the hippocampus and the PHG were preferentially active during retrieval of spatial compared to non-spatial object relations. In contrast, Ekstrom and Bookheimer (2007) used a VR 'taxi driver game' to compare retrieval of spatial context (customer locations), temporal context (customer order) and objects (landmark

recognition), but only the PHC was preferentially active during retrieval of spatial context. Other studies have also found preferential activation during retrieval of spatial versus non-spatial context in the PHC (Burgess et al., 2001) and the PHG (Hayes et al., 2004), but not in the hippocampus. However, Kumaran and Maguire (2005) have suggested that the hippocampus responds selectively to tasks that require flexible use of large-scale spatial representations. In their study, participants were asked to mentally navigate through a spatial environment (home city) and a social environment (network of friends), as well as to visualize individual places and faces (spatial and non-spatial non-relational conditions). The hippocampus was more active during mental navigation in the spatial domain than in the social domain, but equally active in the two non-relational conditions.

The above findings are in line with other fMRI evidence for PHC involvement in spatial processing. In the posterior PHC, a region known as the 'parahippocampal place area' is preferentially active when subjects view pictures of scenes and spatial layouts, compared to pictures of objects, faces, or houses (Epstein and Kanwisher, 1998, but see Bar et al., 2008). PHC activation has also been associated with successful encoding (Brewer et al., 1998) and retrieval (Hayes et al., 2007) of visuospatial scenes, encoding of object locations (Sommer et al., 2005; Buffalo et al., 2006) and recognition of objects that are relevant for navigation (Janzen and van Turennout, 2004). The findings are also consistent with the view that parahippocampal structures serve domain-specific functions in memory (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007). This was nicely demonstrated in a recent study by Litman et al. (2009). Litman et al. found a double dissociation between preferential responses to objects in the anterior PER, and to spatial scenes in the posterior PHC. They also suggest that the responsiveness to objects and scenes shifts gradually along the anterior-posterior axis of the PHG.

The above findings suggest that the hippocampus is not necessarily more involved in spatial than in non-spatial memory tasks, but rather performs a domain general function. FMRI studies that compare activations across other domains than spatial and non-spatial memory provide additional support for this view. For example, the hippocampus has been shown to respond similarly to successful encoding of faces and scenes (Preston et al., 2009), and to encoding and retrieval of semantic and perceptual associations (Prince et al., 2005). In contrast, the PHC responded preferentially to scenes (Preston et al., 2009) and perceptual associations (Prince et al., 2005). It is largely unknown whether

the hippocampus generalizes across sensory modalities as well. One study compared encoding and retrieval of auditory and visual source memory (Peters et al., 2007a). During encoding, subsequent memory effects for both modalities were found in the anterior hippocampus/PER. During retrieval, successful judgments of auditory and visual source were associated with selective activation in the PHC and PER/EC, respectively, but no significant hippocampal activation was detected.

Pattern completion, pattern separation, and mismatch detection

A handful of fMRI studies have attempted to separate activations within subfields of the hippocampus. Studies comparing effects of encoding and retrieval (Zeineh et al., 2003; Eldridge et al., 2005) were discussed above. Others have tested hypotheses derived from computational models and experimental work in animals. Bakker et al. (2008; see also Kirwan et al., 2007) used an incidental encoding task to assess the neural correlates of pattern separation. Subjects were presented with objects that were either identical (targets) or similar (lures) to previously presented objects, or completely new (foils). Activation in the CA3/DG region was higher when subjects viewed a lure than when they viewed a target, and the response to lures was similar as to novel objects. The authors took these findings to suggest that pattern separation occurred in CA3/DG. In other regions in the MTL, including CA1, activation was highest when subjects viewed novel objects, and the responses to lures and targets were similar. This response pattern may reflect pattern completion.

Kumaran and Maguire (2006a) also found support, albeit less direct, for separation of overlapping inputs in the hippocampus. In their study, hippocampal activation correlated with learning rate during encoding of overlapping, but not non-overlapping, temporal sequences. The correlation was particularly strong during presentation of the critical, i.e., overlapping, items. In another study of sequence encoding (Kumaran and Maguire 2006b; see also Kumaran and Maguire, 2007), the hippocampus responded maximally to a sequence of pictures that *partly* overlapped with a previous sequence, rather than a sequence that was completely new. This activation was seen to reflect 'mismatch detection', a novelty response that is contingent upon prior expectations. Activation in the PER/EC responded equally to both conditions, consistent with a more general novelty response. A more recent study (Duncan et al., 2009) found that the

hippocampus responds equally to perceptually matching and mismatching stimuli, if either is relevant for the trial instruction (i.e., 'goal match'). Although these latter studies did not map activation onto specific hippocampal subfields, they nevertheless contribute to the debate about the type of computations that are supported by the hippocampus.

AIMS OF THE THESIS

It is widely agreed that the MTL operates as an associative network that integrates inputs from widespread cortical and subcortical areas to form complex, multimodal representations. The MTL is thought to aid in the formation, storage and later reactivation of these representations, and hereby support performance in multiple cognitive domains, including memory and spatial navigation. Yet, discussions still continue over the type of memory that is supported by the MTL, as well as whether and in what sense different subregions make different functional contributions. **The overall objective of this thesis is to gain further insight in functional differences among subregions of the MTL.** Of primary interest is to differentiate functions of the hippocampus from functions of the parahippocampal structures. Based on previous fMRI research on MTL functions, the objective translates into three more specific aims.

First, MTL activation has been observed in both episodic and semantic memory tasks, as predicted by the declarative theory. However, there is some evidence to suggest stronger activation during recall of autobiographical events, consistent with the multiple trace theory and related accounts of MTL function. It is not clear whether this effect pertains specifically to the hippocampus, but recollective qualities like number of details and personal significance may be among the factors that determine hippocampal involvement. In this thesis we **examine the potential of a naturalistic autobiographical memory paradigm to yield both strong and anatomically precise activation in MTL subregions (Aim 1; Paper 1).**

Second, fMRI studies have consistently shown that the hippocampus is preferentially involved in memory for stimulus relationships and contextual associations. Activation in parahippocampal regions, in particular in the PER, more often correlates with memory for single items. These findings are consistent with predictions from dual-process theories, and with anatomical models of the MTL. However, several studies have shown that also parahippocampal regions are involved in certain types of associative memory. This implies that functional divisions go beyond the dichotomy 'item-associative', a point that is also stressed in the declarative theory. To shed further

light on this issue, we **investigate the contribution of MTL subregions to different types of associative retrieval (Aim 2; Papers 2 and 3).**

Third, as predicted by the cognitive map theory, MTL regions seem to be preferentially involved in spatial memory tasks. This has been shown most consistently for the PHC, in agreement with anatomical and theoretical models that predict domain-specific involvement of the PHC, i.e., in memory for spatial context. It is less clear whether the hippocampus has a special role in spatial memory or rather serves a domain-general function. Since few studies have compared activation across other domains than spatial and non-spatial memory, this thesis will **study the effect of stimulus modality on activation in MTL subregions (Aim 3; Papers 3 and 4).**

In order to achieve these aims, four fMRI experiments were conducted. FMRI was chosen because it is currently the only method that allows brain activation to be measured in neurologically intact humans, noninvasively and with a relatively high spatial resolution.

SUMMARY OF THE PAPERS

PAPER 1

Background: Previous fMRI studies of episodic memory suggest that MTL regions are particularly sensitive to recall of autobiographical events, rich in contextual details and personally significant. In this study, we developed a novel, prospective memory paradigm to measure recall of real-life, autobiographical events. The aim was to test whether this paradigm would yield robust activation in MTL subregions that could be reliably detected in single-subject analyses. This would obviate the need for group analysis and hence image transformations and loss of spatial resolution.

Methods: Events from a real-life birthday party were recorded to construct a surprise memory test. The memory test was administered two weeks later as part of an fMRI experiment, and six subjects who had attended the party participated. Subjects were given a series of questions about episodes from the birthday party and instructed to answer each question covertly. Periods of recall (19 blocks, 5 questions in each) alternated with periods of baseline measurements, during which subjects performed simple perceptual-motor control tasks (23 blocks, 5 tasks in each). Subjects were scanned at 3 Tesla (T) (35 slices; 2x2x3 mm; TR=3 sec). Immediately after scanning, subjects reported their answers to all questions. The data were analyzed for each subject separately.

Main results: The recall task yielded highly significant activation in the MTL. In all subjects, activation was observed in the PHC, whereas two subjects showed extensive activation also in the hippocampus. The other subjects also showed hippocampal activations, but these activations were confined to smaller regions and detected only sub-threshold in two of the subjects. The hippocampal activations were typically observed at a medial location that may correspond to CA1 or the subiculum. In four subjects, there was a significant positive correlation between retrieval performance and level of activation in one or more PHC clusters. The hippocampal activations were not related to performance in any of the subjects.

Conclusions: Our findings suggest that fMRI studies of MTL functions may benefit from using naturalistic paradigms. Recall of real-life autobiographical events triggers strong activation in MTL subregions that is detectable at single-subject level. This may allow a more accurate localization of activation than in conventional group analyses of fMRI data. Our task most consistently activated the PHC, and additional work is needed to identify the exact conditions that determine hippocampal involvement in autobiographical recall.

PAPER 2

Background: Theoretical models propose that the hippocampus has a unique capacity to associate events across time and represent past episodes as temporal sequences of related events. Animal research has largely confirmed this view, but firm evidence from human subjects is lacking. In particular, fMRI studies have often failed to detect MTL activation during retrieval of temporal order, possibly because subjects were asked to judge the relative recency among two previously presented but otherwise unrelated items. We hypothesized that recalling a temporal sequence of life-like events would rely more on the temporal associations proposed to occur in the hippocampus. This prediction was tested in Paper 2.

Methods: The experiment took place across two consecutive days. On day one, subjects (n=20) watched a novel detective movie (89 min). On the next day, subjects recalled the temporal sequence of events from the movie while they underwent fMRI scanning (3T; 26 slices; 1.5x1.5x3.0 mm; TR=2 sec). On each trial (n=15), subjects were shown four scenes from the movie and asked to rearrange these in correct order. Activation was compared to a control condition where subjects used logical inference to identify the correct order of scenes from the same movie. The experiment included trial-by-trial assessments of retrieval performance, effort and strategy. The data were analyzed at group level, and probabilistic maps in the Jülich atlas were used for tentative descriptions of activation within hippocampal subfields.

Main results: Recall of temporal sequences yielded increased activation in the right hippocampus. There was a significant positive correlation between the level of hippocampal activation and accuracy of sequence recall. A region-of-interest analysis

based on the Jülich probabilistic atlas suggested that the hippocampal activation was primarily located in the CA-fields and subiculum. Similar activations were observed in the left hippocampus, albeit sub-threshold. The recall task also yielded increased activation in the bilateral PHC, but this activation was not related to performance.

Conclusions: This study identifies a unique contribution of the hippocampus to correct recall of temporal sequences. The findings are consistent with theoretical accounts of hippocampal function and with fMRI studies that show hippocampal involvement in other forms of sequence memory. Our findings also suggest that the PHC is activated during sequence recall, but that it does not contribute to performance.

PAPER 3

Background: Although declarative memories typically consist of information in multiple modalities, little is known about the role of MTL in crossmodal memory. In this study we investigated the contribution of different subregions in the MTL to retrieval of crossmodal associations. Of main interest was to determine whether retrieval of crossmodal associations relies on domain-general associative capacities of the hippocampus, or on feature conjunction in the PER. We additionally tested whether retrieval of inferred (indirect) associations would specifically involve the hippocampus, and explored the influence of stimulus modality on activation across all MTL subregions.

Methods: Subjects (n=15) learned novel associations between visual, auditory and tactile stimuli. Four unique visual objects (abstract paintings) were presented and subjects learned to associate each one with another visual stimulus (spatial location on screen) as well as with an auditory stimulus (music clip) and a tactile stimulus (textured paper). Each type of association was learned in a separate session towards criterion (85% correct). Immediately after the last session, retrieval was tested during fMRI scanning (3T; 26 slices; 1.5x1.5x3.0 mm; TR=2 sec). On each trial (n=120), one stimulus was presented (visual object, auditory or tactile) and subjects were asked to identify the associated stimulus (visual: object or spatial). The analysis compared retrieval of crossmodal vs. unimodal associations, auditory vs. tactile associations, and inferred vs. learned associations. Modality-specific effects on the latter comparison

were also examined. The data were analyzed at group level. A non-linear registration technique was applied to improve the cross-participant alignment of functional images.

