

Dissecting the Human Medial Temporal Lobe Memory System by functional MRI

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1 Summary

The work presented in this thesis comprises two event-related functional magnetic resonance imaging (fMRI) studies, which aim at dissociating the contributions of different subregions of the human medial temporal lobe (MTL) to declarative memory processes. The first study examines common neural correlates of memory encoding and recognition. Healthy subjects were scanned both while they memorized complex photographs of buildings and landscapes and while they tried to recognize these pictures in a series of new photographs. Confirming earlier findings, declarative memory formation correlated with an activity increase in the MTL and the inferior prefrontal cortex. Further, during recognition, stronger brain responses to correctly identified old items (hits) as compared to correctly identified new items were found in the parietal lobe, the anterior prefrontal cortex, the anterior cingulate and the cerebellum, replicating findings concerning the commonly used old/new effect. As an innovation, a positive and a negative recognition effect were introduced, comparing brain responses to hits and brain responses to misses (old items misclassified as new) during test. This comparison gives a 'purer' measure of neural activity associated with explicit recognition than the commonly used old/new effect. Thus, it can be used to identify decreases and increases in brain activity associated with recognition success. The positive recognition effect, stronger responses for hits than misses, identified activations similar to the old/new effect in prefrontal, parietal, and cerebellar areas. The negative recognition effect, weaker brain responses for hits than misses, which is less contaminated by repetition priming than a reversed old/new effect, offers the possibility to study whether recognition success can also be associated with regional brain activity decreases. In line with electrophysiological findings, this effect identified an activity decrease in the anterior MTL related to recognition success. The main feature this study adds to the existing literature is the fact that memory encoding and retrieval were examined in a single study-test experiment. Thus, it was possible to use a conjunction analysis to directly compare encoding- and retrieval-related activations within subjects. This analysis identified an integrated temporal-cerebellar network, whose activity correlates with both memory formation and retrieval. Stimulus representations that were formed and stored locally during encoding can be effectively re-used by this network during recognition. The results of this study have been published in (Weis et al., 2004a) and (Weis et al., 2004b).

A question that remains open from the results of the above study concerns the nature of the activations identified during memory retrieval. Dual-process models of recognition memory propose that there is a qualitative distinction between the forms of memory that support recognition of an item which is accompanied as opposed to unaccompanied by contextual information. To objectively distinguish between subprocesses within recognition – whether an activation is related to recollection or familiarity - some sort of source memory judgment is needed. To test the hypothesis that distinct MTL operations are associated with either contextual retrieval or item recognition, the same photographs of buildings and landscapes as in the first study were employed as stimuli. As an addition, a context was introduced by transforming the photographs into one of four single-color-scales: red, blue, yellow, or green. In the subsequent old/new recognition memory test, all stimuli were presented as plain grey scale photographs. By this manipulation, a four-alternative source judgment referring to the color in which the stimulus was presented during study could be employed, with the aim to delineate neural correlates of truly recollective memory versus item recognition. As a measure for the neural correlates of contextual retrieval, the positive source memory effect was introduced: the difference in brain activity between hits with and without correct source judgment. This contrast revealed bilateral MTL activation, centered in the hippocampus. In contrast, the item recognition effect, the difference in brain activity for hits with incorrect source judgment as opposed to misses, delineates brain regions involved in item recognition unaccompanied by contextual retrieval. The negative item recognition effect, more activity for misses as opposed to hits without source, identified an activity decrease during item recognition in the anterior MTL, presumably the anterior parahippocampal gyrus. For the first time in the fMRI literature, these results suggest a clear-cut dissociation between human MTL operations that support either contextual retrieval or item recognition, two fundamental mnemonic operations in recognition memory. Currently, there is an intense discussion in the field whether such a dissociation does exist or not. The data presented here clearly support a parsimonious view where the entire MTL supports recognition memory, but by different subprocesses accomplished by different substructures like the (peri)rhinal cortex and the hippocampus. While a reduction of activation in the rhinal cortex is sufficient for item recognition based on a familiarity signal, an activity increase in the hippocampus is essential for successful contextual retrieval and recollective memories.

2 Introduction

What is Episodic Memory?

A basic way to define memory in a way in which many people understand it, is to equate memory with remembering what one has learned and experienced in the past. Further, memory can be characterized as 'the knowledge of an event, or fact, of which in the meantime we have not been thinking with the additional consciousness that we have thought or experienced it before' (James, 1890).

According to this early definition of memory (James, 1890) a number of prerequisites have to be present for a piece of knowledge to be acceptable as a memory. These are: (i) the revival in the mind of a 'copy' of an original event, (ii) the requirement that the present image be held as standing for a 'past original' and (iii) the requirement that the 'pastness' refer not just to the past in general but rather to the personal past of the rememberer.

While the basic concept of memory has not changed since the definition put forward by James (James, 1890), the personal awareness of the experienced past has become more important in the scientific study of memory. It is now referred to as 'episodic memory'.

The meaning of episodic memory can be clarified by the examination of similarities and differences of episodic and semantic memory, both of which comprise subsystems of declarative, or explicit, memory. A variety of similarities exist between these two types of memory. Declarative memory comprises the capacity for conscious recollection of events and facts (Squire and Zola, 1996) and is always either true or false. Further, it is fast, but not always reliable, i.e. forgetting or a retrieval failure can occur, and flexible in the sense that declarative memories are accessible to multiple response systems.

As mentioned above, declarative memory can be further divided into episodic memory, memory for events that compose a unique personal experience, and semantic memory, factual information that is independent of the specific episode in which that information was acquired (Tulving, 1972; Tulving and Markowitsch, 1998). The difference between these two types of memory becomes clear when, for example, one tries to remember the episode that led to the learning of a particular fact. We know that the capital of

Norway is Oslo, even though we are unlikely to remember the exact episode that led to the learning of this fact.

Still, in a variety of ways, episodic and semantic memory are very similar. Both types of memory are large and complex and both can hold practically unlimited amounts of information (Dudai, 1997). It is difficult to distinguish encoding of new information into one of the two systems from encoding of information into the other. Both episodic and semantic memory can receive information through different sensory modalities (Markowitsch et al., 1993) as well as from internally generated sources (Johnson and Raye, 1981). Also, in both systems the processes for encoding of information into memory are quite similar and such acquisition can occur very rapidly, often as a consequence of a single experience of an event or a single exposure to a fact.

The operations of both memory systems obey the principles of encoding specificity and transfer appropriate processing: the effectiveness of given retrieval cues is determined not only by the target information in the memory store, but also by its episodically and semantically encoded context. Finally, and importantly, both systems can be thought of as being concerned with 'remembering that' as opposed to 'remembering how': the results of retrieval from either memory system can be expressed symbolically, for example in language, unlike the skills mediated by procedural memory that can only be expressed through non-symbolic behavior.

In spite of the many similarities between episodic and semantic memory, episodic memory does possess some critical features not shared by the other memory systems. Most important of all, episodic memory is the only form of memory that, at the time of retrieval, is oriented towards the past. Humans who are capable of consciously recollecting past experiences seldom engage in such recollection when they make use of previously acquired semantic information and knowledge. A second important characteristic is the fact that episodic remembering is accompanied by a special kind of 'autonoetic' conscious awareness that is clearly different from the kind of conscious awareness ('noetic' awareness) that accompanies retrieval of semantic information (Tulving, 1993). Even though the remembered experience may now be fragmentary or even false by objective standards, its phenomenal quality is not mistaken for any other kind of conscious awareness. A person can as easily distinguish between recollecting a personal experience and recalling an impersonal fact as we can distinguish between perceiving and imagining. It is this ability of humans that makes possible an

operational definition of autonoetic and noetic awareness in terms of the 'remember'/'know' paradigm (Gardiner et al., 1998; Knowlton and Squire, 1995; Tulving, 1985), which will be discussed further in paragraph 2.2.3 and chapter 5 below.

The landmark study of the amnesic patient H.M. by Scoville and Milner was the first to show that bilateral damage to the MTL severely impairs both the ability to form and to retain long-term declarative memories (Scoville and Milner, 1957). Since the time H.M. was studied, a variety of detailed neuroanatomical studies of the MTL have helped to identify the individual areas important for declarative memory in healthy human subjects (e.g. Squire and Zola, 1996). While these studies have contributed substantially to our understanding of the brain basis of memory, neuropsychological studies of brain-damaged patients can provide only indirect insight into the specific patterns of neural activity that allow humans to form and retain new long-term declarative memories, and to retrieve information from long-term memory. Still, one important point made in these studies was the fact that neurons throughout the MTL can perform both similar as well as distinct memory functions that usually cooperate in signaling declarative memory. Obviously, in the majority of cases, the hippocampus and surrounding cortex signal mnemonic information in different but complementary ways. Therefore, a brief overview of the neuroanatomical organization of this region follows. Still, when considering the results of the imaging studies presented in chapters 4 and 5, it is important to keep in mind that the maximal spatial resolution achievable by fMRI is dependent on the voxel size employed during image acquisition. Thus, the spatial resolution usually ranges on the order of about two to three millimeters, limiting the accuracy of anatomical localization to this range.

2.1 Anatomy of the Medial Temporal Lobe

The MTL is composed of the amygdala, the hippocampus, and surrounding cortical areas, including the entorhinal, perirhinal, and parahippocampal cortices. These structures are interconnected by a variety of topographically organized connections. Therefore, the different substructures of the MTL function together when involved in the formation of new declarative memories or retrieval from memory (Squire and Zola-Morgan, 1991).

On the basis of lesion studies in patients, it has long been believed that the hippocampus is the most critical component of the MTL memory system. However, it has been found that damage to the entorhinal and perirhinal cortices can also cause severe memory impairment (Aggleton and Brown, 1999). Nevertheless, the contribution of these cortical areas to memory processing in humans is not yet fully understood.

Essentially, three cortical areas make up the cortex of the parahippocampal gyrus. These are the entorhinal cortex, the perirhinal cortex and the parahippocampal cortex (Insauti et al., 1998). Most of the parahippocampal gyrus is occupied by the entorhinal area, which is defined as Brodmann area (BA) 28 (Brodmann, 1909). Dorsomedially, the entorhinal cortex is bordered by the periamygdaloid cortex, while caudomedially it is adjacent to the presubiculum and parasubiculum. Laterally, the entorhinal area extends to the medial bank of the collateral sulcus, where it is bordered by the perirhinal cortex (Insauti et al., 1995). The perirhinal cortex follows the collateral sulcus along its full extent and occupies chiefly the fundus and the medial bank of the sulcus. Most of the perirhinal cortex is composed of BA 36, which lies medial to area TE (BA 20). Anteriorly, the perirhinal cortex is continuous with the rostralmost portion of the temporal pole (BA 38). A more detailed description of the components of the human MTL follows (Insauti et al., 1995; Reber et al., 2002).

Temporopolar Cortex

Covering the anterior portion of the temporal lobe, the temporopolar cortex is located rostral to the perirhinal cortex. The temporopolar cortex is surrounded laterally and ventrolaterally by cortex forming the superior and inferior temporal gyri. The boundary between the temporopolar cortex and the neocortex of the superior temporal gyrus lies at the fundus or within the lateral bank of the lateral polar sulcus.

Perirhinal Cortex

The perirhinal cortex borders the temporopolar cortex along the medial surface of the rostral temporal lobe. Rostrally, the perirhinal cortex replaces the temporopolar cortex in the dorsomedial aspect of the temporal lobe. At the more caudal levels, the perirhinal cortex surrounds all but the most medial aspect of the entorhinal cortex. The perirhinal cortex is the lateral cortical area on the anterior portion of the

parahippocampal gyrus. The medial boundary of the perirhinal cortex is defined as the depth of the collateral sulcus. As with the entorhinal cortex, the superior boundary of the perirhinal cortex is the hippocampus. The inferior boundary of the perirhinal cortex is the ventral edge of the parahippocampal gyrus. The anterior edge of the perirhinal cortex is defined as the temporal pole. The posterior edge of the perirhinal cortex is identical to the posterior edge of the entorhinal cortex and is the boundary between the anterior and posterior hippocampal region.

Entorhinal Cortex

The entorhinal cortex is part of the anterior portion of the parahippocampal gyrus covering the medial wall of the gyrus. The superior boundary of the entorhinal cortex is defined as the grey matter of the anterior hippocampus. The inferior boundary of the entorhinal cortex is the ventral edge of the parahippocampal gyrus. The anterior boundary of the entorhinal cortex is defined as occurring at the anterior edge of the amygdala. The posterior boundary of the entorhinal cortex is defined as a projection from the posterior edge of the anterior hippocampus. Thus, the entorhinal cortex is inferior to the anterior hippocampus, while the parahippocampal cortex is inferior to the posterior hippocampus.

Parahippocampal Cortex

The parahippocampal cortex is the posterior cortical area within the parahippocampal gyrus. Whereas the anterior portion of the parahippocampal gyrus is divided into entorhinal and perirhinal cortex, the posterior parahippocampal gyrus is considered to be a single cortical area. The superior boundary of the parahippocampal cortex is the posterior hippocampus. The inferior boundary of the parahippocampal cortex is the ventral edge of the temporal lobe. The anterior boundary of the parahippocampal cortex is the posterior edge of the perirhinal cortex and entorhinal cortex.

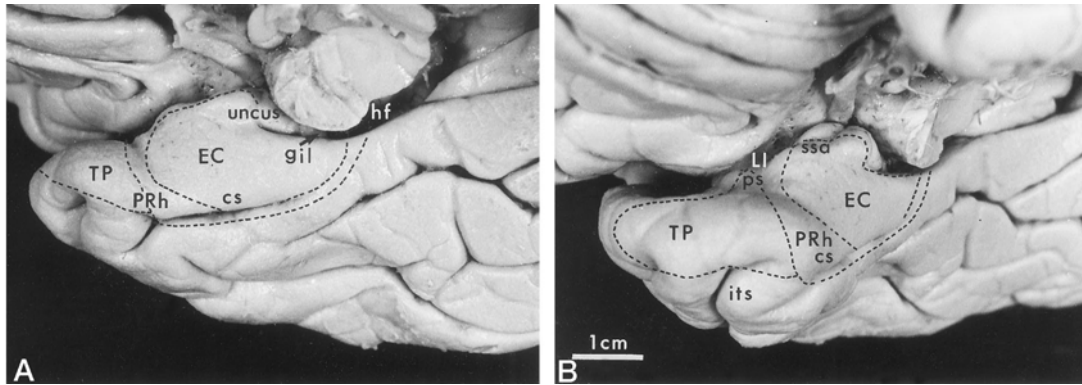


Figure 2-1: Views of the ventral aspect of the brain show location of entorhinal, perirhinal, and temporopolar cortices. *A* is the ventromedial view and *B* is the frontal view of the temporal lobe. cs: collateral sulcus, EC: entorhinal cortex, gil: gyrus intralimbicus, hf: hippocampal fissure, its: inferior temporal sulcus, LI : limen insulae, PRh: perirhinal cortex, ps: temporopolar sulcus, ssa: sulcus semiannularis, TP: temporopolar cortex (from Insauti et al., 1998).

Connections

The MTL is characterized by two major organizing principles. For one, the connections of the MTL are organized in a hierarchy of increasing amounts of sensory convergence. The lowest level of the hierarchy consists of the perirhinal (BA 35 and 36) and parahippocampal cortices. The perirhinal and parahippocampal cortices receive inputs not only from other higher order association areas, including regions of the prefrontal cortex and other polymodal areas within the temporal and parietal lobes, but also unimodal sensory input from visual, somatosensory, olfactory, and auditory areas. The perirhinal and parahippocampal cortices then provide the major input to the next level of the hierarchy, the entorhinal cortex, which in turn provides the major cortical input to the hippocampus via a series of serial and parallel projections. In addition to the prominent projections from the entorhinal cortex to various components of the hippocampus, there is also a direct, though weaker, projection from both the perirhinal and parahippocampal cortices to the hippocampus (Squire and Zola-Morgan, 1991).

A second important characteristic of the MTL connections is the fact that all projections, except those between the different subregions of the hippocampus, are strongly reciprocal. For example, the perirhinal and parahippocampal cortices not only have strong and reciprocal connections with the entorhinal cortex, but also have weaker interconnections with the hippocampus. Thus, the MTL is made up of a complex series of both serial and parallel projections in which any level of the hierarchy has either direct or indirect access to all other levels of the system.

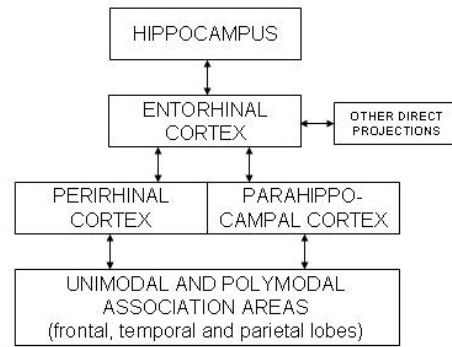


Figure 2-2: Schematic diagram of the projections within the medial temporal lobe (adapted from Squire and Zola-Morgan, 1991).

2.2 Episodic Memory - Evidence from Functional Imaging

Declarative memory is based on at least two fundamental mnemonic operations: memory formation during either implicit or explicit encoding tasks and memory retrieval during for example recognition (Gabrieli, 1998). Until relatively recently, insights into the neural bases of human memory have primarily been derived from neuropsychological studies of humans with select brain lesions. However, since lesions restricted to specific MTL subregions are seldom encountered, it has proved difficult through the study of patients with MTL lesions to determine exactly how the specific substructures in the MTL region mediate episodic memory formation and retrieval. In particular, through lesion studies it has proved hard or impossible to discover whether certain MTL structures mediate the input process of encoding and consolidation, the output process of retrieval, or both of these.

The development of functional neuroimaging studies has made it possible to investigate the relationship between brain structure and function more systematically than was previously possible with lesions studies. In these neuroimaging studies, blood flow in the brain is compared across several conditions. Ideally, these conditions should be similar except for one or very few psychological processes of interest. By the use of 'cognitive subtraction' (Friston, 1998), i.e. the subtraction of brain activity during a control condition from brain activity during an experimental condition of interest, the neural correlates of the process of interest can be identified. Further, since functional neuroimaging can be non-invasively conducted in healthy subjects, lesions studies can be complemented by the examination of clinically developed hypotheses in a normal, unimpaired population.

The two most commonly used neuroimaging techniques are positron emission tomography (PET) and fMRI. PET and fMRI are similar techniques in the sense that both rely on changes in hemodynamic responses which are correlated with changes in neuronal activity: fMRI is sensitive to blood oxygenation level dependent (BOLD) changes in the magnetic properties of blood, while PET is sensitive to local changes in blood flow. In comparison to other neuroimaging methods, such as electrophysiological recordings of event-related potentials (ERPs) which are time locked to the onset of particular stimuli, PET and fMRI offer higher spatial resolution at the cost of a lower temporal resolution. Most important for the study of memory, in contrast to neuropsychological studies of brain-injured patients, these functional neuroimaging techniques allow for a separation between encoding and retrieval processes.

Irrespective of the specific functional neuroimaging method employed, an important distinction is that between transient changes in neural activity that follow a specific event such as the presentation of a stimulus (*item-related activity*), and more sustained modulations of activity that accompany engagement in a specific task and are unaffected by the presentation of specific items (*state-related activity*). Until relatively recently, studies employing functional neuroimaging methods based on the detection of blood flow and oxygenation – the so-called hemodynamic methods of PET and fMRI – were always designed in such a way that item- and state-related brain activity were confounded. Owing to the constraints imposed by the PET methodology, PET images of regional cerebral blood flow (rCBF) are integrated over an acquisition period - and a corresponding block of experimental trials - lasting some 40 – 60 seconds. This restriction makes it impossible to distinguish between item- and state-related activity. The same problem is encountered in so-called 'blocked' fMRI designs, where contrasts are performed on data from two or more blocks of trials, each representing an experimental condition. In both cases, any differences between experimental conditions in patterns of cerebral activity represent an unknown mixture of item- and state-related effects.

In contrast, the recent development of event-related fMRI (efMRI) methods allows for examination of trial-by-trial differences in neural activity during encoding and recognition. Thus, event-related fMRI provides the unique opportunity to study the neural correlates of mnemonic operations with great anatomical detail in healthy human subjects (Dale and Buckner, 1997; Josephs et al., 1997; Zarahn et al., 1997). Furthermore, the application of event-related fMRI procedures to the study of human

memory encoding allows for the examination of what is called the '*subsequent memory effect*' (Sanquist et al., 1980; Rugg, 1995; Wagner et al., 1999), a particularly powerful approach to the study of memory encoding, which provides measures of neural activity correlated with later remembering. In the subsequent memory procedure, neural responses to distinct stimulus events are recorded at the time of study and then classified based on testing the subject's memory for the stimulus at a later time. The key contrast is typically between neural responses to stimuli later remembered and to those later forgotten. Differential neural activity based on memory, sometimes referred to as the *Dm effect* (Paller, 1990), permits the identification and functional characterization of the neural regions that predict subsequent memory, that is, regions that demonstrate a differential response during the encoding of events that are subsequently remembered as opposed to those that are subsequently forgotten.

2.2.1 Encoding

Memory encoding occurs whenever any type of information processing leads to episodic memories. Specifically, this means that during the processing of a stimulus neuronal changes take place, which endure over time. Schacter and colleagues (Schacter et al., 1996b) described memory encoding as 'a special way of paying attention to ongoing events that has a major impact on subsequent memory for them'. Memory encoding can occur both intentionally and incidentally. This means that the processes mentioned above may be engaged both when subjects attempt to remember new materials by intention or when information processing, by means of the kind of task a subject engages in, incidentally encourages memorization of new materials (Craig and Lockhart, 1972).

The main aim in the study of human memory is to answer the question why some experiences are remembered whereas others are forgotten. Considerable behavioral and neuropsychological evidence indicates that the ability to remember a given experience is affected by many factors, including the kind of processing operations that are engaged at the time of encoding and retrieval, and interactions between encoding and retrieval operations.

2.2.1.1 PET and blocked design fMRI studies

From lesion and neuroimaging studies, an involvement of the frontal lobes in memory encoding is undisputed. Findings from patients with frontal lobe lesions seem to

suggest that the frontal lobes are more involved in the more strategic aspects of memory formation as opposed to memory encoding as such (Moscovitch, 1989). Also, damage to the frontal lobes does not necessarily result in major difficulties in clinical tests of episodic memory (Shimamura et al., 1992). In contrast to these findings, functional neuroimaging studies have repeatedly demonstrated a major engagement of the prefrontal cortex in memory processes. Also, differential contributions of the prefrontal cortex to memory encoding and retrieval have been shown.

In a study by Rugg and colleagues (Rugg et al., 1997) the encoding and retrieval of verbal material were studied separately. Subjects were presented with pairs of words either in an intentional or an incidental memory task. When comparing both encoding conditions, the authors found that prefrontal cortex was more active during the intentional as opposed to the incidental task, irrespective of the number of word pairs that were remembered correctly.

In a study by Kapur and colleagues (Kapur et al., 1994), subjects incidentally learned a series of words. The paradigm was designed in such a way as to manipulate the depth of encoding to detect cerebral blood flow differences between superficial and deep encoding (Craik and Lockhart, 1972). While for the shallow encoding task, subjects were instructed to perform an orthographic judgment on the presented word, they performed a semantic task during deep encoding. As expected, memorization of the items, which was assessed after the scan, was more effective in deep than in shallow encoding. Also, in the subtraction of brain activity during the shallow encoding task from the deep encoding task, an involvement of the left inferior prefrontal cortex during deep encoding was found.

This study by Kapur and colleagues (Kapur et al., 1994) was not the only examination of the difference between deep and shallow encoding. Several early PET and block design fMRI studies of episodic encoding have focused attention on the contribution of regions within prefrontal cortex by comparing brain activity during deep encoding tasks, e.g. judging whether a word represents an abstract or a concrete concept, to brain activity during shallow encoding tasks, e.g. judging whether a word is presented in upper- or lower-case letters. Typically, semantic (deep) encoding yields higher subsequent memory performance as compared to non-semantic (shallow) encoding (Craik and Lockhart, 1972). Thus, it might be suggested that the observed activation

differences between deep and shallow encoding tasks reflect encoding processes that directly influence later remembering.

A general finding for verbal material relates to a greater activation in several regions of left inferior prefrontal cortex during deep as opposed to shallow encoding tasks (Fletcher et al., 1995c; Rugg et al., 1997; Wagner et al., 1998b). Moreover, recent studies have also revealed evidence of homologous right inferior prefrontal activation during encoding of non-verbal information, including for example faces (Haxby et al., 1996; Kelley et al., 1998) and abstract visual patterns (Wagner et al., 1998a). Taken together, these results from verbal and non-verbal encoding studies suggest that episodic encoding is facilitated by frontally mediated working-memory processes. The nature of the to-be-learned material or task (Opitz et al., 2000) seems to determine which specific working memory networks are recruited (Buckner and Koutstaal, 1998; Wagner et al., 1998a).

A further central topic of neuroimaging research concerns the role of the MTL and especially the hippocampus in human memory processes. On the basis of lesion studies in patients with damage to the hippocampus as well as ablation studies in monkeys (Squire, 1992; Tulving and Markowitsch, 1997) the involvement of the hippocampus in episodic memory is well established. On the other hand, early PET studies have failed to delineate an involvement of the hippocampus during memory encoding in healthy human subjects. A number of explanations have been put forward for these null results. Some authors refer to technical limitations such as the inadequate spatial resolution of PET and fMRI images. Others blamed the nature of the hippocampal activation, suggesting that it might either be too weak, too diffuse, or too transient to be reliably detected (Fletcher et al., 1995a; Andreasen et al., 1995). One important contribution was made by Haxby (Haxby, 1996). He suggested that the absence of hippocampal activation might be directly related to the subtraction method employed in earlier functional imaging studies, stating that the reference tasks systematically involve encoding, no matter what the cognitive demand.

In contradiction to the above explanation, pioneer studies by Squire and colleagues (Squire et al., 1992) and Grasby and colleagues (Grasby et al., 1993) did clearly demonstrate hippocampal activation, even though both studies employed the subtraction method. In the study by Squire and colleagues (Squire et al., 1992) subjects studied lists of words prior to either silently viewing word stems, completing

word stems to form the first words to come to mind (priming), or trying to recall study words. The authors found an activation of the right hippocampal region when comparing the memory task to either the baseline or the priming condition.

Since these early studies, a variety of functional imaging studies has reported significant hippocampal activation. These studies have tested specific hypotheses about the function of the hippocampus in episodic memory by means of sophisticated paradigms. In a number of studies, MTL activation has been observed under conditions in which exposure to novel stimulus material is compared with exposure to familiar materials (e.g. Dolan and Fletcher, 1997; Gabrieli et al., 1997; Stern et al., 1996; Tulving et al., 1996). For example, Stern and colleagues (Stern et al., 1996) reported that the posterior aspect of the hippocampus and the parahippocampal gyrus were more active during learning of visual scenes which had not been previously presented prior to encoding (*novel stimuli*) as compared with the processing of one visual scene which had previously been presented (*highly familiar stimulus*). Similarly, Gabrieli and colleagues (Gabrieli et al., 1997) reported evidence that, compared with the incidental encoding of familiar pictures, incidental encoding of novel pictures yielded greater posterior MTL activation bilaterally in the parahippocampal cortex.

These studies clearly suggest a link between MTL activity and novelty detection. Still, several studies indicate that MTL activations during encoding extend beyond responses to novelty (e.g. Fernández et al., 1998; Kelley et al., 1998; Wagner et al., 1998b). For example, Wagner and colleagues (Wagner et al., 1998b) reported greater left parahippocampal as well as fusiform activation during a deep encoding task compared to a shallow encoding task. Finally, as with observations that activations within prefrontal regions are affected by the nature of the material being encoded, there have been reports that the encoding of verbal and non-verbal stimuli are differentially associated with left and right MTL regions, respectively (Kelley et al., 1998; Martin et al., 1997).

For example, Kelley and colleagues (Kelley et al., 1998) studied the involvement of dorsal frontal and medial temporal regions during the encoding of words, namable line-drawn objects, and unfamiliar faces. They found that lateralization was strongly dependent on the materials being encoded. While encoding of words was associated with a left-lateralized MTL activation, encoding of unfamiliar faces produced homologous right-lateralized activation. Further, encoding of namable objects yielded

bilateral MTL activation. Just like for frontal activations, these results suggest that both hemispheres are involved with human long-term memory formation and that left and right MTL regions can be engaged differentially according to the nature of the material being encoded.

Another question, which more recent blocked design fMRI and PET studies have attempted to answer, relates to the correlation between MTL activation across an encoding block and the level of subsequent memory for the items in that encoding block. In a study by Fernández and colleagues (Fernández et al., 1998) subjects studied lists of words. After distraction, a free recall of the words in the lists was performed. During encoding, fMRI data was acquired from seven slices perpendicular to the long axis of the hippocampus, extending from the anterior to the posterior extent of the MTL region. In the analysis, the fMRI-signal during encoding blocks was correlated with the number of words recalled from each block for each subject individually. For 11 out of 13 participants a significant positive correlation between the number of recalled words and the signal intensity was found in a posterior hippocampal MTL region. In a subsequent study (Fernández et al., 1999a) the authors showed that five out of six participants demonstrated significant correlations between activation and subsequent memory in bilateral MTL regions that encompassed the posterior extent of the entorhinal cortex, and three out of six participants demonstrated additional correlations in the anterior extent of the entorhinal cortex.

A further hypothesis concerning the role of the hippocampus in memory encoding was suggested by Stern and colleagues (Stern et al., 1996) as well as others (Tulving et al., 1994; Rugg et al., 1997; Fletcher et al., 1997). This hypothesis proposes that the hippocampus is more involved with the encoding of visuo-spatial and complex material than with the encoding of verbal items. This finding might be based on the fact that the presentation of words, which are per se familiar before the memory experiment, does not require the formation of new representations. Also, the proposal is consistent with a finding from animal experimentation (e.g. Nadel, 1994), which suggests that the hippocampus is particularly involved in the processing of spatial data. Owen and colleagues (Owen et al., 1996) specifically tested this hypothesis by comparing brain activity involved with the encoding of object features to the encoding of object locations. Even though they did find differences between these two encoding tasks in inferior temporal and parietal regions, a differential activation of the hippocampus could not be demonstrated.

Nyberg and colleagues (Nyberg et al., 1996) used words as study items to study the neural correlates of the encoding of item, location, and time information. As opposed to location and time information, encoding of item information was found to activate the left hippocampus. Martin and colleagues (Martin et al., 1997) studied incidental encoding of different types of material, namely objects and words. The authors demonstrated that the hemisphere activated and the amount of activation depend on the type of stimulus presented (objects or words), whether the stimulus can be encoded for meaning (real objects and words versus nonsense objects and words), and task experience (first versus second time a task is performed).

A different view has been advanced by Henke and colleagues (Henke et al., 1997) who propose that the hippocampus may be particularly involved in the establishment of associations among components of an episode in memory. In their study, these authors employed four experimental conditions during memory encoding, namely encoding of single items, establishing inter-item associations, novelty detection, and retrieving of recently formed associations. Of these conditions, hippocampal and parahippocampal activation was found only during associative learning. This view is facilitated by a study by Killgore and colleagues (Killgore et al., 2000) who found a left lateralized activation of the hippocampus for the encoding of paired faces as opposed to the encoding of single faces.

Overall, activation of the hippocampal region seems to occur during the encoding of various types of stimuli, with left-sided predominance for words, right-sided predominance for faces and objects and bilateral activations when complex spatial or visual material or the establishment of inter-item associations is involved.

2.2.1.2 Event-related fMRI studies

One main focus of event-related fMRI studies on memory encoding has been the subsequent memory effect, the difference in brain activity during encoding to subsequently remembered and subsequently forgotten items. From the results of these studies it might be suggested that successful as opposed to unsuccessful memory formation is accompanied by more activity in the (posterior) MTL (Brewer et al., 1998; Kirchhoff et al., 2000; Otten et al., 2001; Otten and Rugg, 2001a; Wagner et al., 1998b).

First evidence that the magnitude of frontal and MTL activation during the encoding of individual events is associated with subsequent memory for those events came from two pioneer event-related fMRI studies by Brewer and colleagues (Brewer et al., 1998) and Wagner and colleagues (Wagner et al., 1998b). In the study by Wagner and colleagues (Wagner et al., 1998b) subjects were scanned while they had to decide whether individually presented words were abstract or concrete. In a subsequent non-scanned recognition test, subjects made old/new judgments about studied and non-studied words. Whenever a word was judged as old, the subject also indicated whether this judgment was accompanied by high or low confidence. When brain activity for subsequent high-confidence hits, i.e. later correctly identified old items, was compared to brain activity for subsequent misses, old items later misclassified as new, significant activations were detected in left prefrontal and left temporal regions. In frontal cortex, these activations comprised the anterior and ventral extent of the left inferior frontal gyrus, a more posterior and dorsal extent of left inferior frontal gyrus and the left frontal operculum. Within temporal cortex, effects were observed in the left parahippocampal and fusiform gyri.

Complementary results were obtained in an event-related fMRI study of non-verbal encoding (Brewer et al., 1998). In this study, subjects were shown real-word pictures and judged whether each of these pictures depicted an indoor or outdoor scene. In a non-scanned recognition test, subjects then made old/new judgments for old and new pictures. For pictures judged as old, participants also gave a 'remember' judgment, when they possessed a specific recollection of having seen the picture earlier, or a 'know' judgment, when the picture just seemed familiar to them. It was found, that the activity level in bilateral parahippocampal cortex and in the posterior extent of the right inferior frontal gyrus predicted subsequent remembering or forgetting. There was greater activity during encoding for pictures that were remembered with specific details than for pictures that just seemed familiar, and also for familiar pictures compared with forgotten pictures. Thus one factor influencing the subsequent memorability of non-verbal experiences is the extent to which the processes mediated by right inferior frontal and bilateral parahippocampal regions are engaged during those experiences.

In conclusion, the findings from these event-related fMRI studies, together with earlier findings from blocked design PET and fMRI studies, suggest that frontal and medial temporal regions may act interdependently to promote the encoding of events into

episodic memory. The specific frontal and medial temporal regions engaged during encoding as well as the lateralization of these activations appear to depend on the nature of the processes recruited during encoding, with verbal and non-verbal information resulting in recruitment of distinct mnemonic processes. Verbal experiences may be more memorable when semantic and phonological attributes of the experience are extensively processed via participation of left prefrontal regions (Kapur et al., 1996; Wagner et al., 1998b). Left prefrontal regions may serve to organize these attributes in working memory (Wagner, 1999), with this information serving as input to left medial temporal regions.

In contrast to verbal encoding, non-verbal experiences seem to be more memorable when visuospatial attributes of the experience are extensively processed via participation of right prefrontal regions (Brewer et al., 1998; Kelley et al., 1998; Wagner et al., 1998a). Right prefrontal activations have been shown to be involved with states of alerting and orienting attentional demands (Sturm and Willmes, 2001; Sturm et al., 1999). Furthermore, right prefrontal regions may serve to organize visuospatial attributes in working memory (Smith et al., 1995) with this information serving as an input to bilateral medial temporal regions.

Findings from event-related fMRI studies suggest that a specific experience may elicit the recruitment of frontal and MTL processes to a greater or lesser extent. The variability of activation can be based on a variety of internal and external facts. The source of this variability may include differences in task demands, shifts in subjects' strategies, characteristics of the target items, or attentional modulations during the course of the memory experiment. Regardless of the source of this variability, greater recruitment of frontal and MTL regions will tend to produce more memorable experiences.

2.2.2 Retrieval

To remember an event from the past, information must be retrieved from episodic memory. Episodic retrieval is commonly thought to involve an interaction between a 'retrieval cue' and a memory trace. The retrieval cue can either be provided by the experimental environment, e.g. a word-stem presented to the subject in a word-stem completion task or a stimulus presented in the course of a 'yes'/'no' recognition memory experiment. On the other hand, the retrieval cue can be self-generated as

during free recall of e.g. words that have been learned. The interaction of the cue and the memory trace then results in the reconstruction of some or all aspects of the episode represented by the trace. Whether an episodic retrieval attempt is successful or not is influenced by a variety of factors, not least of which is the way the event was initially encoded into memory.

Usually, studies of episodic memory retrieval have employed memory tests that involve the presentation of cues that are in some way related to the studied items. The simplest and maybe most popular such test is the simple 'yes'/'no' recognition memory test, where the entire studied item is presented to the subject, and it is the subjects' task to answer 'yes' or 'no' to the question whether or not each individual item was presented at study.

Whatever the retrieval task that is employed, retrieval from memory comprises both 'pre-' and 'post-' retrieval processes. Pre-retrieval processing refers to those cognitive operations involved with the attempt to use some internally or externally generated retrieval cue to retrieve information from memory. In contrast, post-retrieval processing relates to those cognitive operations that operate on the products of a retrieval attempt. Among others, post-retrieval processes include the maintenance in working memory of retrieved information and its evaluation.

Importantly, post-retrieval processing and retrieval success are related to different phenomena. Whereas retrieval success, the successful retrieval of some type of information from memory, will always lead to the engagement of post-retrieval processes, retrieval success is not necessary for post-retrieval processes. Even if the result of retrieval from memory is incorrect, some kind of post-retrieval processing will take place, which in this case ultimately will signal a failure of retrieval.

