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Modulating the efficiency of memory formation: Insights from temporal lobe epilepsy and nociceptive arousal

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List of abbreviations

ADC	apparent diffusion coefficient
ADS	Allgemeine Depressions Skala
AED	antiepileptic drug
AMI	Autobiographical Memory Interview
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BDI	Becks Depression Inventory
BOLD	blood oxygenation level dependent
d’	parameter estimate for familiarity
DM	difference due to memory
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
EEG	electro-encephalogram
EEM	emotional enhancement of memory
e.g.	*exempli gratia*, for example
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
FSL	FMRIB’s Software Library
FWHM	full width at half maximum
GLM	general linear model
HF	high frequency
H.M.	initials of a famous patient
HRF	hemodynamic response function
HS	hippocampal sclerosis
i.e.	*id est*, that is
ILF	inferior longitudinal fasciculus
ISI	interstimulus interval
LC	locus coeruleus
LTP	long-term potentiation
MD	mean diffusivity
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
mm	millimeter
ms	milliseconds
MTL	medial temporal lobe

NA	noradrenaline
PCS	Pain Catastrophizing Scale
PET	positron emission tomography
PVAQ	Pain Vigilance and Awareness Questionnaire
R	parameter estimate for recollection
ROC	receiver operating characteristic
ROCF	Rey-Osterrieth-Complex-Figure
ROI	region of interest
RWT	Regensburger Wortflüssigkeitstest
SII	secondary somatosensory cortex
SCR	skin conductance response
$scenes^{+shock}$	scenes followed by shock
$scenes^{no\ shock}$	scenes not followed by shock
sec	seconds
SPM	Statistical Parametric Mapping
STAI	State Trait Anxiety Inventory
T1, T2, T2*	different time constants relevant for MR images
TAP	Testbatterie zur Aufmerksamkeitsprüfung
TBSS	Tract-Based Spatial Statistics
TE	echo time
TLE	temporal lobe epilepsy
TR	repetition time
UF	uncinate fasciculus
VAS	visual analog scale
VBM	voxel-based morphometry
VLMT	Verbaler Lern- und Merkfähigkeitstest
VNS	vagus nerve stimulation
WMS-R	Wechsler Memory Scale-Revised

Abstract

The efficiency of memory formation, i.e. encoding and consolidation, can be modulated by various factors. While some of these factors exert a constant influence on memory processing, others act temporarily. In the present thesis, the effects of two examples of modulating factors were investigated. Study I focused on a neurological disorder constantly affecting the neural correlates of memory formation, and Study II focused on the temporary modulation of consolidation due to arousal. In Study I, different magnetic resonance imaging techniques and memory tasks were implemented to investigate potential reasons for memory deficits in patients with temporal lobe epilepsy of unknown cause. Despite the lack of overt morphological lesions, functional imaging revealed increased hippocampal activity during encoding, but decreased associative memory during recognition for patients compared to healthy controls. The findings suggest that subtle alterations of neuronal microcircuits due to epilepsy exist which impair the efficiency of encoding. Thus, the increase of activity is assumed to reflect a compensatory process for successful encoding within less efficient hippocampal cell assemblies. In Study II, event-related effects of a temporary modulator were investigated. Electrical shocks were applied to healthy participants in order to induce arousal after the initial processing of stimuli probed for memory. Importantly, this paradigm could disentangle effects of arousal from effects of cognitive factors, which usually accompany emotionally arousing stimuli during encoding. Enhanced memory for stimuli followed by electrical shocks in Study II was only found after a retention interval, representing a more efficient consolidation. Since cognitive factors could not account for this effect, the increase of efficiency is most likely due to an enhanced noradrenergic innervation and thus facilitation of neuronal responsiveness in those temporal lobe areas relevant for stimuli processing.

1 Introduction

Memory is a superordinate concept which refers to different mnemonic systems. One major distinction is between *declarative* memory, i.e. conscious recollection about facts and episodes, and *nondeclarative* memory, i.e. procedural learning, priming and conditioning (Squire, 1992). Declarative or explicit memory consists of *semantic* and *episodic* memory (Tulving, 1972). While the former represents factual knowledge, the latter represents memory for specific events that occurred at a particular time and place. Besides its content, memory can also be subdivided into different stages of processing: Encoding, consolidation, storage, and retrieval of information. *Encoding* refers to the acquisition of information, i.e. the transformation of a transient percept into a memory trace (e.g. Wagner, Koutstaal, & Schacter, 1999). In order to become a permanent state, such a new memory representation needs to be stabilized within a gradual, post-experience process called c*onsolidation* (Lechner, Squire, & Byrne, 1999; Müller & Pilzecker, 1900). This term refers to two processes of stabilization: *synaptic* and *systems* consolidation (Dudai, 2004; Frankland & Bontempi, 2005). While synaptic consolidation describes localized molecular and morphological changes in synaptic efficacy or connectivity within minutes to hours, systems consolidation refers to a prolonged reorganization of brain regions supporting memory.

The present thesis focused on a specific component of this heterogeneous and broad concept of memory, namely episodic memory formation comprising encoding and consolidation, and in particular on modulations of the efficiency of episodic memory formation.

For episodic memories, theories on systems consolidation agree on the relevance of the medial temporal lobe (MTL) for encoding and consolidation (Alvarez & Squire, 1994; Frankland & Bontempi, 2005; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). The key structure within the MTL is the hippocampus which is proposed to bind different aspects of an experience into a coherent representation (e.g. Nadel et al., 2000). This integration is necessary, since different neocortical and MTL areas are involved in encoding depending on information content and task demands (Frankland & Bontempi, 2005; Otten, Henson, & Rugg, 2001; Simons & Spiers, 2003). Regarding the MTL, for example, the posterior parahippocampus is of special relevance for the encoding of scenic and contextual information, whereas the anterior

perirhinal cortex is proposed to encode item specific information (Davachi, 2006; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, Yonelinas, & Ranganath, 2007). These processing streams providing domain-specific information from different cortical areas converge in the hippocampus which relates e.g. stimulus identity and context (Eichenbaum et al., 2007); thus, relational representations supported by the hippocampus are assumed to reflect its domain-generality (Davachi, 2006).

The original knowledge about the essential role of the hippocampus and adjacent areas of the MTL in successful memory formation derived from patient studies. In particular, the relevance of certain brain structures for memory was put into the focus of research with the description of the patient H.M. in 1957 (Scoville & Milner, 1957). After a bilateral resection of the medial temporal lobes due to medically refractory epilepsy, H.M. showed a severe amnesia while still having normal intellectual and perceptual abilities. Moreover, the inability to acquire new information was restricted to explicit long-term memory tasks, but not seen in implicit skill learning or short-term memory (Milner, Corkin, & Teuber, 1968). Although this picture of H.M.'s memory performance was refined by many investigations during the following decades (see Corkin, 2002), the initial study was seminal because it suggested that memory is a function which can be localized within the brain and divided into the aforementioned subsystems and stages. The privileged role of the MTL for successful memory formation was confirmed by a multitude of subsequent reports of impaired episodic memory in temporal lobe epilepsy (TLE) with MTL damage and unilateral surgery (Bell, Lin, Seidenberg, & Hermann, 2011; Helmstaedter & Kurthen, 2001; Leritz, Grande, & Bauer, 2006). As in other chronic neurological diseases, for example Alzheimer's disease, MTL damage in TLE is irreversible. Naturally, if a system's "hardware" is damaged, the processes relying on that hardware are malfunctioning. Thus, TLE is one example of a class of factors which constantly affect the efficiency of memory formation, i.e. encoding and consolidation, due to persistent alterations of the underlying morphological substrates.

However, memory deficits in TLE have also been detected in the absence of clearly visible lesions (Bengner et al., 2006; Giovagnoli & Avanzini, 1999). One possible explanation for this finding could be subtle, undetected MTL alterations that diminish the efficiency of neural assemblies. Therefore, Study I

aimed at investigating the relationship of brain integrity, encoding efficiency and memory performance in a group of patients with TLE of unknown cause and healthy controls. Structural magnetic resonance imaging (MRI) techniques were applied in order to investigate brain morphology, while functional MRI (fMRI) was applied in order to investigate the neural substrates of encoding and thereby encoding efficiency. Memory performance was assessed by a sensitive fMRI task in addition to established neuropsychological tests.

Whereas Study I of the present thesis focused on durable alterations of neuroanatomical memory circuits, Study II explored transient modulations of the efficiency of memory formation. Such temporary alterations can be caused by a variety of factors, e.g. behavioral manipulations or pharmacological treatment (see Frankland & Bontempi, 2005). These factors do not affect the hardware of the system, but the efficiency of the "software", i.e. the efficiency of the processes leading to encoding and consolidation. A prominent example of the impact of temporary, behavioral modulators is the superior memory for emotional compared to neutral events (see LaBar & Cabeza, 2006 for review). The beneficial effect of emotion on memory formation is assumed to rely on enhanced consolidation which is mediated by the release of noradrenaline into the amygdala (McGaugh, 2000, 2004). This modulation of consolidation efficiency can even occur on a very short time scale, i.e. event related, due to central noradrenaline release (Strange, Hurlemann, & Dolan, 2003). In general, the noradrenergic system is a very potent neuromodulatory system in the brain (Sara, 2009). However, in the case of emotional stimuli, the effect of arousal is confounded by cognitive factors, as for example selective attention, which also accompany these stimuli and do not act via noradrenaline (Talmi, Luk, McGarry, & Moscovitch, 2007; Talmi, Schimmack, Paterson, & Moscovitch, 2007).

Study II of the present thesis was designed to test the effects of arousal in the absence of the confounding cognitive factors which usually contribute to behavioral and neural effects of emotional memory formation. Therefore, a nociceptive stimulus was chosen to trigger central noradrenaline release from the locus coeruleus and thereby arousal briefly after the processing of neutral stimuli. The impact of this transient modulation was tested at different time intervals in order to differentiate between effects on encoding and consolidation. Functional MRI was implemented to examine changes in the

neuronal pattern of activity that correlated with enhanced efficiency of memory trace formation.

In summary, the present thesis aimed to further investigate the effects of modulating factors on the efficiency of episodic memory formation. Two studies were conducted, which either examined effects of an example of a constant modulating factor or an example of a temporary modulator. Furthermore, the studies focused on different memory stages, i.e. encoding or consolidation. Study I focused on the effects of TLE as a representative of constant modulating factors. Study II was designed to examine temporary effects of arousal. In both studies, MRI techniques were implemented in order to detect structural or functional alterations associated with changes in the efficiency of memory acquisition. The two studies will be described in separate sections. In preparation of both study descriptions, the following chapter will provide an overview of the MRI techniques implemented in the present thesis.

2 Magnetic resonance imaging (MRI)

The present thesis focused on constant and temporary modulations of memory circuits supporting episodic memory formation. In order to investigate the structural integrity of relevant brain areas and the neural substrates of successful encoding, various MRI techniques were applied. The following chapters give an overview of the physical basis of MRI and the specific techniques implemented in Study I and Study II. Moreover, general information about data analysis are given in order to set the stage for understanding the present analyses.

2.1 Physical basis of MRI

Magnetic resonance imaging commonly relies on the magnetic moment of the nuclei of hydrogen. The proton of the nucleus has a positive charge and continuously rotates around its axis. This rotation is termed *spin*. The movement of an electrically charged particle produces a magnetic field. Thus, protons can be characterized as magnetic dipoles. When exposed to a strong external magnetic field (B0), they align parallel or anti-parallel to this magnetic field. Protons are more likely to align parallel to the magnetic field because this orientation is of lower energy than the anti-parallel state. The resultant magnetization is called *longitudinal magnetization*. Inside the magnetic field, in addition to spinning, protons revolve on a conical surface with different velocity (like a spinning top). This rotation is called *precession*; its frequency is called *Lamor frequency* and depends on the strength of the magnetic field intensity and the gyromagnetic ratio of the protons. Basically, protons precess independently. However, the spins can be influenced by a second, time-dependent magnetic field (B1). When a high frequency (HF) pulse is applied, it synchronizes precessing and inverts orientation from parallel to anti-parallel. The protons change because they absorb the applied energy. But, the HF pulse can only transfer its energy to the protons if they have the same frequency. This phenomenon is called *resonance*. When the flipped protons move synchronously, their magnetic fields sum up perpendicular to the external magnetic field (*transversal magnetization*). This changing magnetic field induces a voltage in the receiver coil of the scanner. When the HF pulse is turned off, the spins release the energy to the surrounding environment. They continually dephase and return to their original orientation. This process is called *relaxation*. *Longitudinal relaxation* refers to the fact that the

longitudinal magnetization increases again. The T1-curve describes the time required to gradually release the absorbed energy until the magnetization is realigned with B0. The second time constant T2 represents the decay of transversal magnetization due to phase differences by spin-spin-interaction. This gradual dephasing is termed *transversal relaxation*. Usually, T1 takes longer than T2. The shortest time constant is the third one called T2*. It describes the combined effect of spin-spin-interaction and inhomogeneities in the external magnetic field. Time constants are determined by the characteristics of the tissue. Because relaxation in gray matter for example is different from relaxation in white matter, the signal strength of these tissues is different after a certain time. These differences determine the contrasts between gray and white matter in MR-images. T1-weighted images are usually acquired with a short time interval between excitation and acquisition (*Echo time* or *TE*). Tissues with a short T1 relaxation time (e.g. grey matter) have already gained more longitudinal magnetization and give a higher signal. Tissues with a long T1 relaxation time (e.g. cerebrospinal fluid) give a lower signal at early time points. These images are helpful for assessing anatomical details. In contrast, longer TE is used to create T2-weighted images. They are useful for the illustration of pathological alterations since lesions appear very bright. T2*-weighted images are most important for functional MRI. These images are similar to T2 images, but are more susceptible for magnetic field inhomogeneities which accelerate the T2 relaxation process. Therefore, T2* is faster and useful to observe e.g. changes in blood flow. Moreover, images can rely on motion contrasts which utilize the movement of molecules. These four types of images were used in the present thesis. The different procedures will be described in the following sections.

But, not only the strength of the signal is important for constructing an image. The origin of a signal has to be taken into account as well. Therefore, spatial gradients are used during scanning. Selection of slices is achieved by a gradient slope in the external magnetic field. Thus, protons precess in different frequencies and are only partly resonant to a HF pulse. Two additional gradients within a slice allow unique encoding by influencing frequency and phase of the protons. The origin of a signal can be calculated by a Fourier transform.

2.2 T2 relaxation maps

As stated above, T2-weighted images are sensitive for detecting lesions (Smith et al., 1985). T2 relaxation is governed by the total amount of water and its distribution and interaction with the environment. In case of e.g. edema, neuronal loss or demyelination, the amount of free water in the tissue is increased, and thus T2 relaxation is prolonged (Rugg-Gunn, Boulby, Symms, Barker, & Duncan, 2005).

A more sensitive and objective way than visual inspection to detect abnormalities, is the quantitative evaluation of T2 images with the help of *T2 relaxation maps*. Therefore, a minimum of at least two T2-weighted images with different TE are required. Relaxation times are defined by the equation T2 = (TE2-TE1)/[ln(S1/S2)]; S represents the signal intensity in the early and the late echo images with the echo time TE (Duncan, Bartlett, & Barker, 1996). In order to obtain most accurate measures of T2 relaxation, multiple images at a range of echo times are needed. The rate of T2 relaxation is represented by the exponential signal decay (Pell, Briellmann, Waites, Abbott, & Jackson, 2004). However, in clinical practice, decision about sequences is often made upon a time-quality trade-off: Less echos equals less scan time and more slices (Duncan et al., 1996; Rugg-Gunn et al., 2005). Mostly, a small number of slices covering regions of interest (ROIs) are measured. T2 values are derived from these ROIs and compared between patients and controls. Higher values of patients represent pathological substrates in a variety of conditions, e.g. multiple sclerosis, ischemia etc. In order to examine group differences without biases, i.e. placement of ROI or inter-rater variability, whole-brain T2 mapping with voxel-based analysis has been evolved in the past years (Pell et al., 2004; Rugg-Gunn et al., 2005).

In voxel-based analysis, statistical tests are applied to every voxel of an image. In order to accomplish comparisons between groups, images of different participants need to be preprocessed. Most importantly, all images need to be in the same space. Therefore, in the example of T2 maps, the first step is *normalization*. Images are normalized to a standard template in order to ensure that all data are within the same stereotactic space. In particular, one T2 image is matched to a template using linear steps of translation, rotation, zoom, and shear. In addition, nonlinear warps are applied in order to account for regional anatomic differences. Then, transformation parameters are applied to the T2 maps which are *smoothed,* i.e. blurred, afterwards.

Smoothing improves the signal-to noise ratio and increases the sensitivity of the statistical analysis. Thus, it is a prerequisite for some methods of statistical inference. Spatial smoothing of images is performed by convoluting the image data with a 3-dimensional Gaussian kernel. The shape of the smoothing curve is defined by the Full Width Half Maximum (FWHM). The resultant data are fed into two-sample t-tests. Analyses were conducted using the program SPM (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/). In SPM, standard univariate statistical tests are applied to every voxel in a given analysis. The resulting statistical parameters are assembled into a statistical parameter map. Statistical parametric mapping relies on the use of the general linear model (GLM) which will be described in more detail in the chapter regarding functional magnetic resonance imaging.