Main results: Retrieval of crossmodal associations selectively activated the PER. This activation was independent of stimulus modality, i.e., similar for retrieval of tactile-visual and auditory-visual associations. Activation in other areas, including the hippocampus, the PHC and the EC, was increased during auditory compared to tactile recall. Retrieval of inferred associations yielded increased activation in the hippocampus compared to retrieval of learned associations, but only with tactile stimuli.

Conclusions: This study identifies a unique role of the PER in retrieval of crossmodal associations. This observation is consistent with its proposed capacity for feature conjunction, previously shown to occur within the visual domain. Our findings provide partial support for the view that the hippocampus supports flexible expressions of previously learned associations. Preferential activation during auditory recall may reflect stronger auditory than tactile innervation of the MTL.

PAPER 4

Background: The MTL, and in particular the hippocampus, is proposed to integrate information from multiple modalities and serve domain-general functions in memory. However, most studies of the human MTL have tested memory functions in the visual domain, and little is known about its contributions to memory in other sensory modalities. Paper 3 showed that the hippocampus was more active during auditory than tactile recall, similarly to the PHC and the EC. In this study, we compared activation in MTL subregions during recognition of visual and olfactory stimuli. We also tested whether recognition would yield activation in sensory-specific cortical regions, i.e., reinstatement of cortical memory traces.

Methods: The experiment took place across two consecutive days. On day one, subjects (n=19) encoded 54 unique odors and 54 unique objects, presented once in random order. Subjects identified the stimuli covertly and were discouraged from verbalization. Recognition was tested the next day during fMRI (3T; 40 slices; 3x3x3 mm; TR=3 sec). An old/new recognition paradigm with verbal cues was used in order to identify

modality-specific effects that were independent of sensory input. Subjects were presented with the names of previously studied (old) and unstudied (new) odors and objects, and pressed a button to indicate which stimuli they recognized. The stimuli were grouped in blocks of primarily old/new odors/objects (9x4 blocks, 6 stimuli in each). Post-scan assessment included ratings of retrieval strategy, level of difficulty, and ability to recollect the study episode. All data were analyzed at group level.

Main results: Both identification and recognition of odors was more difficult and less accurate than of objects. Moreover, odor recognition was more often based on a sense of familiarity, rather than recollection of the study episode. The fMRI data showed that successful recognition of objects activated the hippocampus, as well as parietal and frontal regions that have previously been implicated in retrieval of episodic memories. In contrast, successful recognition of odors activated only a subset of these regions, and not the hippocampus. Recognition of objects and odors were associated with increased activation in visual and olfactory cortical regions, respectively.

Conclusions: Our findings suggest that hippocampal involvement in visual memory tasks cannot automatically be generalized to other sensory modalities. Recognition of objects and odors are associated with marked differences in behavioral performance and strategy, and possibly as a result of this yield differences in hippocampal activation. Our study is the first to show cortical reinstatement of olfactory representations during episodic retrieval in a direct comparison with visual stimuli.

DISCUSSION

It is well established that the MTL is important for declarative memory, the conscious recollection of facts and events. Within the MTL, a number of subregions can be distinguished, each with unique architectural, connectional and electrophysiological characteristics. These most likely have functional implications; hence, the different subregions can be expected to make different contributions to memory. Theoretical models make different predictions as to whether and in what sense MTL subregions are functionally distinct. The declarative theory emphasizes that subregions operate in close collaboration to support all aspects of declarative memory. In contrast, dual-process theories suggest that the hippocampus and parahippocampal regions are specialized in associative and item-based memory operations, respectively. Empirical investigations give some support to the latter view, but there is also evidence that the functional divisions are more complex than the item-associative dichotomy suggests. What are the critical dimensions that separate the functional contributions of MTL subregions?

A review of the literature (Introduction) provided us with two ideas. First, both the hippocampus and the parahippocampal regions may form associations in memory, but at different levels of complexity. To investigate this issue, we compared the contribution of MTL subregions to recall of temporal sequences (Paper 2) and retrieval of crossmodal associations (Paper 3). Second, MTL subregions may be differentially responsive to stimuli of a specific content or modality. To investigate this issue, we compared auditory and tactile crossmodal retrieval (Paper 3) and recognition of odors and visual objects (Paper 4). All studies made use of fMRI, since this method allows a non-invasive investigation of MTL functions in healthy human subjects, and has a higher spatial resolution than other functional neuroimaging techniques. Yet, the position of the MTL ventromedially in the skull and the size of its subregions render imaging at the current limit of spatial resolution in fMRI. One source of inaccuracies in the localizations of activity changes is the image transformations required for conventional group analyses. Therefore, we also examined the potential of a naturalistic, autobiographical memory paradigm to yield robust activation in MTL subregions at single-subject level (Paper 1).

This discussion will first deal with some methodological issues that are relevant for the interpretation of our findings. The main findings are then discussed in the context of past research and contemporary theories of MTL function.

METHODOLOGICAL ISSUES

What does the "activation" reflect?

The BOLD signal is measured in arbitrary units and most experimental paradigms, including those adopted here, rely on the method of cognitive subtraction (Donders, 1969). Task effects are expressed as changes in signal intensity relative to a baseline or control condition that involves the same processes as the experimental condition except for the one of interest. At least four issues need to be considered when interpreting signal increases that arise from this type of comparison.

First, a significant increase in signal intensity in a particular region does not mean that the region is not active in the control condition, only that it is "more active" in the experimental condition, and hence sensitive to its unique component(s). Comparisons with a low-level baseline condition can show which brain regions are involved in all components of the task, as described in Papers 1-3. Here, baseline activation was measured during a perceptual-motor task (Paper 1) and a simple arithmetic task (Papers 2 and 3). We explicitly avoided a more passive baseline condition, because levels of MTL activation may increase in the absence of explicit task demands, for example during periods of rest (Stark and Squire, 2001).

Second, increased BOLD signal indicates that there is a relationship between activity in a region and performance of a specific task, not whether the activity is necessary for performance. For example, processing of temporal sequences has been shown to result in increased activation of the prefrontal cortex (Knutson et al., 2004), and crossmodal integration has been associated with activation increases in the superior temporal sulcus (Beauchamp et al., 2004). It is possible that contributions from these and/or other brain

regions could be sufficient for good task performance in Papers 2 and 3. However, our fMRI data offer valuable insights in which regions contribute to these functions under normal circumstances in healthy human subjects.

Third, the method of subtraction assumes 'pure insertion' – that adding one task component does not influence the effect of other task components. This assumption has been questioned because of nonlinearities in the BOLD response (Friston et al., 1996; Logothetis, 2008). Although nonlinearities are most evident at shorter stimulus durations (<4 sec; Vazquez and Noll, 1998; Soltysik et al., 2004) than in most of the current experiments, all results should be interpreted with caution until verified by data from non-subtractive analyses (e.g., parametric; Büchel et al., 1998).

Finally, it is typically assumed that BOLD signal increases reflect increased neuronal firing. The neuronal activity depicted with increased BOLD signal has been shown to correlate best with the local field potential (LFP), which reflects the sum of synaptic activity in a region, or local processing of inputs (Logothetis et al., 2001; Goense and Logothetis, 2008). The BOLD signal correlates less with multiunit spiking activity, which represents the output from a cortical region (Logothetis et al., 2001; Goense and Logothetis, 2008). Thus, the BOLD signal may change without changes in neuronal firing, if the synaptic inputs cause balanced proportional increases in the excitatory and inhibitory conductances (Logothetis, 2008). This uncoupling implies that the observed activations may reflect processes that take place upstream of the area with increased signal intensity. However, despite the potential decoupling, neuronal firing and BOLD are usually well correlated (Mukamel et al., 2005; Nir et al., 2008), in particular when there is coherent spiking at the population level (Nir et al., 2007). This has so far only been demonstrated in neocortical regions.

How accurate are the localizations?

Separating the anatomical subregions of the MTL remains a challenge in fMRI. The accuracy of localization depends on a number of factors, including voxel size, spatial filtering, image registration, and geometric distortions. Paper 1 showed that a naturalistic, autobiographical memory paradigm has the potential to evoke strong activation within subregions of the MTL at single subject level. Single subject analyses

in native space allows more anatomical precision than conventional group analyses, as it avoids extensive spatial filtering and inaccuracies due to imperfections in the cross-participant alignment. However, a group analysis also has its advantages. Specifically, random-effects group analyses in larger samples than in Paper 1 (n=6), allow inferences to be made at the population level (Friston et al., 1999). In the other experiments (Papers 2-4) we opted for random-effects group analyses to improve the generalizability of our findings.

Paper 4 aimed to study retrieval-related activity both within and outside the MTL. In order to obtain whole-brain (approximate) coverage, the voxel size was set to 3x3x3 mm, and standard settings for cross-participant alignment (linear registration to MNI standard space) and spatial smoothing (5 mm) were adopted. Geometric distortions were counteracted by the use of parallel imaging (Bellgowan et al., 2006) and by orienting slices perpendicular to the long axis of the hippocampus (Weiskopf et al., 2006). Because Papers 2 and 3 aimed to differentiate functions of MTL subregions, a reduced field-of-view was adopted to improve the in-plane resolution to 1.5 mm. Additional improvements were sought by minimizing spatial filtering 3 mm (Paper 2) and by the use of a non-linear registration method (Paper 3). As such, these papers may provide a more accurate description of localizations than conventional approaches as exemplified in Paper 4. However, the reported localizations must be interpreted with caution, at least with regard to the hippocampal subfields. Accurate delineation of hippocampal subfields requires a spatial resolution of <1 mm, and geometric distortions and imperfections in the image alignment are likely to remain despite the applied optimizations.

In order to acknowledge some of these uncertainties, activations within hippocampal subregions were expressed in probabilities derived from the Jülich atlas (Amunts and Zilles, 2001). The Jülich atlas contains probabilistic maps of various brain regions, including the hippocampus and the EC (Amunts et al., 2005), that are based on cytoarchitectonic analyses of 10 human postmortem brains. The maps have been transformed to the Montreal Neurological Institute standard template (MNI152), and the reported probabilities reflect the relative frequency with which a structure is present in a given voxel. It has to be considered that the probabilities do not take into account imperfections in the alignment of functional images or possible errors due to interpolation (to 1 mm standard brain), and that the 10 brains on which the maps are

based may not be representative for the population. Still, the Jülich atlas offers a time-effective and reproducible method to express both the location and variability of activations in fMRI data, and is the only probabilistic map of hippocampal subregions currently available.

MAIN FINDINGS

The MTL supports retrieval of episodic and semantic memories

Declarative memory is typically divided in episodic memory, which refers to memory for unique experiences in one's personal past, and semantic memory, which refers to general knowledge or facts. The present work shows that the MTL is activated during retrieval of both episodic (Papers 1, 2 and 4), and semantic (Paper 3) memory. The crossmodal paradigm (Paper 3) is seen to measure semantic memory because subjects learned the associations across multiple learning trials and are therefore likely to have formed general, i.e., context-free, representations in memory. Although most previous fMRI studies of the MTL have tested episodic memory, several studies have also observed MTL activation in tasks of semantic memory (e.g., Maguire and Frith, 2004; Elfgren et al., 2006; Douville et al., 2005; Ryan et al., 2008).

The multiple-trace theory (Nadel and Moscovitch, 1997) and related accounts of MTL function (Vargha-Khadem et al., 1997; Tulving and Markowitsch, 1998) predict that the hippocampus preferentially supports episodic memory, as it requires associations to be formed between a particular experience and its unique spatial and temporal context (Tulving, 1983). This may be particularly evident during recall of autobiographical episodes since these – in contrast to the kind of stimuli used in most laboratory tasks of episodic memory – are personally significant and rich in contextual details (Gilboa, 2004; Cabeza et al., 2004; Cabeza & St. Jacques, 2007). We observed strong activation in both the hippocampus and the PHC during recall of real-life autobiographical events (Paper 1) that was detectable at single subject-level and with a much stricter statistical threshold than typically used in fMRI studies of the MTL. However, since the other types of memory were tested in separate experiments, we cannot make a formal

comparison of their effects to determine whether there is preferential involvement in autobiographical memory. Moreover, contrary to the predictions, activation was most consistent in the PHC, and hippocampal activation was reliably detected in only a few subjects.