According to Tulving (Tulving, 1983), as a prerequisite for a stimulus to be treated as an episodic retrieval cue, the rememberer needs to be in the appropriate cognitive state to begin with. This cognitive state, which makes it possible to make use of a retrieval cue was termed 'retrieval mode'. It relates to a tonically maintained cognitive state entered when there is need to engage in episodic retrieval. Therefore, it follows, that the neural correlates of retrieval mode should be time-locked to the onset of engagement in an episodic retrieval task, and maintained for all the duration of the task. Further, these neural correlates should be revealed by contrasts between classes of tasks rather than between classes of retrieval cues in a recognition memory test.

Moreover, they should demonstrate task invariance, meaning that any pair of tasks, as long as one of them requires episodic retrieval and the other does not, should differentially activate the brain systems supporting retrieval mode. Thus, retrieval mode is the cognitive process which is delineated in blocked fMRI or PET studies of memory retrieval.

On the other hand, processes associated with retrieval success are necessarily item-related. Therefore, their neural correlates are revealed by contrasting the activity elicited by retrieval cues that engender veridical memories with that elicited by cues that either can not, or which fail, to do so. In other words, brain activity related to episodic retrieval success is found when comparing correctly recognized old items to correctly identified new items or to old items misclassified as new in a recognition memory test. Thus, retrieval success is the focus of event-related studies of memory retrieval.

2.2.2.1 PET and blocked design fMRI studies

Lepage and colleagues (Lepage et al., 1998) conducted a series of individual PET studies, each of which involved retrieval from episodic memory. On the basis of a meta-analysis of these studies the authors suggested a functional-anatomic pattern in that activations in the hippocampal region associated with episodic memory encoding are located primarily in the rostral portions of the region, whereas activations associated with episodic memory retrieval are located primarily in the caudal portions. Concerning retrieval mode, it was proposed that activation of the right prefrontal cortex, especially in the vicinity of BA 10, represents the neural signature of retrieval mode.

Other authors found that the right prefrontal activation is invariant with respect to both task (Cabeza et al., 1997) and the nature of the retrieval cue, that is, whether the cue corresponds to a studied or an unstudied item (Kapur et al., 1995; Duzel et al., 1999; Nyberg et al., 1995). Cabeza and colleagues (Cabeza et al., 1997) studied the neural correlates involved in memory recall and recognition of studied word pairs. They found an increase of activation in right prefrontal cortex for both recognition and recall, suggesting that frontal activations in explicit memory tasks are related to the general episodic retrieval mode or retrieval attempt.

Still, these results have been challenged by findings from further studies. Rugg and colleagues (Rugg et al., 1998) acquired PET images during the performance of recognition memory tests and word-stem cued recall. Each task comprised a baseline and two retrieval conditions. In the zero-density retrieval condition, none of the test items corresponded to words encoded in a preceding study phase. Differences in activity between this condition and the baseline were employed to characterize the neural correlates of retrieval effort in each task. In the high density retrieval condition 80% of the test items had been studied previously. Differences in brain activity between this condition and the zero-density condition were taken to represent the neural correlates of successful retrieval. While right anterior prefrontal cortex was not activated more during the zero-density condition as opposed to baseline, it did demonstrate enhanced activity during the high-density condition. Thus, the authors suggested that the right prefrontal activation during episodic retrieval was indeed task-sensitive. This pattern of task sensitivity for right prefrontal activity is difficult to reconcile with the idea that activation in this region reflects the adoption of a task-invariant retrieval mode.

Altogether, activation of the prefrontal cortex has been reported in the majority of functional neuroimaging studies of episodic retrieval (Desgranges et al., 1998; Fletcher and Henson, 2001; Nölde et al., 1998). These findings were not unexpected on the basis of lesion studies which reported relatively subtle memory impairments following frontal lesions (Incisa et al., 1993; Janowsky et al., 1989; Stuss et al., 1994). Still, on the basis of these findings, the right-lateralization of the retrieval-related frontal activations in functional imaging studies was somewhat surprising, especially since the right-lateralization was also found for verbal material. Even though a right-lateralized frontal activation was consistently found during memory retrieval, the findings from blocked studies leave open the question whether the right prefrontal activations reflect task-specific and therefore state-related effects or item-related effects or even some mixture of both.

Based on a review of several PET studies on episodic encoding and retrieval, Tulving and colleagues (Tulving et al., 1994) proposed the so-called hemispheric encoding/retrieval asymmetry (HERA) model of prefrontal activation. This model proposes an asymmetry of prefrontal activations during memory encoding and retrieval. According to the model, encoding involves left prefrontal cortex while during retrieval right prefrontal cortex is activated. Thus, according to the HERA model, both

left and right prefrontal cortex are part of a network involved with episodic remembering, but the two hemispheres play different roles. Several PET and fMRI studies have confirmed the existence of the general HERA pattern (for review: Habib et al., 2003). Still, in a review of a larger number of PET and fMRI studies (Cabeza and Nyberg, 2000), the HERA hypothesis of the predominance of right prefrontal cortex in episodic memory encoding could not fully be confirmed. According to these authors, episodic encoding activations sometimes seem to be left lateralized for verbal material and right lateralized for pictorial stimuli (e.g. Kelley et al., 1998). Therefore, Cabeza and Nyberg suggested, that a full account of the data may require an integration of the verbal/pictorial view of lateralization of prefrontal activations in episodic encoding and the HERA view. Concerning prefrontal activation during episodic retrieval, these authors suggested that the region most strongly associated with the adoption of retrieval mode is the right prefrontal cortex, while activations associated with retrieval effort tend to be left lateralized.

Many reports of profound memory impairment in humans following MTL damage have stressed the importance of the hippocampus and adjacent regions for episodic memory (Squire and Cohen, 1984). In a review of MTL activation detected by PET studies, Lepage and colleagues (Lepage et al., 1998) proposed the hippocampal encoding/retrieval (HIPER) model. The model suggests a division of memory-related labor between the rostral and caudal portions of the hippocampus, in that activations associated with memory encoding are located primarily in the rostral portion of the hippocampal region, while activations associated with episodic memory retrieval are located primarily in the caudal portions.

As compared to PET studies, relatively few blocked fMRI studies have found activation of medial temporal regions during episodic retrieval tasks. Also, reviews of such studies (Schacter and Wagner, 1999; Stark and Squire, 2000a; Stark and Squire, 2000b) failed to find an anterior-posterior distinction between encoding and retrieval. On the contrary, in a review of PET and fMRI studies on episodic encoding and retrieval (Schacter and Wagner, 1999), the authors arrived at the conclusion that PET studies of encoding reveal both anterior and posterior MTL activations. fMRI studies found that the posterior MTL is associated with episodic encoding, while too few fMRI studies on episodic retrieval were available to permit any firm conclusions about their rostrocaudal location.

2.2.2.2 Event-related fMRI studies

As noted above, neural correlates of retrieval success are usually isolated by the use of event-related fMRI study designs, which make it possible to contrast brain responses elicited by hits to brain responses for correct rejections. Two early event-related fMRI studies of recognition memory (Buckner et al., 1998; Schacter et al., 1997) were unable to find any reliable difference between responses elicited by correctly classified old and new words. Similarly, negative findings were reported by McDermott and colleagues (McDermott et al., 1999). These null results were unexpected, since robust old/new effects have been obtained in recognition memory tasks examined by ERPs (Rugg, 1995). Therefore it has been suggested, that almost certainly these null findings reflect no more than the lack of power of event-related fMRI studies to detect differential item-related activity when the interstimulus interval (ISI) is long (16 seconds or more in the above cases; see Josephs and Henson, 1999).

More recent event-related fMRI studies, which employed more sophisticated task designs with a larger number of stimuli and shorter ISIs have consistently reported differences in the activity elicited by hits and correct rejections, i.e. correctly identified new items. The study of Ranganath and colleagues (Ranganath et al., 2000) used an event-related fMRI design to assess prefrontal activation during encoding and retrieval of pictures of objects. The contrast between correctly identified old and new trials during retrieval revealed relatively greater activity for old items in a region of left dorsolateral prefrontal cortex along with a small region demonstrating the opposite effect in the right ventral prefrontal cortex. Findings for regions outside prefrontal cortex were not reported in that study.

In further studies employing simple 'yes'/'no' recognition paradigms, reliable old/new differences were reported in both prefrontal and posterior regions. In the study by Konishi and colleagues (Konishi et al., 2000), who used verbal stimuli, differential activation for hits as opposed to correct rejections was found in left lateral parietal cortex, medial parietal cortex and several regions of left prefrontal cortex. These included bilateral anterior, left ventral and dorsolateral areas as well as anterior cingulate cortex.

In a study by Saykin and colleagues (Saykin et al., 1999), subjects listened to a series of recently learned and novel words. As compared to the novel words, enhanced responses to old items were found in left posterior parahippocampal cortex, as well as

right prefrontal regions including dorsolateral prefrontal cortex, a large area of right temporal cortex, right anterior cingulate and left medial parietal cortex. The reverse contrast revealed greater activity for novel words in left anterior hippocampus. On the basis of these findings, the authors proposed an anterior-posterior functional differentiation within the MTL in processing novel and familiar verbal information.

Donaldson and colleagues (Donaldson et al., 2001b) investigated both item- and state-related activity in a recognition memory task by the use of a mixed blocked and event-related experimental design. Subjects studied a series of word pairs and later performed a 'yes'/'no' recognition task during fMRI scanning. The test trials were interrupted approximately every 2 minutes by a 30 second 'fixation only' rest period. Processes involved with retrieval mode were identified as the difference between activity during the recognition task after removal of the item-related effects, and activity during the inter-block rest periods. Item-related activity was assessed relative to an interstimulus baseline, and in terms of direct contrasts between correctly classified old and new words. From the results, the authors suggested three classes of brain regions supporting recognition memory. These comprise (i) predominantly transient activity, which was found in medial parietal, lateral parietal, and anterior left frontal cortex, reflecting item-related processing associated with retrieval success, (ii) predominantly sustained activity, which identified decreased activity in bilateral parahippocampal cortex, reflecting state-related processing associated with retrieval mode and (iii) concurrent sustained and transient activity, which was found in left middle frontal gyrus, bilateral frontal operculum, and medial frontal gyrus, reflecting a combination of state- and item-related processing. A drawback of this study relates to the fact that the authors did not include a control condition in which words were presented in a context of a task imposing no demand on memory. Therefore, it is not possible to assess which, if any, of these regions exhibited activity concerned specifically with processes involved in recognition memory, as opposed to the more general aspects of word processing.

2.2.3 Event-related fMRI studies on Encoding and Retrieval of Source Memory

Encoding and retrieval of the contextual details in which an item or event was encountered is a critical aspect of episodic memory. The correct retrieval of contextual information plays an important role in daily life, since the ability to recall where and

when a specific event took place enables a person to place a memory appropriately in autobiographical space and time. Memory for contextual details is referred to as 'source memory', and its study involves typical types of experimental paradigms. In all paradigms examining source memory, participants study a series of items in which each item is presented in one of two - or more - classes or sources, for example, words presented to the left or the right of fixation (Yonelinas, 1999), or facts presented in two different lists (Shimamura and Squire, 1991). During the recognition memory test, participants have to discriminate not only between old and new items, but also between the two - or more - sources in which the items were studied. In a typical experiment, subjects would be asked, for example, on which side of fixation the word had been presented, in which list the fact had been learned and so on. Commonly, first an old/new decision is performed which is then followed by a source memory judgment for all items judged as old. Some functional imaging studies have also employed the so called 'remember/know procedure' (Tulving, 1985), where subjects are required to endorse recognized study items according to whether, on the basis of introspection, recognition was - a 'remember' response - or was not - a 'know' response - associated with retrieval of information about the item's encoding context.

The so-called "dual process" models of recognition memory propose that recognition memory is supported by two distinct forms of memory, namely familiarity and recollection or recognition of an item which is accompanied as opposed to unaccompanied by contextual information (e.g. Mandler, 1980; Jacoby and Dallas, 1981; Yonelinas, 1994; O'Reilly and Norman, 2002). In general, these models assume that recollection depends on a relatively slow process, which involves the retrieval of qualitative information about the studied items, e.g. where, when or in what context an item was studied. By contrast, familiarity reflects a purely quantitative, 'strength-like' memory signal.

Behavioral data concerning the nature of these processes are remarkably consistent (Rajaram et al., 2002; Yonelinas, 2002). They showed that recollection does more than familiarity benefit from elaborative encoding (Richardson-Klavehn and Gardiner, 1995), it is slower and requires more attention (Gardiner and Parkin, 1990). Further, recollection is relatively unaffected by an increase of the study-test interval up to several minutes, while familiarity does decline (Gardiner and Java, 1991). Conversely, familiarity is more sensitive to perceptual changes between study and test.

A variety of behavioral studies demonstrating that recollection and familiarity can be dissociated provide strong evidence that these two processes reflect distinct forms of memory. However, alternative 'single process' models have been proposed, in which recollection is assumed to reflect the retrieval of strong, content-rich memories, whereas familiarity is associated with weaker, less specific memories (e.g. Donaldson, 1996).

Henson and colleagues (Henson et al., 1999) investigated the question whether recognition memory judgments with and without recollection reflect dissociable patterns of brain activity. In this study, 60 words were studied incidentally in the context of a lexical decision task. During recognition, subjects made one of three judgments to each word: whether they recollected seeing it during study ('remember' judgments), whether they experienced a feeling of familiarity in the absence of recollection ('know' judgments), or whether they did not remember seeing it during study ('new' judgments). Relative to new words, correctly remembered old words elicited enhanced activity in left ventral and dorsal lateral prefrontal cortex, in left inferior and superior parietal cortex, medial parietal cortex and in the posterior cingulate, a network similar to that identified by the studies of Konishi and colleagues (Konishi et al., 2000) and Donaldson and colleagues (Donaldson et al., 2001a). Items assigned a 'know' judgment elicited greater activity relative to new items in similar left prefrontal regions to those activated by remembered items, as well as in right ventral and dorsal prefrontal cortex, and in the anterior cingulate. Direct comparisons between the two classes of old items revealed relatively greater activity for remembered items in left dorsal anterior prefrontal and inferior as well as superior lateral parietal cortex and the posterior cingulate. On the other hand, items assigned a 'know' judgment elicited relatively more activity in right dorsolateral prefrontal, anterior cingulate and dorsal medial parietal regions. On the basis of these results, the authors suggested that responses of different brain regions do dissociate according to the phenomenology associated with memory retrieval.

A further study using the 'remember'/'know' procedure was reported by Eldridge and colleagues (Eldridge et al., 2000). Unlike Henson and colleagues (Henson et al., 1999), these authors employed a procedure in which subjects first signaled their old/new decision and then made a subsequent 'remember'/'know' decision for those items that had been judged old. The comparison of brain activity for 'remember' judgments as opposed to 'know' judgments delineated activations in left dorsolateral prefrontal

cortex, right inferior prefrontal cortex, bilateral inferior parietal cortex, posterior cingulate cortex and the hippocampus. Thus, the most striking difference from the results obtained by Henson and colleagues (Henson et al., 1999) was the increase of hippocampal activation for 'remember' as opposed to 'know' judgments. It was thus suggested that the hippocampus selectively supports the retrieval of episodic memories.

In a study using pictorial images as test items (Cansino et al., 2002), the task required subjects to classify the items as old or new, and, if old, to signal one of four locations on the screen, where the respective item had been presented during study. These authors employed the contrast between items that were remembered together with a correct location as opposed to those items without a correct location judgment as a measure of recollection. This contrast revealed greater activity in the right hippocampus and left prefrontal cortex for recollected items as opposed to those for which contextual information was forgotten. This finding indicates a role for the hippocampus in the retrieval of episodic information beyond that required for simple item recognition.

A similar finding was reported by Dobbins and colleagues (Dobbins et al., 2003). In this study, subjects were asked to encode words in one of two study tasks. During source recollection, subjects had to judge which of two words had been encoded in a particular encoding task. Correct source judgments were associated with more activity in the hippocampus and adjacent cortex than were incorrect source judgments.

Other studies examined brain activity associated with a familiarity decision, which is often associated with item memory without retrieval of context. In a recent meta-analysis of four event-related fMRI studies using different kinds of study material (Henson et al., 2003), old items were consistently found to elicit less MTL activity than new items. The effects varied in their spatial extent and degree of lateralization, but included a common region identified as right anterior entorhinal and/or perirhinal cortex. Further, the study of Cansino and colleagues mentioned above (Cansino et al., 2002) found equivalent response reductions for recognized items regardless of the accuracy of the associated source judgment, thus demonstrating a dissociation between hippocampal and perirhinal retrieval effects. Consistent with these findings, levels of hippocampal and perirhinal activity elicited by items during study have been

reported to predict subsequent source and recognition memory performance, respectively (Davachi et al., 2003).

The prefrontal region most consistently associated with retrieval success in the results of event-related studies is the anterior prefrontal cortex. In contrast to the findings from blocked design studies, this effect was more often found on the left than on the right. The findings of Henson and colleagues (Henson et al., 1999) that left prefrontal cortex was more active for recognized items accorded 'remember' than 'know' judgments suggests that this region is involved with the processing of retrieved information with a relatively high level of episodic content.

The other prefrontal region activated in some of the event-related studies mentioned above is dorsolateral prefrontal cortex. This activation was mostly detected during tasks with demands that exceed those of simple recognition, e.g. when subjects were required to make an introspective judgment about the recognition decision (Eldridge et al., 2000; Henson et al., 1999). Thus, activity in this region might be related to post-retrieval demands additional to those imposed by simple recognition judgments, possibly operating on the products of retrieval.

Concerning further brain regions involved with contextual retrieval, in the majority of the studies mentioned above, lateral and medial parietal cortex were found to exhibit greater activity for items eliciting successful relative to unsuccessful retrieval, regardless of the exact form of the retrieval task. In most studies, the lateral parietal activations were lateralized to, or at least more extensive, on the left. These findings are consistent with a number of previous studies in which retrieval success was investigated with blocked designs and, broadly speaking, with two meta-analyses of studies employing such designs (Habib and Lepage, 1999; Lepage et al., 1998). Findings from the studies by Eldridge and colleagues (Eldridge et al., 2000) and Henson and colleagues (Henson et al., 1999) which showed that left lateralized parietal activity was greater for items accorded 'remember' than 'know' responses suggest that activity in this region may be related to the amount of episodic information retrieved in response to the test item.

In contrast to the findings for frontal and parietal regions, activation of the MTL in recognition memory is less consistently reported. In the study by Eldridge and colleagues (Eldridge et al., 2000) mentioned above, activation of the MTL was obtained for test items which elicited strong episodic recollection. This finding is consistent with

the proposal that retrieval-related hippocampal activity is associated specifically with this form of memory (Rugg et al., 1997; Schacter et al., 1996a) and more generally, with the view that the hippocampus is specifically involved with episodic memory rather than memory based on non-episodic information such as item familiarity (Aggleton and Brown, 1999). In contrast, old/new decisions can be made on the basis of an acontextual sense of familiarity in the absence of - putatively hippocampally mediated - retrieval of a study episode (Aggleton and Brown, 1999; Yonelinas, 1994). This possibility seems unlikely however to account fully for the inconsistent findings concerning MTL activations in fMRI studies. Also, it has been suggested that item familiarity, the 'non-recollective' basis for recognition, depends mainly upon the perirhinal cortex (Aggleton and Brown, 1999). Therefore retrieval related activation should be found in anterior MTL in cases when recognition is based on familiarity.

Possibly, these seemingly inconsistent findings might reflect the limitations of the fMRI method, since regions in anterior MTL are especially vulnerable to susceptibility artifacts. Another possibility is that the null findings are a consequence of the neural dynamics of the hippocampus, in that retrieval-related neural activity might not generally give rise to changes in BOLD contrast large enough to be detected by fMRI. Finally, the lack of positive findings might be attributed to the fact that MTL activity during retrieval is often overshadowed by encoding related activity. According to this argument (Rugg et al., 1997, but see Gabrieli et al., 1997), the failure to find differential activity for contrasts between responses to old and new items reflects the fact that MTL structures are active both in support of retrieval of old information, and encoding of new information supplied by novel items (Stark and Squire, 2000a; Stark and Squire, 2000b).

2.3 Overview of thesis

This thesis presents two event-related fMRI studies which examine episodic memory processes in the intact human brain. Both memory formation and memory retrieval are studied, but the main emphasis lies on retrieval from episodic memory and subprocesses thereof. Concerning anatomical localization, the main area of interest is the MTL. In this introductory chapter the memory systems of the brain have been introduced. Apart from a short description of MTL anatomy, a review of functional imaging studies of memory encoding and retrieval as well as source memory has been given. The main focus was put on findings from fMRI studies, especially from studies

employing an event-related design. This review clearly demonstrates the suitability of fMRI, and especially event-related fMRI for measuring responses in the MTL.

In chapter 3, the principles of fMRI are introduced. The physics of magnetic resonance as well as the neurophysiology underlying the BOLD signal are described. These are the measures of neural activity in the experiments described in this thesis. The second part of chapter 3 outlines the analysis of fMRI data. Spatial preprocessing of fMRI images is described as well as the statistical models employed in making inferences about task-related regional brain activations.

Chapters 4 and 5 each present one event-related study on episodic memory. In both studies, the same stimulus material, namely complex visual material in form of real-world photographs is used. Also, in both studies, a rapid event-related fMRI design is employed, making it possible to study the formation of episodic memory and retrieval from memory in a common experiment.

The main goal of the study described in chapter 4 relates to the investigation of common neuronal correlates of successful memory formation and retrieval from memory. In this experiment, healthy subjects were scanned while they memorized real-world photographs and subsequently tried to recognize them within a series of new photographs. The results confirm earlier findings in that activity in the MTL and inferior prefrontal cortex correlates with declarative memory formation as defined by the subsequent memory effect, stronger responses to subsequently remembered than forgotten items. Additionally, the findings of this event-related study confirm that activity in specific regions within the parietal lobe, anterior prefrontal cortex, anterior cingulate and cerebellum correlate with recognition memory as measured by the conventional old/new effect, stronger responses for hits than correct rejections. To obtain a purer measure of recognition success, two recognition effects are then introduced by comparing brain responses to hits and misses. The positive recognition effect (hits > misses) reveals a prefrontal, parietal, and cerebellar contribution to recognition, and in line with electrophysiological findings, the negative recognition effect (hits < misses) reveals an anterior medial temporal contribution. Finally, by the use of a conjunction analysis, temporal and cerebellar brain areas are identified that support both declarative memory formation and retrieval. For matching operations during recognition, these areas may re-use representations formed and stored locally during encoding.

The event-related fMRI study presented in chapter 5 was designed to further investigate subprocesses within recognition memory, i.e. retrieval processes associated with contextual retrieval and item recognition. The same stimulus material was used, but now a source memory task was employed to test the hypothesis that distinct MTL operations are associated with either contextual retrieval or item recognition. The positive source memory effect, the difference in brain activity between hits with and without correct source judgment, reveals bilateral MTL activation, centered in the hippocampus. In contrast, the negative item recognition effect, a decrease of activity for hits with incorrect source judgment as opposed to misses identified the anterior MTL, probably the anterior parahippocampal gyrus. Hence, this data show distinct MTL operations that are differentially related to contextual retrieval and item recognition. While an activity increase in the hippocampus is accompanied by successful recollection of contextual information, an activity decrease in the rhinal cortex may provide a familiarity signal that is sufficient for successful item recognition.

Chapter 6 concludes the thesis with some concluding remarks on the findings from the two studies presented in chapters 4 and 5.

2.4 List of Abbreviations

APFC	anterior prefrontal cortex	(page 73)
BA	Brodmann area	(page 10)
BOLD	blood oxygen level dependent	(page 14)
DLPFC	dorso-lateral prefrontal cortex	(page 72)
efMRI	event-related functional magnetic resonance imaging	(page 14)
EEG	electroencephalography	(page 37)
EPI	echo-planar imaging	(page 44)
ERP	event-related potential	(page 14)
fMRI	functional magnetic resonance imaging	(page 5)
FWHM	full width at half maximum	(page 63)

GRE	gradient-recalled echo	(page 44)
GRF	Gaussian random field	(page 53)
HRF	hemodynamic response function	(page 51)
ISI	interstimulus interval	(page 27)
MEG	magnet encephalography	(page 37)
MRI	magnetic resonance imaging	(page 37)
MTL	medial temporal lobe	(page 5)
NMR	nuclear magnetic resonance	(page 38)
PET	positron emission tomography	(page 14)
rCBF	regional cerebral blood flow	(page 14)
RF	radio frequency	(page 39)
SE	spin echo	(page 44)
SNR	signal-to-noise ratio	(page 37)
SPM	statistical parametric map(ping)	(page 46)
TE	time to echo	(page 41)
TR	repetition time	(page 44)

3 Materials and Methods

3.1 Functional Magnetic Resonance Imaging

3.1.1 Non-invasive neuroimaging techniques

A variety of non-invasive neuroimaging techniques are available in brain research today. Recording the electrical activity of the human brain using scalp electrodes, a technique referred to as electroencephalography (EEG) is widely used in clinical practice and experimental neuroscience. This non-invasive technique is, however, limited by the inability to precisely localize the source of electrical activity. Magnet encephalography (MEG), a non-invasive technique which records the minute fluctuations in magnetic fields produced by electrochemical activity in the brain, provides better spatial resolution than scalp-recorded EEG.

However, at present the most widely used techniques for mapping functional neuroanatomy are those that employ a metabolic metric to indirectly measure neuronal activity. The two principal techniques are PET and fMRI. PET uses exogenous radio labeled substances injected into the bloodstream to measure rCBF, whereas fMRI relies on endogenous contrast mechanisms to produce a measure of local levels of blood oxygenation, the BOLD signal. The temporal and spatial resolution of the BOLD signal is better than those afforded by PET measurements of rCBF. Therefore all data in this thesis were acquired using fMRI. Functional brain imaging with fMRI refers to the use of magnetic resonance imaging (MRI) equipment to detect regional changes in cerebral metabolism or blood flow, volume or oxygenation as result of task activation. The technique most frequently used today utilizes BOLD contrast, which makes use of the differing magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) blood. These differences in magnetic susceptibility cause small, yet detectable changes in susceptibility-weighted MRI intensity, but the signal-to-noise ration (SNR) of the BOLD effect is low. Still, modern rapid image acquisition techniques permit statistical analyses for the determination of brain activity foci by generating data sets with hundreds of images for each slice location.

3.1.2 The physics of NMR and MRI

Magnetic resonance imaging is based on the physics of nuclear magnetic resonance (NMR), a property of atomic nuclei, which has a long history of use in chemical analyses. The NMR phenomenon is based on the quantum mechanical property of nuclear spin, i.e. the fact that protons possess a magnetic moment and angular momentum. Among the most commonly used nuclei are ^1H , ^{13}C , ^{19}F , ^{23}Na and ^{31}P . For imaging in biological systems, ^1H - or 'proton' NMR is the most common, primarily due to its high concentration in the human body and high sensitivity. In the absence of a magnetic field, the individual spins are randomly oriented and the bulk material has no net magnetization.

When, however, the object to be imaged, e.g. a human body, is placed in a large static magnetic field the magnetic moments associated with nuclear spin tend to align themselves either parallel or anti-parallel to the static field. This is equivalent to spins residing in low or high energy states, respectively. The combined alignment of all of these protons results in a net magnetic moment; a subject placed within a magnetic field becomes 'magnetized'.

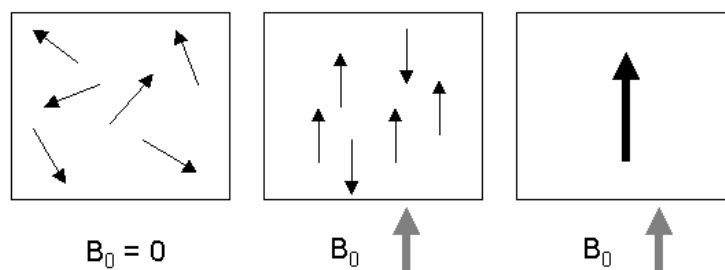


Figure 3-1: Randomly oriented magnetic moments aligning with an applied magnetic field to form a net magnetization (adapted from Shild, 1990).

Since this magnetization is aligned parallel to the static magnetic field, it is called longitudinal magnetization. In biological tissue, this magnetization is exceedingly small, and generally not observable. Because of the angular momentum, the spin, rather than simply aligning with magnetic fields, the individual nuclei precess about it, much as a spinning top would do. The precessional rate, or frequency, is characteristic of the atomic nucleus and is proportional to the strength of the magnetic field. This is called the Larmor relationship:

$$(1) \quad \omega_0 = \gamma \cdot B_0$$

ω_0 is the precessional rate, B_0 is the strength of the applied magnetic field, and γ is a proportionality constant specific to the nuclear species. For example, with ^1H protons, $\gamma = 42.58 \text{ MHz/T}$. For a magnetic field of 1.5T the resonant frequency would therefore be 63.76 MHz. The resulting magnetization can be decomposed into the sum of a stationary – or longitudinal - and a rotational – transverse - component.

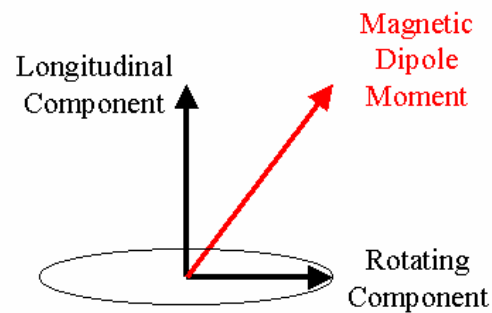


Figure 3-2: The rotating magnetic moment of the proton can be decomposed into a longitudinal component along the applied magnetic field and a transverse component orthogonal to it and precessing about it (adapted from Shild, 1990).

If an oscillating magnetic field at a resonance frequency similar to those of the precessing protons is applied to the object, the spins will absorb energy and become excited. The oscillating magnetic field is called a radio frequency (RF) field, because the frequencies are similar to those used in radio transmission. This process, known as excitation, results in the magnetization being partially or completely tipped into the plane perpendicular to the main magnetic field. In other words, the longitudinal magnetization is reduced as some of the protons are now aligned antiparallel to the main magnetic field. Moreover, the RF pulse causes the protons to precess together, or 'in phase', forming a so-called transverse magnetization, precessing around the static magnetic field at its resonance frequency given in equation (1) above. A coil placed near to the object can detect this precessing magnetization to form an image. These fundamental principles were elucidated more than fifty years ago; among the seminal contributions were those of Felix Bloch (Bloch, 1946) and Erwin Hahn (Hahn, 1950).

Following excitation, magnetization returns to its equilibrium state at an exponential decay rate. This process is called relaxation and consists of both longitudinal and transversal relaxation processes. Therefore, two fundamental temporal parameters are used to describe the MRI signal.

T1 relaxation

Spin-lattice or longitudinal relaxation describes the rate at which the nuclei, once placed in the magnetic field, exponentially approach the equilibrium state, with the magnetization $M_z(t)$ being described by the formula:

$$(2) \quad M_z(t) = M_0 \cdot \left(1 - e^{-t/T_1}\right)$$

where M_0 is the equilibrium magnetization. This exponential process is described by the time constant T_1 . Protons that have been excited to the higher energy state dissipate this energy to molecules of the surrounding structure, the so-called 'lattice', as heat. Protons returning to the lower energy state cause a regrowth of the magnetization vector along the main axis. The exact composition of the environment will affect the constant T_1 . For example, the protons in water have a longer T_1 than those in fat, because the carbon bonds in fat resonate near the Larmor frequency, which facilitates the transfer of energy to the lattice. In the human brain, grey mater contains approximately 71% water, while white matter has a water content of about 84%. This means that T_1 effects can be used to provide contrast between these two tissues.

T2 relaxation

Spin-spin or T_2 relaxation describes the disappearance of coherence of the magnetic moment in the xy plane (the transverse magnetization M_{xy}), occurring at a different rate to the recovery of longitudinal magnetization. The term spin-spin refers to the fact that interactions between protons determine the rate of T_2 relaxation. No energy is lost; rather, in spin-spin relaxation, energy is exchanged between protons, and there is a loss of 'order' or entropy. As neighboring spins pass energy from one to another, their rotations become desynchronized. Their slightly different rotation frequencies result in build-up of phase differences that gradually decrease M_{xy} . The loss of M_{xy} will always be faster than longitudinal relaxation ($T_2 < T_1$), because in addition to energy transfer to the lattice molecules, dephasing represents an extra mechanism of magnetization cancellation.

T2* relaxation

Dephasing will also occur if the applied magnetic field environment is non-uniform, as it usually is. In a non-uniform field, spins in different parts of the object will be rotating at different frequencies and quickly lose coherence and thus become dephased, possessing less net transverse magnetization because of the resulting cancellation. This loss of transverse magnetization due to inhomogeneous fields is often much shorter than the natural T2 signal decay and is characterized by another exponential time constant, T2'. The value of this time constant is determined by the technical implementation of the magnetic field and any field inhomogeneity caused by the properties of the object itself. T2* relaxation reflects the combination of T2 and T2' signal decays. fMRI sequences usually measure T2*, which generally ranges in the order of a few milliseconds to tens of milliseconds. As discussed below, the observed signal decay rate is strongly affected by blood oxygen content.

Pulse Sequences

For generation of an MRI image, not a single RF pulse, but a sequence of pulses is used. By carefully choosing the time between two pulses, such that for one type of tissue longitudinal relaxation has already been completed, while not so for another tissue type, these differences in longitudinal magnetization will show as a difference in signal intensity. This is how a T1-weighted image is generated. T2-weighted (or T2*-weighted) images are generated by the use of an additional RF pulse reversing the precession of the protons after a short period of time, TE (time to echo). By the use of this method, differences in the signal decay rate will become evident as differences in MRI image intensity: tissues with a longer T2 constant will have stronger signal than those with short T2, whose signal decay is more rapid. Modifications to the pattern of RF excitation – the so-called 'pulse sequence' - can modulate the contributions of the various relaxation processes to the resulting MRI signal.

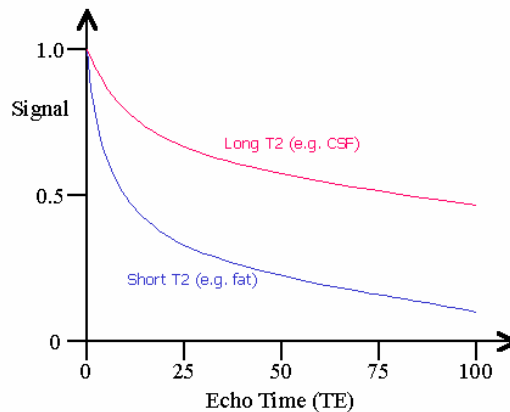


Figure 3-3: Immediately following an RF pulse, the signal decays at a characteristic rate, T2. At the time the MRI signal is sampled, the signal intensity from tissues with long T2 will be greater than that from short T2 tissues. Differences in effective T2 form the contrast basic form most fMRI methods (adapted Shild, 1990).

3.1.3 Image formation: frequency and phase encoding

Placing a sample within a homogenous magnetic field will not produce tomographic MRI images for the simple reason that all protons will experience roughly the same magnetic field. Thus, the frequencies of their emitted signal will all be identical. In MRI, a second magnetic field, which is called a gradient field, is applied so that protons within the sample will emit different frequency signals that are dependent on their spatial position. This is to say, as the magnetic field varies across the object, the resonance frequencies of spins - their Lamor frequencies - also vary. The spins' resonance frequencies are, therefore, determined by their location along the gradient axis. The number of spins resonating at a particular frequency determines the amplitude of that frequency in the spectrum of observable resonance frequencies. For each frequency component of the measured signal, the known value of the applied gradient strength and direction can be used to calculate the position from which the signal came. Therefore, the spectrum of a sample placed in a magnetic field gradient will be a projection of the spin density along the gradient axis (Lauterbur, 1973).

Combining a frequency gradient with a pulse of the appropriate frequency and bandwidth can excite a small slice of the sample. If the signal was acquired immediately after the slice selection, its spectrum would be a one-dimensional projection of the spin density for the spins in the selected slice. To produce a two-dimensional image of spin densities in the sample, encoding along a second axis is

required. While the first axis location is encoded by frequencies, location along the second axis is encoded by phase.

Location-dependent phase is achieved by temporarily switching on a linear gradient along the second axis. An effect of any gradient is an enhanced dephasing of transverse magnetization. During gradient application, local magnetization vectors will rotate with different frequencies depending on their position within the gradient. These spins will possess different histories, reflected in phase differences among their magnetization vectors dependent on their position along this second axis. The duration of the applied phase encoding gradient dictates the degree to which local transverse magnetization is dephased. A series of increasing gradient pulse lengths will enable a reconstruction of the frequencies giving rise to the dephasing of transverse magnetization. Hence, despite the fact that phase is being manipulated in the second axis, the amplitude of spin frequencies are again determined and expressed as a spin density projection along the phase encoding axis.

In summary, a typical imaging procedure starts with slice-selective excitation by the temporary application of a slice-selection gradient. Frequency encoding is determined by applying the frequency encoding gradient in the x-axis during acquisition. This is followed by phase encoding along a second orthogonal axis. During image acquisition, locations are encoded by both frequency and phase of the detected signal.