2.3 Voxel-based morphometry (VBM)

VBM is an automated technique which is implemented to examine brain morphology, i.e. especially grey matter, based on high-resolution structural three-dimensional T1-weighted images (Ashburner & Friston, 2000). In general, raw data are segmented into different tissue types, i.e. grey matter, white matter and cerebrospinal fluid, using information derived from signal intensity and - in most approaches - prior knowledge. However, prior probability maps can only improve the segmentation process if data and priors are registered in the same space. Thus, in serial approaches the quality of segmentation relies on registration accuracy (Ashburner & Friston, 2005; May & Gaser, 2006). In order to reduce this dependency, VBM protocols have been refined constantly.

In SPM5 which was used to analyze the data of Study I, a *unified segmentation* has been applied which comprises *registration, tissue segmentation and bias correction* for intensity nonuniformity within one model (Ashburner & Friston, 2005). In this model, default tissue probability maps are implemented which were provided by the International Consortium for Brain Mapping (ICBM, http://www.loni.ucla.edu/ICBM/ICBM_TissueProb.html). In contrast to previous approaches, there is no need for a customized template since priors are warped to the data and the inverse is used for normalization in order to minimize the impact of the template. Besides its role for segmentation, registration to common space is also a prerequisite for group analysis in order to guarantee that an anatomical structure is represented by

the same voxel throughout the group. However, expansion or contraction of images during spatial normalization may influence the volumes of certain brain regions. In order to correct for those volume changes, an additional preprocessing step, *modulation*, has been proposed. Modulation involves scaling by the amount of contraction so that the total amount of grey matter remains the same as it would be in the original images. Unmodulated images are interpreted in terms of grey matter concentration or density, whereas modulated images are associated with grey matter volume or absolute amount of grey matter (Ashburner & Friston, 2000; Good et al., 2001). The last preprocessing step prior to statistical analysis is spatial smoothing. In order to compare patients and controls, smoothed grey matter images are fed into a two-sample t-test.

However, although VBM is able to detect grey matter differences between groups, the mechanisms underlying these differences remain a matter of debate. Potential correlates of morphometric changes include a change in cell size, growth or atrophy of neurons or glia, as well as synaptic loss (May & Gaser, 2006).

2.4 Diffusion tensor imaging (DTI)

In addition to grey matter, brain morphology can be assessed by white matter integrity. Although VBM of T1-weighted images includes segmentation into grey and white matter, this technique is not optimal for assessing white matter. Instead, the integrity of white matter can be investigated best with diffusion tensor imaging (DTI; Basser, Mattiello, & Le Bihan, 1994; Le Bihan et al., 2001). In general, DTI utilizes principal mechanisms like spin and precession of hydrogen protons as well as applying gradients in order to collect data. But, in contrast to the aforementioned techniques, DTI additionally relies on Brownian motion, i.e. the spontaneous spreading of molecules from higher concentration to lower concentration. In particular, DTI relies on the molecular diffusion of water. Diffusion is *isotropic* if it is equal and unconstrained in all directions (like a drop of ink in a glass of water). In case motion is limited in at least one direction, it is called *anisotropic*. In the white matter of the brain, myelin sheaths of axons represent principal barriers. Therefore, diffusion is nearly limited to a parallel diffusion along the orientation of the fibers. Thus, it is possible to track neural fibers inside the brain in vivo and assess their integrity by imaging diffusion. The relationship of diffusion and white matter

integrity is expressed by an inverse correlation: An abnormal fiber goes along with reduced anisotropy or increased diffusivity, i.e. floating in all directions.

DTI requires special diffusion-weighted sequences which incorporate pulsed magnetic field gradients into standard sequences (Le Bihan et al., 1986). As described earlier, a HF pulse forces protons to precess in phase; after disabling of the HF pulse protons dephase. A very small part of dephasing is due to diffusion in the inhomogeneous field. For static spins, dephasing due to external field inhomogeneities can be eliminated by applying a 180° HF pulse which rephrases the precessing protons again and therefore increases the signal again (*spin echo*). In contrast, the signal in some voxels will be attenuated in relation to diffusion (*spin-echo attenuation*), since this cause of dephasing is not disabled by the HF pulse. As molecular displacements occur along the direction of the gradient, changes of gradient directions are necessary to reveal effects of anisotropy (Le Bihan et al., 2001). To quantify the amount of signal loss due to diffusion, an additional unweighted image - the B_0 image - is acquired. Using a mutual information cost function, each diffusion image is aligned to the B_0 image. This step also corrects for shears and stretches that are caused by eddy currents. These currents arise from the fast switches of the gradients in a diffusion-weighted MRI sequence.

After preprocessing, diffusion tensors are fitted to the data. The different gradients applied during data collection can be imagined as different viewpoints on the shape of the observed matter. The shape of diffusion is best described by an ellipsoid. An ellipsoid is mathematically defined by its orientation in space and its extension in each direction. The orientation in space is described by 3 eigenvectors and the extension is defined by 3 eigenvalues. The largest of these eigenvalues characterizes the principal eigenvector which indicates the principal direction of diffusion (Behrens et al., 2003; Le Bihan et al., 2001).

The extraction of eigenvectors and referring eigenvalues in order to gather information on the principal direction of diffusion is usually done by fitting the data onto a model applying multiple linear regression. Often, the parameters of the diffusion tensor model are chosen to be the six elements derived from the tensor and the signal strength in the unweighted image (Behrens et al., 2003). The diffusion tensors are used to derive core values from the images. Reference values most often used in the literature are *mean diffusivity* (MD) and *fractional anisotropy* (FA). The former represents overall diffusion which is the counterpart of the single scalar apparent diffusion coefficient (ADC)

derived in former diffusion-weighted imaging (DWI; Le Bihan et al., 1986). The latter is unique to DTI and characterizes the preference of water to diffuse in an anisotropic matter. A value of 1 indicates that diffusion occurs along a single axis, whereas a value of 0 refers to isotropic diffusion.

The result of such calculations, e.g. FA maps, can be compared between different groups after normalization. This could be done by using univariate statistics as described before. However, further calculations of FA maps concentrating on white matter using tract-based statistics offer the possibility of a sophisticated analysis (Smith et al., 2006). This procedure was chosen in the present thesis and will be described in detail in the corresponding methods chapter of Study I.

2.5 Functional magnetic resonance imaging (fMRI)

The last technique described in this section differs most obviously from all aforementioned techniques in terms of action required from a participant. While participants might even sleep during scanning procedures aiming at investigating brain morphology, they are requested to fulfill certain cognitive actions during fMRI.

More precisely, fMRI enables the non-invasive assessment of neural correlates of cognitive functions by measuring hemodynamic changes related to brain activity. The method is based on an endogenous contrast mechanism called *blood oxygen level dependent (BOLD)-contrast* (Kwong et al., 1992; Ogawa, Lee, Nayak, & Glynn, 1990). It relies on the fact that activity leads to an over-supply of oxygenated blood and a reduction of deoxygenated blood. Oxygenation influences the magnetic characteristics of hemoglobin. While oxyhemoglobin is diamagnetic, i.e. of low magnetic susceptibility, deoxyhemoglobin is paramagnetic - resulting in magnetic field distortions. Neural activation leads to increased energy demand. Energy is delivered to the synapses in the form of glucose and lactate (by glycolysis). Thus, as activity increases, oxygen consumption and cerebral blood flow increases. However, the blood flow supplies the activated region with more oxygenated blood than is consumed. The increase in blood flow is related to a decrease in deoxyhemoglobin concentration and to an increase in oxyhemoglobin concentration. The decrease in deoxyhemoglobin leads to better field homogeneity which results in a long T2* time and consequently in an increase in the fMRI signal. Images are brighter where T2* relaxation times are longer.

The typical BOLD-response shows a decrease shortly after stimulus onset (*initial dip*) and a signal rise about two seconds after the stimulus onset. Four to eight seconds after stimulus onset a maximum value is achieved. Subsequently, with a slight undershooting, the hemodynamic response is back to baseline at about 20-30 sec after onset (Heeger & Ress, 2002; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

As stated above, fMRI is an indirect measure of neuronal activity and the coupling between neural activity and changes in blood flow has been a matter of debate. Considerable evidence suggests that the BOLD-response represents local field potentials (Logothetis et al., 2001).

2.5.1 Preprocessing

The images acquired in an fMRI session have to be preprocessed in order to run statistical analysis. Preprocessing usually comprises the following steps for temporal and spatial corrections: *Slice timing*, *realignment*, *normalization* and *smoothing*.

Slice timing is a temporal preprocessing step adjusting for the sequential acquisition of slices within a volume. A brain volume consists of a number of slices and these slices are each collected at a slightly different time. However, during the statistical analysis it is assumed that all slices of a specific brain volume have been recorded at the same point in time. Therefore, a reference slice is selected and all other slices of the volume are temporally shifted to the reference slice in time via a Fourier transform. Usually, the slice close to areas of interest is chosen as reference in order to minimize errors of the interpolation procedure. In the studies described in this thesis, all images were temporally corrected with reference to the middle slice.

Subsequently, several spatial preprocessing steps are performed in order to reduce variance due to head movement or differences in individual brain anatomy.

Although participants are positioned carefully, with their heads fixated by foams, and instructed not to move, it is likely that they slightly move their head throughout the experiment. *Realignment* corrects for spatial distortions induced by such movements. Head movement causes the same voxel to appear at different locations. But, during statistical analysis, every voxel is assumed to be stationary throughout the whole experiment. In other words, it is assumed that a voxel always represents the same brain structure. To

ensure this assumption, all brain volumes are aligned with the reference image (usually the first image) by rigid-body transformations. This means that images are repositioned by translation and rotation along the x, y and z-axis. Simultaneously to the realignment process, an additional mechanism called *unwarp* can be applied to control for residual movement artifacts, especially stimulus-correlated movements. This mechanism corrects for the interaction of motion and distortion due to magnetic field inhomogeneity.

Since analyses are based on group-data in order to generalize the results, images need to be adjusted according to a standard reference frame so that the same voxel in the brain of each participant represents the same anatomical structure. This step is called *normalization*. The Montreal Neurological Institute (MNI) provides an anatomical template which represents the average of 152 normal MRI scans. Matching the orientation, size and shape of each individual to the orientation, size and shape of the template is done using affine transformations (translations, rotation, zooms, and shears). Non-linear transformations are often performed subsequently to improve results with respect to regional differences.

The final preprocessing step prior to statistical analysis is to blur the fMRI data (*smoothing).* Smoothing improves the signal to noise ratio in the fMRI signal by removing the noise present in the high spatial frequencies. The signal of interest is expressed on a low spatial frequency of several millimeters. Additionally, smoothing decreases small differences that remain after normalization. Therefore, as already stated before, it increases the sensitivity of the statistical analysis and is a prerequisite for some methods of statistical inference. Usually, smoothing is done with a FWHM of about two to three times the voxel size.

2.5.2 Statistical analysis

The statistical analysis attempts to detect brain areas which are significantly activated during the experimental conditions. It relies on the GLM which basically is a linear regression with the following formula:

$$Y = \beta * X + \varepsilon$$

In this formula, Y is a matrix containing the measured signal for each voxel and X is a matrix with the predictor variables. β holds a set of weights (*beta coefficients*) that determine relative heights or amplitudes of the different predictors. The error term is denoted by ε. Therefore, the measured signal in

each voxel is comprised of known variations in BOLD response caused by the experimental manipulation (X) and residual variance caused by confounding factors (ε). The relative strength of relationship between an experimental factor and the BOLD signal is indicated by the beta weights (β). Thus, it indicates the fit of the predicted to the observed data.

Statistical analysis comprises two steps, the analysis of the data of each single participant (*first-level analysis*) and the group statistics (*second-level analysis*). Both processes involve a *model specification* (i.e. selection of regressors) and a *model estimation* (i.e. computation of the parameter estimates). The first step in statistical analysis is to specify a design matrix. In this matrix, regressors of interest, i.e. the events that have been presented to the participant during scanning, are represented in an on/off fashion. The resulting function of onsets is then smoothed with a hemodynamic response function (HRF). The HRF supplies a model of changes in blood flow reflecting underlying neuronal processes. It mathematically captures a hypothetical BOLD response with the help of Gamma functions. In event-related studies like the present ones, this procedure is done for every stimulus.
In a next step, i.e. the model estimation, the hypothetical response function for the variable of interest is fitted to the experimental imaging data. The result is a beta weight for each regressor in each voxel. Weighting the columns of a design matrix according to specific research questions is achieved by setting up contrasts. Statistical maps are created showing which voxels are significantly activated given a certain linear combination of regressors.

In the second-level analysis, the contrast images of the first-level analyses for each participant are used to perform the group analysis. The second-level parameter estimates correspond to the group mean of the first-level parameter estimates of a particular regressor. Subsequent, the second-level parameter estimates are weighted by a contrast vector to generate contrast images. This process enables to identify voxels which are significantly activated for the whole group by a respective condition. An inherent problem of this kind of data analysis is the massive number of tests performed. An fMRI volume mostly contains thousands of voxels. By calculating this immense amount of t-tests, the likelihood of false positive results is high and needs to be corrected.

All preprocessing steps and subsequent statistical analyses are implemented in SPM which was used to analyze the functional imaging data of this thesis.

3 Study I

3.1 Introduction

The previous chapter summarized different MRI techniques which can be implemented in studies on memory. However, they are not the cornerstone of memory research. As mentioned in the general introduction of this thesis, knowledge about memory systems and underlying brain structures first derived from patient and lesion studies. Historically, one important "source of knowledge about...human memory" is temporal lobe epilepsy (Saling, 2009, p. 570) which is one form of epilepsy.

Epilepsies are the most common neurological disorders with a prevalence of 0.4-0.8% (Salmenpera & Duncan, 2005). They are characterized by epileptic seizures. An epileptic seizure is defined as "...a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005, p. 471). Surprisingly for the general public, epilepsy is not an entity but a variety of disorders. According to the international classification system, a major distinction is made between *localization-related* epilepsies in which seizures arise from a specific brain area and *generalized* epilepsies in which seizures indicate a bilateral hemispheric epileptogenic network. In a second step, these forms are classified as *idiopathic, symptomatic, or cryptogenic* (ILAE, 1989). While idiopathic refers to a presumed genetic etiology, symptomatic epilepsies are the consequence of an identifiable structural lesion. Cryptogenic epilepsies are presumed to be symptomatic, i.e. lesional, but the etiology is not known. However, while writing this thesis, the classification system has been modified and a new diagnostic scheme is about to be implemented in clinical practice (Berg et al., 2010). In this new system, the terms generalized and focal will only be used for seizures but not for epilepsies. Instead, epilepsies shall be grouped according to specificity, i.e. into *electro-clinical syndromes, nonsyndromic epilepsies with structural-metabolic causes, and epilepsies of unknown cause*.

In general, epilepsy is diagnosed if at least one seizure has occurred and enduring epileptogenic abnormality is suggested by clinical investigation (Fisher et al., 2005). Enduring abnormality is indicated by typical epileptic discharges in the electro-encephalogram (EEG) or by structural brain damage.

Therefore, magnetic resonance imaging is central to the diagnostic process since it enables the detection of potential epileptogenic substrates (Salmenpera & Duncan, 2005). Moreover, areas of cognitive functioning and their connection to epileptogenic areas can be determined. The identification of such eloquent areas is especially important in the diagnostic process prior to surgery in order to prevent distortions of language or mnestic abilities (Duncan, 1997).

As said before, memory deficits are a common accompanying disorder in focal epilepsies originating from the temporal lobe, even in the absence of an overt brain damage (Bengner et al., 2006; Giovagnoli & Avanzini, 1999). Since the latter phenomenon is hardly investigated, the present study intended to examine memory performance of cryptogenic TLE patients in more detail using various MRI techniques. In preparation of a precise description of the study, the following chapters will provide information about TLE, memory deficits in TLE patients and findings of MRI studies in TLE.

3.1.1 Temporal lobe epilepsy (TLE)

Temporal lobe epilepsy is the most common form of focal epilepsies. In about 70-80% of these patients, MRI abnormalities including hippocampal sclerosis, tumors and heterotopias can be detected. The remaining 20-30% of patients do not show abnormalities on standard MRI (Mueller et al., 2006; Salmenpera et al., 2007). In case the epilepsy is likely to be symptomatic but MRIs are normal, it is referred to as *cryptogenic* (ILAE, 1989) or *probably symptomatic* (Engel, 2001). According to the upcoming classification system, this form of epilepsy will be subordinated to *epilepsies of unknown cause* (Berg et al., 2010). Moreover, *mesial TLE with hippocampal sclerosis (HS)* will be treated as a distinct constellation different from other temporal lobe epilepsies which can be associated with structural or metabolic conditions (Wieser, 2004). Since this new classification requires long and precise expressions, the term *symptomatic* will be used in the present thesis for the sake of brevity and legibility in order to characterize those patients with overt lesions other than HS. In order to refrain from beliefs, some authors use the term *MRI-negative* instead of cryptogenic (e.g. Rugg-Gunn et al., 2005). Since this description might be confusing when referring to previous studies and own results, the terms *cryptogenic* and *TLE of unknown cause* will both be used throughout the text.