The results of Paper 1 did not indicate in what sense the hippocampal and PHC activations may reflect different mnemonic operations, nor did they provide a clear explanation for the lack of hippocampal activation in some subjects. Activation was measured during events with variable content and compared to activation in a low-level baseline condition. Although the prospective method allowed more experimental control than in most studies of autobiographical memory, several variables that may affect MTL activation (e.g., memory strategy [Kondo et al., 2005] and quality of memories [Addis et al., 2004]) could have varied but were not measured. In order to obtain more insight in the functional roles of MTL subregions, the subsequent experiments included task manipulations and behavioral data that measured more specific aspects of retrieval.

What is the role of the hippocampus?

In Paper 2 we identified a unique contribution of the hippocampus to recall of temporal sequences. In this experiment, naturalistic stimuli from a movie were used to mimic "mental replay", i.e., a vivid recollection of how past events unfold over time, which is seen as a central feature of episodic memory (Tulving, 1983). This makes our study similar to studies that measure recall of autobiographical episodes and that also report hippocampal and parahippocampal activation (Steinvorth et al., 2006; Addis et al., 2007). However, our task was more constrained in that subjects were explicitly asked to retrieve the temporal order of events, and the control condition allowed us to subtract out effects of other mnemonic processes. Although activation was observed in both the hippocampus and the PHC, the performance-based analysis showed that the ability to accurately recall the temporal sequence of events uniquely involves the hippocampus.

Hippocampal involvement in sequence recall was predicted by theories suggesting that the hippocampus is essential for forming associations across time (Rawlins, 1985) and representing past episodes as temporal sequences of related events (Eichenbaum et al.,

2004). So far, most evidence for this has been derived from research in animals. For example, hippocampal lesions have been shown to disrupt sequence learning in rats (Honey et al., 1998), and electrophysiological recordings from hippocampal neurons have revealed several types of sequence coding, including theta phase precession (O'Keefe and Recce, 1993) and replay (Skaggs & McNaughton, 1996). In humans, fMRI studies have shown that the hippocampus contributes to encoding of overlapping sequences (Kumaran and Maguire, 2006a) and temporal sequence mismatch detection (Kumaran and Maguire, 2006b; 2007). Lesion studies suggest that the hippocampus is critical also for recall of temporal sequences (Mayes et al., 2001; Holdstock et al., 2005), and our study is the first to confirm this with imaging data from healthy subjects. A more recent fMRI study (Ross et al., 2009) found additional support for hippocampal involvement in both encoding and retrieval of temporal sequences.

The mechanisms of sequence coding are yet poorly understood but typically ascribed to the associative capacities of the recurrent collaterals in CA3 (Levy, 1996; Lisman, 1999). Paper 2 offered a tentative description of the localization of activation within the transversal plane of the hippocampus, but found no clear evidence for a specific role of CA3. The hippocampal activation was focused in CA and the subiculum, but the different CA fields could not be separated. Based on anatomical studies it is proposed that CA1 and the subiculum form parts of the same functional circuit (Witter et al., 2000b; Knierim et al., 2006), hence the results could be seen to reflect involvement of CA1. It has been argued that CA1 recodes information from CA3 into a more compressed form (Rolls, 1996) and performs temporal pattern separation to support accurate sequence recall (Kesner et al., 2004; Rolls and Kesner, 2006). Relatively little is known about the functions of the subiculum. Animal studies report that subicular neurons fire during delay intervals in working memory tasks, suggesting that it participates in short-term retention of information (Deadwyler and Hampson, 2004) and that it cooperates with CA1 to support performance across long time intervals (Deadwyler and Hampson, 2006). FMRI studies have suggested that the subiculum is particularly important during memory retrieval (Gabrieli et al., 1997, Zeineh et al., 2003; Eldridge et al., 2005), but subicular activation has also been associated with successful encoding (Preston et al., 2009). Previous fMRI studies of sequence memory did not separate between hippocampal subregions, hence whether or not the

CA/subicular region is involved in or necessary for temporal processing awaits further confirmation.

The hippocampus is proposed to associate past events with their unique spatio-temporal context (Davachi, 2006). This view is supported by fMRI studies that show increased hippocampal activation during correct versus incorrect retrieval of contextual features associated with an item, like screen location (Cansino et al., 2002) or color (Weis et al., 2004). However, previous fMRI studies have tested retrieval of *temporal* context by asking subjects to judge the relative recency of two previously presented items and often failed to detect hippocampal activation (e.g., Suzuki et al., 2002; Hayes et al., 2004; Rajah & McIntosh, 2006; Ekstrom & Bookheimer, 2007). This is possibly because recency judgments can be based on indices of relative item strength or familiarity (Hintzman, 2005). Recalling a sequence of multiple related events is more likely to require retrieval of temporal relationships or "order codes" (Friedman, 1993). Hence, in light of previous null findings, our results suggest that hippocampal involvement in retrieval of temporal context depends on the associative demands, as argued by others (Konishi et al., 2006; Aggleton et al., 2007). This is similar to observations of preferential hippocampal activation during item recognition based on recollection rather than familiarity (e.g., Eldridge et al., 2000; Dolcos et al., 2005; Woodruff et al., 2005).

Is the hippocampus involved in all forms of associative memory? Many studies have compared hippocampal involvement in associative versus item-based memory, but only few have compared different types of associative memory. Konkel et al. (2008) tested three types of 'relational memory' in patients with hippocampal lesions, including 'spatial' (object location on screen), 'sequential' (order of object presentation) and 'associative' (co-occurrence of objects in set), and found that patients were impaired on all tasks relative to controls. This suggests that the hippocampus supports different types of associative memory. However, it has been argued that the hippocampus is particularly important for tasks that require flexible expressions of previously learned associations (Eichenbaum et al., 1994, 2004). An example of this type of task is transitive inference, where subjects first learn a set of overlapping stimulus pairs (e.g., AB and BC) and are then asked to identify a stimulus pair that was only indirectly associated during learning (e.g., AC). A similar function was measured in Paper 3 by comparing retrieval of learned (direct) and inferred (indirect) crossmodal associations.

We found partial support for the above hypothesis, as there was increased activation in the hippocampus during retrieval of inferred versus learned associations, based on tactile cues. However, inferential recall based on auditory cues was not associated with increased hippocampal activation, and the main effects showed increased activation during retrieval of learned associations, both in the hippocampus and the PHC.

Hippocampal involvement in transitive inference is supported by lesion studies in rats (Bunsey and Eichenbaum, 1996) and imaging studies of visual recognition in humans (Heckers et al., 2004; Preston et al., 2004). As discussed in Paper 3, increased activation during retrieval of learned associations could possibly reflect new learning on these trials. It has previously been shown that incidental encoding occurs during retrieval (Stark and Okado, 2003). A performance-based analysis may have yielded clearer results. Because the stimulus associations were learned across multiple trials until the subjects had reached a predefined criterion of performance (>85% correct), there were too few incorrect responses to allow a comparison between successful and unsuccessful trials. Although performance was high and similar on both learned and inferred recall trials, performance-based analyses can be used to identify purely mnemonic effects of both encoding (e.g., subsequent memory effects) and retrieval (e.g., hits vs. misses or correct rejections) and may help to separate the functional contributions of different subregions, as shown in Paper 2 and in other fMRI studies (e.g., Danckert et al., 2007).

What is the role of the parahippocampal structures?

In Paper 3, we showed that also the PER supports associative memory. The PER was the only region that was more active during retrieval of crossmodal associations (tactile-visual, auditory-visual) than during retrieval of unimodal associations (visual: object-location). This observation seems to challenge evidence that suggest the PER is specialized in familiarity judgments and other forms of item memory (Brown and Aggleton, 2001; Eichenbaum et al., 2007). However, it has recently been argued that the PER supports memory for intra-item or within-domain associations, i.e., when different stimulus features are combined to form a unitized representation (Mayes et al., 2007). In Paper 3, subjects learned the stimulus associations across multiple trials and may therefore have created unitized, multimodal representations in memory. In support of this interpretation, previous imaging studies have shown that PER activation is

associated with unitization of word pairs during encoding (Haskins et al., 2008) and predicts subsequent memory for associations between items and item-related features (Staresina and Davachi, 2008).

A related view of PER function is articulated in the 'perceptual-mnemonic/feature conjunction' (PMFC) model (Bussey et al., 2005). Here, the PER is said to operate at the end of the ventral visual stream, throughout which increasingly complex object representations are built. As such, it is proposed to form complex, conjunctive representations of visual object features in support of both perception and memory. This model predicts that the PER is required for object discrimination in conditions with high levels of feature ambiguity (e.g., AB+, CD+, BC-, AD-), which is confirmed by lesion studies in monkeys (Bussey et al., 2002) and humans (Barense et al., 2005). A previous fMRI study suggested that the PER also integrates features across modalities, since the level of PER activation differed during presentation of congruent versus incongruent auditory-visual stimulus pairs (Taylor et al., 2006). Paper 3 extends these findings by showing that the PER contributes also to retrieval of crossmodal associations, and that this effect is independent of stimulus modality (see below).

How does the above suggested function of the PER relate to hippocampal contributions to associative memory? The 'configural association theory' (Sutherland and Rudy, 1989), claims that conjunctive representations are formed in the hippocampus. The hippocampus is said to be essential for configural learning, i.e., tasks where the solution is not given by the individual stimuli but contingent upon the particular combination of stimuli; for example when stimulus A is rewarded only if it appears together with B but not if it appears together with C (i.e., AB+, AC-). This is, however, similar to tasks with high levels of feature ambiguity, which according to the PMFC model rely on the PER. Indeed, several studies have found that rats with hippocampal damage are unimpaired on tasks of configural learning, forcing a revision of the configural association theory (Rudy and Sutherland, 1995). According to one view, the hippocampus is only required for rapid, incidental learning of stimulus configurations, whereas cortical areas learn more slowly by extracting regularities across repeated experiences (O'Reilly and Rudy, 2001). Hence, the PER activation observed in Paper 3 could reflect that the crossmodal associations had been learned gradually across multiple trials rather than through "one-shot", hippocampal-dependent learning (see Nakazawa et al., 2003). O'Reilly and Rudy (2001) suggest that pattern completion and pattern separation underlie hippocampal

contributions to rapid, incidental coding and may also be relevant for certain forms of flexible memory. Another view is that the hippocampus is only needed for configural learning that involves 'structural discrimination', i.e., when the solution is given not only by which stimuli are combined but also how they are combined in terms of their spatial arrangement or temporal order (Aggleton et al., 2007). Rats with hippocampal lesions are selectively impaired on this type of configural learning (Sanderson et al., 2006). Structural discrimination, as defined above, was not required for crossmodal retrieval in Paper 3, which could possibly explain the lack of hippocampal activation. This interpretation has appeal in the present context because it predicts hippocampal involvement in sequence memory, which coincides with the results of Paper 2.

Paper 1 suggested that the PHC has a central role during recall of past events, but the data did not identify its specific functional contributions. In Paper 2, increased activation was observed in the PHC during recall of temporal sequences, but the level of activation was not related to accuracy. In light of previous findings we reasoned that the activation could reflect encoding/perception of visual scenes (Epstein and Kanwisher, 1998) or retrieval of spatial context (Burgess et al., 2001; Ekstrom and Bookheimer, 2007), not sufficiently matched in the experimental and control conditions. PHC activation was also observed in the direct comparison of object versus odor recognition (Paper 4), which could also reflect retrieval of visuospatial information, in particular since object recognition was frequently accompanied by recollection of the study context. However, since none of the conducted experiments included a formal test of scene encoding/perception or retrieval of spatial context, the data are only suggestive of these functions. In Paper 3, the PHC responded to many of the same task manipulations as the hippocampus (e.g., main effects of unimodal>crossmodal, learned>inferred, auditory>tactile), as found in several other fMRI studies of associative memory (e.g., Eldridge et al., 2000; Cansino et al., 2002; Davachi et al., 2003; Kirwan and Stark, 2004) and consistent with the view that the PHC is sensitive to both spatial and non-spatial associations (Bar et al., 2008).

What is the effect of stimulus modality?

Early research on amnesia showed that MTL damage disrupts memory performance regardless of the sensory modality in which information was presented (Milner, 1972).

The MTL integrates information from all sensory modalities (Lavenex and Amaral, 2000) and is believed to serve domain-general functions in memory (Squire et al., 2004). In particular the hippocampus is ascribed a domain-general function (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007), since it represents the highest level of integration. Yet, most research on MTL functions has tested visual memory and little is known about its contributions to memory in other sensory domains. We observed that the hippocampus was activated during visual object recognition but not during odor recognition (Paper 4). The hippocampus was also more active during auditory compared to tactile recall, similarly to the EC and the PHC (Paper 3). Together, these findings suggest that MTL functions are sensitive to stimulus modality.