Step-wise increases in both gradients divide the sample into small cubes, so-called voxels (volume elements). Spins in one voxel experience the same frequency and phase encoding. Therefore, the signal of a given voxel is the sum of all spin contributions; hence spins within a voxel cannot be distinguished from each other. The resolution of the image depends on the size of the voxels, which is determined by the step size of the gradients. Increasing the size of the voxel increases the signal and therefore its SNR. However, larger voxels are more likely to encompass groups of spins with different behavior, which could evoke a misleading signal.

Image contrast is based on the difference in signal intensity between areas of different structure in an image. The signal intensity from a given voxel arises from a complex interaction of many different factors, including T1 and T2 relaxation times, proton density, RF pulse characteristics and magnetic susceptibility. Magnetic susceptibility refers to the fact that the net field experienced by a given nucleus depends on other magnetic spins in this nucleus' environment. The relative contribution of some of these

factors to the transverse magnetization can be manipulated by controlling the timing of the RF pulse. The timing parameters are the repetition time TR, the time required to acquire each image volume, i.e. the time between two consecutive 90° RF pulses, and the echo time TE. Therefore, a careful selection of the appropriate pulse sequence with adequate parameters is of high importance for the quality of the acquired images.

3.1.4 Ultra fast MRI sequences: Echo-Planar Imaging

The most commonly used MRI acquisition parameters comprise the so-called spin-echo (SE) sequences. However, SE sequences can take up to minutes to acquire each slice. Improving the speed of MRI acquisition is important for imaging dynamic processes. Although gradient-recalled echo (GRE) sequences brought imaging time down to seconds (Hasse et al., 1986), the introduction of echo-planar imaging (EPI; Mansfield, 1977) sequences meant that it was theoretically possible to obtain a whole brain image in a fraction of a second

The major difference between EPI and other MRI sequences is the way in which the data is sampled. Once acquired, MRI data is Fourier transformed. The Fourier transform converts MRI data from the time domain to the frequency domain. The two orthogonal gradients applied during phase encoding and frequency encoding mean that MRI data must be considered as lying in 2-dimensional frequency space (the so-called k-space) Typical MRI sequences sample one line of 2D k-space after each RF pulse, whereas EPI measures all lines of k-space after a single excitation. EPI therefore greatly reduces imaging time and makes it an ideal sequence for dynamic MRI techniques such as fMRI.

3.1.5 fMRI and the magnetic properties of blood

The cellular component of blood contains red blood cells, the erythrocytes, which contain hemoglobin, the protein responsible for oxygen transport. Oxygen binds to iron, which is a constituent of the hem component of hemoglobin. When hemoglobin has no oxygen bound, each hem group has a net magnetic moment because of iron's four unpaired electrons (Pauling and Coryell, 1936). As soon as oxygen is bound, this net moment disappears due to a redistribution of the available electrons between iron and oxygen. The magnetic state of blood will therefore reflect its level of oxygenation.

The $T2^*$ constant of water protons is influenced by interactions between the protons themselves and also by local magnetic field inhomogeneities caused by different magnetic properties of various molecules. Paramagnetic molecules, such as deoxyhemoglobin, have a local magnetic field gradient. This local gradient will contribute to the decay of transverse magnetization and consequently shorten the $T2^*$ decay time. Thus changes in the levels of deoxyhemoglobin should result in changes in $T2^*$. This effect was demonstrated empirically in vivo (Ogawa and Lee, 1990), showing that experimental manipulation of the oxy- to deoxyhemoglobin ratio - usually by hypoxia - produced detectable contrast changes in blood vessels, and, critically, within the tissue water surrounding vessels. Later it could also be shown that the difference in $T2^*$ signal produced by deoxyhemoglobin concentrations in vivo in humans was sufficient to act as a contrast source (Kwong et al., 1992; Ogawa et al., 1990). This signal source was termed blood oxygenation level dependent, or BOLD, contrast.

3.1.6 Neurophysiology and BOLD

It has been established for long that physiological functions in the brain regionally respond to brain activity, but still, the relationship between increases in neuronal electrical activity and change in blood oxygenation is not fully understood (Villringer and Dirnagl, 1995). Agreement, however, exists about the following causal chain of events. Task-related neuronal activity increases in specific areas of brain grey matter. Therefore, the rates of oxygen and glucose usage in these areas are increased (Hyder et al., 1997) causing a decrease in blood oxygenation in the capillary bed supplying the neuronally active tissue (Vanzetta and Grinvald, 1999) approximately 100ms after sensory stimulation. This in turn evokes a release of vasodilatory compounds, producing increased blood flow to, and dilation of, these capillaries (Duelli and Kuschinsky, 1993). The oxygen supply to electrically active tissue begins to exceed demand and blood oxygenation increases in the capillaries and venules that drain them (Villringer and Dirnagl, 1995). If enhanced neuronal activity continues, vascular and metabolic changes reach equilibrium in 1-3 minutes. If, however, neuronal activity returns to baseline, blood flow also returns to baseline, but blood volume in draining venules remains elevated for 30-60 s after blood flow has re-equilibrated (Mandeville et al., 1999). These observations suggest a triphasic model of the BOLD response. The initial, transient decrease in oxygenation produces a small, transient decrease in the BOLD response - the 'initial dip'. Next, local blood volume increases and thirdly, local blood flow increases approximately 500 ms – 1 s after sensory stimulation. The third

phase of the neurovascular response causes a much larger decrease in deoxyhemoglobin concentrations than the initial increase. The BOLD contrast increase evoked by this deoxyhemoglobin decreases is the signal that is typically measured in fMRI experiments.

As a consequence of this chain of events, the dynamics of the neurovascular response cause the BOLD signal to be delayed in time. Whereas neuronal dynamics occur in the millisecond time frame, the BOLD response takes a number of seconds to evolve. This means that although several fMRI images can theoretically be acquired in a second, the temporal smoothing of the underlying neuronal signal, affected by the BOLD response, ultimately dictates fMRI's effective temporal resolution.

A further point to keep in mind relates to the magnitude of signal changes. As blood occupies only a small fraction of grey matter, BOLD signal changes are of the order of a few percent at best. These small changes require the implementation of sophisticated image processing and analysis techniques to ensure that observations reflect true BOLD signal and not noise. These techniques are described in the next section.

3.2 fMRI Data Analysis with SPM

The general goal in using statistical parametric mapping (SPM) for the analysis of fMRI data is to localize a cognitive function to a specific brain region. Functional specialization is a fundamental principle of brain organization, but is important to acknowledge that the brain is also organized on the basis of functional integration. Using SPMs, inferences can be made about differences in comparing one group of subjects to another or, within subjects, about differences between cognitive conditions over a sequence of observations.

Statistical parametric mapping is a voxel-based approach, employing classical statistical inference to make some assertions about regionally specific responses to experimental factors. In order to assign observed responses to specific cortical areas it is obviously essential that the data must confirm to a known anatomical space. Before employing any statistics, it is therefore necessary to spatially transform individual brain data with the aim of reducing artifactual variance components in each voxel time series.

The imaging time series is first realigned to a common reference frame to correct for subject movement during scanning. After realignment, the data are transformed using linear and nonlinear mappings into a standard anatomical space (Friston et al., 1995a). This normalization procedure allows averaging data across subjects and permits data reporting within a standardized reference co-ordinate system. Following this preprocessing, a statistical model is created in order to draw inferences about differences in regional brain activity between different conditions (Friston et al., 1995c). Finally, these inferences must be corrected to guard against excessive Type 1 error.

Thus, the analysis of functional neuroimaging data involves many steps, which can be broadly divided into (i) spatial processing, (ii) estimation of the parameters of a statistical model and (iii) making inferences about those parameter estimates with their associated statistics.

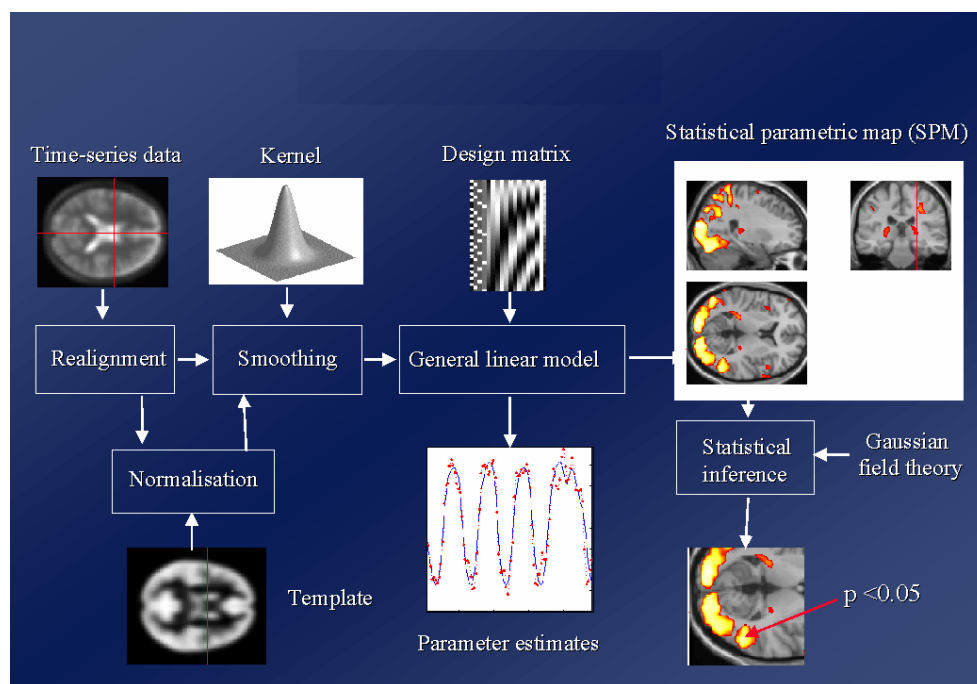


Figure 3-4: Overview over the transformations that start with an imaging data sequence and end with a statistical parametric map as employed (Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk).

3.2.1 Spatial preprocessing

3.2.1.1 Realignment

Spatial

A serious confound in functional imaging experiments, particularly in fMRI studies, arises from subjects' head motion, which, even with cooperative subjects, ranges on the order of up to several millimeters. Realignment, the correction for head movement, removes variance from a time series which would otherwise be attributable to error and hence decrease sensitivity to evoked effects, i.e. if movement is correlated with the cognitive task. The realignment procedure consists of two steps. Firstly, a set of six parameters of an affine 'rigid-body' transformation are estimated. This transformation minimizes the – sum of squared – differences between each successive scan and a reference scan, usually the first scan of the time-series or the mean of all scans. In three dimensions, a rigid body transformation can be defined by six parameters, typically three translations and three rotations about orthogonal axes (Friston et al., 1995a). In a second step, the appropriate transformation is applied to each single data scan by the use of standard interpolation methods.

Temporal

Apart from spatial realignment, temporal realignment must also be taken care of. In multislice acquisition, different slices are acquired at slightly different times. Most important in event-related studies, temporal realignment ensures that data from any given volume were sampled at the same time. This is usually performed only when (i) the temporal dynamics of the evoked response are of interest and (ii) the TR is sufficiently small to permit interpolation and is achieved using sinc interpolation over time.

3.2.1.2 Spatial Normalization

For group studies and to report spatial coordinates of activations it is essential, that the data conforms to some standard anatomical space, e.g., in the case of SPM, the space of the Talairach and Tournoux atlas (Talairach and Tournoux, 1998). A mean image of the series or some co-registered anatomical image is commonly used to estimate warping parameters mapping onto a template which conforms to this space. There are

several models in use for the mapping, including (i) a 12-parameter affine transformation, where the parameters constitute a spatial transformation matrix, similar to that used during realignment, but also including zooms and shears (ii) low frequency basis functions (a discrete cosine set or polynomials) where the parameters to be estimated are the coefficients of the basis functions employed or (iii) a vector field specifying the mapping for each control point, e.g. voxel. Estimation of the parameters of these models can be achieved in a Bayesian framework, trying to find the deformation parameters that have the maximum posterior probability given the data. The deformation is updated iteratively to minimize the sum of squared differences between the template and the deformed image and reflects the probability of actually getting that image if the transformation was correct. Prior information about the likelihood of a given transformation is incorporated by weighting the least squares (Ashburner et al., 1997).

3.2.1.3 Spatial Smoothing

After normalization, the fMRI data are smoothed by applying a Gaussian kernel, a point spread function, of known width to each voxel. The motivations for spatial smoothing are fourfold: (i) by the matched filter theorem, the optimum smoothing kernel is to correspond to the size of the expected effect. According to high-resolution optical imaging experiments, the spatial scale of the hemodynamic response is about 2 – 5 mm. An equivalent smoothing is suggested for most applications. (ii) By the central limit theorem, smoothing will render the error distribution of the data more normal and thus ensure the validity of inferences based on parametric tests. (iii) When employing Gaussian random field theory for making inferences, one of the assumptions is that the error terms are a reasonable lattice representation of an underlying smooth Gaussian field. This necessitates smoothness to be substantially greater than voxel size. (iv) In the context of inter-subject averaging, it is often necessary to smooth more, e.g. on the order of about 8 mm for fMRI data, to project the data onto a spatial scale where homologies in functional anatomy among subjects are expressed.

3.2.2 Statistical parametric mapping

3.2.2.1 The general linear model

Statistical parametric mapping, the method of analysis used for data analysis in this thesis, refers to the construction of spatially extended statistical processes to test

hypothesis about regionally specific effects (Friston et al., 1991). Each and every voxel is processed using a standard, univariate, statistical test. The resulting statistical parameters are then assembled into an image – the SPM. This SPM is interpreted as spatially extended statistical processes by referring to the probabilistic behavior of Gaussian fields (Friston et al., 1994b; Worsley et al., 1996; Worsley et al., 1992), in which ‘unlikely’ excursions of the SPM are interpreted as regionally specific effects and attributed to some cognitive process, which has been manipulated experimentally.

Statistical analysis of imaging data proceeds in two steps: (i) modeling of the data to partition observed responses into components of interest, confounds and error and (ii) making inferences about the interesting effects in relation to error variance, either by a direct comparison of the variance due to an experimental variation of interest to the error variance (F statistic) or by estimating the response or difference of interest divided by an estimate of its standard deviation (t statistic).

The general linear model comprises a variety of ways to analyze PET and fMRI data, including (i) simple t-tests on scans assigned to one condition or another, (ii) correlation coefficients between observed responses and boxcar stimulus functions in fMRI, (iii) inferences made using multiple linear regression, (iv) evoked responses estimated using linear time invariant models and (v) selective averaging to estimate event-related responses in fMRI. Mathematically they are all identical. The GLM is an equation

$$(3) \ y_j = x_{j1} * \beta_1 + \dots + x_{ji} * \beta_i + \dots + x_{jL} * \beta_L + \varepsilon_j$$

that expresses the observed response variable Y in terms of a linear combination of L explanatory variables X plus an error term (Friston et al., 1995c). The betas are unknown parameters, corresponding to each of the L explanatory variables for the jth observation of Y. The errors are assumed to be identically and independently normally distributed. For J observations of Y, the GLM can be expressed in matrix notation:

$$(4) \ y = X\beta + \varepsilon_j$$

The matrix X, which contains the explanatory variables, e.g. experimentally manipulated effects, is called the ‘design matrix’. These explanatory variables might, for example, consist of a boxcar smoothed with the hemodynamic response, or a confound of some kind. This matrix has one row per observation and one column per

model parameter, i.e. each column corresponds to some experimental effect or a confound - i.e. the explanatory variables. The number of parameters L is – usually - less than the number of observation J , hence the simultaneous equations implied by the GLM cannot be solved, as it is over determined. Therefore, some method is required for estimating parameters that 'best fit' the data. The method adopted in SPM is that of least squares.

Each column of X has an associated unknown parameter, some being of interest, e.g. the effect of a cognitive condition, and some of no interest and pertaining to confounding effects, e.g. the effect of being a particular subject. Inferences about parameter estimates are made using their estimated variance, which allows to test the null hypothesis that all the estimates are zero using F statistic to give an $SPM\{F\}$ or that some particular linear combination of the estimates is zero using $SPM\{t\}$. The t -statistic is obtained by dividing a contrast, specified by contrast weights of the ensuing parameter estimates, by the standard error of that compound.

An important assumption in the analysis of time-series is that the residuals are identically and independently normally distributed. However, the hemodynamic response is of longer duration than the typical scan acquisition time, which leads to serial correlations among the error terms. The GLM incorporates factors like correlation among the error terms and allows for some specified temporal filtering of the data. This leads to the notion of *effective degrees of freedom*, which are less than the conventional degrees of freedom, since temporal correlations reduce the effective number of independent observation (Worsley and Friston, 1995).

Temporal basis functions

The simple linear framework for making statistical inferences about activations in fMRI with the GLM is that evoked neuronal responses are convolved with a hemodynamic response function (HRF) to give the measured hemodynamic response (Boynton et al., 1996; Friston et al., 1994a). An impulse response function is the response to a single stimulus, measured at a series of time points after the input. Knowing the form the HRF can take is especially important, not at least because it allows for better statistical models of the data. The HRF may vary from voxel to voxel. To allow for different HRFs in different brain regions, the notion of temporal basis functions was introduced, to model evoked responses in fMRI (Friston et al., 1995b; Josephs et al., 1997). The basic

idea behind temporal basis functions is that the hemodynamic response induced by any given trial type can be expressed as a linear combination of several basis functions of peristimulus time. The convolution model for fMRI responses takes a stimulus function encoding the supposed neuronal responses and convolves it with a HRF to give a regressor that enters the design matrix. In contrast, when using basis functions, the stimulus function is convolved with all the basis functions to give a series of regressors. The associated parameter estimates are the coefficients that determine the combination of basis functions that best models the HRF for the trial type and voxel examined. A commonly used basis set consists of the canonical HRF and its derivatives with respect to the key parameters determining its form, i.e. latency and dispersion. Using this approach, differences among evoked responses can be partitioned into differences in magnitude, latency or dispersion, simply by testing for specific contrasts with an SPM{T} (Friston et al., 1995b).

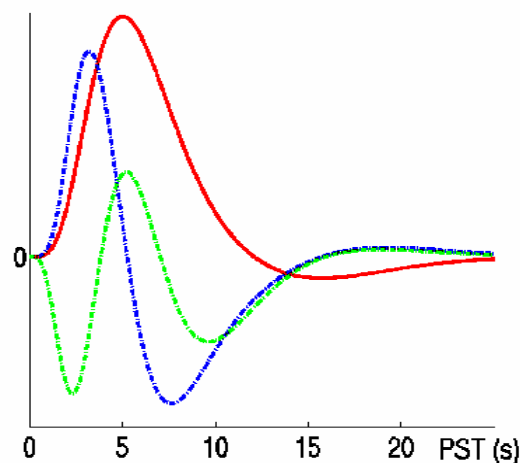


Figure 3-5: Temporal basis function used in the analysis of event-related fMRI data: canonical HRF (red), temporal derivative (blue) and dispersion derivative (green) (Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk).

3.2.2.2 Statistical inference

As already described, in an SPM the significance of brain activity is assessed in a voxel-wise manner. However, in many instances, one cannot have an a priori prediction for the precise voxel which is going to be activated in a particular condition.

Thus, there are two sorts of inferences using SPMs, depending on whether one has an a priori hypothesis about the particular region of the brain engaged. The uncorrected p-value associated with the height of the activation peak or the extent of a connected cluster of activated voxels in the SPM can be used to test anatomically constraint

hypotheses about effects in a particular brain region. A correction for multiple non-independent comparisons is necessary with a hypothesis which is anatomically not constrained. This corresponds to a null hypothesis that there is no effect anywhere in the brain. The theory of Gaussian random fields (GRFs) provides a way of correcting the p-values that takes into account the fact that neighboring voxels are not independent. With sufficiently smooth data, the GRF correction is less severe, and therefore more sensitive, than a Bonferroni correction. Essentially, a Bonferroni correction would control the expected number of false positive voxels, whereas GRF theory controls the expected number of false positive regions. To achieve this, essentially the GRF correction discounts voxel size by expressing the search volume in terms of smoothness or resolution elements (Resels) instead of in terms of single voxels. This intuitive perspective is expressed formally in terms of differential topology using the Euler characteristic (Worsley et al., 1992).

3.2.2.3 Conjunction Analysis

In the process of localizing cognitive functions to specific brain regions it is sometimes of interest to identify brain areas which are conjointly involved with several different cognitive conditions. A conjunction analysis assesses the conjoint expression of two or more effects. The conjunction analysis is based on the minimum t-field test statistic (Friston et al., 1999b). This essentially means that in each voxel the SPM is the minimum of the component SPMs defined by the multiple contrasts.

The distributional results used for minimum fields require the component SPMs to be identically distributed and independent. Independence is roughly guaranteed for large degrees of freedom and independent data by ensuring that the contrasts are orthogonal. It is important to note that it is not the contrast weight vectors per se that are required to be orthogonal, but the subspaces of the data space implied by the null hypotheses defined by the contrasts.

The null hypothesis for the minimum t-field test statistic states that there is no activation in any of the comparisons. A conjunction SPM comprises the minimum t-values of the component SPMs. These minimum t-values have their own distributional approximation which allows one to compute both corrected and uncorrected p-values, just like ordinary SPMs.

Thus, a conjunction analysis is simply a way of regimenting the evidence against a null hypothesis in the special case that the null hypothesis can be decomposed into several null hypotheses; the ensuing probability of the conjunction reflects the evidence against a family of null hypotheses. It is important to note though, that a conjunction analysis is not trying to make an inference about the consistency of the activation of several conditions of interest, it is merely testing the null hypothesis that the area did not respond in any of the contrasts.

3.2.2.4 Inference about subjects and populations

The critical issue in making inferences about groups of subjects is whether one wants to make an inference about the effect in relation to *within-subject variability* or with respect to *between subject variability*. This distinction relates directly to the difference between *fixed-effects analyses* and *random-effects analyses* (Friston et al., 1999a; Friston et al., 1999b; Holmes and Friston, 1998).

In the former, error variance is estimated on a scan to scan basis, assuming that each scan represents an independent observation and thus ignoring serial correlations. Here, the degrees of freedom are essentially the number of scans minus the rank of the design matrix. Conversely, in a random-effects analysis, the error variance is based on the activation from subject to subject, where the effect per se constitutes an independent observation and the degrees of freedom fall dramatically to the number of subjects minus one.

Both types of analysis are valid, but only in relation to the inferences being made: Inferences based on fixed-effects analyses are about the particular subjects studied. The fixed effects inference is drawn from the effect size relative to the within subject variability. The limitation of this type of analysis is that an effect size may be primarily driven by a few subjects (Friston et al., 1999a; Friston et al., 1999b; Holmes and Friston, 1998).

In contrast, random-effects analyses are usually more conservative, but allow inferences to be made about the population from which the sample of subjects was drawn. One observation per subject per condition is entered into a random effect analysis, usually a contrast of parameter estimates from a subject-specific fixed effects analysis. Hence the effect size is compared against the between subject variability. This type of analysis is, therefore, not at risk of being biased by strong effects in a

subset of subjects. Thus more subjects are required to achieve a significant result with random effects analyses, as the degrees of freedom depend on the number of subjects, a suitable minimum number of subjects being about 12. Random effects analyses are used for all analyses presented in this thesis.

3.3 Event-related fMRI

Event-related fMRI can be defined as the use of fMRI to detect transient hemodynamic responses to brief stimuli or tasks (Josephs et al., 1997). Event-related or trial-based measurement is already standard in electrophysiology, namely stimulus-locked event-related potentials. Previous functional imaging methods, such as PET, have limited temporal resolution necessitating measurement of prolonged states of brain activity. Such state-based designs were initially adopted in fMRI and referred to as blocked designs. Improvements in sensitivity and temporal resolution of fMRI have allowed an event-related approach. The event-related approach offers several advantages (Josephs and Henson, 1999):

- The order of trials can be randomized; hence the response to a trial is neither confounded by a subject's cognitive set nor systematically influenced by previous trials.
- Individual trials can be categorized or parameterized post-hoc according to a subjects' performance. An example is the categorization of event-related responses to presented pictures according to whether a particular picture was subsequently remembered or forgotten
- Some experiments involve events that cannot be blocked, such as 'oddball' paradigms where the event of interest is a stimulus that violates the prevailing context.
- Some events can occur unpredictably and can only be indicated by the subject.
- Event-related fMRI allows more direct comparison with other techniques such as ERP or psychophysics.
- Extensions to blocked designs. A state can be modeled, to first order, as a continuous train of events, each representing one trial within a block. This method also enables stimulus or response parameters to be modeled within a block.

As alluded to above, in analyzing event-related data, the explanatory variables are created by convolving a set of delta functions, indicating the onset times of a particular event, with a small set of basis functions that model the hemodynamic response to those events (Josephs et al., 1997). The approach adopted here, which is standard in SPM analyses of event-related fMRI data, was to employ a multivariate Taylor expansion of a mixture of gamma-functions which approximate a canonical HRF (Friston et al., 1998). The higher order basis functions in this expansion include the partial derivative of the HRF with respect to time (see Figure 3-5). This approach has the advantage that the parameter for each covariate is interpretable in terms of response magnitude – the canonical HRF - and latency – the temporal derivative.

4 Neural Correlates of Successful Declarative Memory Formation and Retrieval: The Anatomical Overlap

4.1 Introduction

As mentioned in chapter 2, event-related fMRI studies on episodic memory encoding have repeatedly shown that successful memory formation, measured as the difference in brain activity between subsequently remembered and forgotten items, is accompanied by activity increases in medial temporal and inferior prefrontal areas (e.g. Brewer et al., 1998; Wagner et al., 1998b; Kirchhoff et al., 2000; Davachi et al., 2001; Otten et al., 2001; Otten and Rugg, 2001a; Strange et al., 2002; Morcom et al., 2003; Paller and Wagner, 2002). Few studies have also examined activity decreases during successful memory encoding and found decreases in posterior cingulate, parietal and dorsolateral prefrontal areas to be predictive for subsequent memory (Otten and Rugg, 2001b). In examining data acquired during retrieval from episodic memory, event-related fMRI studies have mostly studied the so called old/new effect. Therefore, fMRI data is acquired during recognition memory tests and the difference in brain activity between hits and correct rejections is examined. The old/new effect has been associated with activations in the anterior prefrontal cortex, parietal cortex, insula, and medial-frontal areas including the anterior cingulate (e.g., Henson et al., 1999; Konishi et al., 2000; Donaldson et al., 2001a; Donaldson et al., 2001b; for review: Rugg and Henson, 2002). The event-related fMRI studies on episodic memory mentioned above have either been concerned with memory formation or memory retrieval, very few have examined both tasks in a single-experiment setting. The first aim of the present study is to replicate these subsequent memory and old/new effects, which were so far obtained in separate encoding and retrieval experiments, within a single study-test experiment.

Based on this empirical foundation, it is a further aim of the study to explore whether recognition success can be associated with both regional brain activity increases and decreases. Brain activity increases for hits as compared to correct rejections (the classical old/new effect) have been interpreted as related to the successful recovery of information from declarative memory (Donaldson and Buckner, 1999; Konishi et al., 2000; Donaldson et al., 2001a; Donaldson et al., 2001b). Still, there is no reason to assume that successful retrieval from memory can only be based on an increase of

activity. A reversed old/new contrast, however, cannot delineate cleanly a brain activity decrease related to recognition success, because it would be heavily contaminated by neural correlates of repetition priming (Buckner and Koutstaal, 1998; Donaldson et al., 2001a; Henson et al., 2000). Repetition priming is an implicit memory phenomenon that improves processing efficacy of repeatedly processed items and that is regularly accompanied by weaker brain activity to old as compared to new items (Tulving and Schacter, 1990; but see Henson et al., 2000). However, it has been shown that repetition priming does not support conscious recognition (Donaldson et al., 2001a). Thus, the question that remains open is: Can only repetition priming or also conscious recognition correlate with a decrease in neural activity (see Henson et al., 2003)? Further evidence comes from electrophysiological data in animals and humans. These data suggest that recognition can also be accompanied by brain activity decreases (Brown et al., 1987; Smith et al., 1986; Miller and Desimone, 1994; Brown and Aggleton, 2001; Fernández et al., 2001). As outlined above, the old/new effect can not simply be reversed to study activity decreases associated with successful recognition. Rather, in analogy to the subsequent memory effect, brain activity during test to hits is compared to brain activity to misses. In this contrast, henceforth called the *recognition effect*, all items are studied once before, but recognition success differs. Hence, a negative recognition effect (misses > hits) seems to be less contaminated by repetition priming than a reversed old/new effect, at least when primed and recognized items show stochastic independence in the sense that performance in the two tasks is uncorrelated at the level of individual items (Shimamura 1985). In addition, the recognition effect might generally be more closely related to recognition success than the old/new effect, because it does not include any difference related to the actual study status of the items. Thus, it is the second goal to identify increases and decreases in brain activity associated with recognition success as indexed by a positive and a negative recognition effect. A recent meta-analysis of four event-related fMRI studies employing different kinds of study material suggested that less anterior MTL activity is related to the amount of familiarity across a variety of stimulus materials (Henson et al., 2003). Another event-related fMRI study (Rombouts et al., 2001) found anterior parahippocampal activation in a comparison of new to often seen items, but this study did not control for performance. In line with these findings as well as with electrophysiological data (Smith et al., 1986; Miller and Desimone, 1994; Brown and Aggleton, 2001; Fernández et al., 2001), the hypothesis pursued in this study expects

to find a negative recognition effects in inferior temporal areas including the anterior MTL.

Given the encoding and recognition results of event-related fMRI studies reported above, there seems to be no or almost no overlap between brain areas involved in both memory formation and recognition (see also Gabrieli et al., 1997). Still, memory formation and recognition have not yet been studied in a single event-related fMRI experiment. If a brain area would support both these operations, neural representations stored locally during encoding could be re-used during recognition. Such a module would not only be efficient and intuitive, its existence is supported by electrophysiological data. For instance, the so called anterior MTL-N400, a negative component in event related potentials recorded invasively in epilepsy patients from the anterior MTL, probably from the perirhinal cortex (McCarthy et al., 1995) shows an amplitude difference between subsequently remembered and forgotten items during encoding (Fernández et al., 2002; Fernández et al., 1999b) as well as between correctly identified old and new items during a recognition memory test (Smith et al., 1986). Therefore, this neural node within the anterior MTL seems to be critically involved in both memory formation and retrieval. However, since most studies to date have examined either memory encoding or retrieval they have therefore not been able to directly compare encoding- and retrieval-related activations within subjects. The third aim of the present fMRI study is thus to characterize this node within a single study-test experiment by a functional imaging approach through the use of a conjunction analysis of the subsequent memory effect and either the positive or the negative recognition effect. Moreover, it is the aim to identify further brain areas whose activity is correlated with both successful memory formation and recognition by whole brain coverage.

Complex color pictures have been used as stimuli in a number of fMRI studies. For example (Stern et al., 1996) reported that the posterior aspect of the hippocampus and the parahippocampal gyrus were more active during the learning of visual scenes which had not been previously presented prior to encoding compared with familiar stimuli. Similarly, (Gabrieli et al., 1997) reported evidence that compared with the incidental encoding of familiar pictures, incidental encoding of novel pictures yielded greater posterior MTL activation situated bilaterally in parahippocampal cortex. As opposed to verbal material the encoding of pictorial material puts higher demands on the formation of new memories. For one, a real-world photograph is of much higher

complexity than a verbal stimulus would be. Further, since to a certain degree words are familiar already before the study phase of the experiment, they do not require the formation of completely new representations, while pictures used as stimuli do. Therefore both experiments reported in this thesis employ complex real-world photographs as stimuli.

4.2 Material and Methods

4.2.1 Subjects

Sixteen healthy volunteers without any significant abnormal neurological history participated in the experiment. All of the 8 male and 8 female subjects had normal or corrected-to-normal vision and were consistent right-handers according to the Edinburgh Handedness Inventory (mean EHI = 88, range: 73-100) (Oldfield, 1971). Their mean age was 30 years with a range of 20 to 49 years. Following approval by the Medical Ethics Committee of the University of Bonn, all subjects gave their written informed consent according to the Declaration of Helsinki (1991). They were paid for their participation.

4.2.2 Stimuli

Stimuli consisted of color photographs of either buildings or natural landscapes without any buildings (Figure 4-1 and Figure 4-2). For each category, 240 images were selected to be similar in complexity, brightness, and contrast.



Figure 4-1: Example of a stimulus: color picture of a building.



Figure 4-2: Example of stimulus: color picture of a natural landscape

4.2.3 Task

Study

During the study phase, 120 randomly selected pictures of buildings were randomly intermixed with 120 pictures of landscapes without any man-made buildings. These 240 stimuli were presented in a pseudo-randomized sequence for 800 ms each. The ISI was randomly varied between 2000 ms and 3000 ms, the mean ISI being 2500 ms. In between the presentation of the stimuli, subjects viewed a black screen. Sixty null events were randomly intermixed in between the stimuli. Since the null events also consisted of a black screen, subjects were not able to distinguish null events from the interstimulus baseline. Subjects were required to press one of the response keys for pictures showing any man-made building, and another response key for pictures showing landscapes without any buildings. The key press was executed with the index and little finger of the right hand. Subjects were also instructed to view the pictures carefully and to memorize them to be able to recognize them in a later memory test.

Recognition

The recognition phase was executed about five minutes after the study phase. During the break, subjects remained inside the MRI scanner and rested. During recognition, all the stimuli from the study phase were presented. 120 new color pictures of buildings and 120 new landscape stimuli were randomly intermixed. Again, stimuli were shown

for 800 ms each. The presentation rate was self-paced by subjects' responses, resulting in a mean ISI of 2065 ms (SD 229 ms). If for any specific stimulus the subject had not reacted within 3000 ms, the next stimulus was shown automatically. Subjects were instructed to press one of three response keys according to the following response categories: picture seen before with high confidence, picture uncertain to be seen before or not, picture not seen before with high confidence. Again, all key presses were executed with the right hand.

4.2.4 fMRI Data Acquisition

Whole-brain scanning was performed on a 1.5 T Symphony scanner (Siemens, Erlangen, Germany) using a standard circularly polarized head coil and standard gradients. The entire imaging session lasted about 1 hour. Scout images were first collected to align the field of view to the centre of the subject's brain. Then, for anatomical localization, a structural image was obtained by use of a T1-weighted 3D-FLASH sequence with the following parameters: repetition time TR = 11 ms, echo time TE = 4 ms, matrix size = 256 x 256, in plane resolution = 0.89 x 0.89 mm², field of view = 230 x 230 mm², number of slices = 120, slice thickness = 1.5 mm, no interslice gap. For echo planar imaging (Kwong et al., 1992; Ogawa et al., 1990; Mansfield, 1977) a T2*-weighted axial EPI-sequences with BOLD contrast and the following parameters was employed: repetition time TR = 2.95 s, echo time TE = 50 ms, matrix size = 64 x 64, inplane resolution = 3.43 x 3.43 mm², field of view = 220 x 220 mm², number of slices = 30, slice thickness = 4 mm, interslice gap = 0.4 mm. Functional images were positioned parallel to the AC-PC line. For each subject, two series of images were acquired. Each series included eight initial dummy scans to achieve equilibrium of longitudinal magnetization. The first of the two series comprised the study phase, while the second series was acquired during recognition. The encoding run consisted of 282 whole-brain acquisitions per subject. During recognition, 282 to 402 whole brain volumes per subject (mean number of scans: 336) were acquired, depending on the individual response times.

Stimuli were presented using the Experimental Run-Time System (ERTS; <http://www.erts.de/>). Pictures were back-projected onto a translucent screen, which was positioned about two meters opposite the magnet bore using an LCD-projector. Subjects lay in a supine position with their head stabilized by an individually molded vacuum cushion. They wore earplugs to reduce the scanner noise. Stimuli were viewed

by way of a mirror mounted on the head coil. Subjects received detailed instructions on the tasks before they were positioned inside the scanner. Before the study run as well as the recognition run, subjects were reminded of the instructions by way of an intercommunication system.