In general, the diagnosis of epilepsy requires the presence of seizures. Seizures that characterize TLE can be defined by specific signs and symptoms which can be covert or overt, i.e. visible to observers, and which can be accompanied by an impairment of consciousness (Marks & Laxer, 1998; Serles, Caramanos, Lindinger, Pataraia, & Baumgartner, 2000; Wieser, 2004). For example, a conscious subjective ictal phenomenon which is not be detected by observers is called an *aura*. Most common are epigastric or déjà vu auras. The former is a feeling of abdominal discomfort which rises to the chest; the latter is the feeling of having experienced a situation before. If consciousness is impaired, patients are not responsive but this reduction of responsiveness might not be evident at first glance although patients might exhibit speech or motor arrest. On the other hand, impaired consciousness goes along with automatisms which are key features of TLE. Typically, oroalimentary automatisms occur, i.e. lip smacking, swallowing, and chewing. Other repetitive motor activity is likely to follow. Clearly visible motor symptoms such as dystonic arm posturing or postictal paralysis have high lateralizing value. Clear ictal speech indicates seizure origin from the non-dominant hemisphere (Marks & Laxer, 1998). Patients are amnesic for the seizure afterwards and show a gradual recovery from postictal confusion. In general, a seizure only lasts several seconds to a few minutes. Specialized epilepsy centers offer the possibility of continuous video-EEG monitoring in which apparent seizures can be evaluated according to the presence or absence of simultaneous EEG abnormalities (Manford, 2001). Interictal or ictal EEG abnormalities associated with TLE are repeatedly detectable and definite spike-slow-waves localized at temporal and fronto-temporal electrodes. The appearance of interictal sharp waves is facilitated by drowsiness and superficial sleep (Wieser, 2004). Although a clear distinction might be difficult in the absence of MRI, some features of semiology and EEG are also reported to distinguish between lateral and mesial TLE: For example, epigastric auras and contralateral hand dystonia as well as anterior temporal spikes are more likely to reflect mesial than neocortical TLE (Madhavan & Kuzniecky, 2007; Wieser, 2004).

The common treatment of epilepsies is the prescription of antiepileptic drugs (AEDs). However, a third of all patients with focal epilepsies are refractory to anticonvulsant therapy (Kwan & Brodie, 2000; Salmenpera & Duncan, 2005). Most frequently, medically intractable epilepsy is seen in TLE with HS

(Blumcke, 2009; Wieser, 2004). Thus, in those patients, surgical treatment might be superior to medication (Wiebe, Blume, Girvin, & Eliasziw, 2001). The best outcome in terms of seizure control is reported for patients with definite HS and a clear disease history (Stefan et al., 2009). But, also patients with normal MRI can benefit from surgery given careful consideration with accurate identification of ictal onset zone and unilateral EEG patterns (Holmes et al., 2000; Madhavan & Kuzniecky, 2007; Sylaja, Radhakrishnan, Kesavadas, & Sarma, 2004). Besides effects on seizure control, benefits and risks of surgery do also exist according to cognitive outcome. One of the risks of temporal lobe surgery is memory impairment as described below (Baxendale, 2008; Helmstaedter & Kurthen, 2001; Lee, Yip, & Jones-Gotman, 2002; Madhavan & Kuzniecky, 2007).

3.1.2 Memory Disorders in TLE

Since the description of H.M., who suffered severe memory loss after removal of the medial temporal lobes (Scoville & Milner, 1957), the nature of memory deficits in TLE and the potential risk of further loss after surgery have been investigated intensely (Helmstaedter & Kurthen, 2001). TLE predominantly affects the formation of episodic memory (Bell et al., 2011; Helmstaedter & Kurthen, 2001; Wieser, 2004); thus stressing the pivotal role of intact medial temporal structures for this kind of memory. A second assumption which has dominated the investigation of memory in TLE is *material-specificity*. Early studies on effects of unilateral surgery suggested that memory loss is modality-specific, i.e. related to verbal or nonverbal information (Milner, 1966; Milner et al., 1968); thus, offering the possibility to distinguish between left and right TLE with the help of concordant memory tasks. While the left temporal lobe was associated with verbal memory, the right temporal lobe was associated with nonverbal memory. For decades, studies on TLE were interpreted within this reference frame (see Baxendale, 2008). Meta-analyses of effects of temporal lobe resection on memory have strengthened the association of left-sided surgery and verbal memory deficits, but failed to show a consistent relationship of nonverbal memory and right-sided surgery (Lee et al., 2002; Vaz, 2004). Therefore, some authors question the utility of specific memory tests since these may not assess nonverbal memory adequately due to verbalization and task demands (Vaz, 2004; but see Gleissner, Helmstaedter, Schramm, & Elger, 2004). Based on this literature, ‘atypical’ findings of cognitive deficits and fMRI studies (e.g. Kennepohl, Sziklas,

Garver, Wagner, & Jones-Gotman, 2007), some authors recently challenge the idea of material-specific memory systems in general. Instead, they suggest that memory performance is mostly influenced by task demands (for review Saling, 2009). For example, memory for verbal material can be unremarkable in left TLE patients if they can rely on semantic associations or established language abilities. On the contrary, these patients perform badly on tasks which are not structured meaningfully. In summary, material-specificity could be subordinated to other features of a task like novelty and associations between stimuli (Bell et al., 2011; Saling, 2009).

In general, cognitive functioning in epilepsy is influenced by a variety of interacting factors (Baxendale & Thompson, 2010; Elger, Helmstaedter, & Kurthen, 2004; Jokeit & Schacher, 2004; Kwan & Brodie, 2001; Wieser, 2004). A summary of these reversible and irreversible modulators is depicted in Figure 3-1.

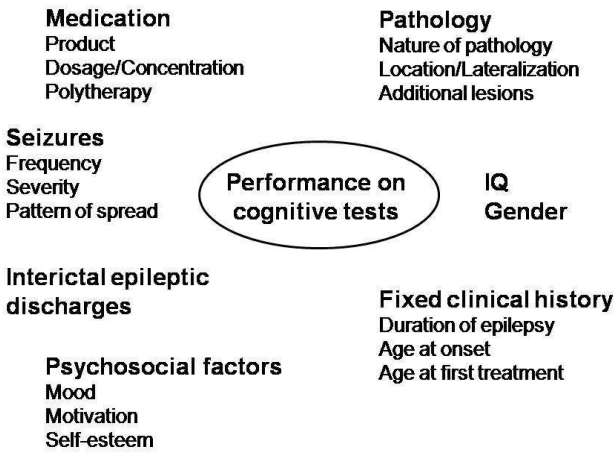

Figure 3-1 Factors influencing cognitive performance of patients with epilepsy
Reversible factors are depicted on the left, irreversible factors on the right.

As can be concluded from this figure, memory deficits can be assigned to a certain type of epilepsy (Jokeit & Schacher, 2004) or a certain lesion (Elger et al., 2004; Kwan & Brodie, 2001), but may also be influenced for example by the type of drug, the drug level, or a recent change of medication (Dodrill & Ojemann, 2007; Jokeit, Kramer, & Ebner, 2005). Moreover, paroxysmal epileptic discharges and subtle seizures can disrupt long-term potentiation (LTP; Aldenkamp & Arends, 2004; Meador, 2007). Deficits might extend poor

memory performance, if seizures frequently spread or generalize, or if additional lesions are detected (Bell et al., 2011; Elger et al., 2004; Jokeit & Schacher, 2004).

Figure 3-1 also implies that many factors need to be considered when predicting the risks of surgery (Baxendale & Thompson, 2010). Currently, risks of surgery are predicted according to a model of *functional adequacy* (Chelune, 1995); this model proposes that postoperative memory decline is inversely proportional to the functional adequacy of the (medial temporal lobe) tissue to be resected. In line with this assumption, high preoperative performance is the best predictor of deterioration (Baxendale, Thompson, Harkness, & Duncan, 2006). Demographic and clinical factors such as age at surgery and IQ may explain additional variance (Baxendale, 2008; Baxendale et al., 2006).

The relevance of knowledge about risks of surgery is one reason for intensely investigating memory in patients with overt lesions. Another reason might be the notion that "TLE provides an opportunity to study aspects of memory that have been theorized to rely on the medial temporal lobe" (Leritz et al., 2006, p. 10). Most often, studies on memory in TLE rely on patients with hippocampal sclerosis (Elger et al., 2004; Jokeit & Schacher, 2004). Patients without overt brain damage have rarely been investigated. If at all, the reports are inconsistent. Two studies concluded that (material-specific) memory distortions present in one but not the other group of TLE patients could solely be based on the etiology, i.e. HS (Alessio et al., 2004; Hermann, Seidenberg, Schoenfeld, & Davies, 1997). On the contrary, another group of authors reported memory impairments irrespective of the presence of overt brain damage (Giovagnoli & Avanzini, 1996, 1999). They concluded that clinical and treatment-related factors, e.g. the epileptogenic focus, might be more important than underlying pathology. A more recent study suggests that the specificity of memory deficits seem to differ between symptomatic and cryptogenic TLE (Bengner et al., 2006). While patients with right TLE and HS recognized less faces compared to controls in an immediate and delayed recognition test, impaired performance in cryptogenic TLE was only seen after a 24 hours retention interval. In particular, only this group of patients showed a significant decline of performance from immediate to delayed recognition.

In summary, mechanisms underlying memory processes in TLE of unknown cause remain less explored. On the one hand, the functional integrity of

neuronal ensembles may be negatively influenced by epileptic discharges leading to less efficient mnemonic processes in the absence of any morphological lesion. On the other hand, subtle abnormalities could not be excluded by any of the cited studies. A possible reason for the conflicting results might lie in the date of the early studies incorporating cryptogenic TLE; it is possible that morphological alterations might not have been detected by the MRI techniques of that time. But, also the later studies did not include detailed neuroimaging. In all studies, author's decision about structural integrity relied on visual inspection of individual structural MRI data. Therefore, the present thesis intended to test the relationship of brain morphology and memory performance in cryptogenic TLE in more detail. A comprehensive MRI-assessment was implemented which will be described in the following section.

3.1.3 MRI and TLE

In clinical routine, standard imaging protocols encompass various structural magnetic resonance images. Diagnoses regarding epileptogenic substrates are usually based on visual inspection of these images by radiologists and neurologists. The patients included in the present study were classified as cryptogenic due to unremarkable morphology according to this procedure.

However, individual assessment of images is not suitable for group studies. In addition, subtle tissue damages might not be detected by this procedure. Therefore, in the present study, all techniques described in the general introduction to MRI (see chapter 2) were implemented in order to investigate structural and functional alterations in patients with TLE of unknown cause. Since most sequences covered the entire brain, damages and structural-functional relations could be detected precisely without bias, e.g. due to placement of ROIs or anatomical expertise. Moreover, all analyses conducted rely on automated procedures and voxel-wise statistics.

The following chapters provide a summary of findings from different studies focusing on morphological abnormalities in patients with cryptogenic TLE and correlations of brain structure and cognitive abilities in patients with TLE.

3.1.3.1 T2 relaxation maps and TLE

T2 relaxation times are widely used in clinical routine for the assessment of mesial TLE. Thus, image acquisition is mostly restricted to the hippocampus. Enhanced T2 relaxation times of patients compared to controls are assumed

to reflect gliosis and/or neuronal loss (Briellmann, Kalnins, Berkovic, & Jackson, 2002; Duncan, 1997). Early studies using sequences with one to six slices could successfully detect enhanced T2 relaxation times ipsilateral to the epileptic focus in patients with HS proven by reduced hippocampal volume on T1-weighted images. But, only half of the patients with cryptogenic TLE showed enhanced T2 relaxation times (Namer et al., 1998; Woermann, Barker, Birnie, Meencke, & Duncan, 1998), probably related to histopathological evidence of neuronal loss and gliosis (Bernasconi et al., 2000). A more recent study applying whole-brain voxel-based analysis of T2 maps also reported abnormalities of T2 relaxation in only 50% of cryptogenic TLE when tested individually against controls (Rugg-Gunn et al., 2005). When tested in a group comparison, cryptogenic TLE patients showed significant enhancement of T2 relaxation times in temporal lobe white - but not grey - matter. Taken together, the authors concluded that minor structural abnormalities are likely to exist. However, it is not clear whether these abnormalities are underlying etiologic factors or the result of seizures. While *voxel-based relaxometry* (Pell et al., 2004) in patients with HS showed enhanced T2 relaxation times in accordance with volumetric ROI-approaches, the pattern of changes is only partly overlapping with results of other voxel-based structural analysis like VBM (Pell, Briellmann, Pardoe, Abbott, & Jackson, 2008; but see Richardson, Strange, & Dolan, 2004). Thus, the different techniques might relate to different pathological states. Comparisons of different whole-brain voxel-based techniques revealed low specificity and concordance in detecting structural changes in patients with normal conventional MRI. Only 31% of the patients showed abnormalities in line with the epileptic focus revealed by video-EEG-monitoring in at least one MRI technique; enhancement of T2 relaxation times in line with EEG and semiology was found in 16% of the patients (Salmenpera et al., 2007).

The relationship of T2 relaxation times and cognition is not fully understood. While some authors found a significant negative correlation of (verbal) memory performance and (left) T2 relaxation (Kalviainen et al., 1997; Lillywhite et al., 2007) others could not detect a simple correlation (Baxendale et al., 1998; Bengner, Siemonsen, Stodieck, & Fiehler, 2008; Namer et al., 1998). But, enhanced T2 was associated with low performance when combined with spectroscopy (Namer et al., 1999), in regression analysis with various MRI- and epilepsy-related predictors (Baxendale et al., 1998) or when

using differences scores, i.e. right-left T2 relaxation times (Bengner et al., 2008). The latter study extended the aforementioned findings of a marked decline from immediate to delayed face recognition performance in a group of patients with right cryptogenic TLE (see Bengner et al., 2006). Whereas a simple correlation of memory performance and T2 relaxation times in different ROIs (Hippocampus and fusiform gyrus) did not yield significant results, higher combined T2 values in the right than the left hippocampus and fusiform gyrus correlated with immediate face recognition. No such relationship was seen for delayed face recognition. The study could not report correlation analysis for controls since these were not referred to memory testing. Thus, the study could not clarify the nature of this specific memory distortion. The authors suggest that delayed recognition might rely on a broader network of areas (Bengner et al., 2008).

3.1.3.2 VBM and TLE

In general, T1-weighted high resolution images are scanned in order to detect structural abnormalities related to epilepsy. With regard to TLE, the most common finding is hippocampal sclerosis which can be detected by visual inspection. In order to detect abnormalities carried by many patients, e.g. in group studies, images can be fed into automated quantitative procedures, e.g. VBM, which do not rely on investigator expertise and offer the possibility of examining the entire brain. A meta-analysis of 18 studies using VBM in TLE compared to controls found that reduction of grey matter is most frequent in the medial temporal lobe ipsilateral to the epileptic focus. Structural abnormalities of the hippocampus were reported by 82.35% of all studies, followed by parahippocampal (47.06%) and entorhinal (23.52%) cortex (Keller & Roberts, 2008). By contrast, extratemporal atrophy was reported to be bilaterally distributed and most prominent in the thalamus (50% of all studies). These results confirmed findings from ROI studies, i.e. manual morphometry studies, but also revealed that atrophy can be detected beyond predetermined structures. One recent study suggests that the pattern of abnormalities is related to treatment success, i.e. that atrophy is more widespread in refractory epilepsy (with HS) compared to non-refractory epilepsy (Bilevicius et al., 2010). Authors of another study postulate that extrahippocampal atrophy is explained by two factors, namely excitotoxic injury from seizure spread and hippocampal deafferentiation, i.e. fiber disconnections in limbic structures as confirmed by a combination of VBM and DTI (Bonilha et al., 2010; also see

Mueller et al., 2006). If not focusing on the pattern but the finding of a reduction itself, *atrophy* and *neuronal loss* are the most common interpretations (Keller, Mackay, et al., 2002; Keller, Wieshmann, et al., 2002; Mueller et al., 2006). But, the exact pathological basis of grey matter reduction is uncertain (Eriksson, Free, et al., 2009).

VBM findings regarding cryptogenic TLE are inconsistent. On the one hand, in opposition to patients with HS, patients with no signs of HS did not deviate from controls in the concentration and amount of grey matter (Mueller et al., 2006; Woermann, Free, Koepp, Ashburner, & Duncan, 1999). On the other hand, a study with a large sample size of drug-responsive TLE patients (n=95) reported hippocampal and thalamic atrophy for both, HS (n=34) and non-HS (n=61), patient groups compared to controls. Reduction of grey matter was less prominent for the non-HS group and only seen at an uncorrected statistical threshold (Labate, Cerasa, Gambardella, Aguglia, & Quattrone, 2008). Another study did also find differences of grey matter volume between cryptogenic TLE patients and controls, but not in the presumed seizure onset zone, i.e. medial temporal (Riederer et al., 2008).