Although research in humans has focused on visual memory, odor stimuli are often used to assess memory functions of the rodent hippocampus (Eichenbaum, 1998). Rodents have a highly developed sense of smell and the hippocampus receives strong olfactory inputs via the PER and the EC (Burwell, 2000). In primates, vision is the dominant sense and the PER receives no direct olfactory input, whereas olfactory input to the EC is limited (Suzuki and Amaral, 1994). Therefore, the human hippocampus is likely to be less responsive to olfactory than to visual stimuli. However, the complete absence of hippocampal activation during odor recognition was unexpected. Our behavioral data suggest that the lack of hippocampal activation reflects qualitative differences in the processing of odors and objects. Odors were more often recognized by a sense of familiarity, which likely does not involve the hippocampus (Brown and Aggleton, 2001; Eichenbaum et al., 2007). The absence of hippocampal activation during recognition of odors, but not objects, could also reflect differences in performance. The ability to discriminate old from new odors was significantly lower than the ability to discriminate old from new objects. In order to obtain unbiased estimates of odor and object recognition effects, the event-related analysis was based on correct trials only (hits versus correct rejections). However, recognition accuracy could not be verified, given the combination of covert labeling/identification during encoding and verbal cues during retrieval. It is possible that other task conditions may have facilitated performance and/or recollection during odor recognition and yielded hippocampal activation also on those trials. Although most fMRI studies of episodic odor memory have failed to detect MTL activation, one study observed hippocampal activation during

odor recognition (Cerf-Ducastel and Murphy, 2006). Human lesion studies also suggest that the hippocampus contributes to olfactory memory (Levy et al., 2004).

The PER and the PHC have been hypothesized to support domain-specific functions in memory (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007), based on differential innervations by regions in the ventral ('what') and dorsal ('where') visual streams, respectively (Suzuki and Amaral, 1994). Paper 3 suggests that parahippocampal responses may differ also between sensory modalities. PER activation during crossmodal retrieval was independent of modality, but the PHC was more active during auditory compared to tactile recall. This result is consistent with anatomical studies in monkeys, showing that auditory association areas in the superior temporal gyrus project predominantly to the PHC and much less to the PER (Suzuki and Amaral, 1994). It is also consistent with previous imaging (Peters et al., 2007a) and lesion data (Peters et al., 2007b) suggesting that the PHC is particularly sensitive to auditory memory. Peters et al. (2007a) observed increased activation in the PHC during successful retrieval of auditory source (speaker voice associated with object during encoding), and increased activation in the PER during successful retrieval of visual source (picture background associated with object during encoding).

In contrast to the study of Peters et al. (2007a), Paper 3 found increased PHC activation in a direct comparison between auditory and tactile recall. It is possible that auditory stimuli were easier to associate with the visual stimuli, similar to the effectiveness of verbal cues in odor versus object recognition, discussed in Paper 4. Speaking against this interpretation is the finding that there was no difference in performance on auditory-visual and tactile-visual recall trials. The most parsimonious explanation for the modality effects may be that the PHC receives stronger auditory than tactile input (Suzuki and Amaral, 1994), and that this causes stronger responses to the former. This implies that the hippocampus and the EC receive stronger auditory input (via the PHC) than tactile input, which could explain why also these regions were more active during auditory than tactile recall. The PER receives most cortical afferents from visual areas, and projections from both auditory and tactile somatosensory areas are weak (Suzkui and Amaral, 1994). This could explain why the PER was not sensitive to the comparison of auditory and tactile recall.

Where are memories stored?

Permanent memory traces are thought to reside in the neocortex (Mishkin, 1982; Fuster, 1997; Harris, 2001), stored as synaptic modifications among neurons that were involved in processing the original experience (Hebb, 1949). According to the cortical reinstatement hypothesis (James, 1890; Damasio, 1989), memory retrieval will therefore involve reactivation of sensory processing areas. This prediction was tested in Paper 4 by comparing whole-brain patterns of activation during recognition of odors and objects. We found that recognition of odors and objects were associated with activation in olfactory and visual cortical regions, respectively. Since these activations occurred in the absence of different sensory input, triggered merely by a verbal cue to retrieve either an odor or object, they most likely reflect reinstatement of cortical memory traces. Previous fMRI studies have demonstrated activation in sensory-specific cortical regions during retrieval of visual and auditory stimuli (Nyberg et al., 2000; Wheeler et al., 2000), but our study is the first to show a similar effect in a direct comparison of visual and olfactory stimuli.

The MTL can be seen to have a coordinating function during memory encoding and retrieval, interacting with neocortical storage sites. Several theories have proposed that the hippocampus stores memories in a compressed form, e.g., as an 'index' (Teyler and DiScenna, 1986), 'summary sketch' (McNaughton, 1989) or 'link system' (Murre, 1996), that identifies the neocortical modules that represent the various sensory features of an experience. The hippocampus is said to bind these modules together and hereby allow the complete memory trace to be reactivated at the time of retrieval (McClelland et al., 1995). Also parahippocampal structures are thought to assist in this process, forming intermediate layers of association. However, the standard consolidation theory (Alvarez and Squire, 1994; McClelland et al., 1995) claims that the MTL has only a time-limited role in retrieval. Over time, repeated reactivations of a memory trace will gradually strengthen the direct connections between the neocortical modules, whereby retrieval becomes independent of the representation in the MTL.

In our experiments, MTL activation was observed after study-test intervals of 10 min (Paper 3), 1 day (Papers 2 and 4) and 2 weeks (Paper 1). Since we did not test effects of consolidation, it is not known to what degree the length of these intervals may have affected the activations. However, it seems unlikely to have had a major effect, since

consolidation is considered to be a slow process (McClelland et al., 1995; but see Tse et al., 2007) and temporal gradients in amnesia are typically observed across several years or decades (Squire and Bayley, 2007). Moreover, according to the multiple-trace theory, the MTL has a permanent role in retrieval of contextually rich, episodic memories (Nadel and Moscovitch, 1997; Moscovitch et al., 2005), which is the type of memory that was tested after the longest, 2-week interval (Paper 1). In support of this view, several fMRI studies of autobiographical memory have found that the level of hippocampal activation does not vary with the age of the retrieved memories (Ryan et al., 2001; Steinvorth et al., 2006) but rather depends on recollective qualities like vividness and personal significance of the retrieved memories (Addis et al., 2004; Gilboa et al., 2004).

CONCLUSIONS

The aim of this thesis was to characterize functional differences among subregions of the MTL. The conducted experiments allow us to draw three general conclusions.

First, recall of real-life autobiographical events yields strong responses in MTL subregions, and most consistently in the parahippocampal cortex. The experimental paradigm has high ecological validity and allows an anatomically precise description of activations, as well as of individual variation herein. These factors should be taken into consideration in future fMRI studies of functional differentiations within the MTL.

Second, both the hippocampus and parahippocampal structures serve associative functions in memory, but at different levels of complexity. Accurate recall of temporal sequences was uniquely related to activation in the hippocampus. This suggests that the hippocampus associates events across time to represent temporal sequences. In contrast, retrieval of crossmodal associations uniquely engaged the perirhinal cortex. This suggests that the perirhinal cortex associates different stimulus features to facilitate storage of coherent, multimodal representations in memory.

Third, MTL subregions are sensitive to stimulus modality. Whereas perirhinal activation during crossmodal retrieval was independent of modality, both the hippocampus as well as the parahippocampal and entorhinal cortices responded more to auditory than to tactile stimuli. This likely reflects stronger auditory innervation of these regions. The hippocampus was also found to be activated during successful retrieval of objects, but not odors, and this may reflect that visual and olfactory stimuli evoke different responses at the behavioral level.

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CONTRIBUTIONS

Papers 1-4 are included on the following pages.

Paper I

Is not included due to copyright

Paper II

Behavioral/Systems/Cognitive

A Specific Role of the Human Hippocampus in Recall of Temporal Sequences

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There is a growing interest in how temporal order of episodic memories is represented within the medial temporal lobe (MTL). Animal studies suggest that the hippocampal formation (HF) is critical for retrieving the temporal order of past experiences. However, human imaging studies that have tested recency discrimination between pairs of previously encoded items have generally failed to report HF activation. We hypothesized that recalling a naturalistic sequence of past events would be particularly sensitive to HF function, attributable to greater involvement of associative processes. To test this prediction, we let subjects watch a novel movie and later, during functional magnetic resonance imaging, asked them to rearrange and "replay" scenes from the movie in correct order. To identify areas specifically involved in retrieval of temporal order, we used a control condition where subjects logically inferred the order of scenes from the same movie. Extensive MTL activation was observed during sequence recall. Activation within the right HF was specifically related to retrieval of temporal order and correlated positively with accuracy of sequence recall. Also, the bilateral parahippocampal cortex responded to retrieval of temporal order, but the activation here was not related to performance. Our study is the first to unequivocally demonstrate that correct sequence recall depends on HF.

Introduction

Memories of past experiences (episodic memories) are thought to be organized by order of occurrence (Tulving, 1983; Eichenbaum, 2004). The medial temporal lobe (MTL) supports episodic memory, and accumulating evidence from animal research (Skaggs and McNaughton, 1996; Fortin et al., 2002; Kesner et al., 2002; Dragoi and Buzsáki, 2006; Pastalkova et al., 2008) suggests that temporal order is represented in the hippocampal formation (HF). This view is consistent with theoretical models of hippocampal function that propose a critical role in associating events across time (Rawlins, 1985; Wallenstein et al., 1998), possibly drawing on the recurrent connections in area CA3 (Levy, 1996; Lisman, 1999). Human imaging studies are less conclusive about hippocampal involvement in memory for temporal order. Most studies do not report preferential HF responses but instead emphasize the importance of the prefrontal cortex (Nyberg et al., 1996; Cabeza et al., 1997; Suzuki et al., 2002; Dobbins et al., 2003; Fujii et al., 2004; Hayes et al., 2004).

Previous imaging studies may not have been sensitive to the type of temporal order memory that involves HF. Typically, subjects were asked to make recency discriminations between pairs of stimuli, in which they could rely on feelings of relative trace strength or familiarity (Yonelinas and Levy, 2002; Hintzman, 2005). Familiarity judgments are most likely mediated by parahippocampal structures, in particular the perirhinal cortex (Brown and Aggleton, 2001; Eichenbaum et al., 2007). This interpretation is supported by observations of more parahippocampal than hippocampal activation during recency judgments (Rekkas et al., 2005; Dudukovic and Wagner, 2007; St. Jacques et al., 2008). Prefrontal involvement in recency judgments may reflect familiarity monitoring (Henson et al., 1999; Rajah and McIntosh, 2006), temporal integration (Fuster, 2001), or logical ordering (Knutson et al., 2004).

The HF is proposed to selectively support associative memory, like recollection (Davachi, 2006; Eichenbaum et al., 2007; but see Squire et al., 2007), and appears to be preferentially active when recency judgments involve retrieval of temporal relationships, rather than item familiarity (Konishi et al., 2006). Sequence recall represents a special case of temporal order memory which likely depends in particular on hippocampal function. Remembering the temporal order within a series of related events increases the demand for relational processing and may involve reactivation of "order codes" (Friedman, 1993). Recent functional magnetic resonance imaging (fMRI) experiments have demonstrated hippocampal contributions to temporal order mismatch detection and disambiguation of overlapping sequences during sequential exposure to unrelated, single items (Kumaran and Maguire, 2006a,b, 2007).

The aim of the present study was to assess the contribution of subregions in the human MTL to recall of the temporal sequence

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of related events. Unique to our study is the use of naturalistic and meaningfully related stimuli that resemble real-life event sequences in episodic memory. We let subjects watch a novel movie and later, during fMRI, presented sets of four scenes from the movie and asked subjects to rearrange these in correct order. Based on previous work, we expected this task to specifically activate HF, as opposed to parahippocampal structures.

Materials and Methods

Subjects

Twenty-three healthy females (23–29 years; all right handed according to self-report) without a history of neurological or psychiatric disease participated in this study. The subjects were recruited among students and staff at the Norwegian University of Science and Technology and St. Olavs Hospital in Trondheim, Norway. Two subjects were excluded from the analysis because of excessive head motion, and one subject was excluded because of poor task compliance, resulting in a final sample of 20 subjects. All subjects provided written informed consent before participation, and the study was approved by The National Committee for Medical Research Ethics in Norway.