4.2.5 fMRI Data Analysis

The functional MRI images were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk, Friston et al., 1995c) implemented in MATLAB 6.1 (Mathworks Inc., Sherborn, MA, USA). Functional imaging runs were first preprocessed. The application of a multislice EPI sequence resulted in a time gap of approximately 100 ms between subsequent slices. To correct for these between-slice timing differences, induces by their different acquisition times, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time. Thereafter all images were realigned to the first image to correct for head movement. By using the transformation matrix calculated from the first EPI-scan of each subject, each volume was normalized to a standard EPI template volume, which is based on the MNR reference brain (Cocosco et al., 1997), and resliced using a sinc-interpolation in space. Afterwards, the normalized data with a resliced voxelsize of 4x4x4 mm were smoothed with an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel to accommodate further intersubject variation in brain anatomy. Finally, functional volumes were proportionally scaled to eliminate confounding effects of differences in global activity within and between subjects. The structural volumes were also normalized, and a mean of all participants' structural images was calculated to depict the localization of group activations. Population inference was made through a two-stage procedure: In the first-stage models, the volumes acquired during each session were treated as a time-series. These time-series were low pass filtered by a Gaussian function of 4 mm FWHM and high pass filtered with a high pass filter whose cut-off frequency was individually computed for each session and each participant (Holmes et al., 1997). The cut-off frequency was calculated as two times the maximal distance between two events of the same type. All analyses were restricted to trials on which encoding responses were correct. For each subject, stimuli in the study phase were individually classified according to three event-types: subsequently remembered, subsequently forgotten and subsequently classified as 'uncertain'. Then, for each subject individually, stimuli in the recognition phase were sorted into: hits, misses,

correct rejections, false alarms and items classified as 'uncertain'. The expected hemodynamic response at stimulus onset for each event-type was modeled by two response functions, the synthetic, canonical HRF (Friston et al., 1998; Josephs et al., 1997) and its temporal derivative. The temporal derivative was included in the model to account for the residual variance resulting from small temporal differences in the onset of the hemodynamic response, which is not explained by the canonical HRF alone (Friston et al., 1998). Through the inclusion of the temporal derivative in the model, a broader range of hemodynamic responses, e.g. those with a steeper increase than the canonical HRF function, can also be modeled. The functions were convolved with the event-train of stimulus onsets to create covariates in the general linear model. During recognition, the presentation rate was self-paced; hence reaction time to recognition trials was included in the model as a nuisance variable to discount the possibility of a confounding effect of differences in reaction times. Session-specific parameter estimates pertaining to the height of the HRF regressor for each effect of interest were calculated from the least mean squares fit of the model to the time series in each voxel. Parameter estimates for the temporal derivative were also computed, but not considered in any contrast. Subsequently, effects of interest were specified by appropriately weighted linear contrasts of the HRF parameter estimates and determined using planned comparisons on a voxel-by-voxel basis; the corresponding linear combination of parameter estimates for each contrast were stored as separate contrast-images for each subject. For the sake of the study goals, trials related to 'uncertain' responses were modeled by separate regressors, but not considered in any contrast. As outlined above, the following effects of interest were considered in the analysis: the *subsequent memory effect*, i.e. the difference in brain activity during study between hits and misses, the *negative subsequent memory effect*, i.e. the difference during study between misses and hits, the *priming effect*, i.e. the difference during recognition between new and old items irrespective of being correctly identified or not, the *old/new effect*, i.e. the difference during recognition between hits and correct rejections, the *positive recognition effect*, i.e. the difference during recognition between hits and misses and the *negative recognition effect*, i.e. the difference during recognition between misses and hits.

An SPM99 group analysis was performed by entering contrast images into one-sample t-tests, in which subjects are treated as random variables. Voxels with a significance level of $p < 0.005$ uncorrected belonging to clusters with at least 10 voxels are reported.

Since the subsequent memory effect and the recognition effect were computed bi-directionally, this effectively results in a two-sided threshold of $p < 0.01$. Activations are shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. For all images shown, coronal slices are ordered from posterior to anterior, numbered according to coordinates of Talairach and Tournoux (Talairach and Tournoux, 1998) and oriented according to the neurological convention with the left side of the brain displayed on the left side of the image. Further, activations are also shown overlaid onto a canonical brain rendered in 3D. The reported voxel coordinates of activation peaks were transformed from MNI space to the space defined by the atlas of Talairach and Tournoux (Talairach and Tournoux, 1998) by non-linear transformations (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>). To address further the question of overlap between areas involved in both encoding and recognition, a conjunction analysis of the subsequent memory effect and the positive and the negative recognition effect respectively was employed.

4.3 Results

4.3.1 Behavioral Data

During encoding, the building/landscape decision task was performed with a mean accuracy of 92% with a range of 85% - 98%. Incorrect responses were recorded for 5% of trials with a range of 2%-10% and no responses were given for 3% of trials with a range of 0% - 7% of all encoding trials. All trials with incorrect or no responses in the orientation task (building/landscape decision) were excluded from further analyses, because subjects might not have attended to these items. There was no significant difference between reaction times to building and landscape stimuli, with the mean reaction time for building stimuli being 735 ms (SD: 89 ms) and the mean reaction time for landscape stimuli being 739 ms (SD: 91 ms). We can therefore assume that there is no systematic reaction time difference between responses with the index and the little finger.

Reaction time differences during recognition can thus be attributed to experimentally induced effects. Recognition memory performance and reaction times are listed in Table 4-1.

	Old		New		
	Hits	Misses	Correct rejections	False alarms	Uncertain
Number	130	65	140	50	95
SD	28	23	23	19	62
RT (ms)	1382	1479	1462	1445	1727
SD	194	214	187	196	103

Table 4-1: Mean Recognition Performance and Reaction Times (RT) with their Standard Deviations (SD).

Accuracy of recognition was assessed by the difference in probabilities of a correct old judgment as compared to an old judgment for a new item, i.e. it was calculated as $Pr = \text{probability hit} - \text{probability false alarm}$. The mean recognition performance for stimuli depicting buildings was $Pr_{\text{building}} = 0.40$ (SD: 0.14), while the mean performance for landscape stimuli was $Pr_{\text{landscape}} = 0.43$ (SD: 0.15). Hence, the recognition performance did not differ between stimuli classes ($t_{15} = 1.019$, n. s.), but at $Pr = 0.41$ (SD: 0.13), it was well above chance level ($t_{15} = 13.01$; $p < 0.0001$). Collapsing across building and landscapes stimuli, a sufficient number of trials for each response category were available to reach an adequate contrast-to-noise ratio for the event-related fMRI analyses. The number of trials contributing to the analyses was 78 – 153 trials per subject for hits, 58 – 113 for misses, 93 – 170 for correct rejections, and 52 – 97 for false alarms.

An ANOVA comparing reaction times (Table 4-1) for hits, misses, correct rejections, and false alarms revealed a reliable effect of response category ($F_{3,45} = 8.42$, $p < 0.005$). Post-hoc paired-sample t-tests showed that reactions to correctly identified old items were faster than incorrect reactions to old items ($t_{15} = 3.78$, $p < 0.005$), correct reactions to new items ($t_{15} = 3.21$, $p < 0.01$), and incorrect reactions to new items ($t_{15} = 5.99$, $p < 0.0001$). All other post-hoc tests did not reveal any reliable difference (max $t_{15} = 1.51$, n. s.).

4.3.2 Imaging Data

In an exploratory analysis, encoding activity to pictures showing buildings was directly compared to encoding of pictures showing landscapes. Processing of building stimuli

compared to processing of landscape stimuli showed small bilateral activation in superior temporal areas, which was more pronounced on the left side. As shown in Figure 4-3, Figure 4-4 and Table 4-2, the maxima of these activations were located in BA 38 bilaterally. As shown in Table 4-2, the peak of the activation in the right hemisphere is located at Talairach and Tournoux (Talairach and Tournoux, 1998) coordinates x: 52, y: 8, z: -16. In the left hemisphere, the maximum is located at the coordinates x: -44, y: -4, z: -16.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right superior temporal gyrus	38	52	8	-16	4.26	13
left superior temporal gyrus	38	-44	-4	-16	3.92	17

Table 4-2: Maxima of the regions activated more for processing of stimuli depicting buildings as opposed to landscape stimuli during study ($p < 0.005$ uncorrected, minimal cluster size 10 voxels).

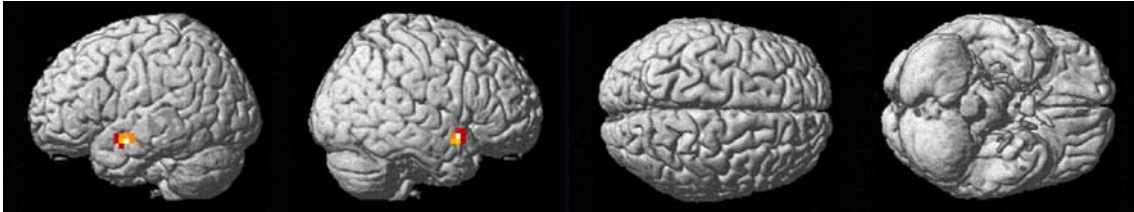


Figure 4-3: Regions activated more for processing of stimuli depicting buildings as opposed to landscape stimuli during study. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

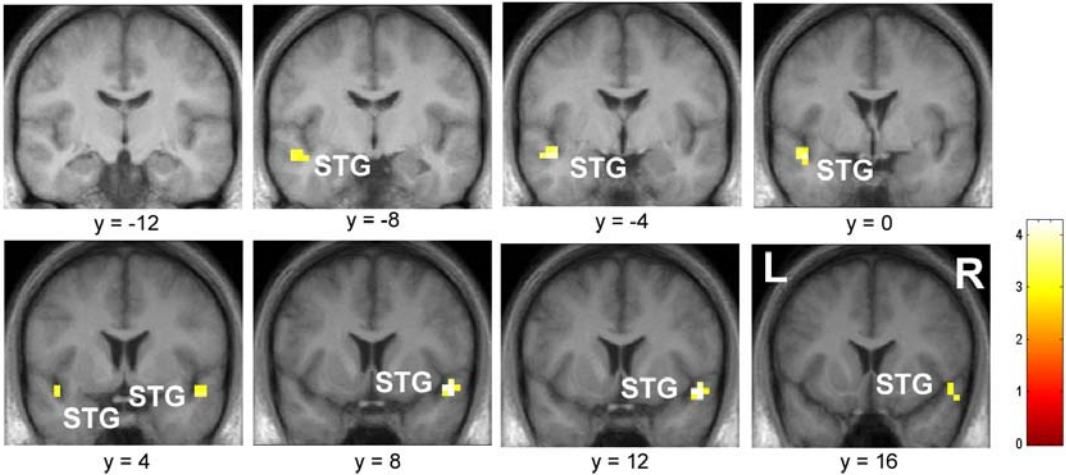


Figure 4-4: Regions activated more for processing of stimuli depicting buildings as opposed to landscapes stimuli during study. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. STG: superior temporal gyrus.

As shown in Figure 4-5, Figure 4-6 and Table 4-3 processing of landscape stimuli as compared to stimuli depicting buildings showed more activity in a small area in BA 9 of the right middle frontal gyrus (Talairach and Tournoux coordinates: x: 40, y: 20, z:

40). These findings may indicate a slightly higher degree of verbal coding for buildings and non-verbal visual-perceptual coding for landscapes (Kelley et al., 1998). However, these small differential effects are not of primary interest for the purpose of this study. Further, there is no difference in recognition performance, hence both stimuli classes were pooled together to increase statistical power for all further analyses.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right middle frontal gyrus	9	40	20	40	3.74	16

Table 4-3: Maximum of the region activated more for processing of stimuli depicting landscapes as opposed to building stimuli during study (p<0.005 uncorrected, minimal cluster size 10 voxels).

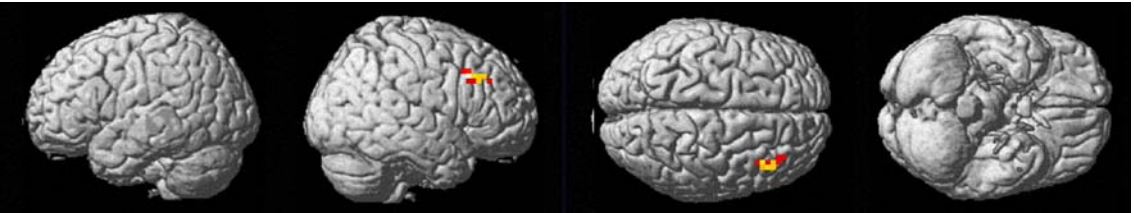


Figure 4-5: Region activated more for processing of landscape stimuli as opposed to stimuli depicting buildings during study. The activation map (p<0.005 uncorrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

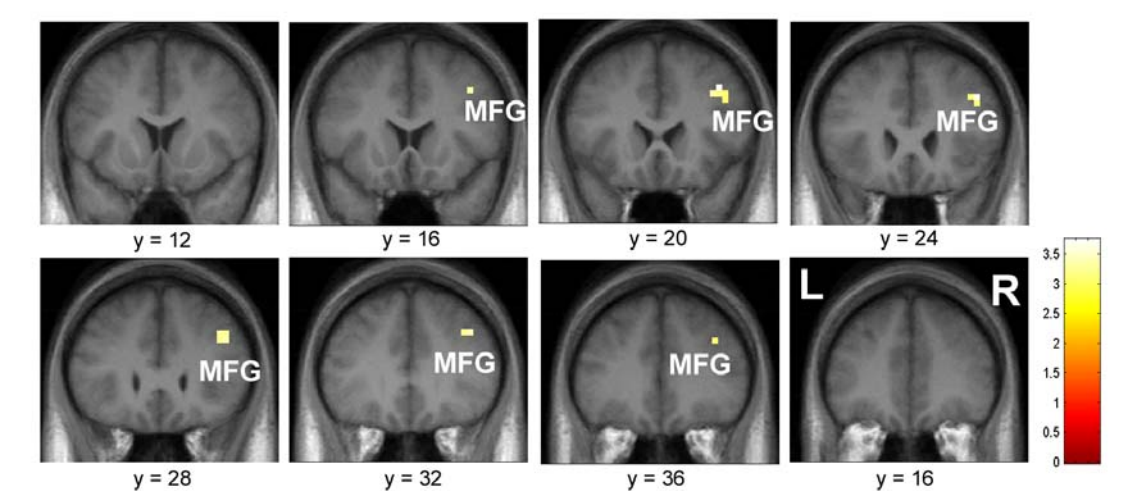


Figure 4-6: Region activated more for processing of landscape stimuli as opposed to stimuli depicting buildings during study. The activation map (p<0.005 uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. MFG: middle frontal gyrus.

The Subsequent Memory Effect

Initially, it is important to verify prior results regarding brain regions involved in successful formation of new declarative memories. Addressing this question requires a comparison between learning events that lead to the successful and unsuccessful formation of memories. As in previous studies, brain responses to each item were

acquired during the study phase. Then, contrasts were conducted to compare learning events that were subsequently remembered and those that were subsequently forgotten as measured by the subsequent recognition memory test during the second experimental run.

Figure 4-7, Figure 4-8 and Table 4-4 show brain regions that exhibit significantly more activity to subsequently recognized than forgotten items. In line with previous findings, this encoding network comprises bilateral medio-temporal and frontal activations. In both hemispheres, the medio-temporal activations extend over areas in the fusiform gyri, parahippocampal gyri and possibly the hippocampi. Activations extend into the inferior temporal gyrus bilaterally. The activations comprise BA areas 20, 28, 35, 36 and 37. In line with the HERA-model (Tulving et al., 1994), frontal activations were found in the left basal and lateral frontal cortex. This cluster extends into the inferior and middle frontal gyrus, comprising BA 9, 45 and 47.

Additionally, an activation cluster was found in the left parietal lobe. This cluster is centered in the left precuneus, but extends into the angular gyrus and the superior parietal lobule, covering BA 7, 19 and 39. Further, there was a small activation cluster in the right lingual gyrus and the right cuneus (BA 17 and 18). Overall, activations appear to be more pronounced in the left than in the right hemisphere.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left fusiform gyrus	20	-44	-48	-28	6.15	85
right fusiform gyrus	37	24	-56	-16	4.31	37
left parahippocampal gyrus	35	-20	-8	-36	4.15	11
right parahippocampal gyrus	35	36	-12	-36	6.60	27
left inferior frontal gyrus	47	-44	44	-12	4.56	36
left inferior frontal gyrus	45	-40	12	28	6.60	40
left precuneus	19	-28	-72	40	5.27	23
left inferior temporal gyrus	20	-52	-12	-28	4.81	15
right lingual gyrus	18	16	-96	-4	4.15	11

Table 4-4: Maxima of the regions activated in the *Subsequent Memory Effect*, i.e. regions activated more in case of successful as opposed to unsuccessful memory formation during encoding ($p < 0.005$ uncorrected, minimal cluster size 10 voxels).

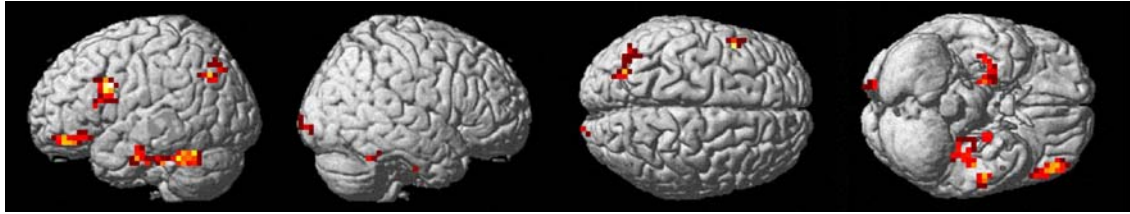


Figure 4-7: *Subsequent Memory Effect*. Regions activated more in case of successful as opposed to unsuccessful memory formation during encoding. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

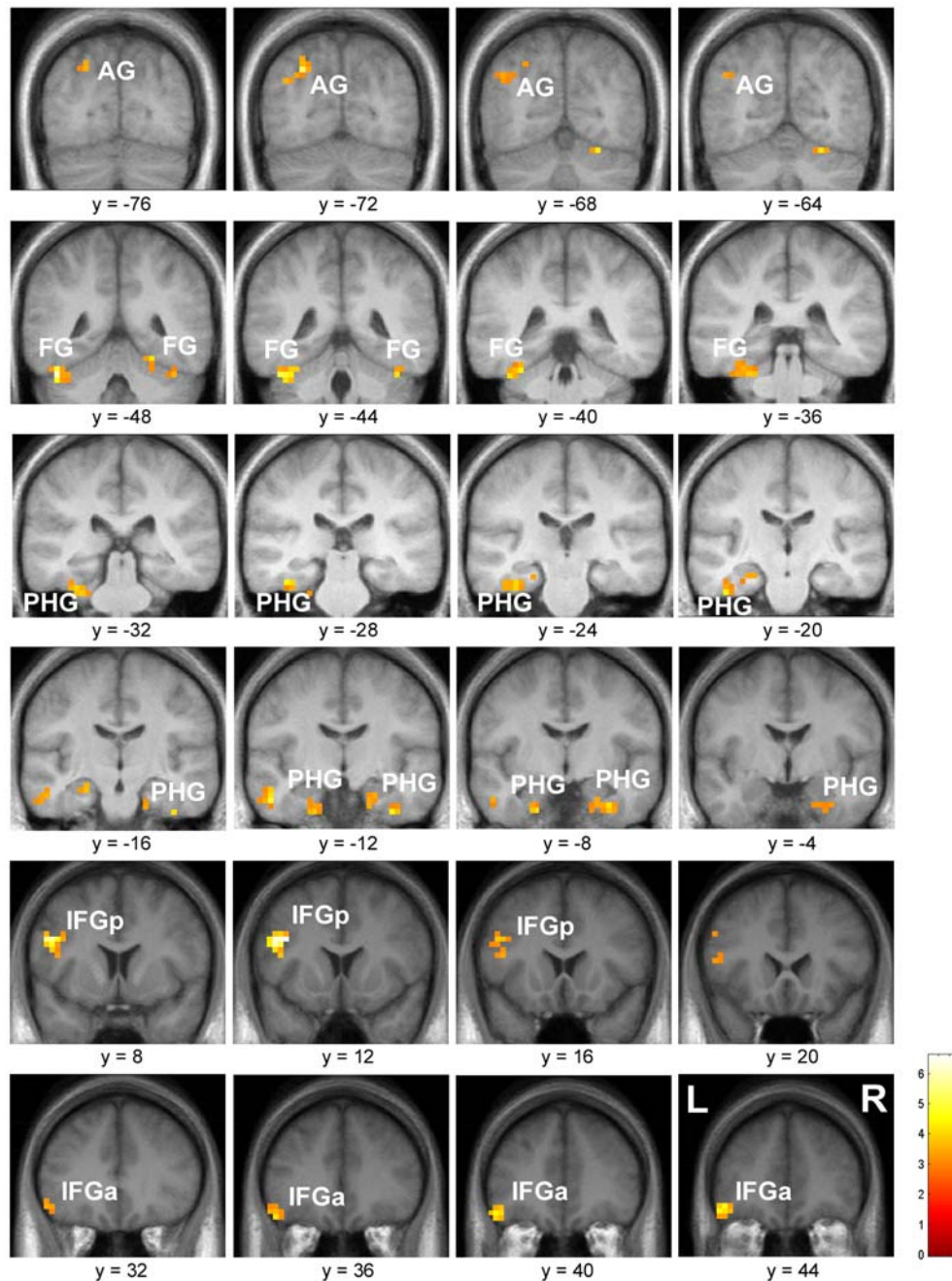


Figure 4-8: *Subsequent Memory Effect*. Regions activated more in case of successful as opposed to unsuccessful memory formation during encoding. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. AG: angular gyrus, FG: fusiform gyrus, IFGa: anterior aspect of the inferior frontal gyrus, IFGp: posterior aspect of the inferior frontal gyrus, PHG: parahippocampal gyrus.

The Negative Subsequent Memory Effect

In addition to areas predicting subsequent memory by an increase of activation, areas in which a decrease of activation is predictive for subsequent memory, were also identified. Figure 4-9 and Table 4-5 show areas that exhibit significantly more activity during learning for subsequently forgotten as opposed to subsequently remembered items. For this contrast activations were found in right medial parietal cortex, comprising the precuneus and the paracentral lobule, extending into BA 7 and 31. Further, there is a small activation cluster in left cingulate cortex (BA 24).

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right precuneus	7	8	-48	52	3.94	18
left cingulate gyrus	24	-16	4	36	5.30	11

Table 4-5: Maxima of the regions activated in the *Negative Subsequent Memory Effect*, i.e. regions activated more in case of unsuccessful as opposed to successful memory formation during encoding ($p < 0.005$ uncorrected, minimal cluster size 10 voxels).

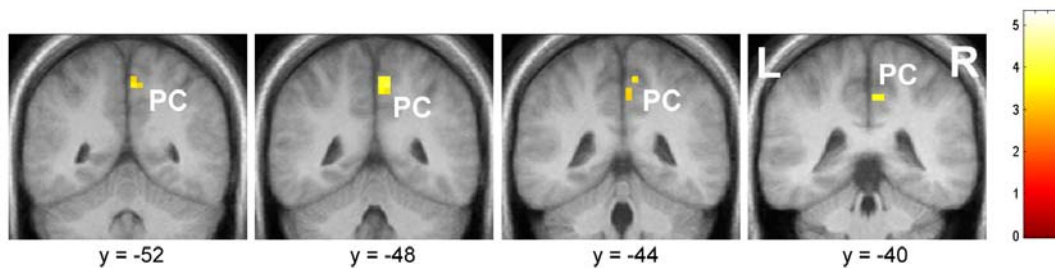


Figure 4-9: *Negative Subsequent Memory Effect*. Regions activated more in case of unsuccessful as opposed to successful memory formation during encoding. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. PC: precuneus.

Repetition Priming Effect

Repetition priming refers to an implicit memory phenomenon that improves processing efficacy of repeatedly processed items and is therefore accompanied by weaker brain responses to old as opposed to new items. Figure 4-10, Figure 4-11 and Table 4-6 show brain regions exhibiting a decrease of activation to previously seen stimuli as opposed to new ones. As expected, an effect of repetition priming was found in bilateral middle occipital gyri covering BA 18 and 19. Further, there was an activation cluster in the left lingual gyrus (BA 19).

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left middle occipital gyrus	19	-36	-92	8	5.15	17
left middle occipital gyrus	18	-20	-92	20	4.47	14
Right middle occipital gyrus	19	28	-84	0	3.68	12
left lingual gyrus	19	-32	-64	-4	4.81	15

Table 4-6: Maxima of the regions activated in the *Repetition Priming Effect*, i.e. regions activated more for new as opposed to old stimuli during test ($p < 0.005$ uncorrected, minimal cluster size 10 voxels).

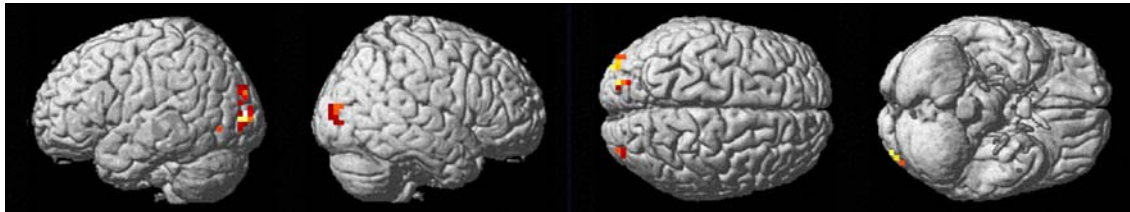


Figure 4-10: *Repetition Priming Effect*. Regions activated more for new as opposed to old stimuli during recognition. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

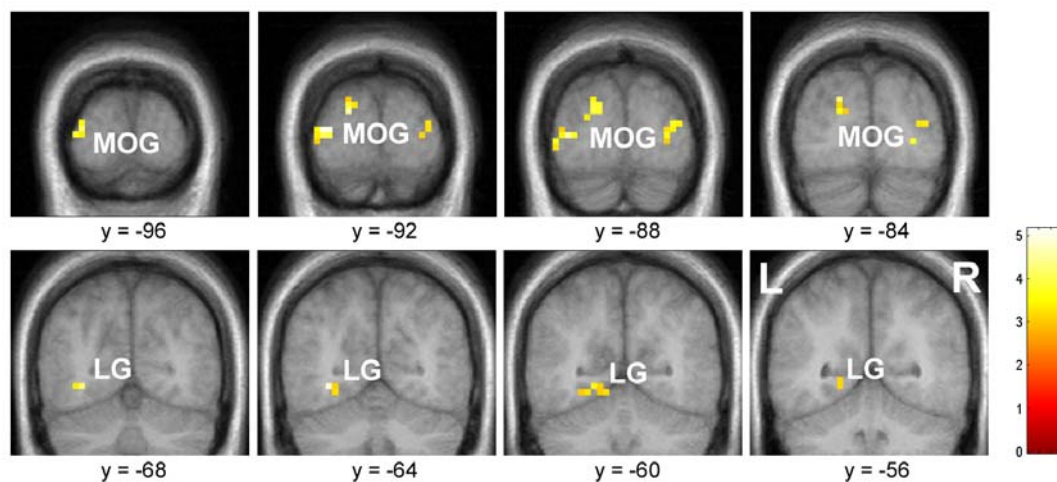


Figure 4-11: *Repetition Priming Effect*. Regions activated more for new as opposed to old stimuli during recognition. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. LG: lingual gyrus, MOG: middle occipital gyrus.

The Old / New Effect

Figure 4-12, Figure 4-13 and Table 4-7 show brain regions that exhibit more neural activity for hits than for correct rejections during recognition. For this contrast, correctly identified old items are compared to correctly identified new items. These areas comprise (1) A dorsolateral prefrontal cortex (DLPFC) area, which covers a medial-superior frontal area including bilateral superior frontal gyri medially and laterally, the anterior cingulate, and pre- as well as supplementary motor areas (BA 6

and 32); (2) an area in right anterior prefrontal cortex (APFC), located in the right superior frontal gyrus (BA 10); (3) bilateral, left lateralized areas in the parietal lobe extending into the superior and inferior parietal lobules (BA 7 and 40); (4) an area in the left insula cortex (BA 13); (5) and finally, bihemispheric activations in the cerebellum.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left superior parietal lobule	7	-32	-64	52	5.56	176
left inferior parietal lobule	40	-56	-32	40	5.05	19
right inferior parietal lobule	40	36	-40	40	5.26	53
right fusiform gyrus	37	40	-48	-16	5.37	10
left superior temporal gyrus	22	-60	-48	16	3.99	10
left cerebellum		-20	-56	-36	6.32	36
left cerebellum		-44	-60	-48	4.68	39
right cerebellum		20	-60	-36	4.18	22
right cerebellum		48	-64	-40	4.08	12
left insula	13	-36	-4	16	4.09	13
left precentral gyrus	6	-40	0	36	5.18	22
left superior frontal gyrus	6	0	16	56	6.03	94
right cingulate gyrus	32	-4	36	28	7.08	34
right superior frontal gyrus	10	32	60	16	5.53	17
right inferior frontal gyrus	47	32	20	-16	4.15	13
right middle frontal gyrus	32	12	12	44	3.86	11
left cingulate gyrus	23	-4	-12	24	4.79	27
Thalamus		-20	-24	12	5.31	42

Table 4-7: Maxima of the regions activated in the *Old/New Effect*, i.e. regions activated more for hits as opposed to correct rejections during test ($p < 0.005$ uncorrected, minimal cluster size 10 voxels).

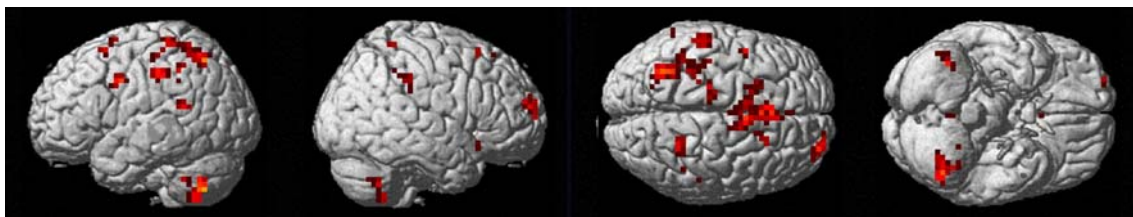


Figure 4-12: *Old/New Effect*. Regions activated more for hits as opposed to correct rejections during test. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

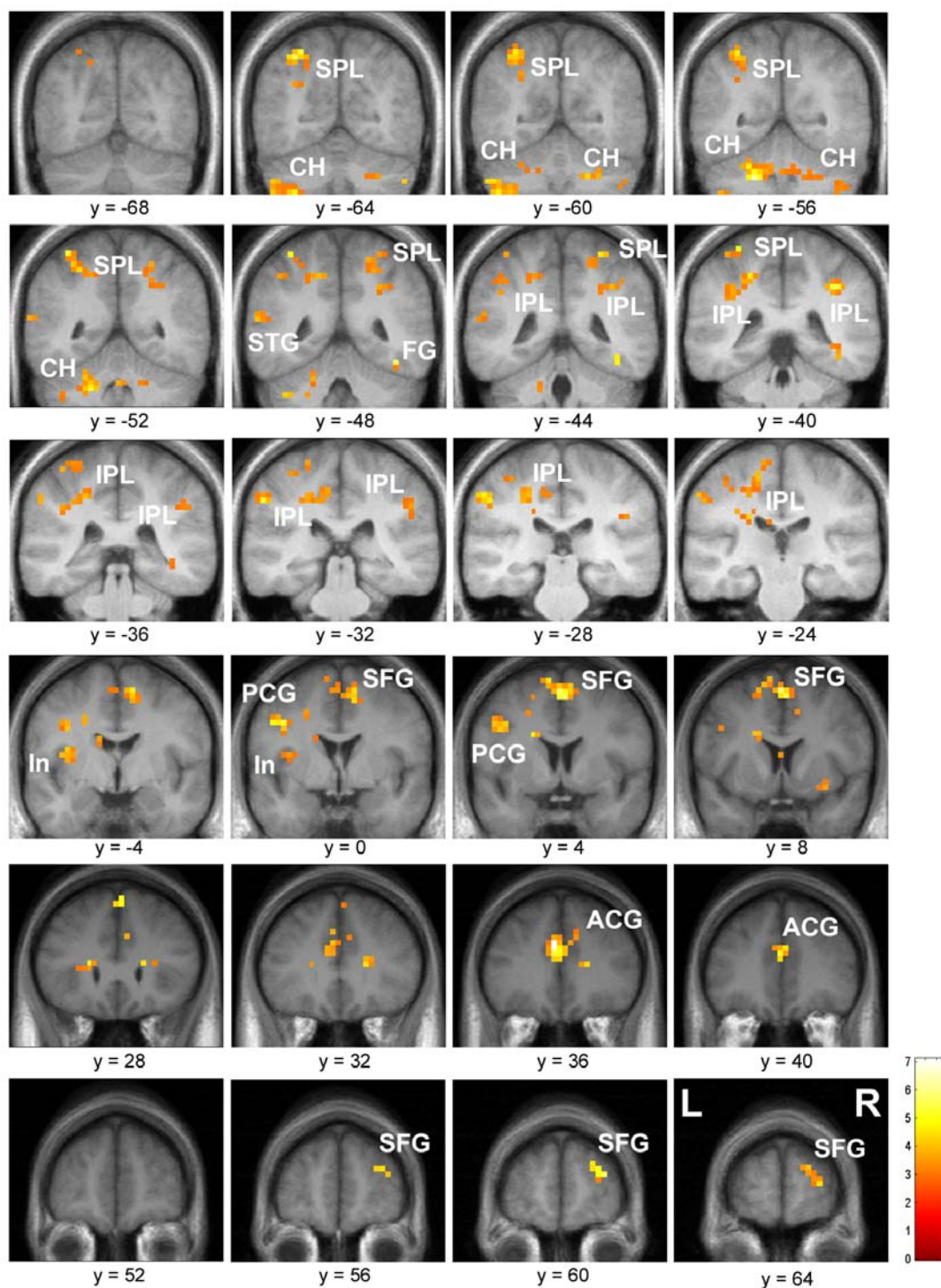


Figure 4-13: *Old/New Effect*. Regions activated more for hits as opposed to correct rejections during test. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. ACG: anterior aspect of the cingulate gyrus, CH: cerebellar hemisphere, In: Insula, IPL: inferior parietal lobule, PCG: precentral gyrus, SFG: superior frontal gyrus, SPL: superior parietal lobule, STG: superior temporal gyrus.

The Positive Recognition Effect

To explore in more detail brain areas engaged in successful memory retrieval, the positive recognition effect is employed which examines the difference in brain responses during test to hits to misses. This contrast, which is shown in Figure 4-14, Figure 4-15 and Table 4-8 reveals a set of activations which have a quite similar location as those seen in the old/new effect, but there are some differences: (1) The right prefrontal activation is centered in the middle frontal gyrus (BA 6) instead of area BA 10; (2) contrary to the cerebellar old/new effect, the cerebellar recognition effect appears to be stronger and more pronounced at midline structures like the vermis, the intermediate cerebellar hemispheres, and the tonsils and it is extended to the relay station for cerebellar afferents, the pons; and (3) there is an activation of the right angular gyrus, which is not seen in the old/new-effect. Nevertheless, the positive recognition contrast reveals a prefrontal-parietal-cerebellar network as the old/new contrast does.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right angular gyrus	39	40	-60	32	3.73	11
Vermis, cerebellum		0	-60	-20	4.82	42
left pons		-16	-48	-24	5.63	52
right middle frontal gyrus	6	16	-12	56	4.86	13
left cerebellum		-20	-72	-28	4.18	15

Table 4-8: Maxima of the regions activated in the *Positive Recognition Effect*, i.e. regions activated more for hits as opposed to misses during test ($p < 0.005$ uncorrected, minimal cluster size 10 voxels).

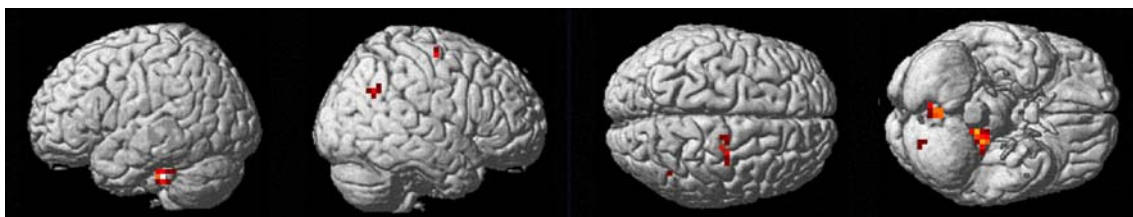


Figure 4-14: *Positive Recognition Effect*. Regions activated more for hits as opposed to misses during test. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

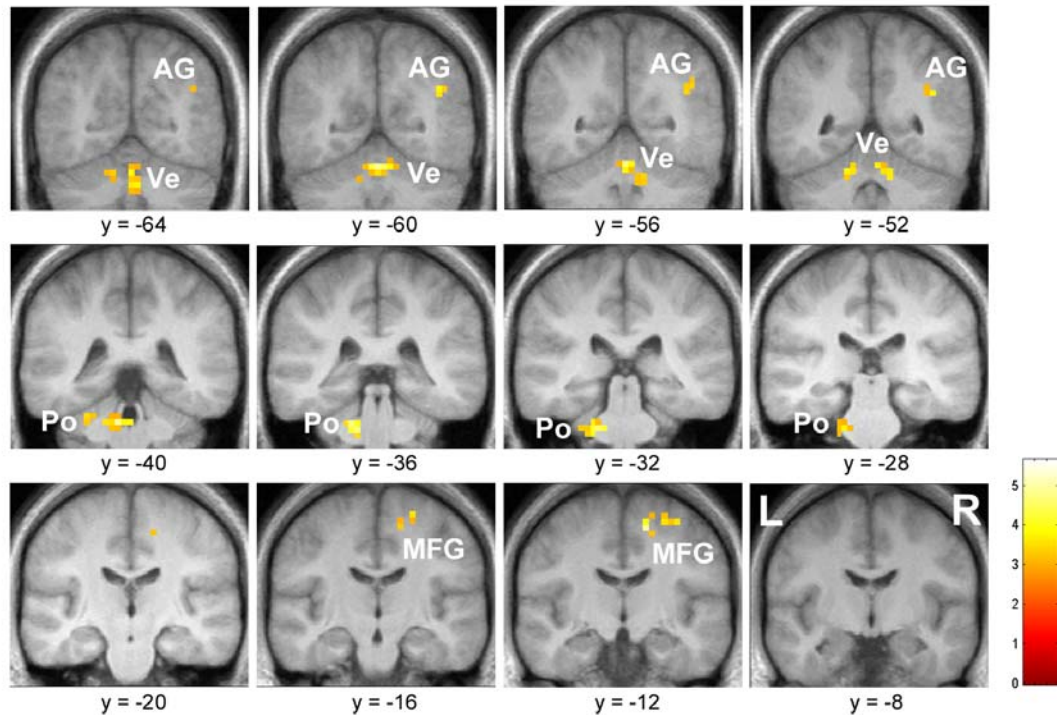


Figure 4-15: Positive Recognition Effect. Regions activated more for hits as opposed to misses during test. The activation map ($p < 0.005$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. AG: angular gyrus, MFG: middle frontal gyrus, Po: Pons, Ve: vermis.