Inconsistency also holds true for investigations of anatomical-functional relations, e.g. correlations of grey matter and memory performance. While some correlation analysis showed that reduced left hippocampal volume is associated with impaired immediate story recall (Kalviainen et al., 1997), deficits in delayed story recall and delayed recall of a learned list of words (Kalviainen et al., 1997; Stewart et al., 2009), other studies failed to show such a relationship - although behavioral results differed significantly between left and right HS (Baxendale et al., 1998). However, in a regression analysis, left hippocampal volume predicted immediate story recall and right hippocampal volume predicted delayed figure recall (Baxendale et al., 1998). But, this study also revealed that different test scores were predicted by a variety of factors, i.e. T2 relaxation times, age and age at onset of epilepsy. Similarly, the few studies using whole-brain analysis provide limited evidence for specific anatomical-functional relations. One study revealed that multiple brain areas are connected to the verbal memory score of the Wechsler Memory Score, i.e. story recall and paired associate learning, in patients with left TLE and HS (Bonilha et al., 2007). In another study, memory performance of 49 patients with TLE and left HS was associated with the global grey matter volume; no relationship was found for 40 right TLE patients. Moreover, this relationship

was only found for recognition scores for words and faces, but not for list learning, story or figure recall (Focke, Thompson, & Duncan, 2008).

3.1.3.3 DTI and TLE

Electrical impulses producing seizures originate in neurons; thus epilepsy is basically considered a "… grey matter disease" (Concha, Beaulieu, Collins, & Gross, 2009, p. 312). But, white matter tracts are assumed to play an important role in seizure propagation. This is one of the reasons for applying DTI in epilepsy. Reference values for comparisons between patients and controls are typically ADC in older DWI studies and MD and/or FA in DTI studies. In general, TLE patients show reduced FA and increased ADC or MD when compared to controls (Yogarajah & Duncan, 2008). This pattern has been reported to successfully localize the epileptogenic zone (Assaf et al., 2003; Concha, Beaulieu, & Gross, 2005; Gross, Concha, & Beaulieu, 2006; Thivard et al., 2005), but might also extend beyond the ipsilateral temporal lobe (Concha et al., 2005; Gross et al., 2006; Thivard et al., 2005). The latter finding has led to the assumption that DTI might be more sensitive than standard MRI (Yogarajah & Duncan, 2008; but see Focke, Yogarajah, et al., 2008; Londono, Castillo, Lee, & Smith, 2003). However, similar to the VBM studies cited above, it is not clear whether reduced FA and increased MD reflect etiologic factors, i.e. the cause, or acquired damage or effects of repeated seizures, i.e. the consequence of epilepsy (Rugg-Gunn, Eriksson, Symms, Barker, & Duncan, 2001). The second analogy to VBM refers to findings in cryptogenic TLE. Normal diffusion parameters have been found in up to 50% of individual patients with normal structural MRI in various studies (Chen et al., 2008; Londono et al., 2003; Rugg-Gunn et al., 2001), but group effects of altered parameters compared to controls have been reported as well (Rugg-Gunn et al., 2001; Shon et al., 2010). However, the latter studies differ according to findings in left vs. right TLE and the sensitivity of MD vs. FA. Moreover, in case of diffusion abnormalities, concordance with electroclinical localization of seizure in individual patients is poor (Chen et al., 2008). Some authors conclude that the epileptic focus in cryptogenic TLE might not be disruptive enough to cause clear alterations; this interpretation goes along with the assumption that subtle lesions occur in areas of naturally low anisotropy (Rugg-Gunn et al., 2001).

Recently, studies emerge which investigate the link of deterioration or asymmetries of white matter and cognition in TLE. In the first studies, correlations of memory scores and diffusion parameters from hippocampal or parahippocampal ROIs were estimated; material-(un)specific effects were found at a liberal uncorrected threshold (Lui et al., 2005) or for left TLE, only (Yogarajah et al., 2008). A similar group effect was found in a study focusing on a specific tract, i.e. the uncinate fasciculus (UF) and its correlation with memory indices of the Wechsler Memory Scale (Diehl et al., 2008): In a heterogeneous group of left mesial and lateral TLE patients, verbal memory scores were associated with increased MD in left UF ROIs, whereas nonverbal memory was associated with reduced FA in right UF ROIs. The correlation of verbal memory (story recall) and MD in the left UF was confirmed by another group of authors (McDonald et al., 2008). While verbal memory was also associated with other tracts, e.g. the right arcuate fasciculus, nonverbal memory (recognition of faces) was not associated with any manually traced tract. The latest study used voxel-wise statistics of FA values in a first step to derive clusters of tracts which differ between TLE patients (10 left, 2 right) and controls (Riley et al., 2010). Mean FA values of an ipsilateral anterior temporal cluster comprising UF and inferior longitudinal fasciculus (ILF) was positively correlated with delayed memory (including verbal and visual material), while mean FA in a mesial temporal cluster of fornix and ILF was associated with immediate verbal memory. In contrast to the aforementioned studies, these correlations were conducted for the combined group of patients and controls. When tested separately, only the correlation of anterior temporal FA and memory remained significant in the group of TLE patients. In the control group, no significant effect was found.

3.1.3.4 FMRI and TLE

For TLE patients, functional MRI is most important prior to surgery. To date, language lateralization on the basis of fMRI is a standard procedure in many tertiary epilepsy centers (Duncan, 2009). Language dominance assessed by fMRI can also explain additional variance in postoperative memory outcome (Binder et al., 2008; Duncan, 2009; Labudda, Mertens, Aengenendt, Ebner, & Woermann, 2010). Memory fMRI itself may be as useful in predicting the risks of a surgery, but has not been established in clinical routine. This may be due to the variety of experimental tasks and problems in identifying patterns of activity in individual participants (Bonelli et al., 2010; Golby et al., 2002; Powell

et al., 2007). In the first fMRI studies on memory in TLE, block designs were used in order to lateralize activity during encoding. The majority of such studies reported asymmetric lateralization indices in favor of a reorganization of memory processes. In particular, activity during encoding of modality-specific stimulus material is reallocated contralateral to the epileptic focus, i.e. to the right in patients with left TLE and HS for verbal material and to the left in right TLE with HS for nonverbal material (Detre et al., 1998; Dupont et al., 2000; Golby et al., 2002; Jokeit, Okujava, & Woermann, 2001a; Rabin et al., 2004; Vannest, Szaflarski, Privitera, Schefft, & Holland, 2008). In line with the hypothesis of functional adequacy, activity in the ipsilateral medial temporal lobe during encoding in the associated modality predicted memory decline after surgery (Rabin et al., 2004).

However, regarding memory, activity in block designs is ambiguous because activity during successful memory formation cannot be separated from unsuccessful processes. Thus, doubts exist whether contralateral activity reflects a true reallocation of memory or attentional processes related to acquisition attempts (Vingerhoets et al., 2004). Merging successful memory formation and failure becomes even more problematic in terms of interpreting patterns of activation, if the ratio of hits and misses differs significantly between groups of patients and controls (Richardson, Strange, Duncan, & Dolan, 2003). Using event-related fMRI, events during encoding can be classified by subsequent performance, i.e. post-hoc by later recognition success (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Paller, Kutas, & Mayes, 1987; Wagner et al., 1998). Thus, this technique enables the detection of true memory activity during encoding by separating or contrasting successful and unsuccessful trials. Therefore, differences between patients and controls can be interpreted more easily in terms of memory processing than in block designs. Nevertheless, studies on event-related memory fMRI in TLE are rare. Data up to now almost exclusively rely on patients with HS, and on left TLE in particular (Powell et al., 2007; Richardson et al., 2003; Richardson, Strange, Duncan, & Dolan, 2006). In a series of studies, Richardson and coauthors investigated encoding of a word list which was probed in a later recognition test using the distinction of *remembering* vs. *knowing* an item (Tulving, 1985); while remembering refers to a vivid recollection of an item, knowing describes the feeling that an item seems familiar but is not definitely remembered. The differences between correctly

recognized words of both classifications were further analyzed (e.g. Richardson et al., 2003). Other studies including right and left TLE used lists of words, faces and objects which were probed in a simple *yes-no recognition* test (Bonelli et al., 2010; Powell et al., 2007).

In all studies, impaired memory of patients compared to controls was associated with enhanced asymmetric, i.e. enhanced contralateral, MTL activity during encoding. The degree of reorganization seemed to be proportional to the severity of pathology (Powell et al., 2007; but see Bonelli et al., 2010). Moreover, ipsilateral activity was associated with better preoperative performance and postsurgery memory decline, thus stressing the functional adequacy of the ipsilateral hippocampus (Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2006; Richardson, Strange, Thompson, et al., 2004). One of the studies on patients with left TLE and HS included several voxel-based analyses, i.e. VBM, T2 relaxation and fMRI, in order to precisely localize structural and functional abnormalities (Richardson, Strange, & Dolan, 2004). The study confirmed that memory performance and ipsilateral fMRI activity decreases are related to increased left hippocampal pathology measured by VBM and T2 relaxation.

In order to minimize the risk of causing a deficit by surgery, it is important to choose fMRI paradigms that are appropriate to test functions of the area which is going to be resected (Salmenpera & Duncan, 2005). Recent studies question the utility of specific previous approaches like mental navigation to test anterior MTL functions (e.g. Beisteiner et al., 2008). Moreover, evidence for a substantial role of the MTL in associative memory is provided by a variety of theoretical and empirical studies. However, relational memory is hardly ever probed in functional imaging of TLE patients. One positron emission tomography (PET) study and two fMRI studies using blocks of relational learning in symptomatic TLE confirmed postsurgical deficits in relation to the degree of presurgical ipsilateral MTL activity during encoding (Frings et al., 2008; Henke et al., 2003). As stated before, block designs prevent investigating activity of successfully encoded in contrast to forgotten associations.

In summary, fMRI studies suggest that epilepsy influences the functional neuroanatomy of memory. However, reorganization is mostly associated with impairment and thus interpreted as being inefficient (Powell et al., 2007; Vannest et al., 2008).

Patients with TLE of unknown cause have rarely been investigated in fMRI studies. If included in a sample, they were not separated from patients with HS (Maccotta, Buckner, Gilliam, & Ojemann, 2007; Rabin et al., 2004). Thus, functional mechanisms underlying memory processes in this patient group are not explored.

3.2 Aim and hypotheses of Study I

The previous chapters have highlighted findings of neuropsychological assessment and MR imaging in patients with TLE. In summary, memory deficits represent the major cognitive impairment in this group of patients. Different MRI techniques have been implemented in order to investigate the neural correlates of this memory decline. However, most studies focus on patients with overt morphological abnormalities, especially hippocampal sclerosis. The mechanisms underlying memory impairments in patients with TLE of unknown cause are less explored. Therefore, the present study intended to investigate brain-related factors of memory performance in a group of patients with cryptogenic TLE. In other words, the study aimed at clarifying whether subtle morphological or functional abnormalities exist which are related to less efficient memory acquisition.

In contrast to most previous studies, the imaging protocol of the present study included various imaging techniques (T2 relaxation times, VBM, DTI, and fMRI) aiming at an extensive assessment of the brain morphology of patients and matched controls. Thus, it could be tested whether memory performance is influenced by the degree of structural and functional integrity of the hardware required for processes of encoding and consolidation.

In particular, it was hypothesized that

1. patients with cryptogenic TLE exhibit memory impairments compared to controls.
2. these impairments are related to morphological alterations of grey or white matter.

In addition, functional MRI was employed in order to directly study the neural correlates of encoding efficiency. FMRI might identify potential functional differences in the absence of any well-defined anatomical pathology.

It was assumed that

3. patients with cryptogenic TLE show altered functional responses when compared to controls, i.e. a different pattern of activation during successful encoding.

In contrast to previous fMRI studies in TLE, the present study implemented an associative memory paradigm. The formation of associations between previously unrelated stimuli is a vital aspect of episodic memory and crucially relies on the hippocampus, as indicated by fMRI (Davachi, 2006; Mayes, Montaldi, & Migo, 2007) and lesions studies (Hannula, Tranel, & Cohen, 2006; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). Thus, associative memory might be more suitable than list learning to test for differences between TLE patients and controls (see Bell & Giovagnoli, 2007; Saling, 2009).
In summary, the present study intended to combine a variety of MRI techniques in order to better characterize patients with cryptogenic TLE. Moreover, the study aimed at investigating the correlation of memory performance and structural or functional neural substrates. Since the origin of seizures suggests a dominant influence of the medial temporal lobe, analyses were focused but not restricted to the MTL. All but one technique provided the detection of abnormalities across the whole brain.

3.3 Methods

3.3.1 Participants

Patients with TLE were recruited from the Protestant Hospital Alsterdorf in Hamburg between September and December 2006. All patients had been referred to video-EEG-monitoring for diagnostic reasons before. EEG-electrodes were placed according to the 10/20 system with additional electrodes according to the 10/10 system; EEG and video was continuously measured for 24 up to 72 hours. The diagnosis was ideally based on seizures documented by video, with the aforementioned semiology (e.g. epigastric aura, automatisms, lateralizing signs) and corresponding unilateral EEG abnormalities. Otherwise, classification was based on seizures observed by physicians during hospitalization, plus seizure semiology stated in the case history and interictal epileptic abnormalities.

In total, 14 patients classified to suffer from unilateral mesial TLE were selected for MRI scanning. One patient did not finish scanning because of claustrophobia; another patient was excluded due to a dual pathology. Four patients were detected as TLE with hippocampal sclerosis (2 left, 2 right) by conventional clinical MRI on a 1.5T system, i.e. by signs of atrophy on T1-weighted images and increased T2-weighted signal intensity (Duncan, 1997; Woermann et al., 1998). According to visual inspection of standard images by experienced radiologists, the remaining patients were classified as cryptogenic. In six patients the epileptic focus was determined to be right-sided, and in two patients left-sided. Thus, only the group of 6 patients with right TLE (5 male; age range 18-47 years, mean 32.8) was further analyzed. All patients were on anticonvulsant medication (see Table 3-1 for details). No seizure was reported at least 24 hours prior to scanning.

Table 3-1 Demographic and clinical characteristics of the patient group with right TLE

Patient	Age	Sex	Years of education	Age at onset	Seizures per month	Drug
1	28	m	10	13	5	Lamotrigine
2	42	m	13	12	0.3	Carbamazepine
3	31	m	10	27	4	Valproic acid
4	47	f	10	11	2	Topiramate
5	30	m	9	22	2	Lamotrigine
6	18	m	13	16	0.2	Oxcarbamazepine

m = male, f = female, age/age at onset in years

The group of TLE patients was compared to a control group which was recruited by advertisement during the same time. In total, 20 participants were scanned. Six participants were excluded because of the following reasons: two had visible brain lesions, one a history of alcoholism, one a beginning dementia, and the remaining two sets of MRI data were unusable due to artifacts. Thus, the control group consisted of 14 participants (10 male; age range 21-55 years, mean 39.4). Since patients and participants did not perfectly match, gender, age and educational background (years of school education) were used as covariates in all analyses.

All patients and control participants were free of psychiatric disorders, right-handed, and native German speakers. All patients were believed to have typical language dominance based on speech during seizures; typical language dominance in controls could only be assumed based on

handedness. Ethics approval was obtained from the ethics committee of the Protestant Hospital Alsterdorf.

3.3.2 Neuropsychological assessment

Cognitive functioning of patients and controls was examined with a comprehensive neuropsychological assessment. Learning and memory for verbal information was assessed with the German version of the Auditory Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest-VLMT; Helmstaedter, Lendt, & Lux, 2001) and the subtest *logical memory* of the Wechsler Memory Scale - Revised (WMS-R; Härting et al., 2000). This latter test requires the *immediate and delayed* recall of two stories which are read out loud by the experimenter. The sum of correctly recalled details indicates memory performance in the respective condition. In the VLMT, 15 words are presented aurally and have to be learned by the participant in 5 trials of presentation and immediate recall. *Learning* capacity is governed by the sum of correct responses in these learning trials. Memory performance is reflected by the delayed free *recall* after approximately 30 minutes and the *difference* between this recall and the last learning trial (trial 7 minus trial5; trial 6 represents the recall of a distractor list after the first learning trials and will not be considered further). In addition, a *recognition* test is applied subsequent to delayed free recall. Performance is indicated by correct responses minus false responses. Nonverbal memory was assessed by the *recall* of the *Rey-Osterrieth-Complex-Figure* which had been copied by patients and participants in order to check for visuospatial abilities (ROCF; Rey, 1941; Spreen & Strauss, 1998). Second, the *face memory test* used by previous studies in Alsterdorf was applied (Bengner et al., 2006). Originally, this computerized test requires an immediate and a 24-hours-delayed *recognition* of 20 previously shown faces out of 40 faces. Because participants were not willing to take part in the study on two consecutive days, delayed recognition was omitted. Another test was omitted from the protocol, too. Since autobiographical memory is a vital aspect of episodic memory, the *Autobiographical Memory Interview* (AMI; Kopelman, Wilson, & Baddeley, 1990) was first incorporated into the test protocol. However, participants were not willing to report autobiographical information and/or not willing to extend the test session. Moreover, data could not be verified. *Working memory* was assessed via the homonymous subtest of the Testbatterie zur Aufmerksamkeitsprüfung (TAP; Zimmermann & Fimm, 2002). The test

requires a fast reaction if a number matches the one next to the last. Since the present thesis focused on long-term episodic memory, this test was not considered in correlation analyses with brain structure, although performance in short-term memory might be based on the MTL as well (Ranganath, Cohen, Dam, & D'Esposito, 2004).