Overview of the experimental procedure

Subjects took part in two experimental sessions, organized across two consecutive days. On day 1, subjects watched a commercial movie (encoding). On day 2, they were asked to remember the temporal order of scenes from this movie (retrieval) during fMRI scanning. None of the subjects had seen the movie before the experiment. Before encoding, subjects were instructed to concentrate on the movie and memorize as much of it as possible. They were made aware of the intention to test their memory of the movie the following day; however, they were not informed about what type of information they would be tested on. Before retrieval, subjects were told that they would be shown sets of four pictures from the movie and that their task was to indicate the temporal order of these pictures. They were not instructed to use a particular strategy, nor informed about our expectations regarding choice of strategy (see below). Subjects received detailed task instructions with examples of the different screen displays and familiarized themselves with using the MRI compatible joystick. Example stimuli were not used in the fMRI experiment. The total scan session lasted ~60 min. Immediately after scanning, subjects were debriefed to obtain additional information about their task responses.

Stimuli

At encoding, subjects watched an 89-min movie from the Swedish television series *Beck* (Movie 4: *Øye for øye*, by Kjell Sundsvall, 1997). The movie portrays professional and personal events in the life of chief inspector Martin Beck and his colleagues during a murder investigation. The events take place over a few weeks and are both of the ordinary kind (e.g., breakfast at home, office meeting) and more exceptional (e.g., autopsy, knife attack). The movie depicts events in a realistic Scandinavian environment with true-to-life characters and has a sensible plot; thus, watching it can be viewed as mimicking "real-life" events unfolding over time. Advantages of using cinematic material to probe episodic memory have previously been recognized in the literature (Furman et al., 2007; Hasson et al., 2008).

The retrieval test made use of 120 unique movie scenes pictures. The pictures were whole-screen captures taken at different time points during the entire movie, distinguishable by the specific action, situation, and/or setting in which the persons and/or objects were depicted. The pictures were grouped into 30 fixed sets of four pictures each, of which one-half was used for Retrieve trials and the other half for Infer trials (see below, Cognitive paradigm). On Retrieve trials, pictures were of a kind that promoted the use of memory. There was no apparent or logical order among the pictures, i.e., subjects were expected to retrieve temporal relationships from memory to reconstruct the sequence of events (Fig. 1*A*). On Infer trials, pictures were of a kind that promoted the use of logic. The order of the pictures could be observed as a chain of causality or a stereotypical script, i.e., subjects were expected to apply logical rules to infer the correct sequence of events (Fig. 1*A*). Pilot studies were conducted to ensure that the selected pictures were easy to recognize and that the two trial types were matched on level of difficulty. The temporal and spatial distance among the scenes varied across trial conditions (both were typically shorter on Infer trials). The event sequences were taken at face value to require either retrieval or inference of temporal order. The validity of the operationalization was assessed in a separate behavioral experiment (see below).

Cognitive paradigm

The retrieval task (Fig. 1) included one experimental condition (Retrieve temporal order), one control condition (Infer temporal order), and one baseline condition (Calculus). In addition, Retrieve and Infer trials were always followed by a response condition (Retrieve-r and Infer-r) and an evaluation condition (Evaluate). Brief periods of rest (Fixation) were included before the onset of each Retrieve, Infer, and Calculus trial.

Retrieve. Subjects were shown four pictures of movie scenes, randomly placed in each quadrant of the screen and with the question "Which order?" written above. Subjects were instructed to figure out the correct order of the scenes and to reconstruct the sequence of events in their mind. They were told to focus on the temporal order of the pictures until prompted to respond. Given the nature of the pictures that were used (see above, Stimuli) (Fig. 1*A*), the condition intended to measure retrieval of temporal order information (sequence recall). All trials had a fixed duration of 32 s.

Retrieve-r. This condition followed immediately after each Retrieve trial. The four pictures remained visible, but now with the request to "Indicate order:" written above, and with a green cross hair in the center of the screen. Subjects used the joystick to indicate the correct order of the pictures, moving the cross hair and clicking on each picture in turn. This phase was included to obtain a continuous record of performance that could be used in subsequent analyses. All trials were self-paced with a max duration of 20 s each.

Infer. Screen layout, timing, and instructions were identical to Retrieve trials, but a different type of pictures was used (see above, Stimuli) (Fig. 1*A*). This condition intended to measure logical inference of temporal order (sequence reasoning) and was used as a high-level control condition in the experiment. Subjects were expected to perform the task mainly without specifically retrieving information about temporal order. This enabled us to identify brain activation specifically related to temporal sequence recall while subtracting the impact of other cognitive operations, such as visual perception/re-encoding, scene recognition, recollection of visuo-spatial details, and general ordering of information.

Infer-r. This condition followed immediately after each Infer trial but was otherwise identical to Retrieve-r.

Evaluate. This condition followed immediately after each Retrieve-r and Infer-r trial. First, subjects indicated the amount of cognitive effort required by the preceding trial. The question "How much effort did you exert?" appeared on the screen together with a five-point rating scale (1 = very little, 5 = very much), and the subjects used the joystick to indicate the appropriate rating. Next, subjects indicated what strategy was used on the preceding trial. The question "How did you arrive at your answer?" appeared on the screen together with three response alternatives: "Tried to see a logical order," "Tried to remember the order," and "Other." The Evaluate phase was included to obtain continuous records of perceived effort and strategy, to be used in subsequent analyses. All trials were self-paced with a max duration of 20 s (10 s for each rating).

Calculus. Subjects were shown a series of simple sums (e.g., $3 + 6 = 9$; $4 + 5 = 11$) on top of four scrambled pictures, and their task was to indicate with a right or left button press whether or not the sum was correct. The presentation of each sum was self-paced with a max duration of 4 s. This condition was included to measure the baseline activation level, as a common reference for the other task conditions. All trials had a fixed duration of 32 s.

Fixation. A white cross hair centered on a black screen was shown for a variable duration of 0.2–2.0 s to allow synchronization with the scanner.

In total, there were 15 Retrieve trials, 15 Infer trials, and 33 Calculus trials, equally divided across three experimental runs. A Retrieve or Infer trial was always followed by a Calculus trial. The order of Retrieve and Infer trials was randomized across subjects and runs. Presentation (Neu-

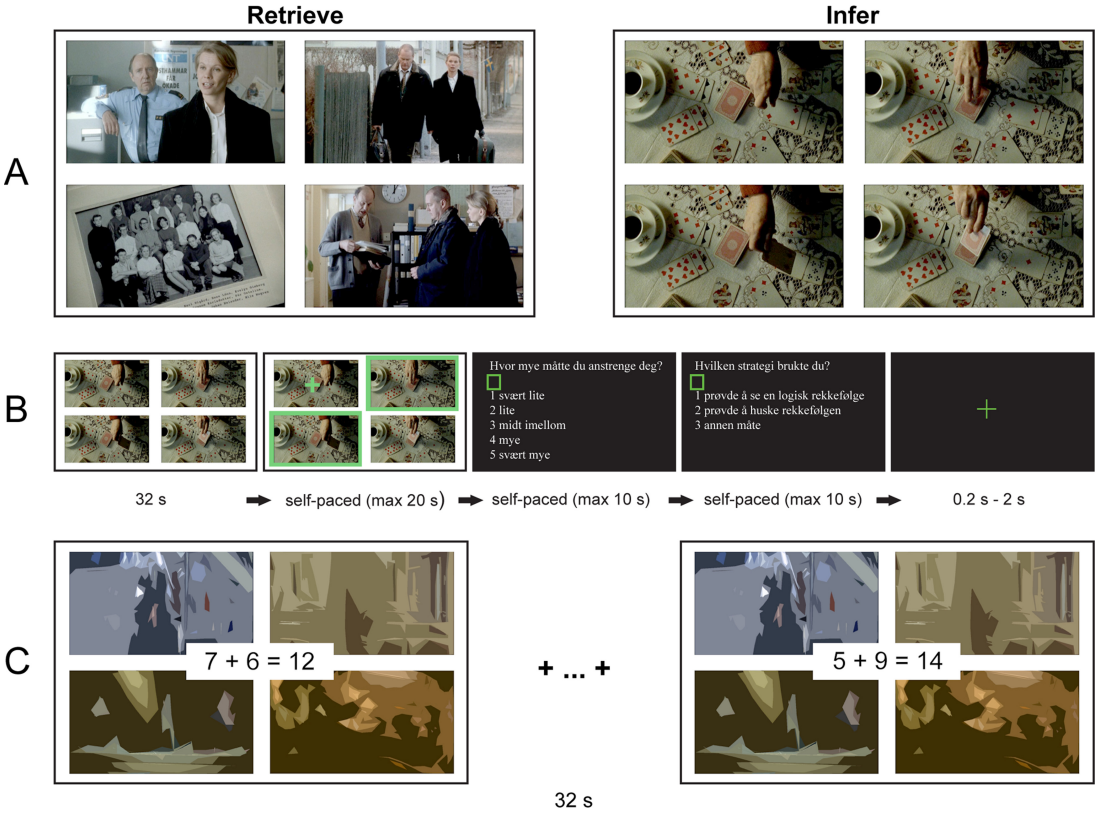

Figure 1. Outline of the cognitive paradigm used in the fMRI experiment. ***A***, Example of stimuli used in conditions Retrieve (left) and Infer (right). ***B***, Four conditions with fixed order of presentation, from left to right: Retrieve/Infer (shown here, Infer), Retrieve-r/Infer-r (shown here, Infer-r), Evaluate (two separate displays for effort rating and indication of strategy), and Fixation. ***C***, Example of stimuli used in the baseline condition Calculus with either a correct (right) or an incorrect (left) sum. See Materials and Methods for further details. The pictures are reprinted with permission from Filmlance International AB (Stockholm, Sweden).

robehavioral Systems) was used for stimulus presentation, response collection, and logging of trial events during the fMRI experiment. Stimuli were presented to the subjects through fiber-optic goggles (NordicNeuroLab AS), mounted on the head coil. Subjects responded to the task using a fiber-optic joystick with two side buttons (Current Designs). A SyncBox (NordicNeuroLab AS) was used to synchronize stimulus presentation with image acquisition.

Image acquisition

Scanning was performed with a 3T Siemens Trio magnet, equipped with an eight-channel head coil for parallel imaging [GRAPPA (Generalized Autocalibrating Partially Parallel Acquisition)] (Griswold et al., 2002). A vacuum pillow and foam pads were used to minimize head motion. During the retrieval task, echo planar images (EPIs) sensitive to blood oxygen level-dependent (BOLD) contrast were acquired with a single-shot gradient-echo pulse sequence [rectangular field of view (FoV), 96 mm; acquisition matrix, 64 × 64; 26 coronal/oblique slices; in-plane resolution, 1.5 × 1.5 mm; slice thickness, 3.0 mm, repetition time (TR), 2.0 s; echo time (TE), 30 ms; interleaved slice acquisition; GRAPPA, 2; 410–474 volumes per run]. A restricted FoV (i.e., no whole-brain coverage) was chosen to enable high-resolution sampling within the MTL. This allowed a more accurate localization of activation within hippocampal and parahippocampal subregions. The slices were oriented perpendicular to the long axis of the hippocampus, or as close to perpendicular as possible without shifting the phase-encoding direction (head–feet). The most posterior slice was located just behind the tail of the hippocampus, and the most anterior slice was taken through the temporal pole. For anatomical reference, a T1-weighted three-dimensional (3D) volume was acquired with an MPRage pulse sequence (192 slices; TE, 2.94 s; TR, 2300 ms; FoV, 256 × 256; in-plane resolution, 0.5 × 0.5 mm; slice thickness, 1.0 mm). In addition, three T2-weighted images were acquired to optimize the registration of the small FoV BOLD images to the anatomical 3D volume (see below): two turbo spin-echo (TSE) scans acquired coplanar to the EPIs (42 slices; TE, 77 ms; TR, 4270 ms; FoV, 200 × 200; in-plane resolution, 0.78 × 0.78 mm; slice thickness, 2.0 mm) and one sagittal reference scan [22 slices, TE, 89 ms; TR, 4500 ms; FoV, 220 × 220; in-plane resolution, 0.69 × 0.69 mm; slice thickness, 4.0 mm (with a 1.2 mm gap)].