The Negative Recognition Effect

Negative recognition effects were obtained by comparing brain responses to misses with responses to hits. As described above, this effect is not equally contaminated by repetition priming as a reversed old/new effect would be. Applying the same minimal cluster size as used for all other contrasts did not lead to a reliable negative recognition effect. However, considering clusters consisting of five voxels or more reveals a left anterior MTL activation, which is shown in Figure 4-16 and Table 4-9. The finding of this activation is exactly in line with the hypothesis which was formulated in the introduction based on electrophysiological findings in humans (Smith et al., 1986) and animals (Brown and Aggleton, 2001). The activation is centered in the anterior parahippocampal gyrus, but, as can be seen in Figure 4-16, the activation might extend into the hippocampus.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left parahippocampal gyrus	35	-24	-20	-16	3.77	6

Table 4-9: Maximum of the region activated in the Negative Recognition Effect, i.e. the region activated less for hits as opposed to misses during test ($p < 0.005$ uncorrected, minimal cluster size 5 voxels).

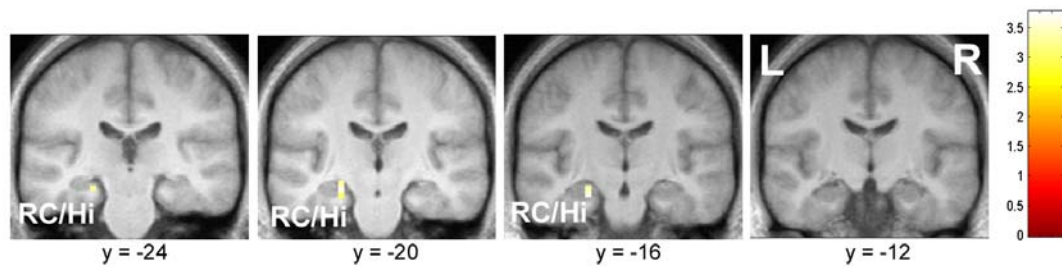


Figure 4-16: *Negative Recognition Effect.* Region activated less for hits as opposed to misses during test. The activation map ($p < 0.005$ uncorrected, minimal cluster size 5 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. RC/Hi: rhinal cortex/hippocampus.

Conjunction of the Subsequent Memory Effect and the Positive Recognition Effect

To identify brain areas showing increased activity for both successful declarative memory formation and retrieval, a conjunction analysis of the subsequent memory effect and the positive recognition effect was employed. Figure 4-17, Figure 4-18 and Table 4-10 show regions that are activated conjointly by these two contrasts. In line with the hypotheses regarding the critical role of inferior and medial temporal areas this analysis identified an activation in the anterior half of the inferior temporal cortex. In both hemispheres, this area reaches the depth of the collateral sulcus, which is covered by perirhinal cortex (Amaral and Insausti, 1990) (BA 20). Additionally, there is major activation in the cerebellar vermis and its afferent relay station, the pons. Further activations are located in the right angular gyrus (BA 39) and in bilateral cerebellar hemispheres.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left cerebellum.		-12	-64	-24	2.93	10
vermis, cerebellum		0	-60	-20	3.21	10
right angular gyrus	39	40	-60	32	2.80	11
left pons		-28	-36	-28	3.06	41
left inferior temporal gyrus	20	-52	-12	-24	3.67	16
right cerebellum		20	-60	-40	2.48	12

Table 4-10: Maxima of the regions activated in the conjunction of the *Subsequent Memory Effect* and the *Positive Recognition Effect*, i.e. regions activated more during successful as opposed to unsuccessful memory formation and more for hits as opposed to misses during test ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

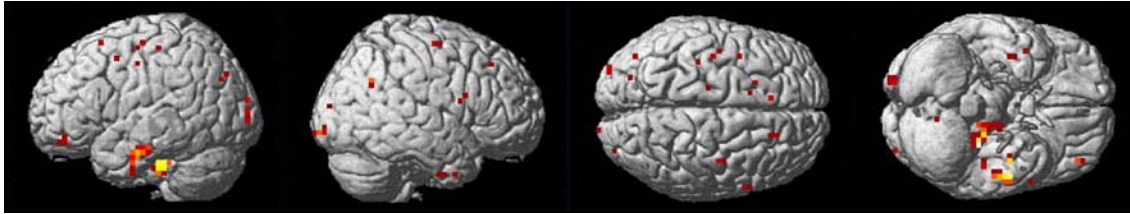


Figure 4-17: Conjunction of the *Subsequent Memory Effect* and the *Positive Recognition Effect*. Regions activated more during successful as opposed to unsuccessful memory formation and more for hits as opposed to misses during test. The activation map ($p < 0.001$ uncorrected) is shown overlaid onto a canonical brain rendered in three dimensions.

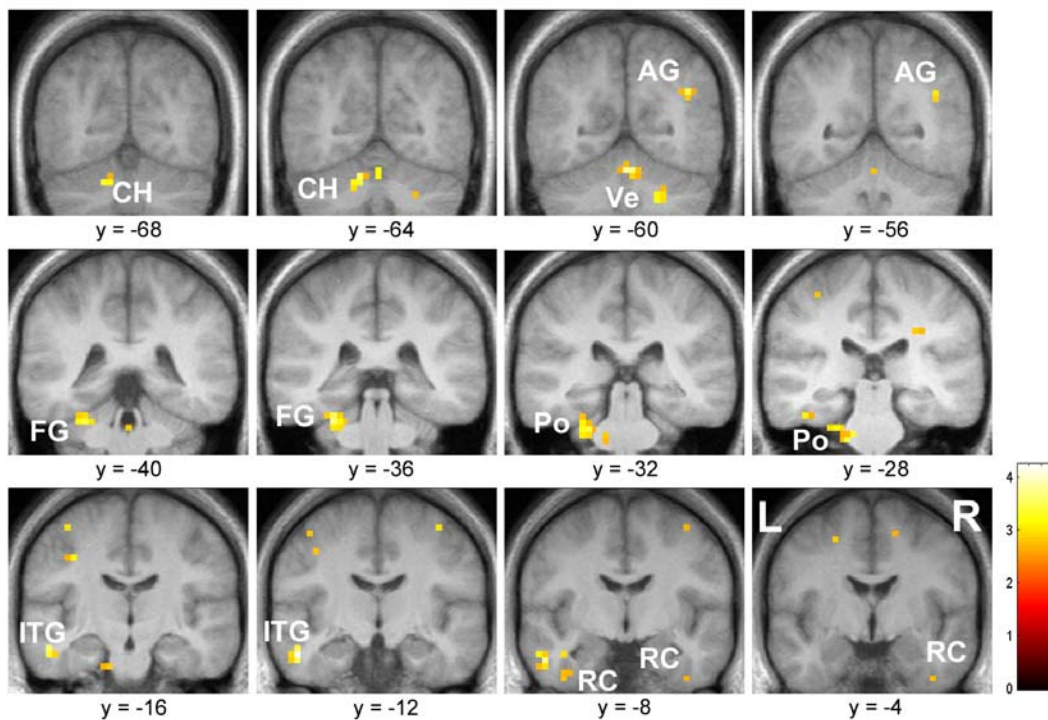


Figure 4-18: Conjunction Analysis of the *Subsequent Memory Effect* and the *Positive Recognition Effect*. Regions activated more during successful as opposed to unsuccessful memory formation and more for hits as opposed to misses during test. The activation map ($p < 0.001$ uncorrected) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume. AG: angular gyrus, CH: cerebellar hemisphere, FG: fusiform gyrus, ITG: inferior temporal gyrus, RC: rhinal cortex, Po: pons, Ve: vermis.

Conjunction of the Subsequent Memory Effect and the Negative Recognition Effect

The conjunction analysis of the subsequent memory effect and the negative recognition effect allows the identification of brain areas associated with activity increases during successful memory formation and activity decreases during successful memory retrieval. Figure 4-19, Figure 4-20 and Table 4-11 show brain areas exhibiting such a pattern of reactivity. Again, in line with the hypotheses this analysis revealed an

anterior MTL activation including the left hippocampus, but centered in the left parahippocampal gyrus (BA 28).

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left parahippocampal gyrus	28	-24	-16	-16	2.99	10
left cerebellum		-44	-48	-28	2.69	12

Table 4-11: Maxima of the regions activated in the conjunction of the *Subsequent Memory Effect* and the *Negative Recognition Effect*, i.e. regions activated more during successful as opposed to unsuccessful memory formation and less for hits as opposed to misses during test ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

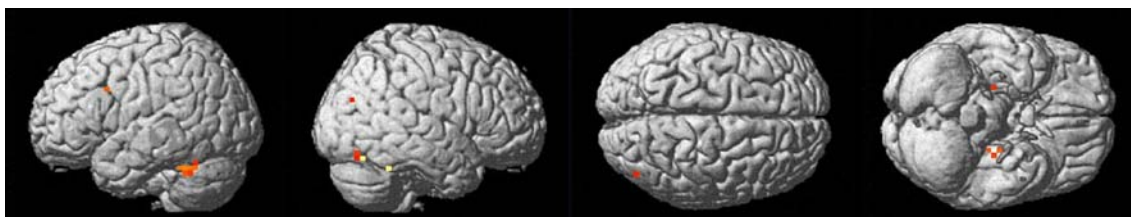


Figure 4-19: Conjunction of the *Subsequent Memory Effect* and the *Negative Recognition Effect*. Regions activated more during successful as opposed to unsuccessful memory formation and less for hits as opposed to misses during test. The activation map ($p < 0.001$ uncorrected) is shown overlaid onto a canonical brain rendered in three dimensions.

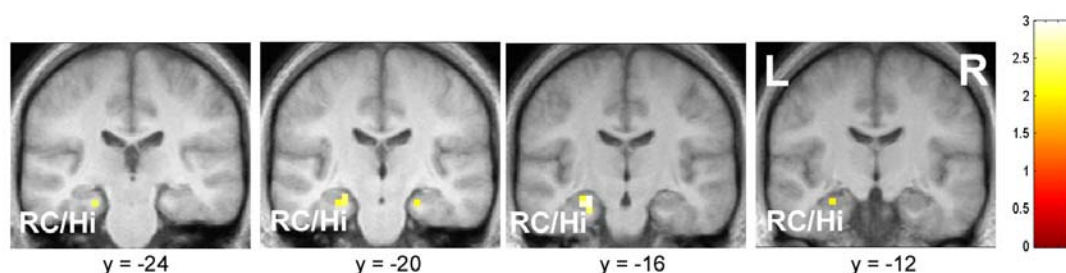


Figure 4-20: Conjunction analysis of the *Subsequent Memory Effect* and the *Negative Recognition Effect*. Regions activated more during successful as opposed to unsuccessful memory formation and less for hits as opposed to misses during test. The activation map ($p < 0.001$ uncorrected) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

4.4 Discussion

In a first step, the data acquired during study was examined. Essentially, these data replicate findings from earlier event-related fMRI studies, in that they revealed subsequent memory effects in a fusiform and parahippocampal and two left inferior frontal areas, one in the posterior and one in the anterior aspect of the inferior frontal gyrus (Brewer et al., 1998; Wagner et al., 1998a; Kirchhoff et al., 2000; Davachi et al., 2001; Otten et al., 2001; Otten and Rugg, 2001a; Strange et al., 2002). Additionally, subsequent memory effects were found in the parietal lobe and the cerebellar hemispheres. These were previously less often reported (Davachi et al., 2001; Otten and Rugg, 2001a), but can be explained by the nature of our stimulus material, which

requires the recruitment of brain areas involved with visuospatial analysis. The left lateralization of the subsequent memory effects found here is not exactly in line with other studies which have also used pictures as stimuli (Brewer et al., 1998; Kirchhoff et al., 2000). It might be explained by the additional use of verbal codes for picture details (Kelley et al., 1998; Opitz et al., 2000) in the highly complex stimulus material used here. Anyway, in line with all earlier studies, the results concerning the encoding data confirm that prefrontal and medial temporal areas are involved in declarative memory formation. Specifically, the prefrontal cortex may execute working memory operations associated with maintenance, selection, and organization of incoming information (Wagner, 1999; Fletcher and Henson, 2001) while the MTL may execute a rather specific operation of declarative memory formation in the hippocampus and a subordinate support operation in the parahippocampal region. This support operation is necessary to make semantic representations of each study item available in the service of comprehension, semantic-associative processing, and memory formation (Nobre and McCarthy, 1985; Fernández et al., 2002).

The negative subsequent memory effect, more activity for subsequently forgotten than subsequently remembered items, revealed only two small clusters of activated voxels in the precuneus and the cingulate gyrus. The location of these activations is roughly congruent with activations described in the initial reports of this effect (Otten and Rugg, 2001b; Wagner and Davachi, 2001). These positive correlates of forgetting have been interpreted as being related to task-appropriate and task-inappropriate allocation of neurocognitive resources away from the process leading to effective memory formation (Otten and Rugg, 2001b; Wagner and Davachi, 2001).

Next, the data acquired during recognition, was studied. Initially, the classical old/new effect was examined. This contrast revealed major activations in the parietal lobe, in frontal midline structures – the anterior cingulate and the superior frontal gyrus - , the left insula, and the right anterior aspect of the superior frontal gyrus and in both cerebellar hemispheres. Activations are more pronounced in the left hemisphere. As intended, these findings replicate earlier efMRI findings that suggest distributed cerebral and cerebellar brain regions participating in recognition memory (Henson et al., 1999; Konishi et al., 2000; McDermott et al., 2000; Cabeza et al., 2001; Donaldson et al., 2001a; Donaldson et al., 2001b). Among these regions, the midline structures activated, i.e. the anterior cingulate and the superior frontal gyrus might control subject responses by evaluating stimulus representations restored in the specific areas

of the parietal lobe (Buckner et al., 1996; Fletcher et al., 1996). Especially with the large number of very complex stimuli used here, a high degree of interference or response competition makes an effective control of response selection and inhibition necessary (Carter et al., 1998; Braver et al., 2001; Potts and Tucker, 2001; Stern et al., 2001; Levy and Anderson, 2002). Together with the left prefrontal subsequent memory effect described above, the right anterior prefrontal activation is fully in accord with the HERA model (Tulving et al., 1994). The right anterior prefrontal activation might correlate with post retrieval monitoring processes and not with the actual process of memory retrieval (Rugg et al., 1996; Schacter et al., 1997; Buckner et al., 1998). The old/new effects in cerebellar hemispheres indicate that the cerebellum plays a role in memory retrieval (Bäckman et al., 1997; Cabeza et al., 1997; Andreasen et al., 1999). The implication of this finding will be discussed below, interpreted in the context of the areas involved in both memory formation and retrieval.

The newly introduced positive recognition effect, depicting increased brain activity to hits as opposed to misses during test, revealed activations in the frontal and parietal lobe that are close to activations revealed by the old/new contrast, but without direct overlap. In comparison to the old/new effect, the cerebellar activation in the positive recognition effect is more centered at midline structures like the vermis, intermediate cerebellar hemispheres, and tonsils, and extended to pontine areas where input from prefrontal, parietal, and temporal cortices is relayed to the cerebellum (Schmahmann 1996). The failure to find exact overlap between the positive recognition effect and the old/new effect must, like all null results, be treated with caution. This is especially so, given that the power to detect a recognition effect was lower than the power to detect an old/new effect, a consequence of fewer misses than correct rejections. Nevertheless, these findings seem to support the view that frontal, parietal and cerebellar regions are involved in the successful recovery of declarative memories during a recognition memory task.

The small negative recognition effect indicates that less activity in the anterior MTL is related to recognition success. This finding is in line with the hypothesis and electrophysiological studies (Smith et al., 1986; Riches et al., 1991; Miller and Desimone, 1994; Brown and Aggleton, 2001; Miller et al., 1991; Fahy et al., 1993). It is unlikely that this effect is solely based on repetition priming, because both classes of items have been encountered once before. However, since the study design employed here does not provide a behavioral measure of repetition priming, it is impossible to

test stochastic independence between primed and recognized items. However, the location of priming effects in occipital areas only (Figure 4-11) makes a repetition priming account for the negative recognition effect in the anterior MTL highly unlikely. Nevertheless, there seem to be alternative interpretations for the negative recognition effect: Old items misclassified as new could be re-encoded during the test phase leading to an encoding related activity increase (Buckner et al., 2001), or the subjects' 'new' decision could be accompanied by an activity increase related to novelty detection (Tulving and Kroll, 1995; Tulving et al., 1996). The latter interpretation obviously seems to be less plausible, because a reversed old/new contrast comprising more items and thus more statistical power did not show any activation in the anterior MTL. Also, the first interpretation is not mutually exclusive with the recognition account, as is further discussed below.

Given the study design employed here, it is impossible to dissociate between sub processes within recognition, since subjects did not classify their responses as being based on a 'remember' or a 'know' judgment. Therefore, it is not possible to decide whether activation is related to recollection or familiarity (Mandler, 1980). This issue could be further evaluated by a study design including for instance a source memory judgment (Cansino et al., 2002). This question will be further pursued in the study presented in chapter 5 below. However, following Brown and Aggleton (Brown and Aggleton, 2001) or Brown and Bashir (Brown and Bashir, 2002), the negative recognition effect in the anterior MTL might rather support a familiarity-based decision than an actual recollective experience (Henson et al., 2003). It may reflect a process enabling recognition by more efficient processing of recognized stimuli with reduced neural activity during an active memory search (Jiang et al., 2000), or by a neural activity increase in the presence of novel stimuli or old stimuli incorrectly classified as new (Brown and Bashir, 2002).

As a final stage of the analysis, the fact that both memory formation and recognition were examined in a common experiment was utilized to delineate brain areas commonly involved with memory formation and recognition. The largest activation clusters of the conjunction analysis of the subsequent memory effect and the positive recognition effect are located in the inferior and anterior MTL as well as cerebellar and pontine regions. When considering the conjunction analysis of the subsequent memory effect and the negative recognition effect, activations are located in the MTL.

Thus, the anterior inferior temporal cortex including the anterior parahippocampal region seems to be conjointly involved in both successful encoding and recognition. This finding confirms suggestions based on across-study comparisons of electrophysiological findings in epilepsy patients (Smith et al., 1986; Fernández et al., 1999b; Fernández et al., 2001; Fernández et al., 2002). Such a module has originally been described on the basis of electrical recordings in non-human primates showing that this brain area is sensitive to both object encoding and object recognition (Desimone et al., 1984; Riches et al., 1991; Miller and Desimone, 1994). During recognition, the neural representation of each test stimulus, i.e., a unique pattern of activation that is evoked by a visually perceived item during recognition, may be matched with stored representations previously formed locally during encoding. Moreover, the inferior and medial temporal cortex is ideally located for this efficient pattern matching, because it is the final route of the ventral visual pathway, providing integrated visual and semantic information (Ungerleider and Mishkin, 1985; Haxby et al., 1991; Nobre and McCarthy, 1995; Büchel et al., 1998; Lerner et al., 2001).

The findings of this event-related fMRI study suggest an important role of the cerebellum and its afferent relay station, the pons, in declarative memory. Functional imaging studies provide mounting evidence that the cerebellum coordinates diverse aspects of cognitive processes (for review: Desmond and Fiez, 1998). Up to now, however, it is unclear whether the cerebellum provides domain-general computations supporting diverse cognitive operations or different operations with specific roles in particular cognitive domains. Several proposals have been made for a general operation, including a central timing processor (Keele and Ivry, 1990) for sequential parsing of temporally complex material (Llinas, 1974; De Zeeuw et al., 1998). Thach (Thach, 1998) proposed that cerebellar processing entails stimulus-response linkage by grouping single-response elements into larger task adequate combinations. The cerebellum also seems to be involved in processes contributing specifically to learning and memory. It is not only critically involved in basic delay conditioning, where it is the locus of memory formation, consolidation, and storage (Thompson and Kim, 1996; Attwell et al., 2002); it is also involved in spatial learning and memory (Pellegrino and Altman, 1979; Lalonde and Botez, 1990; Goodlett et al., 1992). Humans with acquired cerebellar lesions have, however, only minor deficits in declarative memory (Schmahmann, 1996). In imaging studies of declarative memory, cerebellar activations were rather obtained during retrieval than encoding tasks (Desmond and Fiez, 1998),

suggesting that a cortical-cerebellar network self-initiates and monitors conscious retrieval (Bäckman et al., 1997; Andreasen et al., 1999) or that the cerebellum generates candidate responses during a search and selection process (Cabeza et al., 1997; Desmond et al., 1998). The results presented here clearly show that the cerebellum participates in both memory formation and retrieval. However, the fact that cerebellar lesions cause only minor deficits in declarative memory suggests that the cerebellum is not directly involved in storage and retrieval operations. It might rather support mnemonic operations by providing auxiliary processes, as for example a temporal structure for a coherent episode.

In conclusion, by replicating efMRI studies investigating either memory formation or recognition, this study has provided within-study confirmation for brain areas involved in two fundamental mnemonic operations: the formation and the retrieval of declarative memories. Based on this empirical foundation, this is the first study to describe brain regions supporting successful memory retrieval by both activity increases, which were found in frontal, parietal and cerebellar areas, and decreases, which were detected in the anterior MTL. Finally, the study design employed here made it possible to initially identify within subjects and within one common event-related fMRI experiment inferior- and medial-temporal as well as cerebellar areas supporting both memory formation and retrieval. Such integrated modules may re-use stored representations formed locally during encoding for efficient matching operations during recognition.

Acknowledgments

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5 Neural Correlates of Contextual Retrieval and Item Recognition are dissociated within the Human Medial Temporal Lobe

5.1 Introduction

As mentioned in the remarks on source memory processes above, episodic memory can be viewed as consciously accessible memory for an item together with the spatiotemporal context in which the item was encountered (Tulving, 1985). In contrast to single-process models, which suggest that the difference relates merely to memory strength, dual-process models of recognition memory propose that there is a qualitative distinction between the forms of memory that support recognition of an item which is accompanied as opposed to unaccompanied by contextual information (e.g. Mandler, 1980; Atkinson and Juola, 1974; Jacoby and Dallas, 1981; Yonelinas, 1994; O'Reilly and Norman, 2002). In the light of these models, recollection, meaning recognition of an item that is accompanied by contextual information, is truly episodic memory, while recognition unaccompanied by contextual information can rely upon a sense of familiarity which might be based on neurally and functionally distinct processes (Tulving, 1985; Mandler, 1980; Jacoby and Kelley, 1992; Gardiner and Java, 1993; Brown and Aggleton, 2001; Gardiner et al., 2002).

Also, results from behavioral and functional neuroimaging experiments have suggested that recognition based on familiarity and recollection are supported by distinct neural mechanisms. Behavioral studies have shown a clear-cut dissociation between recollection and familiarity (Rajaram et al., 2002). For example, recollection does more than familiarity benefit from elaborative encoding (Richardson-Klavehn and Gardiner, 1995), it is slower and requires more attention (Gardiner and Parkin, 1980). Further, recollection is relatively unaffected by an increase of the study-test interval up to several minutes, while familiarity does decline (Gardiner and Java, 1991).

Various experimental approaches have been used to measure the neural correlates of these distinct forms of recognition memory. Some functional imaging studies employed the so-called 'remember/know procedure' (Tulving, 1985). This procedure requires subjects to respond 'remember' to a recognized item if they are able to recall specific information about the item's study context and 'know' if they do not. Clearly, this method relies on the subject's introspection, but not on an objective measure of

contextual retrieval, thus leaving it open if the results of those studies reflect differences between recognition with and without retrieval of context, or whether instead they are more likely to reflect the neural correlates of relatively strong versus weak recognition memory (Rugg and Henson, 2002; Cansino et al., 2002). In contrast, in tests of source memory, subjects are required to discriminate studied from non studied items and further to judge in which of two or more encoding contexts, or sources, the item was learned. This procedure provides a more objective differentiation between item recognition and retrieval of contextual information.

Human lesion studies identified the MTL as a crucial structure for recognition memory (e.g., Levy et al., 2003; Manns et al., 2003), but the specific role of MTL subregions in item recognition and contextual retrieval still is highly disputed (Haist et al., 1992; Aggleton and Shaw, 1996; Reed and Squire, 1997; Holdstock et al., 2000; Mayes et al., 2002). Since lesions limited to a certain MTL subregion are hardly available in humans, functional imaging seems to be optimally suited to dissociate these mnemonic operations. One central point of controversy relates to the question whether the hippocampus and perirhinal cortex make similar or distinct contributions to recognition memory (Gaffan, 1994; Eichenbaum, 2000; Brown and Aggleton, 2001; Squire, 1998).

At an anatomical level, the perirhinal cortex receives input from visual association areas (Suzuki, 1996) as well as from semantic association cortices (Ricci et al., 1999; Newman et al., 2001), while parahippocampal cortex receives input mainly from visuospatial association areas (Suzuki and Amaral, 1994; Goldman-Rakic et al., 1984). On the other hand, the hippocampus receives the majority of its input from entorhinal cortex, which in turn is supplied by afferences from perirhinal and parahippocampal cortices (Witter and Amaral, 1991). Thus, the hippocampus is well situated to associate contextual information with an item during encoding to create an integrated representation. It has been suggested, that the hippocampus binds together the different components of a learning event by linking neuronal activation in distributed brain regions (Squire and Zola-Morgan, 1991; Squire, 1992; Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994).

In a direct comparison of relational and item-based learning (Davachi and Wagner, 2002), it could be shown that relative to item-based processing, relational processing of pairs of items was associated with greater activation of bilateral hippocampus. Still, an activation of the hippocampal was also found for item-based processing. Further,

hippocampal activation was correlated with later memory. In a verbal associative encoding task (Jackson and Schacter, 2004), authors found that encoding activity in the hippocampus and surrounding MTL was greater for successfully bound word pairs as opposed to successfully recognized single words from the pairs.

The general finding from neuroimaging studies suggests that encoding activity in ventrolateral prefrontal cortex, the hippocampus and posterior parahippocampal cortex increases for items that are subsequently recollected as opposed to forgotten (Brewer et al., 1998; Davachi et al., 2003; Davachi and Wagner, 2002; Fernández et al., 1999a; Henson et al., 1999; Kirchhoff et al., 2000; Otten et al., 2001; Reber et al., 2002; Strange et al., 2002). In contrast, encoding activity resulting in familiarity-based recognition has seldom been studied. One efMRI study (Davachi et al., 2003) using words encoded under different conditions, reading the word backwards or imagination of a place characterized by the word, found that the magnitude of encoding activity in the hippocampus, parahippocampal and perirhinal cortex correlated with different forms of subsequent memory. While engagement of the hippocampus and parahippocampal cortex was associated with later source recollection, encoding activity in perirhinal cortex was predictive of item recognition. Thus, the roles of the hippocampus and surrounding parahippocampal cortices during the formation of new episodic memory are not fully understood.

Concerning the involvement of these structures during recognition, efMRI studies tackling recognition success associated with contextual retrieval reliably found hippocampal activation. In an event-related fMRI study using pictorial images as test items (Cansino et al., 2002) subjects were required to classify the items as 'new' or, if 'old', to indicate the one of four locations on the screen where they had been presented during study. It was found that activity in the hippocampus differed according to the amount of contextual information retrieved. In an earlier study employing the remember/know procedure and words as stimuli (Eldridge et al., 2000), an increase of hippocampal and adjacent MTL activity was found for items which were judged as recollected as opposed to items endorsed as known. The authors suggested that the function of the hippocampus during retrieval is to help to reinstate the complex conjunctions of features that compose a particular event. A similar finding was also reported in a study using words which were encoded in one of two study tasks (Dobbins et al., 2003). Subjects subsequently judged which of the two old words had been encoded in a given task. Correct judgments were associated with more activity in

the hippocampus and adjacent MTL than were incorrect judgments. Thus, event-related fMRI studies tackling recognition success associated with contextual retrieval reliably found hippocampal activation.

However, MTL activations in studies tackling item recognition are remarkably missing. efMRI studies employing the classical old/new effect revealed that successful item recognition is associated with activity increases in distributed brain regions including prefrontal and parietal cortices, but not in the MTL (e.g., Henson et al., 1999; Konishi et al., 2000; Donaldson et al., 2001a; Donaldson et al., 2001b; Rugg and Henson, 2002). This failure to find MTL activations associated with item recognition success might be explained by findings from electrophysiological studies, showing that anterior parahippocampal activity does not increase, but decrease during item recognition (Brown et al., 1987; Miller et al., 1991; Fahy et al., 1993). This line of thought is supported by a recent meta-analysis of four event-related fMRI studies suggesting that less anterior MTL activity is related to the amount of familiarity across a variety of stimulus materials (Henson et al., 2003).

In the study presented in chapter 4 above, the negative recognition effect, less activity during test for hits as opposed to misses, revealed an anterior parahippocampal effect, indicating that less activity in the rhinal cortex is related to recognition success. However, in that study there was no formal dissociation between recollection and item recognition implemented. Therefore, it remains to be shown, whether a decrease of anterior parahippocampal activity is associated with simple, a-contextual item recognition.

Thus, in the study reported here, the findings from chapter 4 are extended by employing a source memory task to objectively determine whether recognition memory was accompanied by retrieval of contextual information or not. The event-related design of the study is similar to the design of the study presented above. Again, the same complex photographs of buildings and landscapes were used as stimuli. To introduce a context, during study the stimuli were transformed into one of four single-color-scales: red, blue, yellow, or green. By adding a four-alternative source judgment during test, which referred to the color in which the stimulus was presented during study, the neural correlates of truly recollective versus item memories can be delineated. On the basis of each subjects' individual behavioral data, old items can be divided into misses and hits with and without correct source judgment, thus making it

possible to disentangle MTL processes associated with either contextual retrieval or simple item memory.

The *positive source memory effect*, the difference in brain activity during test between hits with and without correct source judgment, delineates neural correlates of contextual retrieval, while the *item recognition effect*, the difference between hits with incorrect source judgment and misses, shows areas involved in item recognition. It is hypothesized that an activity increase in the hippocampus is associated with contextual retrieval, while item memory is related to an activity decrease in the anterior parahippocampal gyrus. Also, this study design will make it possible to examine the involvement of sub structures of the MTL during the encoding of simple item memory as opposed to the association of an item to its context. These processes will be examined by the use of the *subsequent source memory effect*, more activity during study for items subsequently remembered together with contextual information as opposed to those items subsequently remembered, but without correct source judgment and the *subsequent item memory effect*, more activity during study for items subsequently remembered without correct source judgment as opposed to items subsequently forgotten.

5.2 Material and Methods

5.2.1 Subjects

Twelve healthy volunteers with normal or corrected-to-normal vision participated in the experiment. All 6 male and 6 female subjects were native German speakers and consistent right-handers according to the Edinburgh Handedness Inventory (mean EHI= 89, range: 82-100) (Oldfield, 1971). Their mean age was 28 years with a range of 20 – 34 years. No subject had a history of substance abuse, a neurological or psychiatric illness. Informed consent was obtained in a manner approved by the Medical Ethics Committee of the University of Bonn and according to the Declaration of Helsinki (1991). Subjects were paid for their participation.

5.2.2 Stimuli

Stimuli consisted of 360 gray-scale photographs of either buildings or natural landscapes without any man-made buildings that were selected to be similar in complexity, brightness, and contrast. The set of 360 pictures comprised 180 landscape

and 180 building stimuli. To counter-balance stimuli across subjects, pictures were randomly divided into three sets of 60 buildings and 60 landscapes each. During study, two of the three sets of pictures were selected for each subject, resulting in four subjects seeing the same 240 pictures during study. For each of these four subjects, different subsets of 60 pictures each were transformed into red-, blue-, yellow- and green-scale, so that no two subjects saw the pictures in the same color (see Figure 5-1). During recognition all 360 pictures were presented as plain gray-scale photographs. Thus, during test, subjects encountered 240 old and 120 new stimuli (see Figure 5-2).

5.2.3 Task

The experiment was divided into four study–test cycles. In each of the four study phases, 30 pictures of buildings were randomly intermixed with 30 pictures of landscapes. The four colors red, blue, yellow and green had the same probability in each set. Stimuli were presented sequentially for 800 ms each with a randomized ISI of 3600 to 5600 ms, the mean ISI being 4600 ms. In between the presentation of the stimuli, subjects viewed a black screen. 30 null events, consisting of a black screen shown for 2000 ms were randomly intermixed. Since the null events also consisted of a black screen, subjects were not able to distinguish null events from the inter stimulus baseline. Subjects were required to press one of the response keys for pictures showing any man-made buildings, and another response key for pictures showing landscapes without any buildings. The key press was executed with the index and little finger of the right hand. Subjects were also instructed to view the pictures carefully and to memorize them with their color to be able to recognize them in a later memory test (Figure 5-1).



Figure 5-1: Exemplary part of an encoding run comprising building and landscape stimuli in blue-, red-, yellow- and green-scale.

Each of the four recognition phases was executed about five minutes after the respective study phase. During the break, subjects remained inside the MRI scanner and rested. In each of the recognition phases, all stimuli from the preceding study phase plus 30 new, previously not presented photographs of buildings (15) and landscapes (15) were shown in grey-scale sequentially and again randomly intermixed at the same presentation rate as during study. Additionally, 45 null events were randomly intermixed. Subjects were required to make an old-new decision by right hand key-press. For those stimuli judged as old, four colored squares were displayed on the screen for 800 ms. The time between the presentation of the stimulus and the colors varied between 1200 and 2400 ms, with a mean of 1600 ms. Subjects were required to indicate by appropriate right hand key-press the color in which the item was presented during encoding (Figure 5-2).



Figure 5-2: Exemplary part of a recognition run comprising building and landscape stimuli in grey-scale and the color display for items classified as old by the subject.

5.2.4 fMRI Data Acquisition

Whole-brain scanning was performed on a 1.5T Symphony scanner (Siemens, Erlangen, Germany) using standard gradients and a circular polarized phase array head coil. The entire imaging session lasted about 90 minutes. Scout images were first collected to align the field of view to the centre of the subjects' brain. Then, for anatomical localization, a structural image was obtained by use of a T1-weighted 3D-FLASH sequence with the following parameters: repetition time TR = 11 ms, echo time TE = 4 ms, matrix size = 256 x 256, in plane resolution = 0.89 x 0.89 mm², field of view = 230 x 230 mm², number of slices = 120, slice thickness = 1.5 mm, no interslice gap. For each subject, eight series of functional EPI images were acquired, one for each of the four study phases and for the four recognition phases. For echo planar imaging (Kwong et al., 1992; Ogawa et al., 1990; Mansfield, 1977) a T2*-weighted axial EPI-sequences with BOLD contrast and the following parameters was employed: repetition time TR = 2.95 s, echo time TE = 50 ms, matrix size = 64 x 64, inplane resolution = 3.43 x 3.43 mm², field of view = 220 x 220 mm², number of slices = 30, slice thickness = 4 mm, interslice gap = 0.4 mm. Functional images were positioned parallel to the AC-PC line. Each series included eight initial dummy scans to achieve equilibrium of longitudinal magnetization. Each of the encoding runs comprised 127 whole-brain acquisitions. During the recognition runs, 194 to 236 whole brain volumes were acquired depending on the individual number of items judged as old and thus requiring a source judgment, the mean number of scans being 218.

Stimuli were presented using the Experimental Run-Time System (<http://www.erts.de/>). Pictures were back-projected onto a translucent screen, which was positioned about two meters opposite the magnet bore using an LCD-projector. Subjects lay in a supine position with their head stabilized by an individually molded vacuum cushion. They wore earplugs to reduce the scanner noise. Stimuli were viewed by way of a mirror mounted on the head coil. Subjects received detailed instructions on the tasks before they were positioned inside the scanner. Before each of the study runs as well as the recognition runs, subjects were reminded of the instructions by way of an intercommunication system.

5.2.5 fMRI Data Analysis

The functional MRI images were analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK,

<http://www.fil.ion.ucl.ac.uk>) implemented in MATLAB 6.1 (Mathworks Inc., Sherborn, MA, USA). Functional imaging runs were first preprocessed. All images were realigned to the first image to correct for head movement. Unwarping was used to correct for the interaction of susceptibility artifacts and head movement (Andersson and Skare, 2002). After realignment and unwarping, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time to correct for their different acquisition times. By using the transformation matrix calculated from the mean EPI-image of each subject, each volume was normalized to a standard EPI template volume, which is based on the MNR reference brain (Cocosco et al., 1997), and resliced using a sinc-interpolation in space. Afterwards, the normalized data with a resliced voxel size of 4x4x4 mm were smoothed with an 8-mm FWHM isotropic Gaussian kernel to accommodate intersubject variation in brain anatomy. The time series data were band-pass filtered to remove artifacts due to cardio-respiratory and other cyclical influences. The structural volumes were also normalized, and a mean of all participants' structural images was calculated to depict the localization of group activations.