In order to control for other cognitive functions that could influence memory performance, tests for attention and executive functions were also administered: the TAP-subtests *divided attention* and *flexibility* and a test for *verbal fluency* (RWT; Aschenbrenner, Tucha, & Lange, 2000). In addition, *crystalline verbal intelligence* was assessed by a vocabulary test (Wortschatztest; Schmidt & Metzler, 1992). Moreover, all patients and participants filled in self-report questionnaires estimating the presence of depression and anxiety, i.e. the *Becks Depression Inventory* (BDI; Hautzinger, Bailer, Worrall, & Keller, 2000) and *State Trait Anxiety Inventory* (STAI; Laux, 1981).

Performance in all tests was compared between patients and controls using analyses of covariance (ANCOVA); in the following, the value of the test statistic and the significance value will be reported in case of significant results, only.

3.3.3 T2 relaxation maps

3.3.3.1 Image acquisition

All image series of the present study were acquired on a 3T system (Siemens Trio) using an 8-channel head coil. Functional MRI was always scanned first and all other sequences were randomly applied; the total scan time was roughly 2 hours per participant.

For the T2 maps, four T2-weighted images were acquired using a turbo-spin echo sequence (TE1: 16 ms, TE2 98 ms, TR 12210 ms, 70 slices, 1 mm slice thickness, flip angle 180°, field of view 256 x 176 mm, 1 repetition).

3.3.3.2 Image analysis

All image series in Study I were analyzed using SPM5. For the T2 maps, in a first step, all images were corrected for inhomgeneities using the bias correction option implemented in the segmentation algorithm (Ashburner & Friston, 2005). This correction can be applied without actually segmenting the images (see next chapter for segmentation). Since the standard normalization

procedure might not be optimal for a restricted field of view, T2 images were coregistered on the individual high resolution T1-weighted image. The normalization parameters obtained by normalization of the T1 image on a T1 template were applied to the T2 images. In the last step, T2 images were smoothed with a 3D Gaussian filter with a kernel of 10 mm FWHM. Using SPM ImCalc, T2 relaxation maps were constructed by applying the standard equation when using two echo times:

(TE2-TE1)/(ln((image1+image3)/(image2+image4)))

Image 1 and 3 represent the images of the first echo, image 2 and 4 the images of the second echo (see Duncan et al., 1996).

On the second level, patients were compared with controls using a two sample t-test with age, gender and education regressed out as covariates of no interest. In a second analysis, memory scores derived from neuropsychological assessment (see chapter 3.3.2: VLMT, logical memory, ROCF recall, and face memory) were correlated with T2 relaxation times. Therefore, all test scores and T2 maps were fed into a regression analysis in SPM. In both analyses, results were considered significant at $p < 0.05$ corrected for multiple comparisons.

3.3.4 VBM

3.3.4.1 Image acquisition

A whole-brain T1-weighted structural MRI was acquired for each participant using a 3D-FLASH sequence (1 mm slice thickness, TR 15 ms, TE 4.9 ms, flip angle 25°, field of view 256 x 256 mm^2).

3.3.4.2 Image analysis

Data were analyzed with the toolbox VBM 5.1 (Christian Gaser, http://dbm.neuro.unijena.de/vbm), an extension of the segmentation algorithm of SPM5. In general, images were spatially normalized, segmented into different tissue classes and smoothed prior to statistical analysis. The unified segmentation approach in SPM5 consists of segmentation, bias correction and warping prior images to the data (Ashburner & Friston, 2005). In the toolbox, this core process has been extended by two aspects which were used in the present data analysis. Information about prior probability of tissue classes was refined by implementing a model of spatial constraints (*Hidden Markov Random Fields Model*). By eliminating isolated voxels which are

unlikely to belong to a tissue class, the noise level is reduced. Second, VBM 5.1 offers the possibility to correct for non-linear warping only (http://dbm.neuro.unijena.de/vbm/segmentation/modulation). Volume changes due to affine normalization will not be considered; thus, the original differences will be preserved. This option is based on the idea that a correction procedure should be applied directly to the data and not by a global scaling to a statistical model. Thus, there is no need to correct for different brain sizes in later statistical analyses as it would be with the default SPM modulation option (see chapter 2.1.3.3). An example of a grey matter map from the present study is depicted in Figure 3-2.

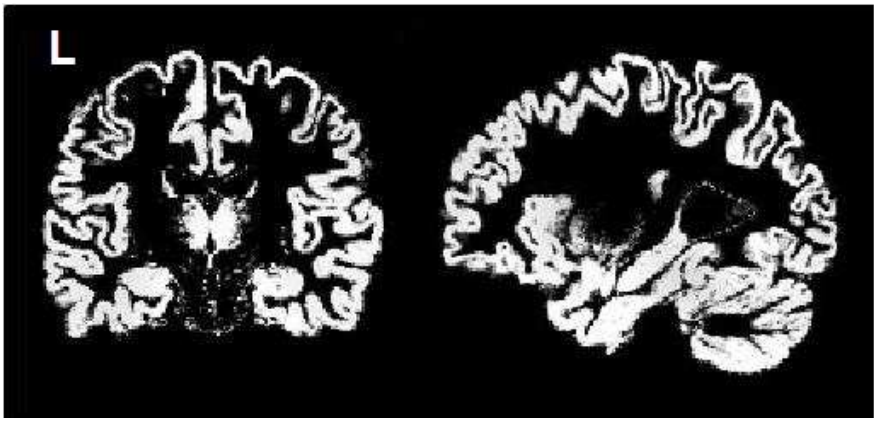

Figure 3-2 Example grey matter map
The grey matter was segmented from an individual T1-weighted image of a control participant.

Approximating the width of the hippocampus, a smoothing kernel of 10 mm FWHM was chosen according to the literature considering optimal detection of abnormalities in TLE (Keller & Roberts, 2008).

As described in the previous chapter, two second-level analyses were conducted. Comparisons between patients and controls were conducted by two sample t-tests with age, gender and education as covariates. The analysis was constrained to grey matter by using grey matter maps only and by an absolute threshold for masking of 0.15. The resultant statistical maps were thresholded at $p < 0.05$, corrected for multiple comparisons at the entire scan volume. Additionally, based on an aforementioned meta-analysis of VBM findings in TLE (Keller & Roberts, 2008), the search volume was reduced to regions of interests in the MTL, namely the hippocampus, parahippocampus and entorhinal cortex using anatomical masks of this regions (Amunts et al., 2005; Tzourio-Mazoyer et al., 2002). Correlation analyses of memory scores and grey matter were also conducted as described above.

3.3.5 DTI

3.3.5.1 Image acquisition

Diffusion-weighted images were obtained with an EPI sequence (60 slices, 2 mm slice thickness, TR 18600 ms, TE 109 ms). The diffusion weighting was isotropically distributed along 60 directions (b-value = 1000 s/mm²). For each direction, 2 volumes and an additional volume with no diffusion weighting (B_0) were acquired.

3.3.5.2 Image analysis

The diffusion-weighted data were processed with the FSL software package (FMRIB's Software Library; Smith et al., 2004). Images were corrected for eddy current and motion induced distortions using FLIRT (FMRIB's Linear Image Registration Tool - linear inter-and intra-modal registration) to apply full affine alignment of each image to the first B_0 image, using the mutual information cost function (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). To exclude non-brain data from further analysis, BET brain extraction was performed (Smith, 2002). Diffusion tensors were derived using a least squares fit of the tensor model to the diffusion data. Fractional anistropy was calculated from the eigenvector‘s eigenvalues of each voxel (Behrens et al., 2003); see Figure 3-3 for example maps.

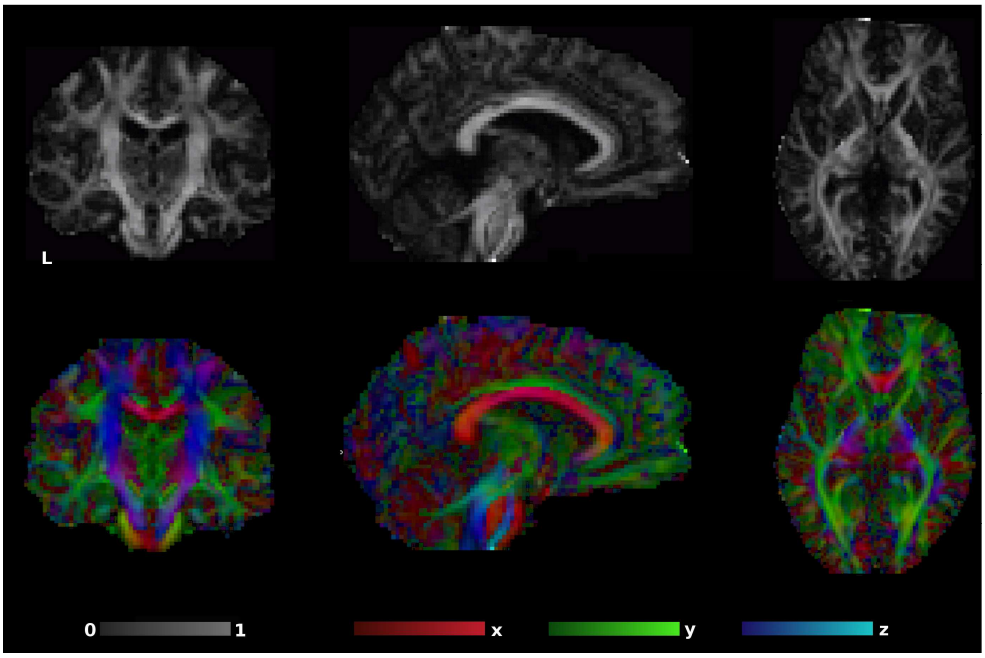

Figure 3-3 Example FA map and corresponding color-coded eigenvector
In FA maps, isotropic diffusion appears dark (e.g. in grey matter), anisotropic areas are bright. The main direction of diffusion is coded in the eigenvector map (left-right in red, superior-inferior in green, and superior-inferior in blue).

Using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), all participants' FA data were then warped nonlinearly onto the FA target implemented in FSL and normalized into a common space using nonlinear registration. Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each participant's aligned FA data was then projected onto this and normalized to MNI space. TBSS was also applied for analysis of mean diffusivity using the nonlinear registration and projection vectors derived from FA data. In contrast to previously described data, this process renders smoothing unnecessary. Group comparisons of patients and controls as well as regression analysis with memory test scores were conducted using FSL randomize, i.e. a permutation-based statistical inference with 5000 permutations. The resulting statistical maps were corrected for multiple comparisons.

In addition to effects in the entire scan volume, the search volume was reduced to the uncinate fasciculus based on the literature described in chapter 3.1.3.3 (e.g. Diehl et al., 2008). This structure should also be of special prominence for memory in general, since it connects temporal and frontal

areas which are relevant in memory processing (Ebeling & von Cramon, 1992; Petrides & Pandya, 1988; Simons & Spiers, 2003).

3.3.6 FMRI

3.3.6.1 Experimental task

As described above, a memory paradigm applied in studies on TLE should be suitable to detect MTL activation or deactivation. Previous event-related fMRI studies have shown hippocampal activation during list learning (e.g. Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003). However, the most prominent role of the hippocampus compared to surrounding structures is relational binding, i.e. (material-unspecific) associative memory processing (see Davachi, 2006). This anatomical relevance fits well into assumptions on optimal tasks for memory assessment in TLE (for review see Bell & Giovagnoli, 2007; Saling, 2009). Testing for associative memory can be accomplished using ecological valid paradigms, i.e. using familiar problems in everyday life like getting to know somebody and remember his name. In fMRI studies, successful encoding of face-name associations has been shown to elicit bilateral hippocampal activations in healthy participants (Kirwan & Stark, 2004; Sperling et al., 2003). Thus, this task appears suitable to test for memory in left and right TLE.

In the present study, all participants were scanned during the encoding of face-name pairs. In total, 66 unfamiliar faces (Karolinska Directed Emotional Faces, http://www.emotionlab.se/databases/kdef) were paired with a first name presented underneath. Participants were informed about the subsequent recognition test and asked to memorize the face-name pairing. They were instructed to use the same encoding strategy which was also implemented in previous studies, namely to decide whether a name fits to a face (e.g. Sperling et al., 2003). Since this decision is highly subjective, no behavioral response was measured. Each pair was shown for 4 seconds in a randomized order. The interstimulus interval (ISI) was jittered (3 to 6 seconds, plus 20% null events). Picture stimuli were presented controlled by a PC using the software Presentation (http://www.neurobehavioralsystems.com). An LCD projector projected the stimuli onto a screen positioned atop the head coil, and the stimuli were viewed by the participants through a mirror (10-15° field of view). The facial stimuli were colored photographs taken from a front perspective. Facial expression was neutral, hair was visible, but there were no

glasses, facial hair, or jewels. The pictures were shown on a grey background with the names and instructions written in black.

Recognition performance was probed immediately after the encoding session. Because encoding was always scanned first, recognition was tested in the scanner. All faces were shown again for 4 seconds each and participants were asked to select the remembered name out of three alternatives - the correct name and two foils - in a forced choice manner. One foil was new and one had already been paired with another face during the encoding session. The latter pairs are termed *re-arranged* in the following (see Figure 3-4 for an overview).

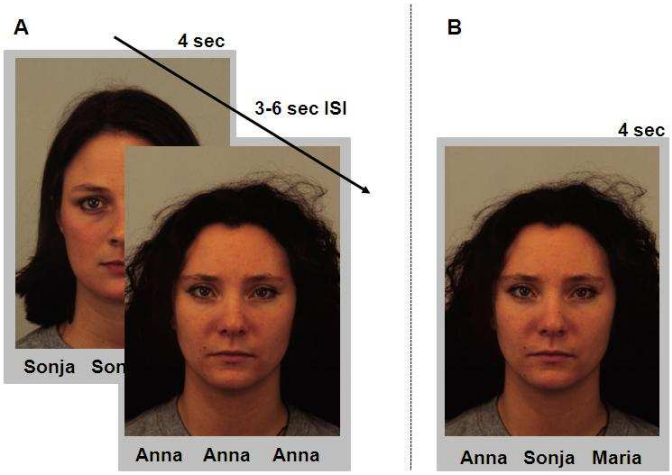

Figure 3-4 FMRI paradigm Study I
A depicts image presentation during encoding, **B** gives an example of image presentation during recognition; see text for details.

Re-arranged pairs are necessarily included because they enable testing for true associative memory (compare Kirwan & Stark, 2004; Sperling et al., 2003). A participant might recognize both aspects of a pair, i.e. has memory for single items seen before, but might fail to remember the exact pairing. This distinction between single item and relational learning could not be tested by simply using new foils as distractors. After each response, participants had to indicate whether they felt confident about their recognition judgment. A 3-point scale using the expressions 'I didn't feel confident', 'I felt quite confident', and 'I felt highly confident' was applied. In general, this procedure is similar to remember-know judgments which have been used before in fMRI studies in TLE (Richardson, Strange, & Dolan, 2004; Richardson et al., 2003, 2006; Richardson, Strange, Thompson et al., 2004). In particular, high confidence recognition decisions are somehow analogue to remember judgments, since they are in most cases accompanied by the recollection of episodic details

(Davachi, 2006; Henson, 2005; Yonelinas, 2002). In the present study, confidence judgments were preferred to remember-know decisions since they are more intuitive and don't require detailed explanation. Responses were entered by pressing buttons on an MR-compatible response box using the index, middle and ring fingers corresponding to the position of the name from left to right and the confidence level from low to high.

In line with the aforementioned memory assessment, ANCOVAs were conducted to compare associative memory performance between patients and controls. In addition, differences scores (hits minus false alarms; hits minus re-arranged pairs) were calculated in order to test performance against chance level in each group, using one-sample t-tests.

3.3.6.2 Image acquisition

Functional MRI was performed with an EPI T2* sensitive sequence in 42 contiguous axial slices (2 mm thickness with 1 mm gap, TR 2.45 sec, TE 25 ms, flip angle 70°, field of view 192 x 192 mm^2, ma trix 64 x 64).

3.3.6.3 Image analysis

The imaging series was realigned, slice-time corrected, spatially normalized into standard anatomical space (MNI), and smoothed with a Gaussian kernel of 10 mm FWHM. An event-related analysis was conducted for each participant on a voxel-by-voxel basis using SPM5. The goal of the functional analysis was the between group comparison of activity only during successful encoding of face-name associations, i.e. the subsequent memory effect. The restriction to successfully encoded items is recommended in case performance between groups differs (Richardson et al., 2003; Vingerhoets et al., 2004). To explore the subsequent memory effect, i.e. to identify voxels where activity during encoding of the face-name pairs is predictive for subsequent retrieval success, a participant-specific design matrix was created. Therefore, the encoding-events were divided post-hoc according to the response during recognition into the 4 possible categories: The participant selected the correct name, the re-arranged foil, the new foil, or no response was given (missing reaction). The events of these categories were modeled as separate regressors by convolving a delta function at the time of onset with the canonical hemodynamic response function. Each of the first three onset regressors was modulated by convolution with a parametric regressor containing the subsequent confidence ratings for each event during retrieval.

As described above, the rationale behind the parametric confidence regressors is their relatedness to remember-know judgments, which have been used before in studies with epilepsy patients (Richardson et al., 2003). Parametric regressors identify areas in which activity increases linearly with an increase in confidence. Realignment parameters were included as covariates in the single-subject design matrix to control for movement artifacts.