Postscan assessments

Immediately after scanning, we asked the subjects whether they had failed to recognize any of the individual pictures used in the task, and if so, to point out the critical picture(s). Next, subjects were given a questionnaire to report (1) how often they had experienced recollection of the pictured event sequences ("mental replay"), using a scale from 1 (never) to 5 (always), and (2) how often they had figured out the answer well within the time limit, on a scale from 1 (never) to 5 (always). The questions were answered separately for Retrieve and Infer trials.

Data analysis

All image analyses were performed in FSL 4.0 (Smith et al., 2004) (FMRIB Software Library, Oxford; www.fmrib.ox.ac.uk/fsl/). First, the functional

images were motion corrected, spatially smoothed (Gaussian kernel full-width at half-maximum, 3 mm), and high-pass filtered (cutoff, 170 s). Next, time course statistical analyses were performed using the general linear model. The expected signal time courses were modeled with a box-car stimulus response function, convolved with a two-gamma hemodynamic response function (Boynton et al., 1996) and its temporal derivative. The model included five predictors, corresponding to the different conditions in the retrieval task (Calculus + Fixation = implicit baseline). Within-subjects parameter estimates were obtained separately for each run and then pooled across runs with a fixed effects model of variance. Group statistics were calculated with a mixed effects model of variance, as implemented in FLAME1 + 2 (FMRIBs local analysis of mixed effects) (Beckmann et al., 2003). Before computing the group statistics, a mask was applied to the functional images to exclude all non-MTL structures. The mask was based on the Harvard–Oxford probabilistic atlases (http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html) and included the left and right hippocampus, parahippocampal gyrus anterior division, and parahippocampal gyrus posterior division (all with max probability >0.25). For significance testing, individual voxels were first thresholded at $z > 3.1$, and voxels that survived this threshold were used to define clusters of activation. Each cluster's significance was then estimated based on random field theory (Friston et al., 1994) and compared with the cluster probability threshold ($p < 0.05$, corrected for multiple comparisons). This threshold reflects the probability under the null hypothesis of obtaining a cluster of a particular size, given the voxel z threshold. The threshold was lowered to voxel $p < 0.005$ (uncorrected for multiple comparisons) and a minimum cluster size of five voxels in exploratory analyses.

Registration of functional to anatomical images was performed by the following procedure, using FLIRT (FMRIBs linear registration tool) (Jenkinson et al., 2002). First, the mean functional image (the average of all scans within a single run) was registered to the mean of the two coplanar T2 TSE scans. Next, the T2 TSE mean was registered to the T2 reference scan, which in turn was registered to the T1 anatomical image. The T1 anatomical image was registered to the Montreal Neurological Institute (MNI)-152 standard template. Finally, the statistical maps were registered to standard space by combining the transformation matrices obtained in the preceding steps. Peak activations are reported in MNI coordinates. To explore potential differences among hippocampal subregions, peak voxels were also localized within the probabilistic maps of the Jülich histological atlas (Amunts et al., 2005), warped to MNI152 space in FSL (http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html). We quantified the responses within six regions-of-interests (ROIs), defined according to the Jülich probabilistic maps (max probability >0.5): left and right cornu ammonis (CA), dentate gyrus (DG), and subiculum (SUB). Subject-specific parameter estimates were obtained from each ROI and compared at group level with repeated measures statistics.

Behavioral data were analyzed in SPSS. Statistical comparisons were made with t tests, or a nonparametric equivalent in cases where the data were not normally distributed. Among the behavioral measures is a sequencing score that reflects the grade of accuracy on Retrieve and Infer trials. Each correct response (i.e., picture in correct temporal position) was awarded one point relative to each remaining response, such that the maximum sequencing score on each trial was 6 (3 + 2 + 1 + 0). Similar scores have been used previously with sequencing tasks (Kumaran and Maguire, 2006b).

Results are presented as mean ± SD in the text.

Behavioral experiment

A separate behavioral experiment was conducted to assess the validity of our paradigm as a measure of temporal sequence recall. Fifteen subjects (23–29 years, all female) were recruited from the same population as the fMRI subjects. All subjects gave oral consent before participation. The subjects were not shown the movie (and assured they had not seen it on any previous occasion) yet completed the same retrieval test as the fMRI subjects. A PC version of the paradigm was used with similar stimulus and timing properties, except that the baseline and evaluation conditions were not included. Subjects indicated the order of the pictures by a series of button presses, and the critical outcome measure was the difference in performance between Retrieve and Infer trials, tested for significance with the Wilcoxon signed-rank test. Performance on retrieve trials was compared with chance level performance using the exact binomial distribution of the number of correct answers by chance (0.625).

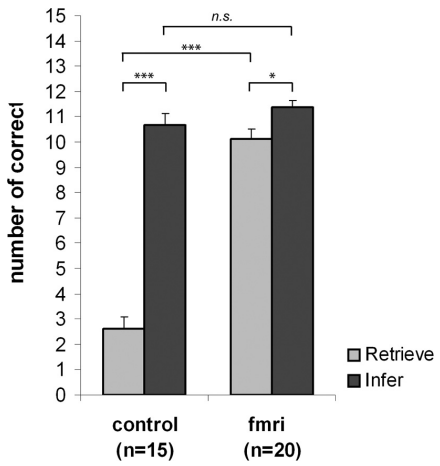

Figure 2. Performance in control versus fMRI subjects. Mean performance in control and fMRI subjects on Retrieve and Infer trials. Performance was measured as the number of trials (out of 15 Retrieve and 15 Infer trials in total) where subjects identified the correct temporal sequence. Error bars indicate SEM. Means were compared with the Wilcoxon signed ranks test (within groups) and Mann–Whitney test (between groups); $^{*}p < 0.05$; $^{***}p < 0.001$; n.s., not significant.

Results

Task validation

Subjects in the unexposed control group were able to identify the correct temporal sequence on 2.60 ± 1.88 of the 15 Retrieve trials and on 10.67 ± 1.84 of the 15 Infer trials (Fig. 2). Their performance on Retrieve trials was significantly lower than on Infer trials (Wilcoxon z, −3.42; $p < 0.001$) yet significantly above chance level (0.625; $p < 0.005$). Subjects in the fMRI group were able to identify the correct temporal sequence on 10.10 ± 1.86 of the Retrieve trials and 11.35 ± 1.31 of the Infer trials. This difference is (marginally) significant (Wilcoxon z, −1.96; $p = 0.050$). fMRI subjects performed significantly better than control subjects on Retrieve trials (Mann–Whitney U; z, 5.03; $p < 0.001$) but not on Infer trials (Mann–Whitney U; z, 1.15; $p = 0.248$). These results indicate that performance on Retrieve trials relies more on memory for temporal order than performance on Infer trials. Still, the fact that control subjects performed above chance level on Retrieve trials suggests that, at least on some trials, it is possible to determine the correct temporal sequence without the retrieval of temporal order information.

fMRI task performance

The trial-by-trial self reports obtained during the fMRI experiment revealed that subjects adopted the intended strategy on the majority of both Retrieve (Tried to remember the order, 88.67 ± 9.45%) and Infer trials (Tried to see a logical order, 96.00 ± 5.88%). The fMRI subjects attempted to infer a logical order on 1.33 ± 2.74% of Retrieve trials and used "Other strategy" on 10.00 ± 9.55%. Subjects reported attempts to retrieve the temporal order on 3.33 ± 5.92% of Infer trials and the use of any Other strategy on 0.67 ± 2.05%. To be able to provide an unam-

Table 1. Behavioral data

Measure (units)	Condition		
	Retrieve	Infer	Retrieve versus Infer
Accuracy I (% correct)	68.90 ± 13.06	76.89 ± 9.94	n.s.
Accuracy II (sequencing score)	63.70 ± 10.14	70.10 ± 7.24	$p = 0.041$
Scene recognition (% hits)	99.42 ± 1.13	97.46 ± 4.25	$p = 0.050$
Effort (rating 1–5)	2.60 ± 0.46	2.49 ± 0.53	n.s.
Mental replay (rating 1–5)	3.35 ± 1.18	2.80 ± 0.83	$p = 0.008$
Processing time (rating 1–5)	3.55 ± 0.61	3.75 ± 0.44	n.s.

Mean behavioral performance in the group of fMRI subjects ($n = 20$). Data were obtained during scanning (accuracy and effort) or immediately afterwards (scene recognition, mental replay, and required processing time). Means were compared with the paired samples *t* test (accuracy and scene recognition) and the Wilcoxon signed ranks test (effort, mental replay, and processing time); n.s., Not significant. See Materials and Methods for further details.

biguous interpretation of our data, we decided to include only trials where the intended strategy was used (on average, 13.0 Retrieve trials and 14.4 Infer trials per subject) in all subsequent analyses.

Subjects were able to identify the correct temporal sequence on 68.90 ± 13.06% of Retrieve trials and 76.89 ± 9.94% of Infer trials. The difference is not significant ($t_{(19)} = 2.04$; $p = 0.055$). The total sequencing score was significantly higher on Infer trials (70.10 ± 7.24) than on Retrieve trials (63.70 ± 10.14) ($t_{(19)} = 2.19$; $p = 0.041$). The average rating of effort level was 2.60 ± 0.46 on Retrieve trials and 2.49 ± 0.53 on Infer trials, not significantly different ($t_{(19)} = 1.24$; $p = 0.231$).

Postscan assessments

The recognition rate of individual pictures was high for both Retrieve trials (99.42 ± 1.13%) and Infer trials (97.46 ± 4.25%), although slightly higher in the former (Wilcoxon *z*, 1.96; $p = 0.050$). Subjects reported to have "mentally replayed" the sequence of events more often on Retrieve trials (3.35 ± 1.18) than on Infer trials (2.80 ± 0.83). The difference is significant (Wilcoxon *z*, 2.67; $p = 0.008$). Ratings of required processing time were similar for both types of trial (Retrieve, 3.55 ± 0.61; Infer, 3.75 ± 0.44; Wilcoxon *z*, 1.41; $p = 0.157$).

The behavioral data are summarized in Table 1.

fMRI data

Retrieve versus Baseline

To determine which MTL regions were engaged during sequence recall, we first compared Retrieve trials to Baseline. Three clusters of significantly increased activation were detected (Table 2, clusters A–C; Fig. 3). Cluster A covered parts of both the HF (mainly medial portion of the anterior half) and the parahippocampal cortex (PHC) (throughout most of its extent) in the right hemisphere. Cluster B covered parts of both the HF and PHC in the left hemisphere and was widely similar to cluster A in localization and extent. Cluster C covered a smaller area laterally in the head of the left HF. For a detailed description of the cluster localizations, see the supplemental text, available at www.jneurosci.org as supplemental material.

Retrieve trials evoke a range of mnemonic processes that are likely to be reflected in the comparison with Baseline. To identify irrelevant activations, we used a high-level control task (Infer) where the order of the four scenes was not retrieved but determined through logical inference but which was otherwise similar to the sequence recall task (Retrieve). Relative to Baseline, Infer trials correlated with increased activation that was similar to that in Retrieve trials but more restricted (see supplemental Table 1 and supplemental text for further details, available at www.jneurosci.org as supplemental material).

Retrieve versus Infer

The primary aim of the present study was to identify MTL regions that were specifically involved in the retrieval of temporal order information. To achieve this, we compared the level of activation in Retrieve and Infer trials directly. Three clusters of increased activation were detected (Table 2, clusters D–F). All clusters overlapped with the activation observed in Retrieve > Baseline but were more limited to specific parts of the HF and PHC (Figs. 3, 4).

Cluster D peaked in the center of the right HF body, medially near the border toward the entorhinal cortex (EC) (Jülich histological atlas probability, 87% SUB). The cluster extended 4 mm in the posterior direction and 5 mm in the anterior direction. At the most posterior levels, the activation was restricted to the HF–EC border area. At more anterior levels, the activation extended slightly in the superior and lateral direction.

Cluster E peaked at the posterior end of the left PHC, at the medial bank of the collateral sulcus (CS). The cluster extended 2 mm in the posterior direction and 5 mm in the anterior direction. At all levels, the activation was confined to the medial bank of the CS.

Cluster F peaked anteriorly in the right PHC, at the medial bank of the CS. The cluster extended 5 mm in the posterior direction and 1 mm in the anterior direction. At all levels, the activation was confined to the medial bank of the CS.