The expected hemodynamic response at stimulus onset for each event-type was modeled by two response functions, the canonical HRF (Friston et al., 1998; Josephs et al., 1997) and its temporal derivative. The temporal derivative was included in the model to account for the residual variance resulting from small temporal differences in the onset of the hemodynamic response, which is not explained by the canonical HRF alone (Friston et al., 1998). The functions were convolved with the event-train of stimulus onsets to create covariates in a general linear model. Subsequently, session-specific parameter estimates pertaining to the height of the HRF regressor for each of the different conditions were calculated from the least mean squares fit of the model to the time series. For the study phase, these conditions comprised items subsequently remembered with correct source judgment, items subsequently remembered without correct source judgment and items subsequently forgotten, while for the test phase there were hits with correct source judgment, hits without correct source judgment, misses, correct rejections and false alarms. Parameter estimates for the temporal derivative were not further considered in any contrast.

An SPM2 group analysis was performed by entering parameter estimates for the main effects of each condition into a within-subject one-way ANOVA, in which subjects are treated as random variables. Estimation of the model included correction for the non-

sphericity induced to the design by the non-independent and non-identically distributed errors of the parameter estimates. Activations are shown overlaid onto a canonical brain rendered in three dimensions as well as projected onto selected coronal slices of the mean high-resolution T1-weighted volume. For all images shown, coronal slices are ordered from posterior to anterior, numbered according to coordinates of Talairach and Tournoux (Talairach and Tournoux, 1998) and oriented according to the neurological convention with the left side of the brain displayed on the left side of the image. Further, activations are also shown overlaid onto a canonical brain rendered in 3D. The reported voxel coordinates of activation peaks were transformed from MNI space to the space defined by the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) by non-linear transformations (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

5.3 Results

5.3.1 Behavioral Results

During encoding, the building/landscape decision task was performed with a mean accuracy of 94% with a range of 90% - 98%. Incorrect responses were recorded for 4% with a range of 2%-6% and no responses for 2% with a range of 0% - 4% of all encoding trials. All trials with incorrect or no responses in the orientation task (building/landscape decision) were excluded from further analyses, because subjects might not have attended to these items. There was no significant difference between reaction times to building and landscape stimuli, with the mean reaction time for building stimuli being 747 ms (SD: 79 ms) and the mean reaction time for landscape stimuli being 751 ms (SD: 81 ms). We can therefore assume that there is no systematic reaction time difference between the index and the little finger. Reaction time differences during recognition can thus be attributed to experimentally induced effects. Recognition memory performance and reaction times are listed in Table 5-1. For the purpose of an event-related fMRI data analysis a considerable proportion of misses is required. Thus, the study was designed in a way to obtain a recognition performance clearly above chance level but with enough misses. Accuracy of item recognition was assessed by the difference in probabilities of a correct old judgment and an old judgment for a new item (Pr = probability hit – probability false alarm). While recognition performance did not differ between stimulus classes (mean $Pr_{building}$ = 0.41 (SD: 0.14) versus mean $Pr_{landscape}$ = 0.40 (SD: 0.17), $t_{11} = 1.069$, n. s.), it was well above the chance level of $Pr = 0$ (mean $Pr = 0.41$ (SD: 0.15), $t_{11} = 8.403$; $p <$

0.00001). The accuracy of source judgments was also well above the chance level of 25 % (mean correct = 53.5%, SD: 11%, $t_{11} = 9.04$, $p < 0.0001$).

Since recognition performance did not differ between building and landscape stimuli, trials were collapsed together, thus obtaining a sufficient number of items for each response category to reach an adequate contrast-to-noise ratio for the event-related analyses (hits with correct source judgment: mean: 70, range: 45 – 133, hits with incorrect source judgment: mean: 76, range: 41 – 108, misses: mean: 94, range: 63 – 130, correct rejections: mean: 98, range: 94 - 102, false alarms: mean: 22, range: 17 – 35).

An ANOVA comparing reaction times (Table 5-1) for hits with correct source judgment, hits with incorrect source judgment, misses, correct rejections and false alarms revealed a reliable effect of response category ($F_{4,66} = 4.351$, $p < 0.05$). Post-hoc paired-sample t-tests showed that reactions to hits with correct source judgments were faster than those to hits with incorrect source judgments ($t_{11} = 4.30$, $p < 0.001$). Reactions to false alarms were slower than reactions to hits with both correct ($t_{11} = 4.78$, $p < 0.001$) and incorrect source judgments ($t_{11} = 3.36$, $p < 0.01$). Correct reactions to new items were faster than reactions to misses ($t_{11} = 2.52$, $p < 0.05$) and reactions to false alarms ($t_{11} = 2.23$, $p < 0.05$). All other post-hoc tests did not reveal any reliable difference (max $t_{11} = 1.81$, n. s.).

	Old			New		
	all	Hits	Misses	Correct rejections	false alarms	
		Item + Source				
		Item only				
Number	146	76	70	94	98	22
%	60.8 ¹	50.8 ²	49.2 ²	39.2 ¹	81.7 ³	18.3 ³
SD	32	24	18	30	9	10
RT (ms)	1491	1455	1529	1564	1482	1591
SD	288	282	303	303	233	344

Table 5-1: Mean item recognition performance and source recognition performance as well as reaction times (RT) with their standard deviations (SD). Note: percentage of all old items¹, all hits², and all new items³.

5.3.2 Imaging Data

Based on the results of the study presented in chapter 4 as well as other functional imaging studies, this study was designed to examine regional specific hypotheses concerning the MTL. Specifically, the hypothesis expects an activity increase in the hippocampus which is associated with the binding of contextual information to an item during encoding as well as during contextual retrieval. Further, in the anterior parahippocampal gyrus an activity increase during encoding and an activity decrease during recognition is expected for simple item memory. Therefore, MTL activations are reported at a statistical threshold of $p < 0.001$ uncorrected for multiple non-independent comparisons and a minimal cluster size of 10 voxels. In all other brain areas, however, the results are reported at a statistical threshold of $p < 0.05$ corrected for multiple non-independent comparisons based on the false discovery rate (Genovese et al., 2002), also at a minimal cluster size of 10 voxels.

Looking at the data acquired during encoding, it was the aim to delineate the neural correlates of the successful formation of item memory as opposed to the establishment of associations between an item and its context. Therefore the behavioral data of each individual subject was used to back-sort the fMRI acquired during the encoding events into items that were later recognized and accompanied by correct contextual retrieval, items that were later recognized without correct source judgment and items that were later forgotten. In a first step all items that were later recognized were pooled together irrespective of correct source judgment to compute the *subsequent memory effect*, more activity for items that were later recognized than those that were later forgotten. Figure 5-3 and Table 5-2 show MTL regions that exhibit significantly more activity to subsequently recognized than forgotten items. In line with previous findings and replicating the results of the study presented in chapter 4, this effect identified extended areas in bilateral MTL (BA 28, 34, 35, 36 and 37) including the hippocampus, the parahippocampal gyrus and medial parts of the fusiform gyrus.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left parahippocampal gyrus	37	-28	-43	-15	5.77	203
right parahippocampal gyrus	28	20	-12	-16	4.07	11
right parahippocampal gyrus	36	28	-43	11	4.63	48

Table 5-2: Maxima of the MTL regions activated in the *Subsequent Memory Effect*, i.e. regions activated more for hits as opposed to misses during study ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

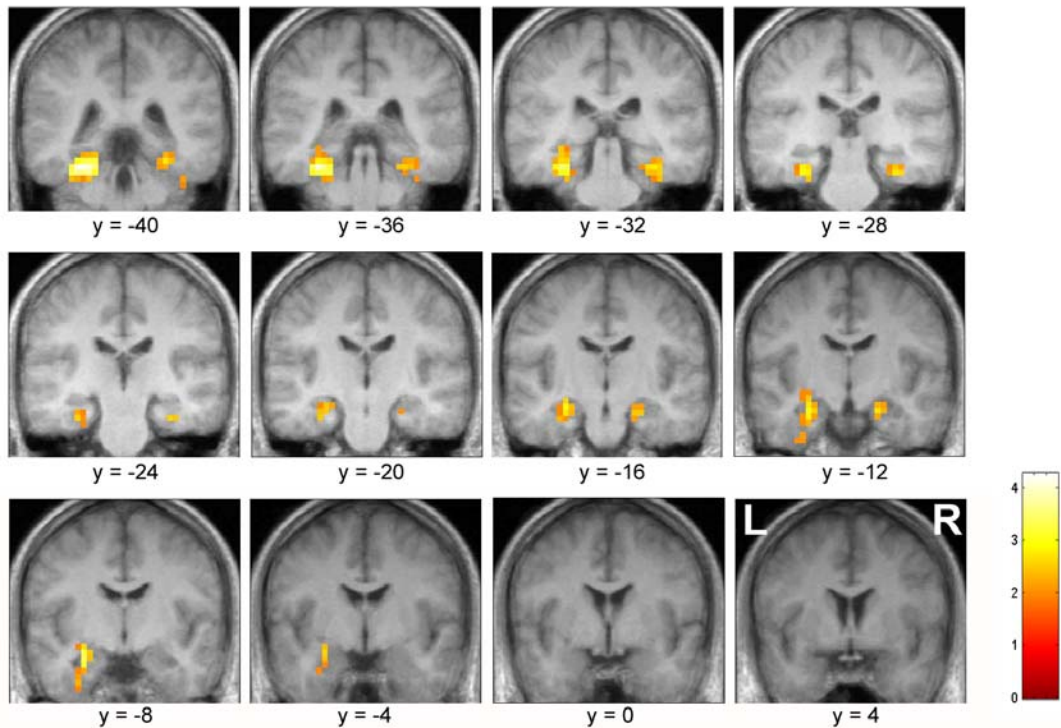


Figure 5-3: *Subsequent Memory Effect*. MTL regions activated more for hits opposed to misses during study. The activation map ($p < 0.001$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

At a neocortical level, as reported in Figure 5-4 and Table 5-3 areas predicting subsequent memory are located in the left ventrolateral prefrontal cortex (BA 46) and in the lateral parts of the fusiform gyrus bilaterally (BA 19 and 37).

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left fusiform gyrus	37	-48	-63	-7	4.84	28
right fusiform gyrus	37	48	-59	-14	4.35	26
left middle frontal gyrus	46	-48	32	13	4.24	13

Table 5-3: Maxima of the neocortical regions activated in the *Subsequent Memory Effect*, i.e. regions activated more for hits as opposed to misses during study ($p < 0.05$ corrected, minimal cluster size 10 voxels).

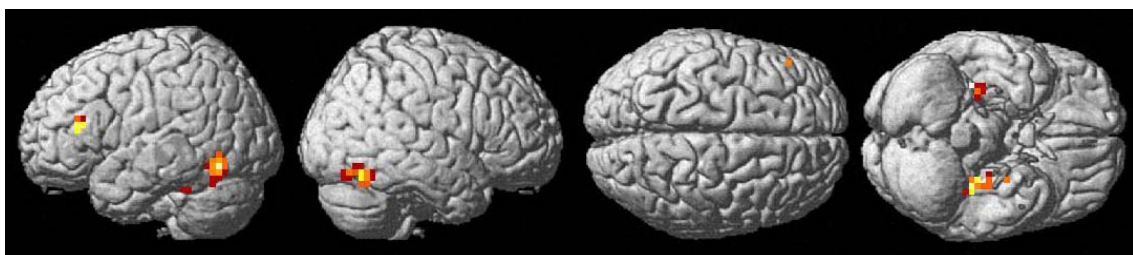


Figure 5-4: *Subsequent Memory Effect*. Neocortical regions activated more for hits opposed to misses during study. The activation map ($p < 0.05$, corrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

In addition to those areas which predict subsequent memory by an increase of activation, areas in which a decrease of activation is associated with subsequent memory were also identified. As shown in Figure 5-5 and Table 5-4, the *negative subsequent memory effect*, an activity decrease during study for subsequently remembered as opposed to forgotten items, is found in the right parietal lobe, extending into the precuneus (BA 47) and the supramarginal gyrus (BA 40). No MTL regions exhibited such a pattern of activation.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right supramarginal gyrus	40	55	-49	39	5.04	33
right precuneus	47	8	-49	39	4.55	21

Table 5-4: Maxima of the neocortical regions activated in the Negative Subsequent Memory Effect, i.e. regions activated less for hits as opposed to misses during study ($p < 0.05$ corrected, minimal cluster size 10 voxels).

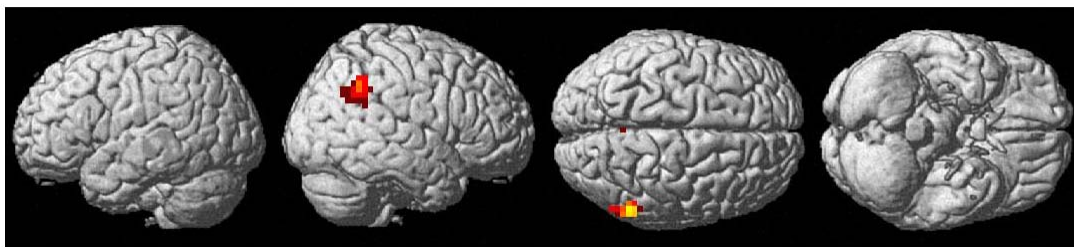


Figure 5-5: *Negative Subsequent Memory Effect*. Neocortical regions activated less for hits as opposed to misses during test. The activation map ($p < 0.05$ corrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

The next step of the analysis aimed at delineating structures whose activity during study correlates with later recollection of contextual details and the association of context to an encoded item. Thus, the *subsequent source memory effect* compares activity during study for items which are later recognized together with a correct source judgment to those items which are recognized but for which contextual retrieval fails. As shown in Figure 5-6 and Table 5-5, bilateral MTL extending into the occipital-inferior temporal region (BA 19, 20 and 37) and covering all MTL subregions – bilateral hippocampi, amygdalae, and parahippocampal regions- as well as bilateral fusiform gyri show more activity during the study phase for later recognized items with correct source assignment than for trials of later recognized items with incorrect source assignment.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left parahippocampal gyrus	35	-32	-5	-17	5.00	99
left parahippocampal gyrus	19	-24	-32	-9	4.26	17
right parahippocampal gyrus	36	48	-35	-8	4.56	135
right parahippocampal gyrus	34	32	-1	-17	4.17	73
left fusiform gyrus	37	-32	-51	-18	3.52	23
left fusiform gyrus	18	-20	-82	-16	4.13	15

Table 5-5: Maxima of the MTL regions activated in the *Subsequent Source Memory Effect*, i.e. regions activated more for hits with correct source judgment as opposed to hits with incorrect source judgment during study ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

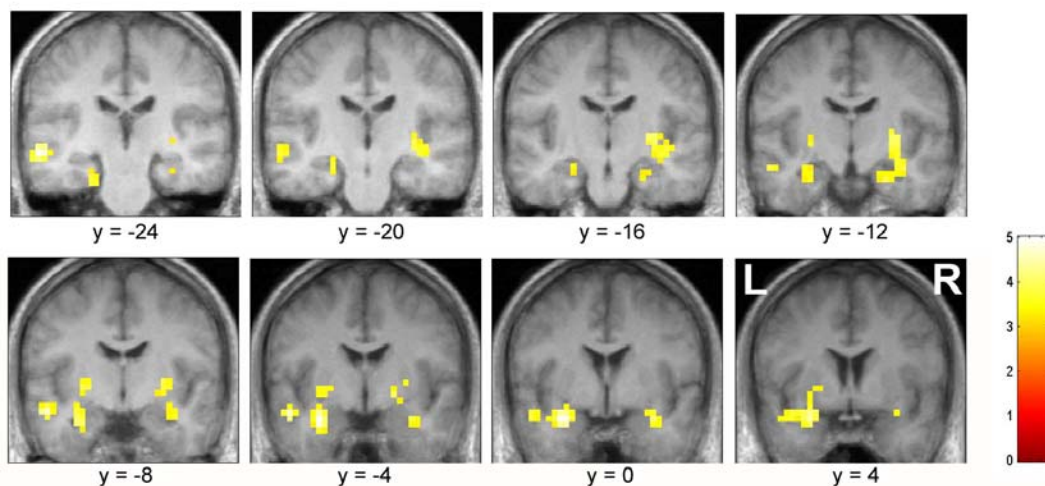


Figure 5-6: *Subsequent Source Memory Effect*. MTL regions activated more for hits with correct source judgment as opposed to hits with incorrect source judgment during study. The activation map ($p < 0.001$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

In addition, at the neocortical level (Figure 5-7, Table 5-6) left basal and ventrolateral prefrontal cortex (BA 11, 45 and 47), left lateral temporal cortex (BA 19 and 21), the left posterior cingulate (BA 30) as well as bilateral insular and cerebellar cortices also predict subsequent recollection of source information.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		X	y	z		
left fusiform gyrus	37	-32	-51	-18	3.52	31
left fusiform gyrus	18	-20	-82	-16	4.13	19
left inferior frontal gyrus	47	-48	27	2	4.53	63
left middle temporal gyrus	21	-59	-24	-6	4.99	38
left middle temporal gyrus	37	-51	-58	-4	3.91	40
left posterior cingulate	30	-20	-66	7	3.61	20
right lingual gyrus	17	20	-92	1	3.74	15
left thalamus		-8	-12	4	4.23	18
left cerebellum		0	-63	-14	3.71	17

Table 5-6: Maxima of the neocortical regions activated in the *Subsequent Source Memory Effect*, i.e. regions activated more for hits with correct source judgment as opposed to hits with incorrect source judgment during study ($p < 0.05$ corrected, minimal cluster size 10 voxels).

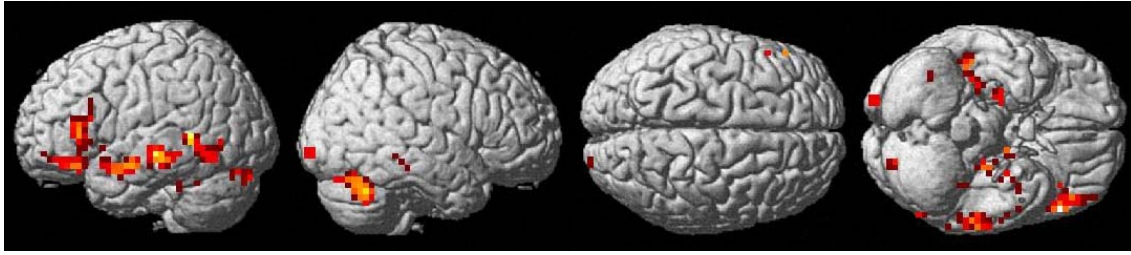


Figure 5-7: *Subsequent Source Memory Effect.* Neocortical regions activated more for hits with correct source judgment as opposed to hits with incorrect source judgment during study. The activation map ($p < 0.05$ corrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

The *negative subsequent source memory effect*, activity decreases during study for hits with correct source judgment as opposed to hits without correct source judgment, revealed no reliable activation, even after lowering the statistical threshold to $p < 0.05$ uncorrected.

As a measure of the neural correlates of item encoding, the *subsequent item memory effect*, the difference in encoding activity between hits without correct source judgment and misses, was examined. As shown in Figure 5-8 and Table 5-7, the only brain area showing a significant difference between encoding of subsequent hits without correct source judgment and misses is located in the left posterior parahippocampal gyrus (BA 36).

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left parahippocampal gyrus	36	-28	-36	-15	3.94	10

Table 5-7: Maximum of the MTL region activated in the *Subsequent Item Memory Effect*, i.e. region activated more for hits with incorrect source judgment as opposed to misses during study ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

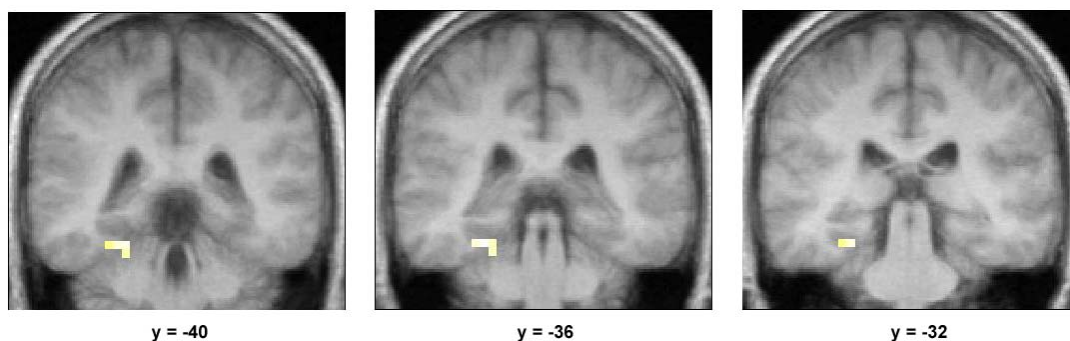


Figure 5-8: *Subsequent Item Memory Effect.* Regions activated more for hits with incorrect source judgment as opposed to misses during study. The activation map ($p < 0.001$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

The *negative item memory effect*, activity decreases during study for hits with incorrect source judgment as opposed to misses, revealed no reliable activation, even after lowering the statistical threshold.

Further, the data acquired during recognition was examined. Initially, the neural correlates of successful contextual retrieval were directly investigated by looking at the *positive source memory effect*, more brain activity for hits with correct source judgment than for hits without correct source judgment. This contrast revealed bilateral MTL activations, which are centered in the anterior hippocampus (Figure 5-9 and Table 5-8) and extend into the amygdala and the parahippocampal gyrus (BA 28 and 34). Outside the MTL, there are no further activations.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left hippocampus		-16	-5	-17	4.47	42
right hippocampus		24	-1	-17	4.01	13

Table 5-8: Maxima of the MTL regions activated in the *Positive Source Memory Effect*, i.e. regions activated more for hits with correct source judgments as opposed to hits with incorrect source judgments during test ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

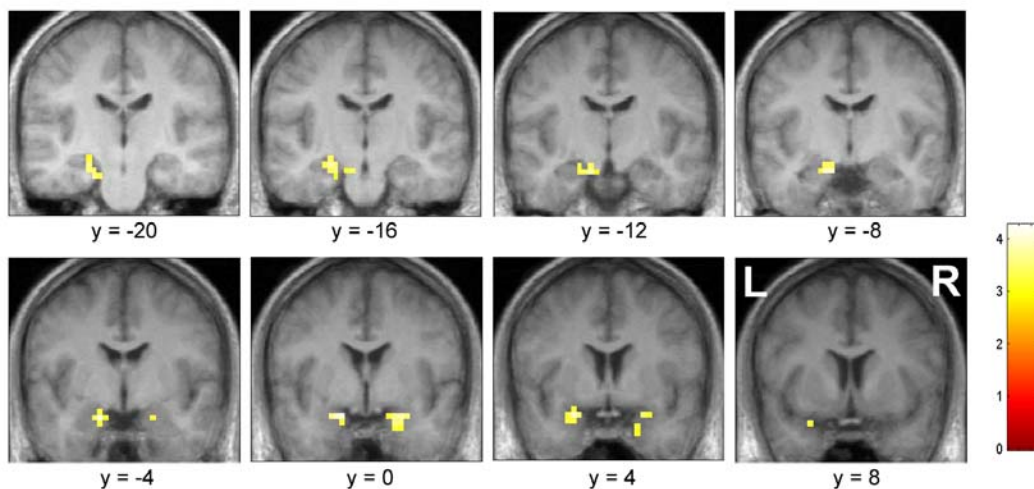


Figure 5-9: *Positive Source Memory Effect*. MTL regions activated more for hits with correct source judgments as opposed to hits with incorrect source judgments during test. The activation map ($p < 0.001$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

The negative source memory effect, weaker activation for hits with correct source judgment as opposed to hits with incorrect source judgment revealed no reliable activation, even after lowering the statistical threshold to $p < 0.05$. Thus, retrieval of contextual information is accompanied by an activity increase in the hippocampus.

In the next step the neural correlates of successful item recognition without contextual retrieval were investigated. The *negative item recognition effect*, a decrease of activity for hits with incorrect source judgment as opposed to misses revealed activation in the right anterior MTL, centered in the parahippocampal gyrus in BA 36 (Figure 5-10 and Table 5-9).

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right parahippocampal gyrus	36	28	-17	-19	3.79	11

Table 5-9: Maximum of the MTL region activated in the *Negative Item Recognition Effect*, i.e. region activated less for hits with incorrect source judgments as opposed to misses during test ($p < 0.001$ uncorrected, minimal cluster size 10 voxels).

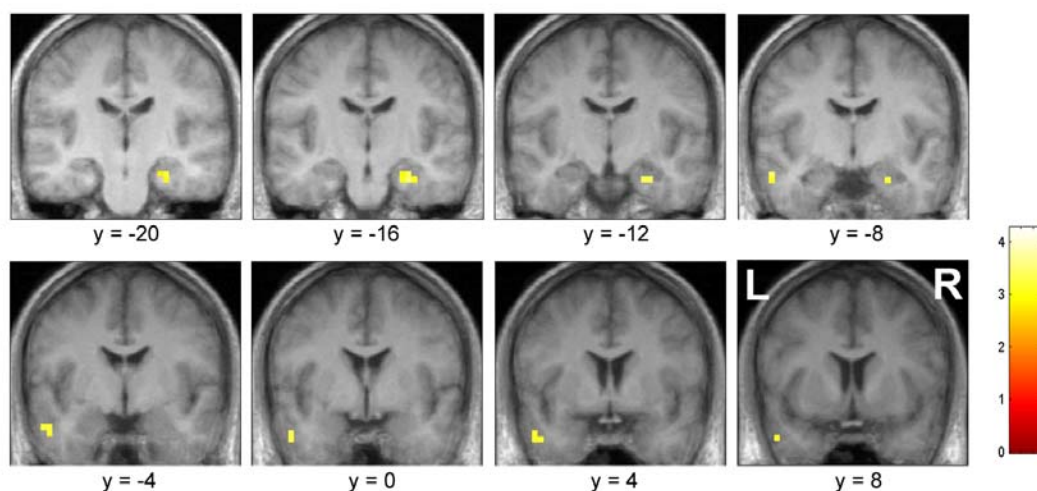


Figure 5-10: *Negative Item Recognition Effect*. MTL region activated less for hits with incorrect source judgments as opposed to misses during test. The activation map ($p < 0.001$ uncorrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

Also, after correction for multiple non-independent comparisons, a cluster of activation in bilateral medial frontal gyrus (BA 10 and 11) remained significant (Figure 5-11 and Table 5-10). Thus, correct item recognition is accompanied by an activity decrease in the anterior parahippocampal gyrus and the medial frontal cortices.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left medial frontal gyrus	10	0	50	-9	4.51	15

Table 5-10: Maximum of the neocortical region activated in the *Negative Item Recognition Effect*, i.e. region activated less for hits with incorrect source judgments as opposed to misses during test ($p < 0.05$ corrected, minimal cluster size 10 voxels).

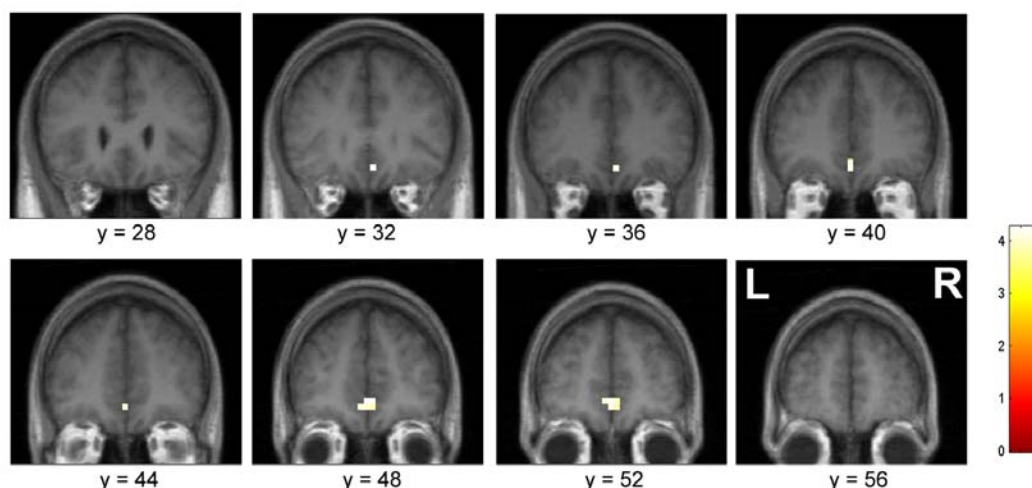


Figure 5-11: *Negative Item Recognition Effect.* Neocortical region activated less for hits with incorrect source judgments as opposed to misses during test. The activation map ($p < 0.05$ corrected, minimal cluster size 10 voxels) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

From the above results it may seem that the positive source memory effect in the MTL is more pronounced on the left, while the negative item recognition effect appears to be more lateralized to the right hemisphere. Therefore, a paired-sample t-test was conducted to directly compared activations of the left and right hemisphere. However, this comparison did not yield any significant lateralization effect neither for the positive source memory effect nor the negative item recognition effect.

The negative item recognition effect can be viewed as less activity for hits with incorrect source judgment than misses or more activity for misses than hits with incorrect source judgment. While the first view would be in line with the idea of an activity decrease associated with a familiarity signal, the latter one would suggest that misses are accompanied by more encoding related activity than already well-encoded items. To further examine this hypothesis, it is necessary to compare the negative item recognition effect with the subsequent memory effect. Hence, the subsequent memory effect computed from the study data was again considered and it was examined whether the subsequent memory effect as found here is conjunct with the negative item recognition effect. This analysis was conducted by way of a conjunction analysis based on the minimum T-field test statistic (Friston et al., 1999b) between both effects. Indeed activity is overlapping in the anterior parahippocampal gyrus bilaterally and extending into the hippocampus (BA 28, 34, 35 and 36) (Figure 5-12 and Table 5-11). All activation outside the MTL does not survive correction for multiple

comparisons. Thus, activity in the same anterior medial temporal area is correlated positively with encoding success and negatively with item recognition success.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left hippocampus		-28	-20	-16	2.42	25
right hippocampus		24	-16	-16	3.73	57
right parahippocampal gyrus	37	28	-43	-8	2.65	17

Table 5-11: Maxima of the MTL regions activated in the conjunction between the *Subsequent Memory Effect* and the *Negative Item Recognition effect*, i.e. regions activated more for hits opposed to misses during study and less for hits with incorrect source judgments as opposed to misses during test ($p < 0.001$ uncorrected).

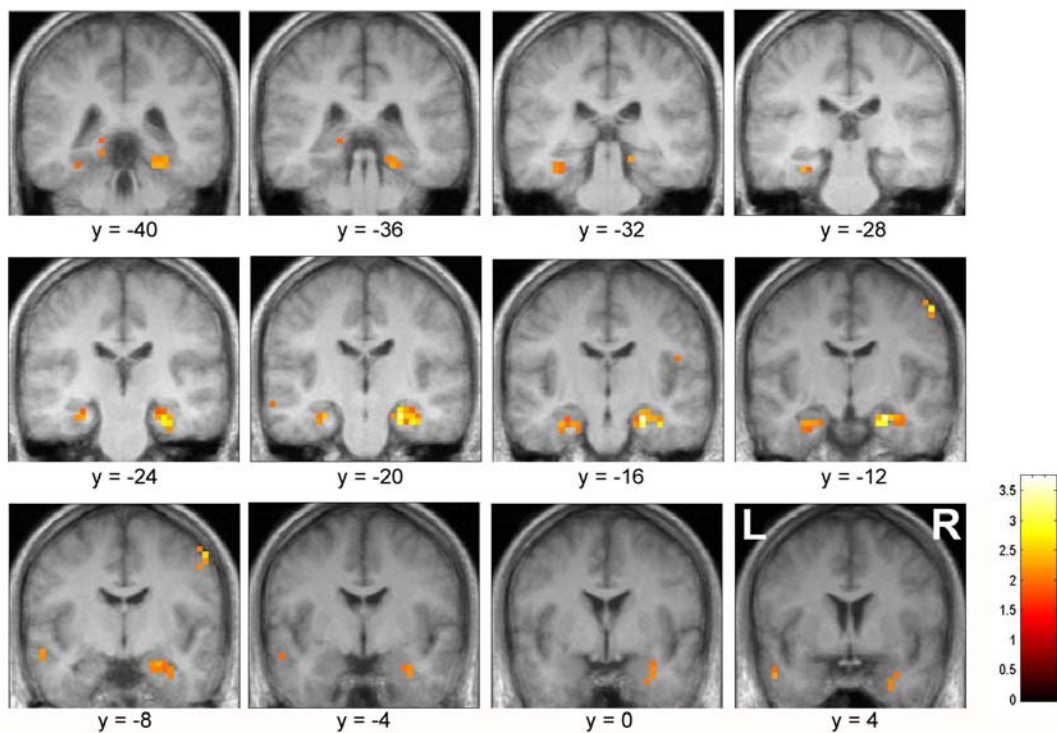


Figure 5-12: Conjunction between the *Subsequent Memory Effect* and the *Negative Item Recognition effect*, i.e. regions activated more for hits as opposed to misses during study and less for hits with incorrect source judgments as opposed to misses during test. The activation map ($p < 0.001$, uncorrected) is shown superimposed onto coronal slices of the mean high-resolution T1-weighted volume.

To search for brain areas that show an activity increase associated with item recognition success, the *positive item recognition effect*, more activity for hits with incorrect source judgment than misses, was computed. This contrast did not show any activation of the MTL. However, it reveals widespread activations across different neocortical areas with a clear left hemispheric dominance. (Figure 5-13 and Table 5-12). Activation was found in the left inferior, middle, superior and medial frontal and the precentral gyrus (BA 4, 6, 8, 9, 10, 44, 45, 46 and 47) and in the right inferior,

middle, superior and medial frontal gyrus (BA 6, 8, 9, 10, 32 and 46). Also, there is bilateral activation of the anterior cingulate (BA 32). In the parietal lobe, activation could be found in the left precuneus, angular and supramarginal gyrus, superior and inferior parietal lobules, and postcentral gyrus (BA 2, 3, 7, 39 and 40). On the right, there is activation of the superior and inferior parietal lobules and the precuneus (BA 7 and 39). In the temporal lobe, only the left hemisphere is activated, namely the inferior and middle temporal gyrus and the fusiform gyrus (BA 20 and 37). Further, there is activation in the left middle occipital gyrus (BA 19) and bilateral cerebellum.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left middle frontal gyrus	9	-51	13	29	7.64	828
left cingulate gyrus	23	-4	-30	27	3.50	15
right middle frontal gyrus	6	32	2	44	3.89	48
right middle frontal gyrus	46	48	32	24	5.67	69
left inferior temporal gyrus	20	-59	-51	-11	4.91	88
left precuneus	7	-8	-67	51	8.34	2525
right cerebellum		8	-75	-23	4.65	17
right cerebellum		16	-52	-21	4.15	114
right lentiform nucleus		20	4	11	3.52	30
right lentiform nucleus		20	11	-4	3.94	22

Table 5-12: Maxima of the neocortical regions activated in the *Positive Item Recognition Effect*, i.e. regions activated more for hits with correct source judgment as opposed to misses during test ($p < 0.05$ corrected, minimal cluster size 10 voxels).

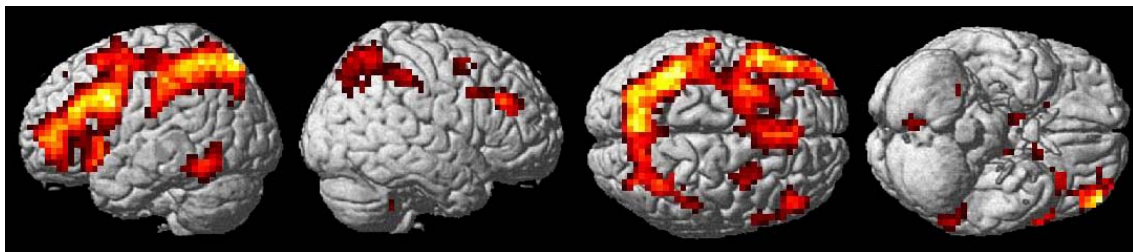


Figure 5-13: *Positive Item Recognition Effect*. Neocortical regions activated more for hits with correct source judgment as opposed to misses during test. The activation map ($p < 0.05$ corrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

To specify further the operations underlying this positive item recognition effect, the positive recognition effect was also computed for hits with correct source judgment. This effect reveals an almost identical pattern of neocortical activations (Figure 5-14 and Table 5-13). Again, this effect did not show any activation of MTL areas at an uncorrected threshold. At the neocortical level, this positive item recognition effect is associated with widespread activations across different neocortical areas with a clear left hemispheric dominance. Frontal activations comprise parts of the inferior, middle, superior and medial frontal gyrus as well as the precentral gyrus (BA 4, 6, 8, 9, 10, 11,

44, 45, 46 and 47) on the left side and the inferior, middle, medial frontal gyrus and the precentral gyrus of the right hemisphere (BA 6, 8, 45 and 46). Furthermore, there is bilateral activation of the anterior cingulate (BA 32). Parietal activations include the inferior and superior parietal lobule, the postcentral, angular and supramarginal gyrus and the precuneus (BA 1, 2, 3, 7, 31 and 40) on the left and right inferior and superior parietal lobule, postcentral gyrus and precuneus (BA 2, 3, 7 and 31). Temporal activations consist of clusters in bilateral inferior and middle temporal as well as lateral fusiform gyri (left hemisphere: BA 20, 21, 28, 34, 35 and 37, right hemisphere: BA 20, 21 and 37). In the occipital lobe, activation was located in the left cingulate and middle occipital gyrus (BA 18 and 19) and the right cuneus, lingual and middle occipital gyrus (BA 17 and 18). Finally, there is bilateral activation of the cerebellum, mainly in midline structures like the vermis.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
right middle frontal gyrus	46	48	32	26	5.77	32
right inferior frontal gyrus	9	59	9	29	4.05	11
left middle temporal gyrus	37	-59	-51	-11	5.17	59
right inferior temporal gyrus	26	56	-48	-20	3.79	26
right cingulate gyrus	31	0	-29	35	4.41	18
left precuneus	7	-8	-67	51	8.34	4098
right middle occipital gyrus	18	20	-100	0	3.38	18
left cerebellum		-24	-59	-17	3.56	38
right cerebellum		28	-63	-20	4.93	306

Table 5-13: Maxima of the neocortical regions activated in the *Positive Item & Source Recognition Effect*, i.e. regions activated more for hits with correct source judgment as opposed to misses during test map ($p < 0.05$ corrected, minimal cluster size 10 voxels).