The contrast images corresponding to the parametric confidence regressor of successfully encoded associations were entered in the second level analysis. Analogue to the aforementioned study (Richardson et al., 2003), these images were contrasted in a two-sample t-test comparing patients against controls. To control for remaining group differences, the covariates age, gender and years of education were included. Based on prior knowledge regarding the neural correlates of encoding face-name associations, the correction for multiple comparisons was based on a reduced volume of interest by employing a cytoarchitectonically defined anatomical mask for the hippocampus (Amunts et al., 2005; Tzourio-Mazoyer et al., 2002). The statistical threshold was set to $p < 0.05$ for the reduced and the entire scan volume.

3.4 Results

3.4.1 Neuropsychological assessment

Memory scores determined by standard neuropsychological tests for patients and controls are listed in Table 3-2 (see appendix Table A- 1 for descriptive results other than memory performance).

Table 3-2 Memory scores of patients and controls

Test	Patients Mean (SD) range	Controls Mean (SD) range
Verbal memory		
Immediate logical memory	25.5 (7.79) 14-38	27.79 (4.79) 20-34
Delayed logical memory	21 (7.12) 9-31	24.38 (4.97) 13-31
VLMT, learning (t1 to t5)	46.5 (9.85) 34-60	48.07 (8.28) 34-62
VLMT, recall (t7)	8.83 (3.06) 6-13	10.79 (2.52) 6-14
VLMT, difference (t7-5)	2.66 (1.75) 0-5	1.75 (1.83) 0-7
VLMT, recognition	11.33 (2.16) 10-15	12.6 (2.1) 8-15
Nonverbal memory		
ROCF, recall	17.83 (3.18) 15-24	19.3 (5.32) 7-30
Face memory (% correct)	65.16 (6.79) 55-85	70.92 (10.76) 55-95

SD = standard deviation, VLMT = Verbaler Lern- und Merkfähigkeitstest, t = trial,
ROCF = Rey-Osterrieth-Complex-Figure, % = percent
Note: Memory scores = raw values/points for each test,
except for face memory which is expressed in percentage of correct answers

As can be seen from the range of values, a few individual scores in both groups were below or above average when compared to normative data. Such individual deviations were not found in more than one variable, e.g. in VLMT recognition only. Moreover, the important comparison for the present study was the direct comparison between the two groups.

Statistical analyses of group differences did not reveal any significant results. Most importantly, this holds true for the control tests, e.g. intelligence or attention, and also for memory. Thus, memory performance on standard tests did not differ between patients and controls included in the present study.

Nevertheless, memory performance could relate to differences in brain morphology. Thus, all memory variables listed above were fed into regression analyses with structural and diffusion imaging data. Potential effects are described in the following sections.

3.4.2 T2 relaxation maps

T2 relaxation times in the medial temporal lobe did not differ between patients and controls. Moreover, T2 relaxation times did not relate to any memory score listed in Table 3-2, neither in the combined group of participants nor in separate groups of patients and controls. All T-values were below 2 and did not exceed the threshold for significance in any contrast.

3.4.3 VBM

The VBM group analysis of grey matter did not display any significant result. No T-value exceeded the threshold for significance (T = 7.47) after corrections for multiple comparisons at the entire brain; the highest T-value (T = 3.93) was found outside the medial temporal lobe, in the right parietal cortex (xyz = 43,-48, 19). Moreover, no effect survived small volume correction using anatomical masks. Thus, differences between patients and controls were neither detected at the entire scan volume nor at the reduced search volume. In other words, patients did not show reduced grey matter volumes compared to controls.

Correlation analyses of grey matter and memory scores assessed by standard neuropsychological tests (see Table 3-2) did not reveal significant results. The highest T-values did not survive corrections for multiple comparisons (VLMT learning & left hippocampus T = 2.6, VLMT learning & right hippocampus T = 3.14; immediate logical memory & left hippocampus T = 3.29, immediate logical memory & right hippocampus T = 3.5). In other words, memory performance was not assigned to specific brain areas in any group.

3.4.4 DTI

When extracting the mean FA and MD values from the uncinate fasciculus and analyzing them outside FSL as done in previous studies (Diehl et al., 2008; McDonald et al., 2008), significant group differences were found (FA: $F(1,14) = 5.36$, $p = 0.03$; MD: $F(1,14) = 10.05$, $p = 0.005$), i.e. patients showed decreased FA and increased MD. A difference between left and right UF was not detected. However, this group result was misleading. When analyzing the

entire volume, a significant difference of FA was seen throughout the entire brain (see Figure 3-5). Thus, decreased FA of patients compared to controls was not restricted to a specific tract. Differences of MD were not found after corrections for multiple comparisons.

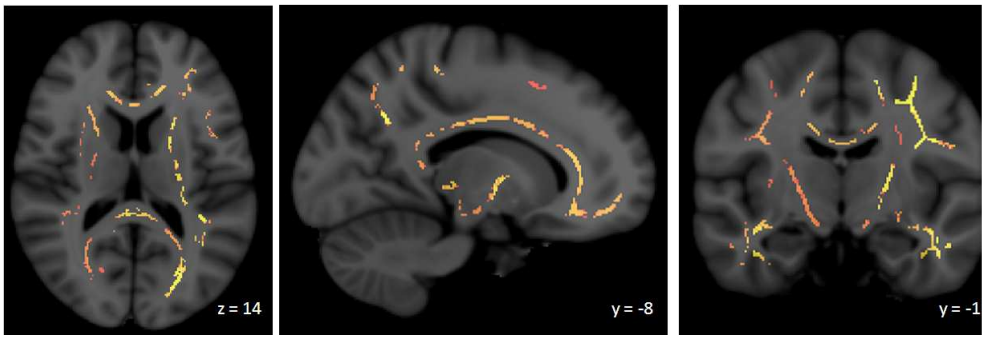

Figure 3-5 Decreased FA of patients compared to controls
For displaying reasons, significant results ($p<0.05$ corrected for multiple comparisons) are overlaid on a standard template including grey and white matter.

Correlation analysis of the mean FA values derived from the ROI approach revealed a significant correlation of FA in left UF and delayed story recall (*delayed logical memory*; $r = 0.72$, $p = 0.003$). This association was only evident in the combined group of patients and controls. Regression analysis of memory scores and FA values within FSL did not reveal any significant results. Correlation of memory and MD were neither significant in the ROI, nor the whole-brain analysis.

3.4.5 FMRI

3.4.5.1 Behavioral results

Behavioral results of both groups for the face-name associative memory task are summarized in Table 3-3.

Table 3-3 Recognition performance of patients and controls in the associative memory task

	Performance (in %) Mean (SD)		Reaction times (in sec) Mean (SD)	
	Patients	**Controls**	**Patients**	**Controls**
Correct pairs	38.38 (5.8)	56.49 (11.6)	2.45 (0.44)	2.47 (0.22)
Low conf.	46.53 (31.2)	28.17 (19.19)	2.63 (0.47)	2.76 (0.40)
Medium conf.	33.4 (18.87)	35.02 (17.35)	2.19 (0.46)	2.48 (0.23)
High conf.	20.05 (24.48)	34.91 (17.78)	1.74 (0.93)	2.09 (0.26)
Re-arranged pairs	33.35 (5.4)	29.56 (8.8)	2.5 (0.48)	2.66 (0.26)
New pairs	19.7 (3.9)	8 (4.7)	2.68 (0.41)	2.92 (0.27)
Missing reaction	8.57 (7.7)	5.95 (4.1)	--	--

% = percent, sec = seconds, SD = standard deviation, conf. = confidence

Note: performance is described by the percentage of answers for all categories
true recognition hits are depicted in the first line of the table
for these correct choices (correct pairs), the percentage of different confidence ratings is given

The group (patients vs. controls) x response (correct, re-arranged, new, missing reaction) ANCOVA revealed a significant interaction of group and condition ($F(1.8,28.3) = 8.14$, $p < 0.001$; see Figure 3-6). Patients retrieved significantly fewer correct face-name associations than controls. In addition, they falsely recognized more new foils as belonging to a face (Tukey HSD, $p < 0.01$). Moreover, scores in the control group differed significantly between conditions (Tukey HSD, $p < 0.01$), whereas patients did not show a difference between correct and re-arranged pairs.

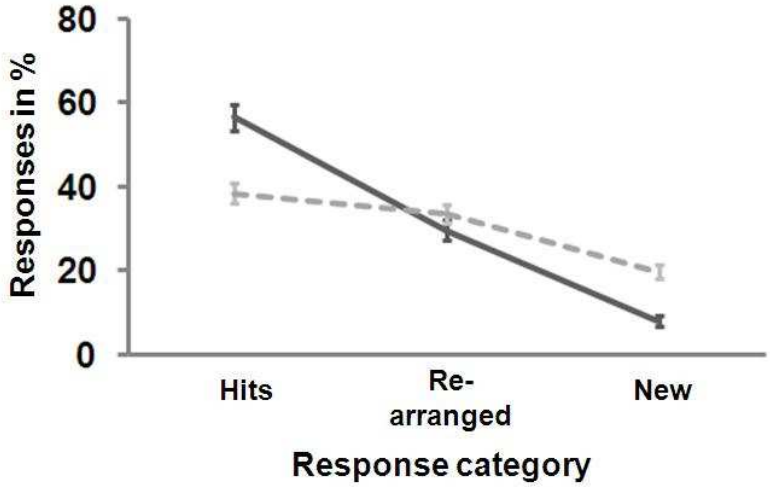

Figure 3-6 Recognition performance of patients and controls in the associative memory task
Amount of responses (in percent) in each category (hits, re-arranged, and new pairs) for patients (dashed line) and controls (solid line). Performance is collapsed across confidence, missing reactions are omitted. Whiskers represent the standard error of the mean.

This difference was also reflected in corrected recognition scores. When subtracting falsely recognized new foils from hits, both groups showed performance above chance level (patients: $t(5) = 8.9$, $p < 0.001$, controls: $t(13) = 12.2$, $p < 0.001$). The difference score of hits and re-arranged pairs was only above chance level in the control group ($t(13) = 5.1$, $p < 0.001$).

In the group x response latency (reaction times during recognition) ANCOVA, no effect reached significance, indicating that reaction times differed neither between patients and controls nor between response categories.

In the following, the correct responses were analyzed in detail because they correspond to the fMRI subsequent memory effect analysis. The group x confidence (low, medium, high confidence) ANCOVA displayed no significant effect, indicating that neither the relative frequency of confidence ranks differed between the groups nor the frequency of the three confidence ranks in general. Also, in the group x confidence latency (reaction times for confidence judgment) ANCOVA, no effect reached significance, i.e. patients were as fast as controls in giving their confidence judgments.

3.4.5.2 Functional results

The fMRI data revealed a greater subsequent memory effect for patients than controls in the right hippocampus (xyz = 24,–18,-20; Z = 4.36, p = 0.003 small volume corrected; Figure 3-7). Thus, the activation for successfully remembered pairs shows a steeper increase with increasing confidence in patients as compared to controls. No effect was seen outside the MTL after correction for multiple comparisons on the entire scan volume.

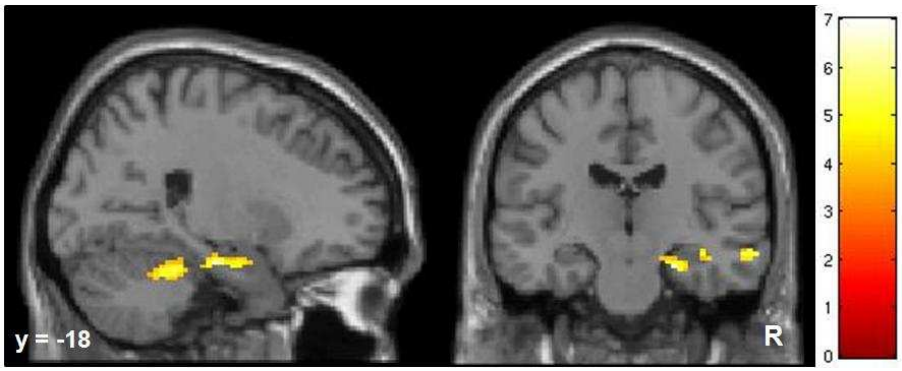

Figure 3-7 Differences of activation during successful encoding between patients and controls

Activity increase of the right hippocampus during successful associative encoding is significantly greater for cryptogenic right TLE patients compared to controls (for displaying reasons thresholded at p<0.001 uncorrected, and superimposed on a standard anatomical image; at the uncorrected threshold, additional activation is found in the lateral temporal lobe and the cerebellum).

The reverse contrast did not reveal an effect, i.e. controls did not show enhanced activation in any brain area compared to patients.

3.5 Discussion

The present study intended to investigate the neural basis of memory performance in patients with TLE of unknown cause using different voxel-based MRI techniques. The techniques were implemented in order to clarify the question whether efficiency of memory formation in this patient group is constantly modulated by structural and functional alterations of the underlying neuroanatomical circuits. The following discussion will be divided according to behavioral, structural and functional imaging results.

3.5.1 Behavioral results

The six patients with right TLE included in the analyses did not differ from a control group on standard neuropsychological tests. Thus, this result was not in line with a previous report of (material-specific) memory impairments of cryptogenic patients compared to controls evident in standard tests as story and figure recall (Giovagnoli & Avanzini, 1999). However, other studies have shown sustained memory in case patients can benefit from semantic cohesion of stimuli or other aspects of meaningfully structured material aiding encoding and retrieval (see Bell & Giovagnoli, 2007; Saling, 2009). Thus, the standard tests such as story or figure recall might not have been difficult enough to result in impairments in the current sample. A group difference as proposed in hypothesis 1 was detected in an experimental test, i.e. the associative memory task employed in fMRI. Patients performed significantly worse than controls, indicated by less hits on old pairs and less correct rejections of new pairs. Nevertheless, the corrected recognition scores, i.e. hits-false alarms, indicated that general memory performance was above chance level in both groups. This was not the case regarding true associative memory. As has been argued in the methods section, the difference between old and re-arranged pairs reflects the difference between item and relational memory. In the patient group, these scores did not differ, indicating impaired associative memory. Therefore, the present data are in line with previous results on associative memory in TLE (Henke et al., 2003) and theories on the relevance of the MTL for relational memory (Davachi, 2006; Mayes et al., 2007). In addition, they are in accordance with assumptions on the importance of task-specificity compared to modality-specificity (Bell & Giovagnoli, 2007; Saling, 2009). Since performance on standard tests did not differ and regression analysis did not yield significant results, the associative memory performance

of patients was not based on a material-specific learning impairment, but on failing to combine a verbal to a nonverbal stimulus. Criticism on this assumption might be based on the fact that list lengths of tests obviously differ, i.e. the fMRI task comprised three times more events than the standard neuropsychological tests. The effect of list length has never been explored in epilepsy so far. Thus, an influence cannot be completely excluded. However, it seems unlikely given the fact that previous fMRI studies with TLE patients have used more than 250 events (Powell et al., 2007; Richardson et al., 2003). In line with the studies of Richardson et al. (2003), patients had difficulties to reject new foils on the one hand. On the other hand, they showed similar ratings of confidence in the case of successfully recognized associations (Richardson, Strange, & Dolan, 2004; Richardson et al., 2003, 2006).

In summary, the present data suggest that memory deficits in cryptogenic TLE might be more subtle and not uncovered with standard tests (Bell & Giovagnoli, 2007; Bengner et al., 2006). One proposal to improve assessment relies on a prolonged retention interval, i.e. on expanding standard test intervals from minutes to hours or days (Bengner et al., 2006; Blake, Wroe, Breen, & McCarthy, 2000; Kapur et al., 1997). But, contrary to the study of Bengner et al. (2006) for example, the impaired ability to memorize associations was seen immediately after encoding in the present study. Thus, it cannot be attributed to an inefficient consolidation process. Therefore, when probing associative instead of item memory, it might not be necessary to prolong the retention interval. However, since testing and scanning took place on one day in the present study, effects of consolidation in addition to inefficient encoding cannot be assessed.

The major limitation of the present study is the small sample size. The present study therefore differs from the aforementioned study reporting group differences (Giovagnoli & Avanzini, 1999). On the other hand, the cited study stated to include cryptogenic TLE patients but did not report MRI findings. Thus, patients with structural abnormalities might have been included. On the contrary, the present study incorporated different structural MRI techniques to investigate subtle lesions. Patients with and without morphological damage differ according to memory (Alessio et al., 2004; Hermann et al., 1997). However, this result is confounded by factors associated with the presence of HS, i.e. duration of epilepsy, severity of seizures and medication (Alessio et

al., 2004). Thus, as has been described before, memory is influenced by a variety of factors in TLE. Although it might be impossible to control for all contributing factors (see Elger et al., 2004; Kwan & Brodie, 2001), future studies are needed which incorporate large samples controlling for structural, clinical and treatment-related factors by investigating patients with and without HS and controls.

3.5.2 Structural and diffusion MRI

In the present study, structural and diffusion imaging were employed in order to characterize brain morphology. According to individual inspection of clinical MR images, all patients were classified as cryptogenic. The voxel-based group analyses revealed inconsistent results. On the one hand, T2 relaxation times and VBM did not reflect differences between patients and controls. On the other hand, DTI data suggest that the group of patients in the present study differs significantly from controls.