Because we had no a priori prediction of lateralized hippocampal activation, we re-examined the contrast Retrieve > Infer with a more liberal statistical threshold ($p < 0.005$, uncorrected; minimum cluster size = 5). With this threshold, five clusters of activation were identified in the left HF (supplemental Table 2 and supplemental text, available at www.jneurosci.org as supplemental material), in addition to clusters at the same locations, but of larger extent, as in the initial maps. Notably, the two largest clusters in the left HF (Fig. 4, clusters G and H) appeared at a similar location as the activation within the right HF (cluster D). An additional cluster (Fig. 4, cluster I) was found at a more lateral position, primarily coinciding with the left HF activation in Retrieve > Baseline (cluster C). The fact that the hippocampal activations were widely similar across hemispheres but stronger on the right is likely to reflect the nature of our stimuli. Previous studies have suggested a right lateralization of memory for visual (Kelley et al., 1998) and nonverbal (Golby et al., 2001) stimuli.

The contrast Infer > Retrieve yielded no significant activation, i.e., no MTL regions responded specifically to logical inference of temporal order. This implies that this function is supported by brain regions located outside the MTL, not scanned in this experiment, most likely in the prefrontal cortex (Knutson et al., 2004).

Correlation with behavioral performance

Because of the low number of incorrect responses and little trial-to-trial variation in sequencing scores, we were unable to obtain a reliable estimation of within-subject, parametric effects of performance. We did analyze a subset of data where different performance levels were represented within the same run and observed significant activation in left and right HF (threshold $p < 0.005$, uncorrected; data not shown). However, having 15 trials per subject and an average level of 69% correct leaves only five trials for the lower levels of performance (sequencing scores 0–5), and typically only two or three different levels were represented within a given run. Therefore, we also performed a between-subjects analysis in selected ROIs, i.e., in clusters that were active in Retrieve > Infer. A significant, positive correlation was observed between the accuracy of sequence recall (sum of

Table 2. Clusters of activation during sequence recall

Contrast	Cluster Index	Size	*z* max	*x*	*y*	*z*	Localization
Retrieve > Baseline	A	2584	5.78	25	−21	−13	Right HF and PHC
	B	2195	5.82	−29	−39	−13	Left HF and PHC
	C	50	4.21	−35	−17	−18	Left HF
Retrieve > Infer	D	134	4.27	21	−21	−15	Right HF
	E	114	3.99	−24	−40	−15	Left PHC
	F	50	4.26	27	−31	−18	Right PHC

Clusters with significant activation in the contrasts Retrieve > Baseline and Retrieve > Infer. Significance level, $p < 0.001$ with cluster correction for multiple comparisons ($p < 0.05$). Size, Number of voxels; *z* max, maximum *z* score within cluster; *x*, *y*, *z*, MNI coordinates of peak voxel; localization, anatomical region covered by the cluster. The clusters are referred to in Results using the same indices as here (A–F). The clusters are shown in Figure 3 (A–F) and Figure 4 (D–F).

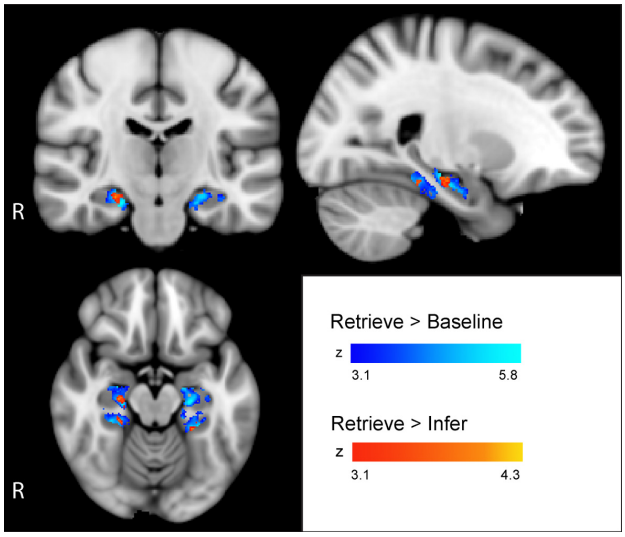

Figure 3. Maps of activation during sequence recall. Areas of significant activation during sequence recall. Areas in blue show increased activation in Retrieve trials relative to Baseline and correspond to clusters A–C in Table 2. Areas in red show increased activation in Retrieve trials relative to Infer trials and correspond to clusters D–F in Table 2. R, Right. Color bars indicate voxel *z* scores. Voxels are significant at $p < 0.001$ with cluster correction for multiple comparisons ($p < 0.05$).

sequencing scores across all trials) and level of activation in the right HF (cluster D, Pearson $r = 0.60$; $p < 0.005$) (Fig. 5). Activation in the left and right PHC was not related to accuracy (left PHC: $r = -0.20$, $p = 0.41$; right PHC: $r = 0.04$, $p = 0.86$). There was no significant correlation between accuracy and the level of (subthreshold) activations in the left HF.

To examine whether the performance effect was confounded by amount of recollection or vividness, we used the rating of mental replay obtained with the postscan questionnaire. Mental replay was not correlated to accuracy of sequence recall ($r = -0.01$; $p = 0.972$), nor to the level of activation in right HF ($r = 0.05$; $p = 0.82$). The correlation between the hippocampal activation and sequence accuracy remained significant after controlling for mental replay ($r = 0.60$; $p = 0.007$).

Comparison of activation within hippocampal subfields

To explore potential differences between hippocampal subfields, we compared the peak activations (averaged across participants) in the left and right CA, DG, and SUB, as defined by the Jülich histological atlas (Fig. 6). In the right hemisphere, the level of activation was significantly higher in the subiculum (Wilcoxon *z*, 3.81; $p < 0.001$) and CA fields (Wilcoxon *z*, 3.92; $p < 0.001$), compared with DG. Also in the left hemisphere, the level of activation was significantly higher in the subiculum (Wilcoxon *z*, 3.92; $p < 0.001$) and CA fields (Wilcoxon *z*, 3.88; $p < 0.001$) than in DG. The level of activation was not significantly different in the subiculum and CA fields in either hemisphere.

Discussion

The aim of this study was to examine the contribution of MTL subregions to a particular manifestation of episodic memory, recall of the temporal sequence of past events. We used high-resolution fMRI to quantify levels of MTL activation while subjects reconstructed the temporal order of life-like events, derived from a movie they had watched the day before. Extensive activation was observed, and effects specifically related to retrieval of temporal order were localized bilaterally in HF and PHC. Across subjects, the right hippocampal activation correlated positively with performance, whereas this was not observed in PHC.

Sequence recall involves HF and PHC

The contrast Retrieve > Baseline revealed that recall of temporal sequences involves the coordinated operation of HF and PHC bilaterally. Unlike in previous imaging studies of memory for temporal order, our paradigm was designed to measure retrieval of complex, naturalistic event sequences, in keeping with theoretical accounts of MTL involvement in episodic memory (Tulving, 1983; Eichenbaum, 2004), and our results clearly support a role for the MTL. The activation in Retrieve > Baseline reflects several mnemonic processes, including scene recognition, recollection of spatial context, and retrieval of temporal order. With exception of the latter, these processes are likely to occur also on Infer trials, which explains the similar activation in Infer > Baseline. However, Infer trials did not require memory for successful performance. Control subjects who had not seen the movie performed well above chance, implying that temporal order could be inferred directly. It is still possible that retrieval contributed to performance; however, the influence hereof would be small because we included only trials where logic was the reported dominant strategy.

HF restores the correct order of events

The critical measure in this study was the comparison between Retrieve and Infer trials, where temporal order was reconstructed from memory or derived from logical rules, respectively. Impor-

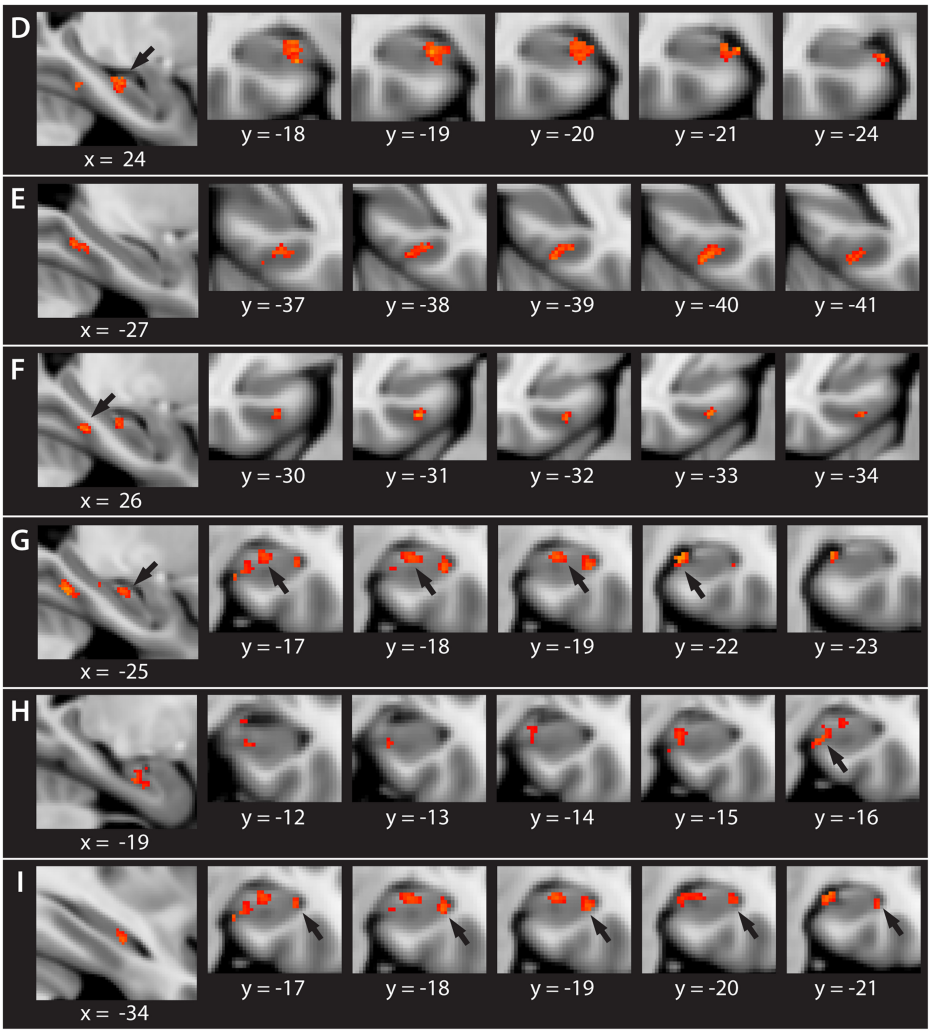

Figure 4. Activation specifically related to retrieval of temporal order (Retrieve > Infer). Areas marked in red show clusters of voxels with increased activation in the contrast Retrieve > Infer. The clusters are referred to in Results using the same indices as here (D–I). Each cluster is shown on a separate row with one sagittal section (leftmost picture) and five coronal sections taken in the anterior–posterior direction (from left to right). The numbers below the pictures are MNI coordinates. Clusters D–F are significant at $p < 0.001$ with cluster correction for multiple comparisons ($p < 0.05$). Clusters G–I are significant at $p < 0.005$, uncorrected.

tantly, the two conditions were comparable in terms of performance and effort and used the same stimulus material to evoke similar processes of scene recognition and context recollection. The observed increase in right hippocampal activation during Retrieve trials, and left hippocampal activation at a lowered statistical threshold, indicate that HF responds particularly to retrieval of temporal order. This result is consistent with current theories of MTL function, suggesting that HF associates episodic items with their spatio-temporal context (Davachi, 2006; Diana et al., 2007).

fMRI studies of temporal order memory have generally failed to observe hippocampal activation, most likely because of the use of recency discrimination paradigms. For example, previous studies that have used naturalistic stimuli, such as persons encountered in a virtual reality game (Ekstrom and Bookheimer, 2007), and photographs of locations that subjects visited before scanning (St. Jacques et al., 2008), measured recency judgments and did not observe significant HF activation specific to temporal order retrieval. We hypothesized that sequence recall would be more sensitive to hippocampal function, because of greater involvement of associative processes. A sequence involves a series of events, rather than a pair; hence, a higher number of temporal associations must be determined. Also, the use of naturalistic events that are meaningfully related may contribute to encoding of their temporal relationship, whereby order judgments can be based on associative rather than item-based retrieval (Friedman, 1993). Partly in support of this is the report that relational encoding of words enhanced hippocampal activation during subse-

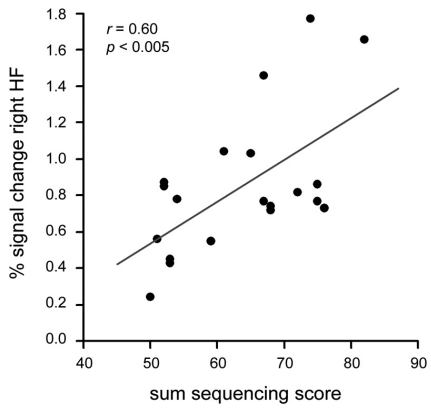

Figure 5. Significant positive correlation between level of activation within the right HF (cluster D, Results) and accuracy of sequence recall. Accuracy was measured as the sum of sequencing scores on all Retrieve trials. Level of activation was measured as the peak voxel's percentage signal change in Retrieve > Infer. Each dot represents an individual subject, and the correlation is shown with the line of best fit.