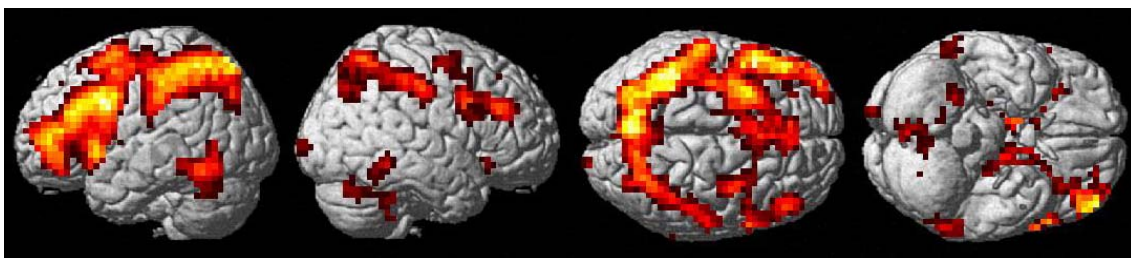


Figure 5-14: *Positive Item & Source Recognition Effect*. Neocortical regions activated more for hits with correct source judgment as opposed to misses during test. The activation map ($p < 0.05$ corrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

Also, a statistical comparison of both positive recognition effects shows stronger activity for the positive recognition effect with correct source judgment than with incorrect source judgment in the left MTL only. This effect is theoretically and in practice identical to the positive source memory effect described above. Thus at first

sight, recognition success with and without correct source judgment seems to be accompanied by an activity increase in identical neocortical brain areas.

However, when contrasting brain responses to false alarms, i.e. new items that were wrongly declared as old, and misses, again an almost identical pattern of neocortical activations was revealed. Frontal activations comprise the inferior, superior, middle and medial frontal gyrus, the precentral gyrus and the anterior cingulate bilaterally (BA 4, 6, 8, 9, 10, 32, 44, 45, 46 and 47). Temporal regions include the superior temporal gyrus and the insula on the left (BA 22, 38 and 13) and the middle and superior temporal gyrus (BA 22) on the right. In the parietal lobe, the angular and supramarginal gyrus, the inferior and superior parietal lobules, the postcentral gyrus and the precuneus bilaterally (BA 1, 2, 3, 7, 19, 39 and 40) are activated. Again, all activations are more pronounced in the left hemisphere. The extend of the activations is somewhat smaller than in the recognition effect, which can be explained by fewer false alarms than hits (Figure 5-15 and Table 5-14). Thus, activity of this large neocortical network might in this certain experimental design not be related to recognition per se, but rather to the source memory task required for all hit and false alarm trials but not for misses.

Anatomical Region	BA	Coordinates			t-value	No. voxels
		x	y	z		
left inferior frontal gyrus	47	-32	16	3	4.51	78
left middle frontal gyrus	46	-48	32	24	4.54	167
left middle frontal gyrus	6	-24	-1	55	4.60	62
right inferior frontal gyrus	9	51	9	33	3.87	31
right superior frontal gyrus	6	0	10	51	4.84	70
right middle frontal gyrus	46	48	32	24	3.51	12
right medial frontal gyrus	25	16	11	-14	4.23	15
right medial frontal gyrus	6	8	33	35	4.97	152
right superior temporal gyrus	22	55	-46	13	3.90	20
left inferior parietal lobule	40	-36	-37	42	6.36	405
right inferior parietal lobule	40	44	-29	42	4.89	92

Table 5-14: Maxima of the neocortical regions activated more for false alarms as opposed to misses during test ($p < 0.05$ corrected, minimal cluster size 10 voxels).

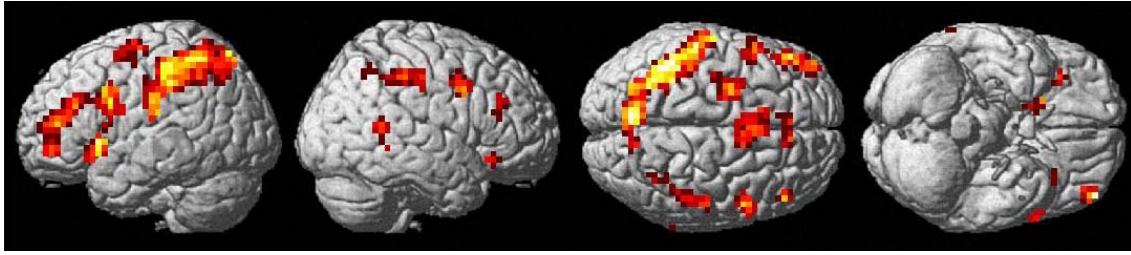


Figure 5-15: *False Alarms > Misses*. Neocortical regions activated more for false alarms as opposed to misses during test. The activation map ($p < 0.05$ corrected, minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions.

5.4 Discussion

It was the aim of this event-related fMRI study to extend the findings of the study presented in chapter 4. Different sub processes of recognition memory were studied, aiming to dissociate human MTL processes associated with either contextual retrieval or item memory. Also the neural correlates of encoding of item memory as opposed to the association of an item to its context were examined. Therefore, the stimuli and the paradigm employed here are very similar to the one used in the study presented in chapter 4 above. A refinement was made by adding a context to each of the studied images, which was realized as one of four colors in which the pictures were presented during study. This manipulation made possible a source memory decision, which not only required subjects to encode and recognize items, but also, during recognition, to make a source judgment about the color in which the items were presented during study. This study design made it possible to distinguish brain activity which resulted in subsequent item recognition and contrast it to the neural correlates of successfully binding a study item with its context. Further, it is possible to compare hemodynamic responses during recognition to hits and misses, and to distinguish between recollection and familiarity by the comparison of hits with correct source judgment to hits without correct source judgment, i.e. those trials, for which the item is remembered but the context is forgotten.

Concerning encoding processes, the subsequent source memory effect, the neural correlates of the successful association of an item and its context during study, revealed an involvement of all MTL subregions including the hippocampus, amygdala as well as the perirhinal and parahippocampal cortex. These results show that an involvement of the hippocampus is especially critical for subsequent recollection, a finding, which is in agreement with the results of several earlier studies (Davachi et al., 2003; Ranganath et al., 2003; Jackson and Schacter, 2004; Henke et al., 1997).

Still, in contrast to those studies, activation of the subsequent source memory effect extends into the amygdala, perirhinal and parahippocampal cortex. These MTL areas are part of the ventral visual pathway where higher order visual processing takes place (Ungerleider and Mishkin, 1985; Nobre and McCarthy, 1995). They have also been shown to be part of the visual working memory system (Ungerleider et al., 1998). As opposed to verbal stimuli, the visuospatial nature and complexity of the pictures used as stimuli here might make an interaction of these higher order visual perception and visual working memory areas with the hippocampus necessary for the association of an item to its context. This is especially so, as both the stimulus itself and the source information, namely the color in which the image is presented during study, both have to be processed as higher order visual information. It has been suggested, that the perirhinal cortex contributes to the processing of relationships between several visual stimuli (Murray and Bussey, 1999). Still, even in this case, the maximum of the activation is located in bilateral hippocampi.

In good accordance with the visuospatial nature of the stimuli, an area in posterior parahippocampal cortex distinguishes subsequent item memory from subsequent misses. A stronger activation of this area, which is associated with higher order visual perception and object recognition during study assumedly results in a familiarity based judgment during recognition.

Also a role of the prefrontal cortex in the encoding of an item together with contextual information as opposed to item information alone has repeatedly been suggested (Cansino et al., 2002; Henson et al., 1999; Buckner, 2003). In accordance with the HERA model of a prefrontal encoding and retrieval asymmetry (Tulving et al., 1994) the prefrontal subsequent source memory effect is located in the left hemisphere.

Concerning the data acquired during recognition, to identify brain areas whose activity is related to item recognition success, the negative item recognition effect was employed, a decrease of activity for hits with incorrect source judgment as opposed to misses. In line with the hypothesis an anterior MTL deactivation was revealed; this decrease of activation was centered in the anterior parahippocampal gyrus, which is covered by ento- and perirhinal cortex (Amaral and Insausti, 1990).

Evidence from studies in experimental animals suggests that this area plays a key role in visual recognition memory (Murray and Bussey, 1999; Meunier et al., 1993; Bachevalier et al., 2002; Gaffan, 2002). Specifically, a decrease in object-selective

responses with repeated exposure has been shown (Brown and Xiang, 1998). Thus, it has been suggested that the perirhinal cortex contributes to recognition memory by assessing relative familiarity, which is based on neuronal response decrements (Brown and Aggleton, 2001). The data presented here suggest a similar mechanism in humans, in which more neural resources may be needed for items that are processed for the first time than for those that have been encountered before and are therefore already familiar. Thus, this processing stage might support item recognition by a familiarity signal, which essentially is based on a reduced processing demand for more familiar items.

While data concerning the role of the perirhinal cortex in recognition memory almost exclusively comes from work with experimental animals, there is some data to suggest that the region has an equivalent role in humans. A meta-analysis of several event-related fMRI studies employing different kinds of study material also suggested that less anterior MTL activity is related to the amount of familiarity (Henson et al., 2003). Also, in the study presented in chapter 4 above, it was shown that a decrease of activity in the anterior MTL is related to recognition success. In line with (Brown and Aggleton, 2001) and (Brown and Bashir, 2002), it was hypothesized that the negative recognition effect in the anterior MTL might rather support a familiarity-based decision than an actual recollective experience (Henson et al., 2003) and that it may reflect a process enabling recognition by more efficient processing of recognized stimuli with reduced neural activity during an active memory search (Jiang et al., 2000), or by a neural activity increase in the presence of novel stimuli or old stimuli incorrectly classified as new (Brown and Bashir, 2002).

However, more activity in this MTL region is associated with a higher probability of successful memory formation (Brewer et al., 1998; Wagner et al., 1998b; Kirchhoff et al., 2000; Davachi et al., 2001; Otten et al., 2001; Otten and Rugg, 2001a; Strange et al., 2002). It follows that another way of looking at the negative item recognition effect concerns the amount of re-encoding activity elicited during test by new items as well as old items misclassified as new (Buckner et al., 2001). Indeed, the subsequent source memory data show that the anterior MTL is related both to item recognition by an activity decrease and declarative memory formation by an activity increase. This finding is in line with electrophysiological data recorded from within this region in epilepsy patients, where the very same event related potential is correlated with both item recognition and encoding success (Smith et al., 1986; Fernández et al., 1999b;

Fernández et al., 2001; Fernández et al., 2002). However, the two explanations are not mutually exclusive, they might rather represent the two sides of the same coin, where familiar items have less processing demands and deeply processed items are subsequently better remembered.

As opposed to mere item recognition, a correct source judgment requires the retrieval of contextual information. Several event-related fMRI studies have found an increase of hippocampal activation when the task required the retrieval of contextual information, respectively when items classified as remembered by the subject were contrasted with those classified as know (Cansino et al., 2002; Eldridge et al., 2000; Dobbins et al., 2003). Thus, the difference in brain activity between hits with and without correct source judgment was analyzed. As predicted, this contrast led to bilateral MTL activation, centered in the hippocampus. In line with prior studies (Eldridge et al., 2000; Cansino et al., 2002; Dobbins et al., 2003), this finding indicates that activation of the hippocampus, which is reciprocally connected to numerous parts of associative cortex (Insausti et al., 1998), is essential for the process of linking an item to contextual information during retrieval. Thus, the hippocampus seems to support truly episodic or associative memory (Eichenbaum, 2001) by linking an item to contextual information during retrieval.

In line with experimental animal data, these findings suggest a clear-cut process dissociation within the human MTL, where contextual retrieval is associated with an activity increase and item recognition goes along with an activity decrease. Thus, these two effects are clearly dissociated. However, given MTL signal distortions due to susceptibility artifacts and spatial filtering during normalization, averaging, and smoothing of the data, it is difficult to confirm a clear-cut anatomical dissociation based on these findings alone. Nevertheless, the focal maxima of the activation clusters are located in different MTL subregions, one in the hippocampus (positive source memory effect) and one in the parahippocampal gyrus (negative item recognition effect). Such anatomical dissociation is also in line with findings from event-related fMRI studies on memory encoding (Ranganath et al., 2003; Davachi et al., 2003), which showed that encoding activity in the rhinal cortex predicted familiarity-based recognition while encoding activity in the hippocampus was predictive for subsequent recollection. Together with these findings, the data presented here also adds to the mounting evidence of a functional dissociation between the hippocampus and the rhinal cortices.

The two positive recognition effects, the contrasts between brain activity for hits with and without correct source judgment as opposed to misses as well as the contrast between false alarms and misses showed very similar patterns of activation in a variety of neocortical areas, including prefrontal and parietal cortices. The missing difference in neocortical activation between hits with and without correct source judgment is in line with prior results (Dobbins et al. 2002) and requires a specific interpretation.

In contrast to miss-trials, all hit- and false alarm-trials are associated with a search task, since for all items classified as old by the subject, the search for contextual information is initiated. Thus, the common main effect depicted in the three contrasts shown in Figure 5-13, Figure 5-14 and Figure 5-15 relates to a difference in task demands rather than a difference in recognition memory. Therefore, it is suggested that this large neocortical network might be related to search processes associated to the source task rather than to recognition memory. Such search process requires the recruitment of brain regions involved with control and evaluation of retrieved information. Several frontal brain regions have been shown to be involved with control processes in memory retrieval (Buckner, 2003). Specifically, it has been shown that the amount of prefrontal activation increases as the amount or difficulty of retrieved contextual information increases (Konishi et al., 2002; Ranganath et al., 2000). Further, it has been suggested (Buckner, 2003) that frontal regions associated with memory retrieval are likely to constitute general computational resources that allow selection and control of context-appropriate representations in many task contexts. Therefore, activations of this large neocortical network might be related to the search for source information which is initiated for both hits with and without correct source judgments but not for misses, since for all items classified as old, subjects are required to try and retrieve contextual information. This process requires the recruitment of brain regions involved with control and evaluation of the retrieved source information. These control processes might be mediated by prefrontal cortex, operating on stimulus representations which are restored in the parietal lobe (Buckner et al., 1996; Fletcher et al., 1996; Buckner, 2003), especially as the stimuli used here are very complex and furthermore visuo-spatial in nature.

In conclusion, the data presented here provide first evidence for a process-dissociation between item recognition and contextual retrieval within the human MTL as previously suggested based on experimental animal data (Brown and Aggleton, 2001). While an activity increase in the hippocampus may play a key role in the re-association of

complex episodes, which is essential for successful contextual retrieval, a reduction of processing activity in the rhinal cortex is sufficient for item recognition, which might be the basis for a feeling of familiarity.

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6 General Discussion

The major focus of this thesis was put on MTL contributions to episodic memory processes. In contrast to lesion studies, functional brain imaging offers the possibility to study the neural correlates of episodic memory in healthy human subjects. Most important and in contrast to lesion studies, the use of functional imaging studies offers the possibility to distinguish between the contributions of distinct brain regions to subprocesses within episodic memory, and thus to delineate processes associated with either the formation of new memories or the retrieval from memory. Therefore, the method adopted in this thesis for the study of episodic memory processes is event-related fMRI.

The first study presented in this work focused on common neural correlates of both the formation of new episodic memories and retrieval from episodic memory. The main feature this study adds to the existing literature is the fact that both memory encoding and recognition were examined in a single event-related fMRI study. In contrast to existing studies, this study design offers the opportunity to directly compare encoding- and retrieval-related activations within subjects, making it possible to delineate brain areas involved with both memory encoding and retrieval. These brain areas were found in inferior and medial temporal as well as in cerebellar brain regions. By the efficient use of matching operations, these neural modules can re-use stored representations during recognition which were formed locally during encoding. Also, by replicating efMRI studies investigating either memory formation or recognition, this study has provided within-study confirmation for brain areas involved in two fundamental mnemonic operations: the formation and the retrieval of declarative memories.

As a further innovation, in this study a positive and a negative recognition effect were introduced, comparing – in analogy to the subsequent memory effect - brain activity during test to hits and misses. This contrast is more closely related to recognition success than the commonly used old/new effect. In addition, the negative recognition effect, which is less contaminated by repetition priming than a reversed old/new effect, offers the possibility to study whether recognition success can be associated with both regional brain activity increases and decreases. Findings from the positive recognition effect support the view that frontal, parietal and cerebellar regions are involved in the successful recovery of declarative memories during a recognition memory task.

Further, the negative recognition effect indicates that less activity in the anterior MTL is related to recognition success. The major findings of this study are summarized in Figure 6-1.

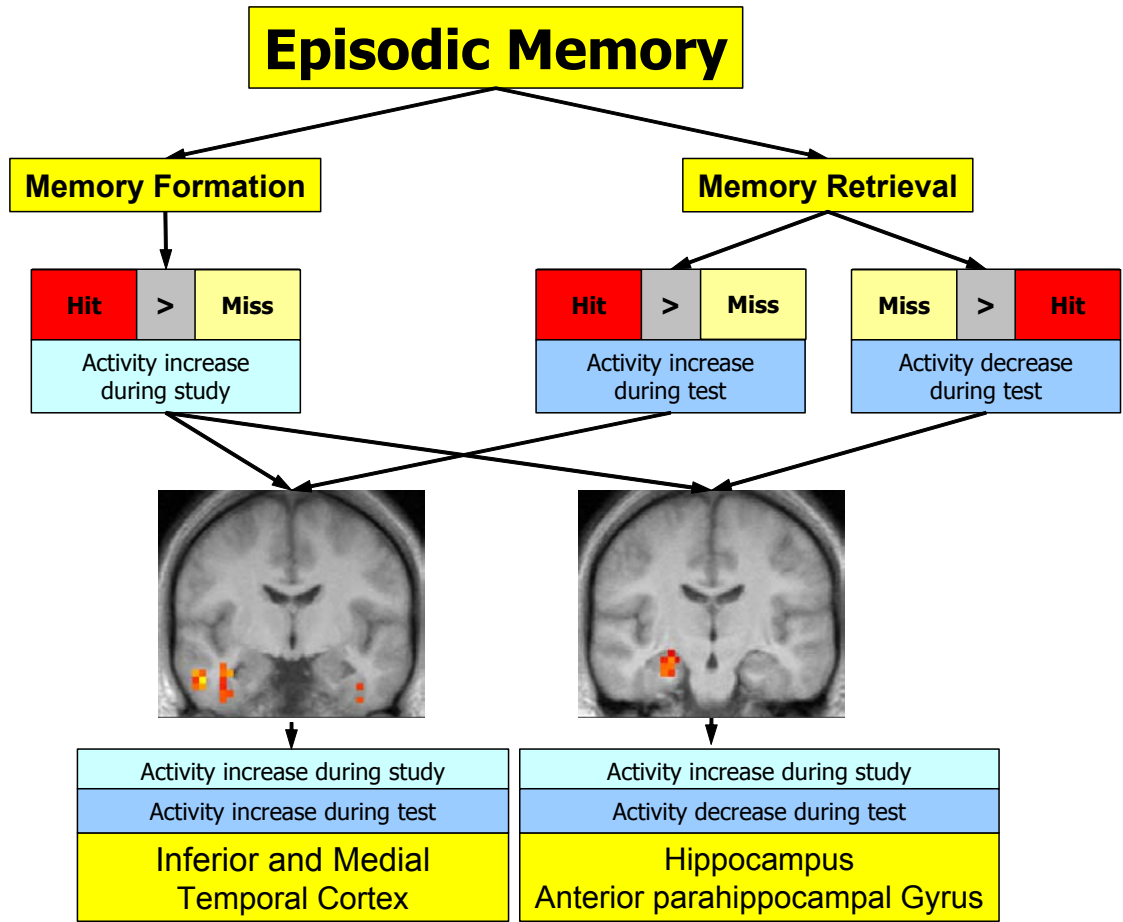


Figure 6-1: Schematic representation of the results of the study presented in chapter 4.

One drawback of the study presented in chapter 4 relates to the fact, that in the design employed it was impossible to segregate hits according to whether they were based on familiarity alone, or accompanied by recollection. Therefore, it was impossible to further analyze the nature of the recognition effects and the differential contribution of MTL subregions to either item memory or contextual retrieval.

This question was addressed in the study presented in chapter 5. The same stimuli and essentially the same study design were now used in the context of a source memory paradigm, thus making it possible to distinguish between subprocesses within recognition and to examine whether an activation is related to mnemonic processes based on recollection or familiarity. Again, both encoding into episodic memory and recognition were studied in the same event-related fMRI experiment, but this time the

main focus was put on subprocesses within recognition. It was the aim of this study to dissociate human MTL processes associated with either contextual retrieval or item recognition.

The neural correlates of successful contextual retrieval were investigated by the use of the positive source memory effect, more brain activity for hits with correct source judgment as opposed to hits without correct source judgment. As a measure of item memory, the item recognition effect, the difference between hits without correct source judgment and misses was employed. By the results of these contrasts, the data presented here suggest a process dissociation within the human MTL, where contextual retrieval is associated with an activity increase in the hippocampus and item recognition is accompanied by an activity decrease in the anterior parahippocampal gyrus. Thus, these data provide first evidence for a process-dissociation between contextual retrieval and item recognition within the human MTL. A key role in the re-association of complex episodes, which is the essential factor in successful contextual retrieval, can be attributed to an activity increase in the hippocampus, while a reduction of processing activity in the rhinal cortex is sufficient for item recognition, which might be based on a feeling of familiarity. By this dissociation, the data presented here clearly supports dual-process models of recognition memory, which propose that recollection and familiarity are supported by qualitatively distinct neural mechanisms, instead of merely reflecting a quantitative difference in the strength of a memory trace. Thus, it might be suggested, that although the hippocampus and the perirhinal cortex will usually function as interacting components of an integrated memory system, their contributions are different and can be dissociated. The major results of this study are summarized in Figure 6-2.

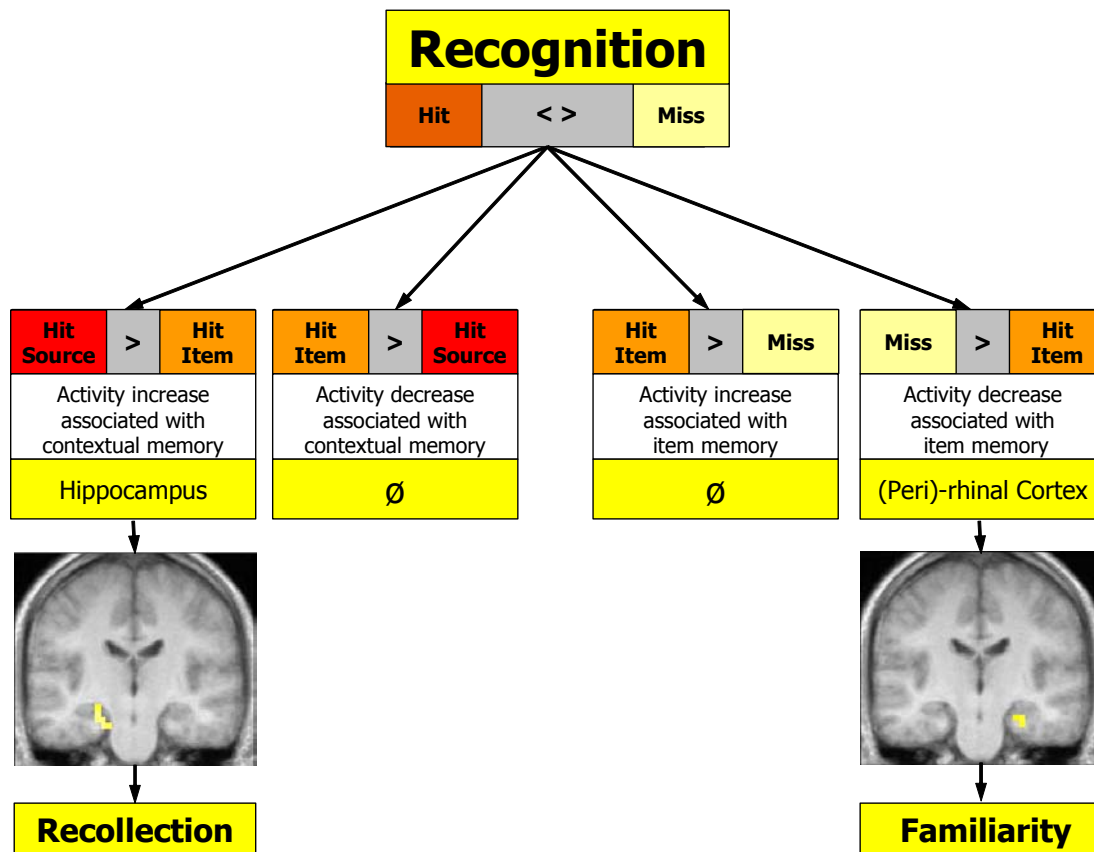


Figure 6-2: Schematic representation of the results of the study presented in chapter 5.

In conclusion, the work presented in this thesis has presented several innovative and important insights into the function of the human MTL memory system. Recognition memory is based on different functional mechanisms; while an activity increase in the hippocampus is essential for the re-establishment of contextual details, an activity decrease in anterior parahippocampal cortex is the basis of a familiarity based item recognition. The very same brain region shows an activity increase during successful memory formation, indicating that neural substrates formed during encoding can be efficiently re-used during item recognition for efficient pattern matching operations. These results are in line with electrophysiological evidence in experimental animals and may explain contradicting findings in human lesion studies, where lesions cleanly confined to one of the MTL substructures cannot be found.

7 References

- Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav. Brain Sci.* 22: 425-444.
- Aggleton JP, Shaw C (1996) Amnesia and recognition memory: a re-analysis of psychometric data. *Neuropsychologia* 34: 51-62.
- Amaral DG, Insausti R (1990) Hippocampal formation. In: *The human nervous system* (Paxinos G, ed.), pp. 711-755. San Diego, CA: Academic Press.
- Andersson JL, Skare S (2002) A Model-Based Method for Retrospective Correction of Geometric Distortions in Diffusion-Weighted EPI. *Neuroimage* 16: 177-199.
- Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Rezai K, Watkins GL, Ponto LLB, Hichwa RD (1995) Short-term and long-term verbal memory: A positron emission tomography study. *Proc. Natl. Acad. Sci. USA* 92: 5111-5115.
- Andreasen NC, O'Leary DS, Paradiso S, Cizadlo T, Arndt S, Watkins GL, Ponto LL, Hichwa RD (1999) The cerebellum plays a role in conscious episodic memory retrieval. *Hum. Brain Mapp.* 8: 226-234.
- Ashburner J, Neelin P, Collins DL, Evans A, Friston K (1997) Incorporating prior knowledge into image registration. *Neuroimage* 6: 344-352.
- Atkinson RC, Juola JF (1974) Search and decision processes in recognition memory. In: *Contemporary Developments in Mathematical Psychology in Learning, Memory and Thinking*. (Vol. 1) (Krantz DH, ed.), pp. 242-293, W.H. Freeman.
- Attwell PJ, Cooke SF, Yeo CH (2002) Cerebellar function in consolidation of a motor memory. *Neuron* 34: 1011-1020.
- Bachevalier J, Namanic S, Alvarado MC (2002) The medial temporal lobe structures and object recognition memory in nonhuman primates. In: *Neuropsychology of memory*. 3rd ed. (Squire LR, Schacter DL, eds.), pp. 326-338. New York: Guilford Press.
- Bäckman L, Almkvist O, Andersson J, Nordberg A, Winblad B, Reineck R, Långström B (1997) Brain activation in young and older adults during implicit and explicit retrieval. *J. Cogn. Neurosci.* 9: 378-391.
- Bloch F (1946) Nuclear Induction. *Phys. Rev.* 70: 460-474.
- Boynton GM, Engel SA, Glover GH, Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci.* 16: 4207-4221.
- Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A (2001) Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cereb. Cortex* 11: 825-836.
- Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD (1998) Making memories: brain activity that predicts how well visual experience will be remembered. *Science* 281: 1185-1187.
- Brodman K (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellbaues*. Leipzig: Barth.
- Brown MW, Aggleton JP (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus. *Nat. Rev. Neurosci.* 2: 51-61.
- Brown MW, Bashir ZI (2002) Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 357:1083-1095.
- Brown MW, Xiang JZ (1998) Recognition memory: neuronal substrates of the judgment of prior occurrence. *Prog. Neurobiol.* 55: 149-189.

- Brown MW, Wilson FA, Riches IP (1987) Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. *Brain Res.* 409(1): 158-162.
- Buckner RL (2003) Functional-Anatomical Correlates of Control Processes in Memory. *J. Neurosci* 23: 3999-4004.
- Buckner RL, Koutstaal W (1998) Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. *Proc. Natl. Acad. Sci. USA* 95: 891-898.
- Buckner RL, Raichle ME, Miezin FM, Petersen SE (1996) Functional anatomic studies of memory retrieval for auditory words and visual pictures. *J. Neurosci.* 16: 6219-6235.
- Buckner RL, Koutstaal W, Schacter DL, Wagner AD, Rosen BR (1998) Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. *Neuroimage* 7:151-162.
- Buckner RL, Wheeler ME, Sheridan MA. (2001). Encoding processes during retrieval tasks. *J. Cogn. Neurosci.* 13: 406-415.
- Büchel C, Price C, Friston K (1998) A multimodal language region in the ventral visual pathway. *Nature* 394: 274-276.
- Cabeza R, Nyberg L (2000) Imaging Cognition II: An Empirical Review of 275 PET and fMRI Studies. *J. Cogn. Neurosci.* 12: 1-47.
- Cabeza R, Kapur S, Craik FIM, McIntosh AR, Houle S, Tulving E (1997) Functional Neuroanatomy of Recall and Recognition: A PET Study of Episodic Memory. *J. Cogn. Neurosci.* 9: 254-265.
- Cabeza R, Rao SM, Wagner AD, Mayer AR, Schacter DL (2001) Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. *Proc. Natl. Acad. Sci. U. S. A.* 98: 4805-4810.
- Cansino S, Maquet P, Dolan RJ, Rugg MD (2002) Brain activity underlying encoding and retrieval of source memory. *Cereb. Cortex* 12: 1048-1056.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998) Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280: 747-749.
- Cocosco C, Kollokian V, Kwan R, Evans A (1997) BrainWeb: Online Interface to a 3D MRI Simulated Brain Database. *Neuroimage* 5:S425.
- Cohen NJ, Eichenbaum H (1993) Memory, amnesia, and the hippocampal system. Cambridge, MA: MIT Press.
- Craik F, Lockhart R (1972) Levels of processing: a framework for memory research. *J. Verb. Learn. Verb. Behav.* 11: 671-684.
- Dale AM, Buckner RL (1997) Selective averaging of rapidly presented individual trials using fMRI. *Hum. Brain Mapp.* 5: 329-340.
- Davachi L, Wagner AD (2002) Hippocampal contributions to episodic encoding: Insights from relational and item-based learning. *J. Neurophysiol.* 88: 982-990.
- Davachi L, Maril A, Wagner AD (2001). When keeping in mind supports later bringing to mind: neural markers of phonological rehearsal predict subsequent remembering. *J. Cogn. Neurosci.* 13: 1059-1070.
- Davachi L, Mitchell JP, Wagner AD (2003) Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. USA* 100: 2157-62.
- Desgranges B, Baron JC, Eustache F (1998) The functional neuroanatomy of episodic memory: the role of the frontal lobes, the hippocampal formation, and other areas. *Neuroimage* 8:198-213.
- Desimone R, Albright TD, Gross CG, Bruce C (1984) Stimulus-selective properties of inferior temporal neurons in the macaque. *J. Neurosci.* 4: 2051-2062.

- Desmond JE, Fiez JA (1998) Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn. Sci.* 2: 355-362.
- Desmond JE, Gabrieli JDE, Glover GH (1998) Dissociation of Frontal and Cerebellar Activity in a Cognitive Task: Evidence for a Distinction between Selection and Search. *Neuroimage* 7: 368-376.
- De Zeeuw CI, Simpson JI, Hoogenraad CC, Galjart N, Koekkoek SK, Ruigrok TJ (1998) Microcircuitry and function of the inferior olive. *Trends Neurosci.* 21: 391-400.
- Dobbins IG, Foley H, Schacter DL, Wagner AD (2002) Executive Control during Episodic Retrieval: Multiple Prefrontal Processes Subserve Source Memory. *Neuron* 35: 989-996.
- Dobbins IG, Rice HJ, Wagner AD, Schacter DL (2003) Memory orientation and success: separable neurocognitive components underlying episodic recognition. *Neuropsychologia* 41: 318-333.
- Dolan RJ, Fletcher PC (1997) Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* 388: 582-585.
- Donaldson W (1996) The role of decision processes in remembering and knowing. *Mem. Cogn.* 24: 523-533.
- Donaldson DI, Buckner RL (1999) Trying versus succeeding: event-related designs dissociate memory processes. *Neuron* 22: 412-414.
- Donaldson DI, Petersen SE, Buckner RL (2001a) Dissociating memory retrieval processes using fMRI: evidence that priming does not support recognition memory. *Neuron* 31: 1047-1059.
- Donaldson DI, Petersen SE, Ollinger JM, Buckner RL (2001b) Dissociating state and item components of recognition memory using fMRI. *Neuroimage* 13: 129-142.
- Dudai Y (1997) How big is human memory, or on being just useful enough. *Learn. Mem.* 3: 341-365.
- Duelli R, Kuschinsky, W (1993) Changes in brain capillary diameter during hypocapnia and hypercapnia. *J. Cereb. Blood Flow Metab.* 13: 1025-1028.
- Duzel E, Cabeza R, Picton TW, Yonelinas AP, Scheich H, Heinze HJ, Tulving E (1999) Task-related and item-related brain processes of memory retrieval. *Proc. Natl. Acad. Sci. USA* 96: 1794-1799.
- Eichenbaum H (2000) A cortical-hippocampal system for declarative memory. *Nat. Rev. Neurosci.* 1: 41-50.
- Eichenbaum H (2001) The hippocampus and declarative memory: cognitive mechanisms and neural codes. *Behav. Brain Res.* 14: 199-207.
- Eichenbaum H, Otto T, Cohen NJ (1994) Two functional components of the hippocampal memory system. *Behav. Brain. Sci.* 17: 449-518.
- Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA (2000) Remembering episodes: a selective role for the hippocampus during retrieval. *Nat Neurosci.* 3: 1149-1152.
- Fahy FL, Riches IP, Brown MW (1993) Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Exp. Brain Res.* 96: 457-472.
- Fernández G, Weyerts H, Schrader-Bolsche M, Tendolkar I, Smid HG, Tempelmann C, Hinrichs H, Scheich H, Elger CE, Mangun GR, Heinze HJ (1998) Successful verbal encoding into episodic memory engages the posterior hippocampus: a parametrically analyzed functional magnetic resonance imaging study. *J. Neurosci.* 18: 1841-1847.
- Fernández G, Brewer JB, Zhao Z, Glover GH, Gabrieli JDE (1999a) Level of sustained entorhinal activity at study correlates with subsequent cued-recall performance: a functional magnetic resonance imaging study with high acquisition rate. *Hippocampus* 9: 35-44.