The T2 relaxation and VBM results are in line with studies reporting alterations in only a very limited number of patients classified as cryptogenic before (Mueller et al., 2006; Salmenpera et al., 2007). Thus, replicating the conclusion from individual assessment, MRIs of patients in the present study might be truly unremarkable. On the other hand, the results could rely on effects of group composition. In general, VBM is most effective in the case of a uniform pattern of atrophy, i.e. patients with HS are homogenous groups which show clear effects in VBM analysis (Keller & Roberts, 2008). Cryptogenic TLE might be less homogenous, with subtle individual abnormalities not detectable in a group comparison (Mueller et al., 2006; Woermann et al., 1999). Thus, instead of belonging to a homogenous non-HS group (Blumcke et al., 2007), patients might be characterized by different etiologies which result in a heterogeneous group (Berg, 2008; Mueller et al., 2006). It has been argued that VBM is only effective in large samples or when using covariates as in the present study (Pell et al., 2008). Since the temporal lobe also show large variations in healthy populations, effects of small samples might not be detected; this “low statistical power in areas with large interindividual variability” also prevents the use of VBM in single case assessment (Eriksson, Thom, et al., 2009, p. 3351). Moreover, difficulties during preprocessing of structural images occurred based on inhomgeneities found in T2- and T1-weighted images. Although a bias correction was applied,

remaining inhomogeneities might have affected normalization and segmentation. Thus, the findings need to be interpreted with caution. Moreover, T2 relaxation was restricted to the medial temporal lobe. If the position of slices was not optimal, the signal might have been suboptimal, too. This, taken together with the general loss of signal-to-noise ratio due to the smaller volume within a voxel, the higher resolution might have failed to result in 'better' images. Therefore, as argued throughout this thesis, whole-brain techniques should be preferred in the case of limited anatomical and radiological expertise.

Regarding the lack of grey matter abnormalities, the amount of diffusion abnormalities is surprising. Although, altered diffusion parameters in cryptogenic TLE have been reported before, the present finding clearly exceeds the pattern of previous findings (Rugg-Gunn et al., 2001; Shon et al., 2010). Reduced FA was not restricted to the ipsilateral temporal lobe, but found in parietal and frontal areas of both hemispheres. Widespread abnormalities are often associated with seizure spread, but not all of the patients included had a history of secondary generalized seizures. Moreover, there is no other group characteristic which could account for this result. In summary, it is not clear whether the present results depict true alterations of diffusion in the absence of grey matter abnormalities.

On the other hand, the present findings illustrated that results from ROI analyses might be misleading. If only focusing on one tract, putative specific differences could be detected which in addition might correlate with memory performance (Diehl et al., 2008; McDonald et al., 2008). But, such an analysis might not reflect the true pattern of alterations. In the present study, no correlation of memory scores and brain volume or diffusion was detected. This is in line with previous studies using simple correlation analysis (Baxendale et al., 1998; Bengner et al., 2008; Focke, Thompson, et al., 2008; Namer et al., 1999). For statistical reasons, reliable relationships between brain morphology and cognition can only be detected in the case of specific abilities which show a large variability or circumscribed learning effects (see Draganski et al., 2004; Maguire et al., 2000, 2003). But, in the case of a small sample with average performance, no such relationship might be detected. The lack of power has also been apparent in the aforementioned studies which could only detect correlations in case of impaired performance for patients compared to controls (McDonald et al., 2008), in larger samples merging mesial and lateral TLE

(Diehl et al., 2008) and when not adjusting for multiple tests, i.e. Type I error (Diehl et al., 2008; McDonald et al., 2008). Since these studies were restricted to specific tracts, another study aimed at identifying areas without this priori bias (Riley et al., 2010). However, TBSS was only used for the detection of differences in FA and MD; mean FA from resulting clusters was subsequently correlated with specific test scores as has been done before.

In summary, previous and present results suggest that memory performance can only be related to brain morphology in case of variability of test performance and large sample sizes. The present study clearly does not fulfill these criteria. Therefore, instead of measuring cognitive performance outside the scanner which can be correlated with structural imaging, it might be more meaningful to assess the neural correlates of behavioral measures directly and during scanning.

3.5.3 Functional MRI

Encoding of face-name associations was performed during fMRI scanning. As proposed in hypothesis 3, the fMRI data revealed differences between patients and controls. Hippocampal activity during successful encoding was enhanced in patients compared to controls. In particular, the increase of hippocampal activity associated with an increase in subsequent memory confidence exhibited a steeper slope in patients than controls. On the other hand, no area exhibited greater activity during encoding in controls than in patients.

The current data suggests that the pattern of encoding related activity differs not only between TLE patients with normal structural MRIs and controls, but between patient groups as well. Whereas the right TLE patients of the current sample show enhanced ipsilateral activity, encoding processes are often reorganized to the contralateral hemisphere in patients with HS (Powell et al., 2007; Richardson et al., 2003, 2006). In particular, regression analyses suggested that the extent of the pathology is proportional to the degree of reorganization (Powell et al., 2007; Richardson, Strange, & Dolan, 2004). The ipsilaterality of activation in the present sample of patients with right TLE of unknown cause thus implies that either morphological lesions do not exist or that they are too small to elicit functional reorganization. With regard to grey matter analysis, this assumption seems likely; but as argued above, a clear decision about morphological integrity is limited in the present study.

It is important to note, that increased activity reflects successful encoding, but is not equivalent to increased performance. As discussed before, overall memory performance was diminished in patients. Simply spoken, the amount of subsequent hits is reduced, but activity associated with these events is enhanced for patients compared to controls.

A plausible interpretation for the increased activity arises from the existing literature on compensatory MTL activity in dementia. While minor structural lesions and mild cognitive impairments are accompanied by hyperactivation of MTL structures, severe dementia is linked to hypoactivation. Hyperactivation is meant to reflect a compensatory but inefficient process since patients are not able to achieve the same performance as controls (Dickerson & Sperling, 2008). This explanation can be transferred to the present findings.

In cryptogenic TLE, increased neural activity is necessary to accomplish successful encoding within less efficient hippocampal cell assemblies. But, since this higher activity threshold is less frequently reached, the process fails to compensate the mnestic deficit - as indicated by impaired memory performance.

In summary, the findings suggest that subtle alterations of neuronal microcircuits due to epilepsy exist which impair the efficiency of encoding.

An alternative interpretation might be that the results are based on complex, and yet underestimated, interactions of interictal epileptic activity with the BOLD effect on the one hand and performance on the other hand (Krakow, 2008). Interictal epileptiform activity can change the BOLD signal, influence the lateralization of activation during cognitive tasks (Janszky et al., 2004) and can also impair memory performance (Aldenkamp & Arends, 2004). Effects of interictal activity were not assessed with the methods employed in the present study. However, it is unlikely that the enhanced activation is solely based on epileptic activity. This has two reasons. First, the analysis of fMRI data was restricted to successfully encoded information, i.e. successful memory formation. Second, unsystematic effects of interictal epileptiform activity throughout the scanning session are unlikely to affect one trial type only; thus, they should be cancelled out by the trial wise analysis.

The present effect in the ipsilateral hippocampus was strong enough to be detected even in a small sample with limited statistical power. The result implies that functional networks in patients with TLE of unknown cause might be different from patients with TLE and HS, and controls. Such a difference

between patient groups would have practical implications. So far, predictions of memory function after surgery are based on patients with definite hippocampal sclerosis. However, patients without overt damage in standard MRI are also referred to amygdalahippocampectomy (Alarcon et al., 2006; Blumcke et al., 2007; Stefan et al., 2009; Sylaja et al., 2004). According to the theory of functional adequacy, patients with residual memory function in the affected hippocampus are at greater risk of impairments postoperatively (Chelune, 1995; Powell et al., 2007; Rabin et al., 2004). Therefore, patients with cryptogenic TLE might be at greater risk of postsurgical memory deficits than patients with symptomatic TLE. As mentioned above, direct comparisons between groups are needed.

As a second potential methodological confound, antiepileptic drugs were not lowered during the scanning procedure. However, the enhancement of activity is unlikely to be due to medication. All medication that lowers excitability would be expected to lower the BOLD signal, as has already been observed for all the substances taken by the patients of the present study (Jansen et al., 2006; Jokeit, Okujava, & Woermann, 2001b; Kida, Smith, Blumenfeld, Behar, & Hyder, 2006). For example, patients on topiramate therapy showed less activation in prefrontal areas during a language task which was accompanied by lower language scores (Jansen et al., 2006). Thus, the enhanced activation seen in the present study does not match the reported effects of medication, e.g. a reduction of activated cluster size with higher drug level (Jokeit et al., 2001b).

3.5.4 Limitations

As stated throughout the discussion, the most obvious methodological restriction of the present study is the small sample size. This was due to a certain issue. The available scanner system was up-graded. Due to the small signal-to-noise ratio in MR imaging, the images are prone to small changes such as changes in the magnetic field, helium levels or temperature. After a complete change of the scanner system, it was no longer possible to scan comparable data of further patients with right cryptogenic TLE, or patients with left cryptogenic TLE, or a group of TLE patients with HS. Thus, the data do not allow a generalization of the findings. The suggested interpretation can only be preliminary and needs further investigation and direct comparisons between groups. Patients were included according to seizure semiology and

EEG abnormalities. However, noninvasive EEG might not be able to definitely differentiate between medial and lateral TLE (see Bengner et al., 2006). Although all signs were clearly in favor of mesial TLE, a definite classification cannot be guaranteed. Moreover, a direct measure of epileptic activity was not included into the test protocol. But, as argued above, a systematic influence is unlikely. In addition, interictal activity accounts much less to study results than previously thought (Aldenkamp & Arends, 2004; Elger et al., 2004).

3.5.5 Conclusion and future directions

In summary, the present study detected subtle memory impairments and functional alterations related to encoding efficiency in cryptogenic TLE. The behavioral results suggest that standard neuropsychological list learning tests might not uncover memory deficits of cryptogenic TLE patients compared to controls. On the contrary, associative memory paradigms might reveal group differences. Successful encoding was associated with enhanced activity in the ipsilateral hippocampus which is likely to reflect a compensational process. Thus, the present data revealed that the efficiency of memory formation is affected by TLE, irrespective of overt brain damage. Nevertheless, the underlying mechanisms of functional alterations need to be explored in more detail in future studies. Although the application of different MRI techniques did not exhibit clear results in the present study, a combination of techniques seems promising given the concordant fMRI and DTI findings on language dominance (Powell et al., 2006).

Given the lack of clear cognitive-structural relationships, some authors argue that cognitive impairments are related to widespread networks (Bell et al., 2011; Duncan, 2009). Affirmative results emanate from studies on resting state activity (Pereira et al., 2010). In contrast to such studies on networks, other studies focus on a detailed analysis of e.g. hippocampal subfields using fMRI or histological specimen. These studies emphasize a correlation of memory and the dentate gyrus (Pauli, Hildebrandt, Romstock, Stefan, & Blumcke, 2006; Zeineh, Engel, Thompson, & Bookheimer, 2003). Moreover, metabolic abnormalities associated with epilepsy are assumed to influence memory (Madhavan & Kuzniecky, 2007; Tramoni et al., 2011).

In summary, no clear anatomical markers of memory impairment in TLE have been found so far (see Bell et al., 2011). Future studies including large samples of patients are needed to further explore the efficiency in memory

formation in TLE. Imaging will remain a main aspect in such studies since a rescan with advanced equipment might characterize some group of patients more precisely (Duncan, 2009). Especially imaging and genetics is assumed to be most helpful in exploring TLE of unknown cause, since this disease is poorly understood (Berg et al., 2010). Studies investigating the impact of genetic predisposition on memory in epilepsy corroborate this assumption (Busch et al., 2007; Gambardella et al., 2005).

4 Study II

4.1 Introduction

Study I of the present thesis demonstrated altered efficiency of memory formation due to temporal lobe epilepsy. TLE is one example of a group of factors which constantly influence encoding and/or consolidation due to persistent alterations of the underlying anatomical substrates. In general, memory formation can also be influenced by temporary alterations of functional processes which either result in enhanced or diminished memory performance. One prominent example of temporary factors facilitating memory formation in experimental settings and everyday life is emotional arousal (for review see LaBar & Cabeza, 2006). Compared to neutral events, processing of emotional events is associated with specific hormonal states and the recruitment of specific brain areas (LaBar & Cabeza, 2006; McGaugh, 2000; Murty, Ritchey, Adcock, & LaBar, 2010). However, as will be illustrated in the following section, the beneficial effect of emotional arousal on memory is confounded by cognitive processes which are additionally initiated by emotional stimuli. Therefore, Study II of the present thesis aimed at investigating temporary effects of arousal on memory formation in the absence of cognitive modulators.

In preparation of the study description, the following chapters will highlight core findings regarding arousal-induced memory enhancement. As said before, the first paragraph focuses on studies using emotional stimuli. The subsequent section focuses on neurotransmitters released as a function of arousing stimuli and its effects on memory acquisition. Of special relevance is the noradrenergic system which is also one of the major neuromodulatory systems influencing the efficiency of synaptic transmission in general (Sara, 2009). Last, ideas from both fields of research will be connected in order to define the hypotheses of the present study.

4.1.1 Emotional enhancement of memory (EEM)

In everyday life, everybody experiences that emotionally arousing information or situations are usually better remembered than neutral ones. This effect is called *the emotional enhancement of memory* (EEM; LaBar & Cabeza, 2006). In experiments of the EEM, words, stories or images of emotional and neutral content are presented and memory performance is contrasted between these

two categories. According to the *modulation hypothesis*, the superiority of emotional memories is based on the release of adrenal stress hormones due to arousal (McGaugh, 2000, 2004). In particular, the release of cortisol and adrenaline and the subsequent noradrenergic innervations of the amygdala are assumed to generate a more efficient consolidation. Consistent with the proposed effect on consolidation, the memory benefit for emotional stimuli is more pronounced after longer retention intervals (Kleinsmith & Kaplan, 1963; Sharot, Verfaille, & Yonelinas, 2007). Moreover, in fMRI studies, enhanced amygdala activity is consistently observed for successful encoding of emotional stimuli, supporting the crucial role of this structure in the EEM (for a meta-analysis on emotional memory and fMRI see Murty et al., 2010).

However, two types of results challenge the practicability of the modulation hypothesis. First, in contrast to a proposed effect on consolidation, superior memory for emotional stimuli is also observed immediately after encoding (Dolcos & Cabeza, 2002; Sharot et al., 2007; Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008). Second, in addition to valence and arousal, emotional stimuli can be defined by further aspects. Emotional stimuli also differ from neutral stimuli according to cognitive characteristics, i.e. *relatedness*, *distinctiveness*, and the attraction of selective attention (Sharot & Phelps, 2004; Sommer, Glascher, Moritz, & Buchel, 2008; Talmi, Luk, et al., 2007; Talmi, Schimmack, et al., 2007). Distinctiveness refers to the fact that emotional stimuli exhibit unique features, i.e. that they are unusual relative to neutral items. Moreover, they have specific semantic relations. Relatedness may improve list organization at encoding and aid retrieval (Gardiner, Craik, & Birtwistle, 1972; Neely & Tse, 2007). Last, emotional stimuli gain attention and therefore achieve enhanced sensory processing (Schupp, Flaisch, Stockburger, & Junghofer, 2006; Talmi et al., 2008). If these factors are removed from the stimuli, the EEM is diminished. Therefore, the *multifactor theory* proposes that the EEM is not only driven by arousal but also by the cognitive characteristics of emotional stimuli that are known to enhance memory performance (Buchanan, Etzel, Adolphs, & Tranel, 2006; Schmidt & Saari, 2007; Sommer et al., 2008; Talmi, Luk, et al., 2007; Talmi, Schimmack, et al., 2007). In other words, effects of emotional arousal and cognition are confounded. This is a problem for interpreting results. If "… arousal is evoked by the same stimulus that is probed for memory" (Anderson, Wais, & Gabrieli,

2006, p. 1599), it is difficult to disentangle for example effects of attention during initial processing from effects of arousal on consolidation.

Directed modulation of consolidation by arousal has been implemented first in animal studies. The following chapter will provide an overview of findings from such studies and adaptations implemented in studies with humans.