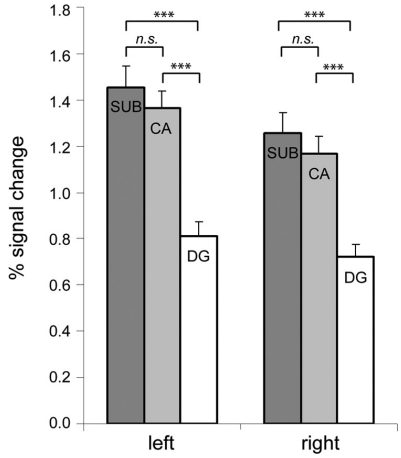

Figure 6. Activation during sequence recall in subregions of the hippocampal formation. Subregions were defined with the probabilistic maps of the Jülich histological atlas. Activation was measured as the peak voxel's percentage signal change in the contrast Retrieve > Infer and averaged across participants. Error bars indicate SEM. Means are compared with the Wilcoxon signed ranks test; $^{***}p < 0.001$; n.s., not significant.

quent recency judgments (Konishi et al., 2006). Moreover, HF participates in sequence learning and mismatch detection of sequences of unrelated items (Kumaran and Maguire, 2006a,b, 2007). Our study is the first to combine a complex sequencing task with naturalistic, related stimuli, and to our knowledge, the first to present robust evidence for HF involvement in retrieval of temporal order.

Memory sequences enable mental replay: vivid recollection of how past experiences unfold over time (Tulving, 1983). Previous fMRI studies reported hippocampal activation when subjects re-experienced autobiographical episodes (Piefke et al., 2003; Addis et al., 2004; Steinvorth et al., 2006), and that hippocampal activation increases with ratings of vividness (Gilboa et al., 2004). In our experiment, autobiographical experiences were mimicked with events from a movie, and subjects were encouraged to replay the event sequences mentally. Replay occurred most often on Retrieve trials, which possibly contributed to stronger hippocampal activation in this condition. Admittedly, mental replay not only involves recollection of temporal but also visuo-spatial information. However, recollection of visuo-spatial details alone is unlikely to explain the observed hippocampal activation because we found a positive correlation between accuracy of sequence recall and level of right HF activation that remained significant after controlling for mental replay. This strongly suggests that HF contributes specifically to correct retrieval of temporal order. The lack of a similar correlation in left HF is possibly related to the stimulus material being visuo-spatial and nonverbal.

Computational models suggest that HF codes associations across time by strengthening synaptic connections between representations of successive events (Levy, 1996; Wallenstein et al., 1998). Gelbard-Sagiv et al. (2008) recently described a human analog of sequence replay in rats (Skaggs and McNaughton, 1996; Foster and Wilson, 2007). Single human hippocampal neurons showed selective and sustained responses to television episodes that later recurred during free recall. Theoretical concepts relate the potential to code sequential information either to the presence of recurrent connections in CA3 (Levy, 1996; Lisman, 1999) or their absence in CA1 (Eichenbaum et al., 1999; Manns and Eichenbaum, 2005; Rolls and Kesner, 2006). It is clear, though, that CA3 and CA1 contribute to memory in fundamentally different ways (Lee et al., 2004; Leutgeb et al., 2004; Hartley et al., 2005; de Almeida et al., 2007). Compelling connectional and functional evidence discriminates between DG and CA3 on the one hand, and CA1 possibly together with subiculum on the other (Witter et al., 2000; Knierim et al., 2006). Our observation of increased activation mainly in the CA field and subiculum argues in favor of a stronger involvement of CA1 in temporal/sequence coding. This is consistent with animal data showing that temporal order memory depends in particular on CA1 (Hoge and Kesner, 2007), possibly by adding a temporal "tag" to subsequent events (Manns et al., 2007). Although it cannot yet be excluded that CA3 is involved (Hoang and Kesner, 2008), temporal order memory does not require DG (Gilbert et al., 2001).

PHC reinstates visuo-spatial contexts

The contrast Retrieve > Infer also showed increased activation in bilateral PHC, consistent with previous findings that both HF and PHC support associative memory (Davachi et al., 2003; Düzel et al., 2003; Kirwan and Stark, 2004). However, unlike the hippocampal activation, the parahippocampal activation was not directly related to task performance. This indicates that HF and PHC have distinct roles during recall of past event sequences. It is possible that PHC is involved in retrieving temporal context, as suggested by studies of recency discrimination (Dudukovic and Wagner, 2007; St. Jacques et al., 2008), albeit in a manner less critical for performance than HF. A more likely interpretation, with more support in the literature, is that the PHC activation reflects processing of visuo-spatial information. Ample evidence suggests specialization of PHC in perception of visuo-spatial scenes (Epstein and Kanwisher, 1998; Bar and Aminoff, 2003; Epstein et al., 2007) and retrieval of spatial context (Burgess et al., 2001; Kahn et al., 2004; Ekstrom and Bookheimer, 2007; but see Bar et al., 2008). In our experiment, Retrieve trials had higher stimulus complexity than Infer trials, in that the scenes had larger temporal spacing and more often depicted different settings. It is conceivable that PHC responded to these properties and that the increased activation during Retrieve trials reflects higher de-

mands for (re-)encoding of visuo-spatial scenes. Alternatively, PHC may have been involved in retrieval of visuo-spatial contextual details that are associated with the scenes, supporting visual imagery and reconstruction that take place during mental replay of past events (Hassabis and Maguire, 2007).

Visuo-spatial contextual details can be combined with general knowledge of temporal patterns to infer the correct order of events (Friedman, 2004). Although we included only trials where subjects reported to have remembered the order of the events, we cannot exclude the possibility of additional inference. This is illustrated by the fact that control subjects performed above chance level on Retrieve trials. However, the use of inferential processes to reconstruct temporal order is believed to occur mainly during recency judgments, especially when indices of relative trace strength are indistinguishable, such as when the temporal distance between items is short (Friedman, 1993, 2004). Notably, a recent fMRI study measured recency judgments under these conditions and found significant activation in PHC but not in HF (St. Jacques et al., 2008). Increased parahippocampal activation as observed in the present study thus most likely reflects reinstatement of visuo-spatial contexts, not related to temporal ordering.

Conclusion

This study provides the first fMRI data on the role of MTL structures in recall of temporal sequences. We have used naturalistic, complex stimuli, and based on our findings, we argue that correct sequence recall depends in particular on the hippocampal formation.

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A specific role of the human hippocampus in recall of temporal sequences

SUPPLEMENTARY MATERIAL

RESULTS

<u>Retrieve > Baseline</u>

Description of cluster localizations

Cluster A peaked in the center of the left HF body, medially near the border towards the entorhinal cortex (EC) *(Jülich histological atlas probability: 82% subiculum [SUB]).* The cluster extended 15 mm in the anterior direction and 17 mm in the posterior direction. In the anterior direction, the activation extended to include most of the HF head. In the posterior direction the activation continued within the HF body and spread inferiorily into the PHC (collateral sulcus [CS] and gyral part). Within the HF, the active voxels were primarily located in the medial part, but extended laterally at the most anterior levels.

Cluster B peaked at the posterior end of the left PHC, at the medial bank of the CS. The cluster extended 32 mm in the anterior direction and 3 mm in the posterior direction. In the anterior direction, the activation continued throughout most of the PHC (CS and gyral part) and spread into the head and body of the HF. Within the HF, the activation peaked at a medial location similar to that of cluster A *(local maximum: x = -23, y = -21, z = -15; max z = 5.39; 89% SUB).* The active voxels were located primarily in the medial part of the HF, but extended laterally at the most anterior levels.

Cluster C peaked in the lateral corner of the left HF head, at the level of the uncal recess *(87% CA).* The cluster extended 4 mm in the posterior direction and 1 mm in the anterior direction, and was located at the same lateral position across all levels.

Infer > Baseline

Supplemental Table 1:

Clusters of activation during logical inference of temporal order

	cluster						
contrast	*index*	*size*	*z max*	*X*	*Y*	*Z*	*localization*
Infer >	1	1874	4.87	24	-38	-15	right PHC and HF
Baseline	2	821	4.78	-31	-40	-11	left PHC
	3	304	4.40	-24	-12	-17	left HF

Clusters of activation in the contrast Infer>Baseline. Significance level: $p<0.001$ with cluster correction for multiple comparisons ($p<0.05$). Size = number of voxels; z max = maximum z-score within cluster; X, Y, Z = MNI coordinates of peak voxel localization. PHC = parahippocampal cortex; HF = hippocampal formation. The localizations of the clusters are described in further detail in the text below.

Description of cluster localizations

Cluster 1 peaked at the posterior end of the right PHC, in the center of the CS. The cluster continued 33 mm in the posterior direction and covered most of the PHC (CS and gyral part). The cluster extended to include parts of the HF body and head. Within the HF, the activation was primarily located in the medial part (local maximum: x = 25, y = -21, z = -12, max z = 4.85; *72% SUB*), but extended laterally at the most anterior levels.

Cluster 2 peaked at the posterior end of the left PHC, in the center of the CS. The cluster continued 2 mm in the posterior direction and 14 mm in the anterior direction and covered most the PHC (mainly CS; spread to gyral part at most anterior levels).

Cluster 3 peaked superiorly in the center of the left HF head (*67% CA*). The cluster extended 12 mm in the posterior direction and 3 mm in the anterior direction. The active cluster was located at a similar position across all levels but shifted in the medial direction at the most posterior levels, where it spread a little into the anterior PHC.

Retrieve>Infer: Sub-threshold activation

Supplemental Table 2:

Activation during sequence recall in the left hippocampal formation (HF)

	cluster					
contrast	*index*	*size*	*z max*	*X*	*Y*	*Z*
Retrieve >	G	105	4.02	-21	-22	-14
Infer	H	65	3.39	-19	-16	-20
	I	47	3.49	-34	-18	-18
	J	11	2.84	-32	-27	-9
	K	11	2.84	-16	-10	-18

Clusters of activation in the left HF in the contrast Retrieve>Infer. Activations were revealed by a post-hoc exploratory analysis with a lowered significance level (voxel $p<0.005$ uncorr. and min. cluster size 5 voxels), without the additional constraint of cluster-level $p<0.05$ corr. that was used in the initial analyses. Size = number of voxels; z max = maximum z-score within cluster; X, Y, Z = MNI coordinates of peak voxel. The clusters are referred to in the text using the same indices as here (G-K).

Description of cluster localizations

Cluster G peaked in the center of the left HF body, medially near the border towards the entorhinal cortex (EC) *(68% SUB).* The cluster extended 5 mm in the posterior direction and 6 mm in the anterior direction. At the most posterior levels the activation was restricted to the HF-EC border area, but at more anterior levels the activation shifted towards a more superior and lateral location.

Cluster H peaked in the center of the left HF head, medially near the border towards the EC *(65% CA).* The cluster extended 2 mm in the posterior direction and 5 mm in the anterior direction. The activation was located at a similar medial position across all levels.

Cluster I peaked in lateral corner of the left HF head *(99% CA).* The cluster extended 4 mm in the posterior direction and 2 mm in the anterior direction, and was located at the same lateral position across all levels.

Cluster J: peaked in the posterior part of the left HF body, at a superior and lateral location (*48% CA).* The cluster extended 3 mm in the posterior direction and 1 mm in the anterior direction, and was located at a similar position across all levels.

Cluster K: peaked in the center of the left HF head, at a superior and medial location near the border towards amygdala *(50% amygdala superficial group).* The cluster extended 2 mm in the posterior direction and 1 mm in the anterior direction, and was located at a similar position across all levels.

Paper III

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38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.

66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

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74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.

135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.

164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.

194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.

219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
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