- Fernández G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dümpelmann M, Van Roost D, Elger CE (1999b) Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science* 285: 1582-1585.
- Fernández G, Heitkemper P, Grunwald T, Van Roost D, Urbach H, Pezer N, Lehnertz K, Elger CE (2001) An inferior temporal stream for word processing with integrated mnemonic function. *Hum. Brain Mapp.* 14: 251-260.
- Fernández G, Klaver P, Fell J, Grunwald T, Elger CE (2002) Human declarative memory formation: segregating rhinal and hippocampal contributions. *Hippocampus* 12: 514-519.
- Fletcher PC, Henson RN (2001) Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124: 849-881.
- Fletcher PC, Dolan RJ, Frith CD (1995a) The functional anatomy of memory. *Experimentia* 51: 1197-1207.
- Fletcher PC, Frith CD, Baker S, Shallice T, Frackowiak RSJ, Dolan RJ (1995b) The mind's eye – activation of the precuneus in memory related imagery. *Neuroimage* 2:196-200.
- Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RS, Dolan RJ (1995c) Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. *Brain* 118: 401-416.
- Fletcher PC, Shallice T, Frith CD, Frackowiak RS, Dolan RJ (1996) Brain activity during memory retrieval. The influence of imagery and semantic cueing. *Brain* 119: 1587-1596.
- Fletcher PC, Frith CD, Rugg MD (1997) The function neuroanatomy of episodic memory. *Trends Neurosci.* 20: 213-218. Fletcher PC, Shallice T, Frith CD, Frackowiak RS, Dolan RJ (1996b) Brain activity during memory retrieval. The influence of imagery and semantic cueing. *Brain* 119: 1587-1596.
- Friston KJ (1998) Imaging neuroscience: principles or maps? *Proc. Natl. Acad. Sci. USA* 95: 796-802.
- Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1991) Comparing functional (PET) images: the assessment of significant change. *J. Cereb. Blood Flow Metab.* 11: 690-699.
- Friston K, Jezzard P, Turner R (1994a) Analysis of Functional MRI Time-Series. *Hum. Brain Mapp.* 1: 153-171.
- Friston K, Worsley K, Frackowiak R, Mazziotta J, Evans A (1994b) Assessing the Significance of Focal Activations Using their Spatial Extent. *Hum. Brain Mapp.* 1: 214-220.
- Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ (1995a) Spatial registration and normalization of images. *Hum. Brain Mapp.* 2: 165-189.
- Friston KJ, Frith CD, Turner R, Frackowiak RS (1995b) Characterizing evoked hemodynamics with fMRI. *Neuroimage* 2: 157-165.
- Friston KJ, Holmes A, Worsley KJ, Poline JP, Frith C, Frackowiak R (1995c) Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* 2: 189-210.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998). Event-related fMRI: characterizing differential responses. *Neuroimage* 7: 30-40.
- Friston KJ, Holmes AP, Worsley KJ (1999a) How many subjects constitute a study? *Neuroimage* 10: 1-5.
- Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ (1999b) Multisubject fMRI studies and conjunction analyses. *Neuroimage* 10: 385-396.
- Gabrieli JD (1998) Cognitive neuroscience of human memory. *Annu. Rev. Psychol.* 49: 87-115.
- Gabrieli JD, Brewer JB, Desmond JE, Glover GH (1997) Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 276: 264-266.

- Gaffan D (1994) Role of the amygdala in picture discrimination learning with 24-h intertrial intervals. *Exp. Brain Res.* 99: 423-430.
- Gaffan D (2002) Against memory systems. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357: 1111-1121.
- Gardiner JM (1988) Functional aspects of recollective experience. *Mem. Cogn.* 16: 309-313.
- Gardiner JM, Java RI (1991) Forgetting in recognition memory with and without recollective experience. *Mem.Cognit.* 19: 617-623.
- Gardiner JM, Java RI (1993) In: *Theories of memory* (Collins A, Conway MA et al., eds.), pp. 163-188. Hillsdale, NJ. Erlbaum.
- Gardiner JM, Parkin AJ (1980) Attention and recollective experience in recognition memory. *Mem. Cognit.* 18: 579-583.
- Gardiner JM, Ramponi C, Richardson-Klavehn A (1998) Experiences of remembering, knowing, and guessing. *Conscious. Cogn.* 7: 1-26.
- Gardiner JM, Ramponi C, Richardson-Klavehn A (2002) Recognition memory and decision processes: a meta-analysis of remember, know, and guess responses. *Memory* 10: 83-92.
- Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15: 870-878.
- Goldman-Rakic PS, Selemon LD, Schwartz ML (1984) Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience* 12: 719-743.
- Goodlett CR, Hamre KM, West JR (1992) Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration (pcd) mutant mice. *Behav. Brain Res.* 47: 129-141.
- Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ (1993) Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain* 116: 1-20.
- Habib R, Lepage M (1999) Novelty assessment in the brain. In: *Memory, consciousness and the brain* (Tulving E, ed.), pp. 265-277, London: Psychology Press.
- Habib R, Nyberg L, Tulving E (2003) Hemispheric asymmetries of memory: the HERA model revisited. *Trends Cogn. Sci.* 7: 241-245.
- Hahn E (1950) Spin Echoes. *Phys. Rev.* 80: 580-594.
- Haist F, Shimamura AP, Squire LR (1992) On the relationship between recall and recognition memory. *Exp. Psychol. Learn. Mem. Cogn.* 18: 691-702.
- Hasse A, Frahm J, Matthai D, Hänicken W, Merboldt KD (1986) FLASH Imaging. Rapid NMR Imaging Using Low Flip-Angle Pulses. *J. Magn. Reson.* 67: 258-266.
- Haxby JV (1996) Medial temporal lobe imaging. *Nature* 380: 669-670.
- Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, Herscoviyh P, Shapiro MB, Rapoport SI (1991) Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc. Natl. Acad. Sci. USA* 88: 1621-1625.
- Haxby JV, Ungerleider LG, Horwitz B, Maisog JM, Rapoport SI, Grady CL (1996) Face encoding and recognition in the human brain. *Proc. Natl. Acad. Sci. USA* 93: 922-927.
- Henke K, Buck A, Weber B, Wieser HG (1997) Human hippocampus establishes associations in memory. *Hippocampus* 7: 249-256.
- Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ (1999) Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *J. Neurosci.* 19: 3962-3972.
- Henson R, Shallice T, Dolan R (2000) Neuroimaging Evidence for Dissociable Forms of Repetition Priming. *Science* 287: 1269-1272.

- Henson RN, Cansino S, Herron JE, Robb WG, Rugg MD (2003) A familiarity signal in human anterior medial temporal cortex? *Hippocampus* 13: 301-304.
- Holdstock JS, Gaffan D, Mayes AR (2000) Perceptual and mnemonic matching-to-sample in humans: contributions of the hippocampus, perirhinal and other medial temporal lobe cortices. *Cortex* 36: 301-322.
- Holmes A, Friston K (1998). Generalisability, random effects and population inference. *Neuroimage* 7: S754.
- Holmes A, Josephs O, Büchel C, Friston K (1997). Statistical modelling of low frequency confounds in fMRI. *Neuroimage* 5: S480.
- Hyder F, Rothman DL, Mason GF, Rangarajan A, Behar KL, Shulman RG (1997) Oxidative glucose metabolism in rat brain during single forepaw stimulation: a spatially localized $^1\text{H}[^{13}\text{C}]$ nuclear magnetic resonance study. *J. Cereb. Blood Flow Metab.* 17:1040-1047.
- Incisa Della Rocchetta A, Milner B (1993) Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia* 31: 503-524.
- Insauti R, Tunon T, Sobreviela T, Incauti, Ponzalo L (1995) The human entorhinal cortex: a cytoarchitectonic analysis. *J. Comp. Neurol.* 335: 171-198.
- Insauti R, Juottonen K, Soininen H, Insauti A, Paranen K, Vainio P, Laakso M, Pitkänen A (1998) MR Volumetric Analysis of the Human Entorhinal, Perirhinal, and Temporopolar Cortices. *Am. J. Neuroradiol.* 19: 659-671.
- Jackson O, Schacter DL (2004) Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage* in press.
- Jacoby LL, Dallas M (1981) On the relationship between autobiographical memory and perceptual learning. *J. Exp. Psychol. Gen.* 110: 306-340.
- Jacoby LL, Kelly C (1992). In: *The neuropsychology of consciousness* (Milner AD, Rugg MD, eds) pp. 201-234. London: Academic Press.
- James W (1890) *Principles of psychology*. New York: Holt.
- Janowsky JS, Shimamura AP, Kritchevsky M, Squire LR (1989) Cognitive impairment following frontal lobe damage and its relevance in human amnesia. *Beh. Neurosci.* 103: 548-560.
- Jiang Y, Haxby JV, Martin A, Ungerleider LG, Parasuraman R (2000) Complementary neural mechanisms for tracking items in human working memory. *Science* 287: 643-646.
- Johnson MK, Raye KL (1981) Reality monitoring. *Psychol. Rev.* 88: 67-85.
- Josephs O, Turner R, Friston KJ (1997) Event-Related fMRI. *Hum. Brain Mapp.* 5: 243-248.
- Josephs O, Henson RN (1999) Event-related functional magnetic resonance imaging: modelling, inference and optimization. *Philos. Trans. R. Soc. Lond B Biol. Sci.* 354: 1215-1228.
- Kapur S, Craik FIM, Tulving E, Wilson AA, Houle S, Brown GM (1994) Neuroanatomical correlates of encoding in episodic memory: Levels of the processing effect. *Proc. Natl. Acad. Sci. USA* 91: 2008-2011.
- Kapur S, Craik FI, Jones C, Brown GM, Houle S, Tulving E (1995) Functional role of the prefrontal cortex in retrieval of memories: a PET study. *Neuroreport* 6: 1880-1884.
- Kapur S, Tulving E, Cabeza R, McIntosh AR, Houle S, Craik FIM (1996) The neural correlates of intentional learning of verbal materials: A PET study in humans. *Cognit. Brain Res.* 4: 243-249.
- Keele SW, Ivry R (1990) Does the cerebellum provide a common computation for diverse tasks? A timing hypothesis. *Ann. N. Y. Acad. Sci.* 608: 179-207.
- Kelley WM, Miezin FM, McDermott KB, Buckner RL, Raichle ME, Cohen NJ, Ollinger JM, Akbudak E, Conturo TE, Snyder AZ, Petersen SE (1998) Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* 20: 927-936.

- Killgore WDS, Casasanto DJ, Yurgelun-Todd DA, Maldjian JA, Detre JA (2000) Functional activation of the left amygdala and hippocampus during associative encoding. *Neuroreport* 11: 2259-2263.
- Kirchhoff BA, Wagner AD, Maril A, Stern CE (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J. Neurosci.* 20: 6173-6180.
- Knowlton BJ, Squire LR (1995) Remembering and knowing: two different expressions of declarative memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 21: 699-710.
- Konishi S, Wheeler ME, Donaldson DI, Buckner RL (2000) Neural correlates of episodic retrieval success. *Neuroimage* 12: 276-286.
- Konishi S, Uchida I, Okuaki T, Machida T, Shirouzu I, Miyashita Y (2002) Neural correlates of recency judgment. *J. Neurosci.* 22: 9549-9555.
- Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Natl. Acad. Sci. USA* 89: 5675-5679.
- Lalonde R, Botez MI (1990) The cerebellum and learning processes in animals. *Brain Res. Brain Res. Rev.* 15: 325-332.
- Lauterbur PC (1973) Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature* 242: 190-191.
- Lepage M, Habib R, Tulving E (1998) Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* 8: 313-322.
- Lerner Y, Hendler T, Ben-Basher D, Harel M, Malach R (2001) A hierarchical axis of object processing stages in the human visual cortex. *Cereb. Cortex* 11: 287-297.
- Levy BJ, Anderson MC (2002) Inhibitory processes and the control of memory retrieval. *Trends Cogn. Sci.* 2002; 6: 299-305.
- Levy DA, Manns JR, Hopkins RO, Gold JJ, Squire LR (2003) Impaired visual and odor recognition memory span in patients with hippocampal lesions. *Learn. Mem.* 10: 531-536.
- Llinas R (1974) Eighteenth Bowditch lecture. Motor aspects of cerebellar control. *Physiologist* 17: 19-46.
- Mandeville JB, Marota JJ, Ayata C, Zaharchuk G, Moskowitz MA, Rosen BR, Weisskoff RM (1999) Evidence of a cerebrovascular postarteriole windkessel with delayed compliance. *J. Cereb. Blood Flow Metab.* 19: 679-689.
- Mandler G (1980) Recognizing: the judgement of previous occurrence. *Psychol. Rev.* 87: 252-271.
- Manns JR, Hopkins RO, Reed JM, Kitchener EG, Squire LR (2003) Recognition memory and the human hippocampus. *Neuron* 37: 171-80.
- Mansfield P (1977) Multi-planar image formation using NMR spin echoes. *J. Phys. C* 10: L55-L58.
- Markowitsch HJ, von Cramon DY, Schuri U (1993) Mnestic performance profile of a bilateral diencephalic infarct patient with preserved intelligence and severe amnesic disturbances. *J. Clin. Exp. Neuropsychol.* 5: 627-652.
- Mayes AR, Holdstock JS, Isaac CL, Hunkin NM, Roberts N (2002) Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus* 12: 325-340.
- Martin A, Wiggs CL, Weisberg J (1997) Modulation of human medial temporal lobe activity by form, meaning, and experience. *Hippocampus* 7: 587-593.
- McCarthy G, Nobre AC, Bentin S, Spencer DD (1995) Language-related field potentials in the anterior-medial temporal lobe: I. intracranial distribution and neural generators. *J. Neurosci.* 15: 1080-1089.

- McDermott KB, Ojemann JG, Petersen SE, Ollinger JM, Snyder AZ, Akudak E, Conturo TE, Raichle ME (1999) Direct comparison of episodic encoding and retrieval of words: an event-related fMRI study. *Memory* 7: 661-678.
- McDermott KB, Jones TC, Petersen SE, Lageman SK, Roediger HL 3rd (2000) Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: an event-related fMRI study. *J. Cogn. Neurosci.* 12: 965-976.
- Meunier M, Bachevalier J, Mishkin M, Murray EA (1993) Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *J. Neurosci.* 13: 5418-5432.
- Miller EK, Desimone R (1994) Parallel neuronal mechanisms for short-term memory. *Science* 263: 520-522.
- Miller EK, Li L, Desimone R (1991) A neural mechanism for working and recognition memory in inferior temporal cortex. *Science* 254: 1377-1379.
- Morcom AM, Good CD, Frackowiak RS, Rugg MD (2003) Age effects on the neural correlates of successful memory encoding. *Brain* 126: 213-229.
- Moscovitch M (1989) Confabulation and the frontal systems: Strategic versus associative retrieval in neuropsychological theories of memory. In: *Varieties of Memory and Consciousness: Essays in Honour of Endel Tulving* (Roediger IHL, Craik FIM, eds.), pp. 133-157. Hillsdale, NJ: Erlbaum.
- Murray EA, Bussey TJ (1999) Perceptual-mnemonic functions of the perirhinal cortex. *Trends Cogn. Sci.* 3: 142-151.
- Nadel L (1994) Multiple memory systems: What and why, an update. In: *Memory Systems 1994* (Schacter DL, Tulving E, eds.), pp. 39-63. Cambridge, MA: The MIT Press.
- Newman AJ, Pancheva R, Ozawa K, Neville HJ, Ullman MT (2001) An event-related fMRI study of syntactic and semantic violations. *J Psycholinguist Res* 30: 339-364.
- Nobre AC, McCarthy G (1995) Language-related field potentials in the anterior-medial temporal lobe: II. Effects of word type and semantic priming. *J. Neurosci.* 15: 1090-1098.
- Nolde SF, Johnson MK, Raye CL (1998) The role of prefrontal cortex during tests of episodic memory. *Trend in Cognitive Sciences* 2: 399-406.
- Nyberg L, Tulving E, Habib R, Nilsson LG, Kapur S, Houle S, Cabeza R, McIntosh AR (1995) Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport* 7: 249-52.
- Nyberg L, McIntosh AR, Cabeza R, Habib R, Houle S, Tulving E (1996) General and specific brain regions involved in encoding and retrieval of events: What, where, and when. *Proc. Natl. Acad. Sci. USA* 93:11280-11285.
- Ogawa S, Lee TM (1990) Magnetic resonance imaging of blood vessels at high fields: in vivo and in vitro measurements and image simulation. *Magn. Reson. Med.* 16: 9-18.
- Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc. Natl. Acad. Sci. USA* 87: 9868-9872.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97-113.
- Opitz B, Mecklinger A, Friederici AD (2000) Functional asymmetry of human prefrontal cortex: encoding and retrieval of verbally and nonverbally coded information. *Learn. Mem.* 7: 85-96.
- O'Reilly RC, Norman KA (2002) Hippocampal and neocortical contributions to memory: advances in the complementary learning systems framework. *Trends Cogn. Sci.* 6: 505-510.
- Otten LJ, Rugg MD (2001a) Task-dependency of the neural correlates of episodic encoding as measured by fMRI. *Cereb. Cortex* 11: 1150-1160.

- Otten LJ, Rugg MD (2001b) When more means less: neural activity related to unsuccessful memory encoding. *Curr. Biol.* 11: 1528-1530.
- Otten LJ, Henson RN, Rugg MD (2001) Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. *Brain* 124: 399-412.
- Owen AM, Milner B, Petrides M, Evans A (1996) Memory for object features versus memory for object location: A positron-emission tomography study of encoding and retrieval processes. *Proc. Natl. Acad. Sci. USA* 93: 9212-9217.
- Paller KA (1990) Recall and stem-completion priming have different electrophysiological correlates and are modified differentially by directed forgetting. *J. Exp. Psychol. Learn. Mem. Cogn.* 16: 1021-1032.
- Paller KA, Wagner AD (2002) Observing the transformation of experience into memory. *Trends Cogn. Sci.* 6: 93-102.
- Pauling L, Coryell CD (1936) The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proc. Natl. Acad. Sci. USA* 22: 210-216.
- Pellegrino LJ, Altman J (1979) Effects of differential interference with postnatal cerebellar neurogenesis on motor performance, activity level, and maze learning of rats: a developmental study. *J. Comp. Physiol. Psychol.* 93: 1-33.
- Potts GF, Tucker DM (2001) Frontal evaluation and posterior representation in target detection. *Brain Res. Cogn. Brain Res.* 11: 147-156.
- Rajaram S, Hamilton M, Bolton A (2002) Distinguishing states of awareness from confidence during retrieval: evidence from amnesia. *Cogn. Affect Behav. Neurosci.* 2: 227-235.
- Ranganath C, Johnson MK, D'Esposito M (2000) Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J. Neurosci.* 20: RC108(1-5).
- Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M (2003) Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia*: in press.
- Reber PJ, Wong EC, Buxton RB (2002) Encoding activity in the medial temporal lobe examined with anatomically constrained fMRI analysis. *Hippocampus* 12: 363-376.
- Reed JM, Squire LR (1997) Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behav. Neurosci.* 111: 667-675.
- Ricci PT, Zelkowitz BJ, Nebes RD, Meltzer CC, Mintun MA, Becker JT (1999) Functional neuroanatomy of semantic memory: recognition of semantic associations. *Neuroimage* 9: 88-96.
- Richardson-Klavehn A, Gardiner JM (1995) Retrieval violation and memorial awareness in stem completion: an empirical analysis. *Psychol. Res.* 57: 166-178.
- Riches IP, Wilson FA, Brown MW (1991) The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. *J. Neurosci.* 11:1763-1779.
- Rombouts SARB, Barkhof F, Witter MP, Machielsen WCM, Scheltens Ph (2001) Anterior Medial Temporal Lobe Activation During Attempted Retrieval of Encoded Visuospatial Scenes: An Event-Related fMRI Study. *Neuroimage* 14: 67-76.
- Rugg MD (1995) Event-related potential studies of memory. In: *Electrophysiology of mind* (Rugg MD, Coles MGH, eds.), pp. 132-170. New York: Oxford University Press.
- Rugg MD, Henson RNA (2002) Episodic memory retrieval: an (event-related) functional neuroimaging perspective. In: *The cognitive neuroscience of memory encoding and retrieval* (Parker AE, Wilding EL, Bussey T, eds.), pp. 7-28. Hove: Psychology Press.

- Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ (1996) Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain* 119: 2073-2083.
- Rugg MD, Fletcher PC, Frith CD, Frackowiak RSJ, Dolan RJ (1997) Brain regions supporting intentional and incidental memory: A PET study. *Neuroreport* 8: 1283-1287.
- Rugg MD, Fletcher PC, Allan K, Frith CD, Frackowiak RS, Dolan RJ (1998) Neural correlates of memory retrieval during recognition memory and cued recall. *Neuroimage* 8: 262-73.
- Sanquist TF, Rohrbaugh JW, Syndulko K, Lindsley DB (1980) Electrocortical signs of levels of processing: perceptual analysis and recognition memory. *Psychophysiology* 17: 568-576.
- Saykin AJ, Johnson SC, Flashman LA, McAllister TW, Sparling M, Darcey TM, Moritz CH, Guerin SJ, Weaver J, Mamourian A (1999) Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. *Brain* 122: 1963-1971.
- Schacter DL, Wagner AD (1999) Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus* 9: 7-24.
- Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS (1996a) Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proc. Natl. Acad. Sci. USA* 93: 321-325.
- Schacter DL, Verfaellie M, Pradere D (1996b) The neuropsychology of memory illusions: False recall and recognition in amnesic patients. *J. Mem. Lang.* 35: 319-334.
- Schacter DL, Buckner RL, Koutstaal W, Dale AM, Rosen BR (1997) Late onset of anterior prefrontal activity during true and false recognition: an event-related fMRI study. *Neuroimage* 6: 259-269.
- Schmahmann JD (1996) From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum. Brain Mapp.* 4: 174-198.
- Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesion. *J. Neurol. Neurosurg. Psychiatry* 20: 11-21.
- Shild HH (1990) MRI made easy (.... well almost). Schering AG.
- Shimamura AP (1985) Problems with the finding of stochastic independence as evidence for the independence of cognitive processes. *Bull Psychonom Soc* 23: 506-508.
- Shimamura AP, Squire LR (1991) The relationship between fact and source memory. Findings from amnesic patients and normal subjects. *Psychobiology* 19: 1-10.
- Shimamura AP, Gershberg FB, Jurica PJ, Mangels JA, Knight RT (1992) Intact implicit memory in patients with frontal lobe lesions. *Neuropsychologia* 30: 931-937.
- Smith EE, Jonides J, Koeppe RA, Awh E, Schumacher EH, Minoshima S (1995) Spatial vs. object-working memory: PET investigations. *J. Cogn. Neurosci.* 7: 337-356.
- Smith ME, Stapleton JM, Halgren E (1986) Human medial temporal lobe potentials evoked in memory and language tasks. *Electroencephalogr. Clin. Neurophysiol.* 63: 145-159.
- Squire LR (1998) Memory systems. *C. R. Acad. Sci. III.* 321: 153-156.
- Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99: 195-231.
- Squire L, Cohen NJ (1984) Human memory and amnesia. In: *The neurobiology of learning and memory* (McGauch JL, Lynch G, Weinberger NM, eds.), pp. 3-64, New York: Guilford Press.
- Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. *Science* 253: 1380-1386.
- Squire LR, Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. USA* 93: 13515-13522.
- Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME (1992) Activation of the hippocampus in normal humans: a functional anatomic study of memory. *PNAS* 89:1837-1841.

- Stark CE, Squire LR (2000a) fMRI activity in the medial temporal lobe during recognition memory as a function of study-test interval. *Hippocampus* 10: 329-337.
- Stark CE, Squire LR (2000b) Functional magnetic resonance imaging (fMRI) activity in the hippocampal region during recognition memory. *J. Neurosci.* 20: 7776-7781.
- Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* 93: 8660-8665.
- Stern CE, Sherman SJ, Kirchoff BA, Hasselmo ME (2001) Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. *Hippocampus* 11: 337-346.
- Strange BA, Otten LJ, Josephs O, Rugg MD, Dolan RJ (2002) Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. *J. Neurosci.* 22: 523-528.
- Sturm W, Willmes K (2001) On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage* 14: S76-84.
- Sturm W, de Simone A, Krause BJ, Specht K, Hesselmann V, Radermacher I, Herzog H, Tellmann L, Muller-Gartner HW, Willmes K (1999) Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia* 37: 797-805.
- Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sayer L, Pogue J (1994) Organisational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychologia* 8:355-373.
- Suzuki WA, Amaral DG (1994) Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J. Comp. Neurol.* 350: 497-533.
- Suzuki WA (1996) The anatomy, physiology and functions of the perirhinal cortex. *Curr. Opin. Neurobiol.* 6: 179-186.
- Talairach P, Tournoux J (1998) A Stereotactic coplanar atlas of the human brain. Stuttgart: Thieme.
- Thach WT (1998) What is the role of the cerebellum in motor learning and cognition? *Trends Cogn. Sci.* 2: 331-337.
- Thompson RF, Kim JJ (1996) Memory systems in the brain and localization of a memory. *Proc. Natl. Acad. Sci. USA* 93: 13438-13444.
- Tulving E (1972) Episodic and semantic memory. In: *Organization of Memory* (Tulving E, Donaldson W, eds.), pp. 381-403. New York: Academic Press.
- Tulving E (1983) *Elements of Episodic Memory*. Clarendon Press.
- Tulving E (1985) Memory and consciousness *Can. Psych.* 26: 1-12.
- Tulving E (1993) What is episodic memory? *Curr. Perspect. Psychol. Sci.* 2: 67-70.
- Tulving E, Kroll N (1995) Novelty assessment in the brain and long-term memory encoding. *Psychonomic. Bull. Rev.* 2: 387-390.
- Tulving E, Markowitsch HJ (1998) Episodic and Declarative Memory: Role of the Hippocampus. *Hippocampus* 8: 198-204.
- Tulving E, Markowitsch HJ (1997) Memory beyond the hippocampus. *Curr. Opin. Neurobiol.* 7:209-216.
- Tulving E, Schacter DL (1990) Priming and human memory systems. *Science* 247: 301-306.
- Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S (1994) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc. Natl. Acad. Sci. U.S.A.* 91: 2016-2020.

- Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S (1996). Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb. Cortex* 6: 71-79.
- Ungerleider LG, Mishkin M (1985) Two cortical visual systems. In: *Analysis of Visual Behavior* (Ingle DJ, Goodale MA, Mansfield RJW, eds.), pp. 549-586. Cambridge, MA: MIT Press.
- Ungerleider LG, Courtney SM, Haxby JV (1998) A neural system for human visual working memory. *Proc. Natl. Acad. Sci. USA* 95: 883-890.
- Vanzetta I, Grinvald, A (1999) Increased cortical oxidative metabolism due to sensory stimulation: implications for functional brain imaging. *Science* 286: 1555-1558.
- Villringer A, Dirnagl U (1995) Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. *Cerebrovasc. Brain Metab. Rev.* 7: 240-276.
- Wagner AD (1999) Working memory contributions to human learning and remembering. *Neuron* 22: 19-22.
- Wagner AD, Davachi L (2001) Cognitive neuroscience: forgetting of things past. *Curr. Biol.* 11:964-967.
- Wagner AD, Poldrack RA, Eldridge LL, Desmond JE, Glover GH, Gabrieli JD (1998a) Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport* 9: 3711-3717.
- Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL (1998b) Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 281: 1188-1191.
- Wagner AD, Koutstaal W, Schacter DL (1999) When encoding yields remembering: insights from event-related neuroimaging. *Phil. Trans. R. Soc. Lond. B* 354: 1307-1324.
- Weis S, Klaver P, Reul J, Elger CE, Fernández G (2004a) Neural Correlates of Successful Declarative Memory Formation and Retrieval : The Anatomical Overlap. *Cortex*: in press.
- Weis S, Klaver P, Reul J, Elger CE, Fernández G (2004b) Temporal and Cerebellar Brain Regions that Support both Declarative Memory Formation and Retrieval. *Cereb. Cortex* 14: 256-267.
- Witter MP, Amaral DG (1991) Entorhinal cortex of the monkey: V. Projections to the dentate gyrus, hippocampus, and subicular complex. *J. Comp. Neurol.* 307: 437-459.
- Worsley KJ, Friston KJ (1995) Analysis of fMRI time-series revisited - again. *Neuroimage* 2: 173-181.
- Worsley KJ, Evans AC, Marrett S, Neelin P (1992) A three-dimensional statistical analysis for CBF activation studies in human brain. *J. Cereb. Blood Flow Metab.* 12: 900-918.
- Worsley K, Marrett S, Neelin P, Vandal A, Friston K, Evans A (1996) A unified statistical approach for determining significant signals in images of cerebral activation. *Hum. Brain Mapp.* 4: 58-73.
- Yonelinas AP (1994) Receiver-operating characteristics in recognition memory: evidence for a dual-process model. *J. Exp. Psychol. Learn. Mem. Cogn.* 20: 1341-1354.
- Yonelinas AP (1999) The contribution of recollection and familiarity to recognition and source-memory judgments: A formal dual-process model and an analysis of receiver operating characteristics. *J. Exp. Psych. Learn. Mem. Cogn.* 25: 1415-1434.
- Yonelinas AP (2002) The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46: 441-517.
- Zarahn E, Aguirre G, D'Esposito M (1997) A trial-based experimental design for fMRI. *Neuroimage* 6: 122-138.

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08/85 – 06/88	High school 'Modellschule Obersberg', Bad Hersfeld, Germany
06/88	High school Diploma, Grade 2.3

Professional Education

09/88 – 08/91	Institute of Economic Sciences, University of Technology, Aachen, Germany
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Education

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02/95 – 10/95	Diploma Thesis: "The classical Banach principle as a unified approach to pointwise convergence assertions in Ergodic and Approximation Theory." Rated top 5%
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10 List of Publications

Publications in scientific journals

Weis S, Klaver P, Reul J, Elger CE, Fernández G (2004) Neural Correlates of Successful Declarative Memory Formation and Retrieval: The Anatomical Overlap. *Cortex* 40:200-202.

Weis S, Specht K, Klaver P, Tendolkar I, Willmes K, Ruhlmann J, Elger CEE, Fernández G (2004) Process Dissociation between Contextual Retrieval and Item Recognition. *Neuroreport*: in press.

Weis S, Klaver P, Reul J, Elger CE, Fernández G (2004) Temporal and Cerebellar Brain Regions that Support both Declarative Memory Formation and Retrieval. *Cereb. Cortex* 14: 256-267.

Klaver P, Fell J, Weis S, De Greiff A, Ruhlmann J, Reul J, Elger CE, Fernandez G (2004) Using visual advance information: an event-related functional MRI study. *Brain Res. Cogn. Brain Res.* 20: 242-255.

Sturm W, Longoni F, Weis S, Specht K, Herzog H, Vohn R, Thimm M, Willmes K (2004). Functional reorganisation in patients with right hemisphere stroke after training of alertness: a longitudinal PET and fMRI study in eight cases. *Neuropsychologia* 42: 434-450.

Sturm W, Longoni F, Fimm B, Dietrich T, Weis S, Kemna S, Herzog H, Willmes K (2004) Network for auditory intrinsic alertness: a PET study. *Neuropsychologia* 42: 563-568.

Tendolkar I, Weis S, Guddat O, Fernandez G, Brockhaus-Dumke A, Specht K, Klosterkötter J, Reul J, Ruhlmann S (2004) Evidence for a dysfunctional retrosplenial cortex in patients with schizophrenia: a functional magnetic resonance imaging study with a semantic-perceptual contrast. *Neurosci Lett.* 369(1):4-8.

Fernández G, Specht K, Weis S, Tendolkar I, Reuber M, Fell J, Klaver P, Ruhlmann J, Reul J, Elger CE (2003) Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. *Neurology* 60: 969-975.

Fernández G, Weis S, Stoffel-Wagner B, Tendolkar I, Reuber M, Beyenburg S, Klaver P, Fell J, de Greiff A, Ruhlmann J, Reul J, Elger CE (2003) Menstrual cycle-dependent neural plasticity in the adult human brain is hormone, task, and region specific. *J. Neurosci.* 23: 3790-3795.

Specht K, Holtel C, Zahn R, Herzog H, Krause BJ, Mottaghy FM, Radermacher I, Schmidt D, Tellmann L, Weis S, Willmes K, Huber W (2003) Lexical decision of nonwords and pseudowords in humans: a positron emission tomography study. *Neurosci. Lett.* 345: 177-181.

Weis S, Grande M, Pollrich S, Willmes K, Huber W (2001) Processing of Homonyms: A Functional MRI Study on the Separation of Word Forms from Concepts. *Cortex* 37(5):745-749.

Weis S, Pollrich S, Erberich SG, Willmes K (2000) Abhängigkeit von Interstimulusintervallen und Aufnahmegeschwindigkeit bei der Bildakquisition schneller ereigniskorrelierter funktioneller MRI. In: Horsch A, Lehmann TM (eds.) *Bildverarbeitung für die Medizin 2000, Algorithmen, Systeme, Anwendungen*. Springer, München: 408-412.

Erberich S, Kemeny S, Krings T, Weis S, Willmes K, Thron A, Oberschelp W (2000) Wissensbasierte Optimierung von selbstorganisierenden Merkmalskarten (SOM) zur Analyse von funktionellen Magnetresonanztomographien (fMRT). In: Horsch A, Lehmann TM (eds.) *Bildverarbeitung für die Medizin 2000, Algorithmen, Systeme, Anwendungen*. Springer, München: 361-365.

Erberich S, Fellenberg M, Kemeny S, Weis S, Krings T, Willmes K (2000) Unüberwachte Zeitreihenanalyse von fMRT-Daten. In: Evers H, Glombitza GP, Lehmann T, Meinzer HP (eds.) *Bildverarbeitung für die Medizin 1999, Algorithmen, Systeme, Anwendungen*. Springer, München: 422-426.

Huber W, Weis S, Grande M, Pollrich S, Willmes K (2000) Processing of homonyms: A functional MRI study on the separation of word forms from concepts. *Brain & Language* 74: 409-411.

Longoni F, Sturm W, Weis S, Holtel C, Specht K, Herzog H, Willmes K (2000) Functional reorganization after training of alertness in two patients with right-hemisphere lesions. *J. Neuropsych.* 11: 250-261.

Citable Abstracts

Weis S, Specht K, Klaver P, Tendolkar I, Willmes K, Ruhlmann J, Reul J, Elger CE, Fernández G (2004) Neural Correlates of Contextual Retrieval and Item Recognition are dissociated within the Human Medial Temporal Lobe. *NeuroImage* 22(1)

Rimol LM, Savoy R, Specht K, Weis S, Hugdahl K (2004) fMRI neuronal activation to single phonemes in left temporal cortex. *NeuroImage* 22(1)

Weis S, Grande M, Willmes K, Huber W (2003) Processing of Word Form and its reorganization: an event-related functional MRI study. *NeuroImage* 19: S 1422.

Weis S, Specht K, Klaver P, Reul J, Elger CE, Fernández G (2003) Encoding and Retrieval of Source Memory for Complex Visual Material: an event-related fMRI study. *NeuroImage* 19: S235.

Weis S, Klaver P, Reul J, Elger CE, Fernández G (2002) Visual encoding and recognition: an event-related fMRI study. *NeuroImage* 16: S276.

Klaver P, Weis S, Reul J, Elger CE, Fernández G (2002) Concrete and abstract words in working memory: an fMRI study. *NeuroImage* 16(2):S469.

Weis S, Huber W, Pollrich S, Willmes K (2001) Analysis of the temporal dynamics of event-related functional MRI activation studies. *NeuroImage* 13: S280.

Weis S, Pollrich S, Willmes K (2001) The temporal dynamics of number processing: an event-related functional MRI study on magnitude comparison. *NeuroImage* 13: S625.

Grande M, Huber W, Weis S, Pollrich S, Willmes K (2001) The separation of word forms from concepts: a functional MRI study. *NeuroImage* 13: S536.

Nuerk HC, Dambeck N, Weis S, Thron A, Willmes K (2001) Functional activation in number processing may be specific to notation, task, and individual strategy. *NeuroImage* 13: S579.

Sturm W, Schmenk B, Fimm B, Kottenhoff R, Liebert M, Weis S, Kemeny S, Erberich S, Willmes K (2001) Overlapping networks for orienting and alerting: an fMRI study. *NeuroImage* 13: S364.

Weis S, Fimm B, Longoni F, Dietrich T, Zahn R, Herzog H, Kemna L, Willmes K, Sturm W (2000) The functional anatomy of intrinsic and phasic alertness - a PET study with auditory stimulation. *NeuroImage* 11: S10.

Weis S, Pollrich S, Willmes K (2000) A comparison of analysis strategies in SPM – Fixed effects, random effects, and conjunction analysis. *NeuroImage* 11: S620.

Weis S, Pollrich S, Willmes K (2000) The impact of interstimulus intervals and repetition times in event-related fMRI. *NeuroImage* 11: S618.

Specht K, Holtel C, Schnitker R, Weis S, Herzog H, Krause BJ, Huber W (2000) Right hemisphere activations after stroke: A PET study. *NeuroImage* 11: S??? .

Weis S, Erberich SG, Kemeny S, Liebert M, Achten B, Willmes K (1999) Effects of interaction between activation and control conditions in block design paradigm fMRI experiments of higher cognitive functions. *NeuroImage* 9: S3.

Achten B, Fimm B, Kottenhoff R, Liebert M, Weis S, Kemeny S, Erberich SG, Willmes K, Sturm W (1999) The functional anatomy of covert and overt orienting of attention: a functional MRI study. *NeuroImage* 9: S740.

Erberich SG, Weis S, Kemeny S, Willmes K, Oberschelp W, Thron A (1999) Preprocessing strategies for MRI data analysis by a self-organizing map (SOM) Neural Networks. NeuroImage 9: S20.

Longoni F, Weis S, Specht K, Holtel C, Herzog H, Achten B, Willmes K, Sturm W (1999) Functional reorganisation after training of alertness. NeuroImage 9: S771.

Specht K, Holtel C, Weis S, Herzog H, Schmidt D, Mottaghy FM, Krause BJ, Huber W (1999) The Functional Anatomy of Auditory Lexical Decision and its Plasticity after Left Hemisphere Damage: A PET study. NeuroImage 9: S719.

Willmes K, Weis S, Kemeny S, Pollrich S, Erberich SG (1999) Evidence for an analogue mental representation of numbers - A fMRI study on number parity judgements. NeuroImage 9: S381.