4.1.2 Effects of stress hormones on memory

As indicated above, the superiority of emotional memory has been ascribed to the release of stress hormones. This assumption stems from a multitude of animal studies aiming at influencing memory acquisition by inducing arousal via post-learning stress, injections of hormones and drugs or selective brain lesions (see van Stegeren, 2008). Memory improvements were seen after inhibitory avoidance training, infusions of adrenaline and corticosterone, as well as beta-adrenoceptor agonists (McGaugh, 2000; van Stegeren, 2008). In contrast, memory was impaired after lesions of the basolateral amygdala and injections of adrenoceptor antagonists into the amygdala (McGaugh, 2005; van Stegeren, 2008). Thus, in summary, memory performance correlated with the levels of noradrenaline (NA) in the periphery and the central nervous system, especially the amygdala (McGaugh & Roozendaal, 2002; van Stegeren, 2008). These findings were cumulated in the modulation hypothesis (Cahill & McGaugh, 1998; McGaugh, 2000, 2004; McGaugh & Roozendaal, 2002). In this framework, arousal is assumed to result in the release of adrenal stress hormones, i.e. the systemic release of corticosterone/cortisol and adrenaline. Since peripheral adrenaline cannot pass the blood-brain-barrier, the central noradrenergic system is activated via vagal afferents projecting to the brain stem. Adrenergic and glucocorticoid effects are assumed to converge in the amygdala which expresses NA and modulates consolidation processes in other brain regions, e.g. the hippocampus (McGaugh, 2000; McGaugh & Roozendaal, 2002). In addition, NA mediates the effects of other hormones and neurotransmitters on consolidation (Roozendaal, McEwen, & Chattarji, 2009). As said before, the basis of the central noradrenergic system is located in the brain stem, more precisely in the locus coeruleus (LC; Berridge & Waterhouse, 2003; Sara, 2009; Tully & Bolshakov, 2010; van Stegeren, 2008). Activity in the LC can be increased by any salient and significant stimulus, i.e. emotional, stressful or noxious stimuli (Berridge & Waterhouse, 2003; Delaney, Crane, & Sah, 2007; Sara, 2009). Projections

from the LC constitute a network which innervates the brain almost entirely (Sara, 2009). This range of influence and the fact that NA activates pre- and postsynaptic receptors demonstrate the potential to modulate functional processes (Berridge & Waterhouse, 2003; Sara, 2009; Tully & Bolshakov, 2010). The relevance of the noradrenergic system for consolidation was stressed by varying intervals of the aforementioned manipulations, e.g. different time intervals between memory encoding, pharmacological treatment, and memory retrieval.

Pharmacological studies aiming at manipulating noradrenergic transmission have also been conducted in humans (Cahill & Alkire, 2003; Cahill, Prins, Weber, & McGaugh, 1994; Strange et al., 2003; van Stegeren, Roozendaal, Kindt, Wolf, & Joels, 2010). However, in the majority of these studies, the manipulation was already active at encoding (see Cahill & Alkire, 2003; LaBar & Cabeza, 2006). Nevertheless, studies using emotional material and pharmacological interventions have shown that modulations of the efficiency of memory formation can occur on a very short time scale, i.e. event related, which can only be explained by a central release of NA (Strange & Dolan, 2004; Strange et al., 2003).

A less invasive method than injections of stress hormones or applications of betablockers to induce and manipulate arousal is the ice water or *cold pressor stress* test. In this test, participants have to put one arm into ice water for a few minutes. For the control condition, the bath is of room temperature. A couple of studies have administered this stress test after a learning phase (Andreano & Cahill, 2006; Cahill, Gorski, & Le, 2003; McCullough & Yonelinas, 2011). Thus, a potential effect on memory cannot be attributed to attentional or perceptual processes during initial encoding. The first study showed enhancing effects for negative but not for neutral stimulus material (Cahill et al., 2003). Since salivary cortisol was enhanced due to the stress test, the authors concluded that post-learning stress hormones interact with emotional arousal during initial encoding. However, the following studies found enhancing effects for neutral information (Andreano & Cahill, 2006; McCullough & Yonelinas, 2011). One of the studies showed a quadratic correlation, i.e. inverted U-function, between cortisol and subsequent memory: Memory was only enhanced at medium levels of cortisol (Andreano & Cahill, 2006).

In summary, the studies replicated the importance of stress-related hormones for memory without using any pharmacological treatment. Thus, post-learning stress induced by a nociceptive stimulus is assumed to enhance arousal across species.

4.2 Aim and hypotheses of Study II

The previous chapters have summarized the findings of enhanced memory performance for emotional stimuli and the relevance of the noradrenergic system for this beneficial effect. However, in standard experiments of the EEM, the neuromodulatory noradrenergic effects on consolidation due to arousal are confounded by cognitive processes elicited by emotional stimuli during initial processing. Therefore, the present study intended to further explore the effects of arousal on memory processes by excluding such interactions. In order to unravel effects of arousal on consolidation from effects on initial processing, basic ideas of event-related studies contrasting neutral and emotional stimuli were combined with basic ideas of studies investigating the neurobiological background.

In particular, the following aspects regarding the paradigm were considered important. First, stimuli probed for memory should not differ according to cognitive characteristics or emotional state at the time of perception. Thus, a modulating arousing factor should be applied after the initial processing only. The effect of arousal should be tested at different retention intervals, since consolidation does require time and also sleep (Diekelmann & Born, 2010; Frankland & Bontempi, 2005). Last, an event-related design suitable for exploring successful memory formation (see Study I) should be used. The exact paradigm will be explained in the following methods section. In brief, neutral scenes acted as memoranda and electrical shocks as arousing modulators. A nociceptive stimulus was chosen, since it does not contain emotional content but activates the noradrenergic system in the same manner as emotional stimuli because of its salience (Berridge & Waterhouse, 2003; Sara, 2009). Moreover, electrical shocks can be applied briefly in an event-related fashion.

By contrasting recognition performance of scenes followed by electrical shocks and scenes without an arousing context, the following hypothesis was tested:

1. After a retention interval, memory performance is enhanced for scenes followed by nociceptive arousal due to a more efficient consolidation.

Furthermore, the present study aimed at investigating the underlying neural correlates of a potential effect. Previous fMRI and patient studies have shown that the MTL is involved in successful encoding of neutral and emotional information (LaBar & Cabeza, 2006). Oftentimes, studies of the EEM have shown enhanced amygdala activity and amygdala-hippocampal coupling (McGaugh, 2004; Murty et al., 2010). Nociceptive stimulation should also innervate amygdala and MTL, since it induces arousal and activates the noradrenergic system (Andreano & Cahill, 2006; Berridge & Waterhouse, 2003; Cahill et al., 2003; Sara, 2009). But, activity associated with arousal-induced subsequent memory might also differ from the EEM, since cognitive factors are excluded.

2. Nociceptive stimulation modulates amygdala and MTL activity during encoding.

In order to test the hypotheses, two different experiments were conducted sequentially. In experiment 1, two behavioral groups were tested in order to examine the time scale of the influence of arousal, i.e. to examine whether arousal influences encoding or consolidation. Therefore, recognition performance was probed immediately after encoding in one group and with a 24 hours delay in the other group. Based on the results of the first experiment, an fMRI study (experiment 2) was conducted to explore the neuronal pattern of activity correlating with enhanced efficiency of memory formation.

4.3 Experiment 1

4.3.1 Methods

4.3.1.1 Participants

Forty healthy volunteers (19 males, mean age 27.3 years) participated in experiment 1 (detailed group compositions are listed in Table A- 2 in the appendix). They were randomly assigned to two behavioral groups, performing encoding and recognition on the same day (termed *day1-group*) or separated by one night (termed *day2-group*). Ethics approval for the study

(experiment 1 and 2) was obtained from the ethics committee of the medical association of Hamburg. All participants gave written informed consent.

4.3.1.2 Experimental Task

During encoding, 80 unfamiliar neutral and non-arousing photos of outdoor scenes (Peelen, Fei-Fei, & Kastner, 2009) were shown for 800ms each, either containing cars or people. The duration of stimuli presentation was chosen according to the literature on the time course of visual processing using the same or other scenic stimuli (Peelen et al., 2009; Rose, Schmid, Winzen, Sommer, & Buchel, 2005) and memory formation (Fernandez et al., 1999; Fernandez, Klaver, Fell, Grunwald, & Elger, 2002). In summary, the chosen duration was assumed to be long enough to enable complete visual processes but short enough to prevent explicit memory encoding via strategies, which would additionally influence memory acquisition. The final duration of 800ms was determined by pilot studies which will not be described in this thesis. Since the scenes were homogenous, interitem variability in memorability was limited.

The paradigm is sketched in Figure 4-1.

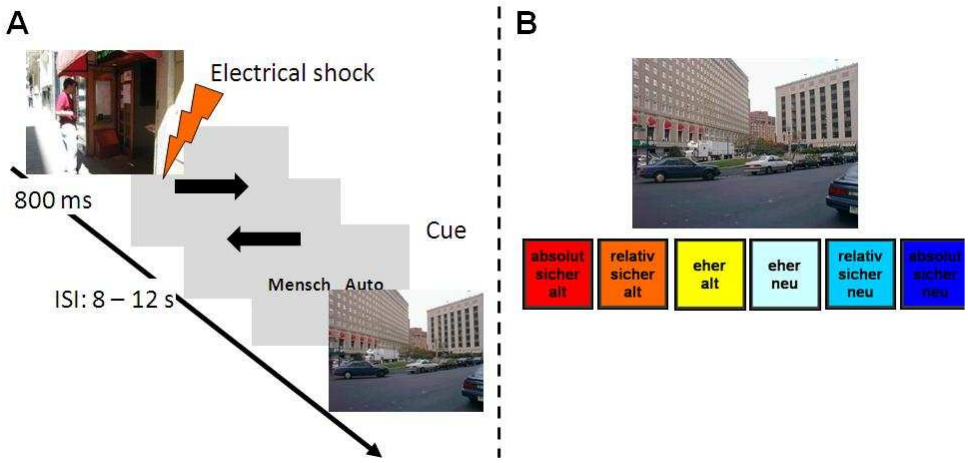

Figure 4-1 Paradigm Study II
A) encoding, **B**) example scene and confidence rating during recognition; see text for details

Participants were asked to classify each scene, i.e. cars vs. people, as quickly as possible by pressing the corresponding button. At stimulus offset (with a 50ms delay), half of the scenes of each category were followed by an electrical shock consisting of a train of four 2 ms pulses that were delivered through an electrode on the left ventral forearm. The order of stimuli was

pseudorandomized with the restriction that five pictures of one condition maximum, i.e. shock vs. no shock, or one category, i.e. cars vs. people, were presented in succession.

The intensity of the electrical stimulation was individually adjusted at the beginning of the experiment. During titration, participants rated the intensity of each shock on a computerized visual analog scale (VAS), which ranged from 0 ('stimulation not perceptible') to 100 ('stimulation intolerable'). The VAS consisted of two white vertical lines representing the two endpoints of the scale, and a horizontal bar that participants could expand to the right or compress to the left via button presses in order to indicate the experienced shock intensity. The intensity representing 70 was delivered throughout the experiment. The VAS was also administered during encoding after the first, middle, and last shock to test for habituation or sensitization.

For the sake of brevity, the scenes followed by shock will be termed *scenes*$^{+shock}$ in the following, while scenes not followed by shock will be termed *scenes*$^{no\ shock}$. In order to suppress intentional encoding after stimulus offset via rehearsal or elaborative strategies, the ISI (jittered 8 to 12 seconds) was filled with a distracting task. The task was chosen according to suggestions for active baseline conditions which do not affect activity related to memory in fMRI studies (Stark & Squire, 2001). Participants had to determine via button press whether arrows presented for 800ms each pointed to the left or the right. For motivational aspects, individual accuracy was shown to the participants at three different time points. After each distraction task, a cue slide pointing to the encoding task indicated the next scene.

Participants were informed about the upcoming memory test, but they were strongly encouraged to focus on the encoding and arrow pointing tasks. In the day1-group, recognition was tested briefly after encoding. Removing electrodes and giving instructions for the recognition test resulted in a temporal delay of approximately 5 minutes. In the day2-group, recognition was delayed by approximately 24 hours. For the recognition task, old scenes were mixed with the same amount of new ones. For each participant, target and lures were drawn randomly from a larger set of scenes. Responses were given self-paced on a 6-point confidence scale (from *high confidence old* to *high confidence new*), represented by six boxes underneath each scene. In case of an *old*-response, participants were asked whether this scene was

followed by shock during encoding using a yes-no forced-choice source memory task.

4.3.1.3 Statistical analysis

Analyses of group composition, shock intensity and ratings, encoding and recognition performance were conducted in STATISTICA using t-tests and analyses of (co-)variances. The value of the test statistic and the significance value will be reported in case of significant results only. Groups were compared according to the perceived shock intensity in order to guarantee that effects cannot rely on differences in perception. Otherwise, groups were analyzed separately.

Regarding recognition, in a first step, performance was evaluated in general. Therefore, a corrected hit rate was calculated by subtracting false alarms (old responses to new scenes) from hits (old responses to old scenes). A value of zero would indicate performance on chance level. Next, recognition performance was compared between scenes^{+shock} and scenes$^{no\ shock}$ by contrasting the total amount of hits in both conditions.

Afterwards, performance was analyzed with respect to confidence. Therefore, the confidence ratings were fitted to the *dual-process signal detection model* of recognition memory in order to derive estimates of *recollection (R) and familiarity (d')* (Yonelinas & Parks, 2007; Yonelinas, Aly, Wang, & Koen, 2010). For brevity, this model will not be described in detail; basic information which are necessary for understanding the present analysis will be outlined. The rationale for using a confidence scale is that recognition can be fulfilled by two different and independent processes, namely recollection and familiarity. Only the first process encompasses a vivid recollection of events, i.e. retrieving specific details. Therefore, it is usually associated with more high confidence ratings than familiarity. The distinction between recollection and familiarity is also reflected by the terms *remembering* vs. *knowing* which were introduced in Study I (Tulving, 1985). The dual-process model assumes that familiarity reflects a signal detection process whereas recollection reflects a threshold retrieval process, i.e. familiarity is a continuous strength dimension and recollection is a discrete retrieval process which can either succeed or fail. Since familiarity and recollection are independent processes in this framework, they rely on different regions of the medial temporal lobe (Diana et al., 2007; Eichenbaum et al., 2007; Yonelinas, 2002; Yonelinas et al., 2010).

Quantitative estimates for both processes were derived according to an open-source algorithm (http://psychology.ucdavis.edu/labs/Yonelinas). In the first step, cumulative frequencies of confidence ratings are plotted for each participant. The first point on the function reflects the most confident responses for hits and false alarms. The second point is additionally determined by the second most confident responses etc. These plots which relate hits to false alarms at different levels of confidence are termed *receiver operating characteristics* (ROC) (Yonelinas, 1994; Yonelinas & Parks, 2007). In the second step of the analysis, a model is fit to the ROC in order to derive estimates of recollection and familiarity (Yonelinas & Parks, 2007).

Last, performance in the source memory task was defined by a corrected hit rate equivalent to the general recognition performance, i.e. by subtracting wrong assignments from correct judgments.

4.3.1.4 Skin conductance response (SCR)

Throughout the experiment, skin conductance was measured continuously via Ag/AgCl electrodes placed on the palm of the left hand. SCR is a measure of eccrine sweat gland activity and a reliable physiologic correlate of arousal (Bradley, Codispoti, Cuthbert, & Lang, 2001; Lang, Greenwald, Bradley, & Hamm, 1993; Venables & Christie, 1973). Due to technical problems, SCR could only be measured in 14 participants of the day1-group and 12 participants of the day2-group. The signal was amplified using a CED 2502 amplifier and sampled at 10 Hz using a CED 1401 analog-digital converter (Cambridge Electronic Design). Skin conductance responses were quantified by subtracting the average skin conductance in the second before the stimulus onset from the maximum skin conductance within the 4 seconds after stimulus onset. Data were z-transformed to account for interindividual differences in physiological reactivity. In order to confirm the arousing effect of the electrical shock in general, the amplitudes for scenes followed by shock and scenes not followed by shock were contrasted. This was done within a condition × subsequent memory ANOVA. Thus, differences in SCR were also related to memory performance. Last, in order to test for effects of habituation and sensitization, the first and the second half of the scenes^{+shock} were contrasted against each other.

4.3.2 Results

The day1-group and the day2-group differed according to the distribution between the sexes ($\chi^2(1) = 4.01$, $p = 0.02$); thus sex was included as a covariate into between-group analyses. The groups did not differ according to real or perceived intensity of the electrical shocks (see appendix Table A- 2 for details). Moreover, the VAS ratings of the electrical shocks did not vary over time in any group. Electrical shocks elicited a significant skin conductance response in both groups, i.e. arousal was enhanced following scenes^{+shock} compared to scenes$^{no\ shock}$ (day1-group: $F(1,13) = 7.35$, $p = 0.02$; day2-group: $F(1,11) = 6.45$, $p = 0.02$). The SCR-amplitude for scenes^{+shock} did not differ between the first and second half of the encoding session. Thus, SCR and VAS ratings indicate that neither habituation nor sensitization to the shock was detected throughout the experiment.

For the encoding task, descriptive results are summarized in Table 4-1.

Table 4-1 Performance during encoding in experiment 1

	Day1-Group	Day2-Group
Classification task		
Percent correct		
scenes$^{no\ shock}$ (M/SD)	98/3.64	94.37/3.23
scenes^{+shock} (M/SD)	96.37/2.74	95/4.44
Classification task		
Reaction times (ms)		
scenes$^{no\ shock}$ (MD/SD)	548.77/97.07	542.14/59.4
scenes^{+shock} (MD/SD)	548.50/102.9	542.74/60.91
Distraction task		
% correct (M/SD)	98.33/1.46	98/1.34

scenes^{+shock} = followed by shock, scenes$^{no\ shock}$ = not followed by shock
ms = milliseconds, M = mean, MD = median, SD = standard deviation, %=percent

Performance in the encoding and the arrow-pointing tasks were highly accurate and did not differ between conditions in any group. The majority of all responses (92%) were executed during image presentation, i.e. before the electrical shock was potentially applied. Accordingly, reaction times did not differ between conditions. In summary, fast reaction times and the high percentage of correct categorization in both conditions in both groups indicate that initial cognitive processing of the majority of scenes was completed by the time of arousal induction.

Recognition performance is summarized in Table 4-2 (see Table A- 3 in the appendix for corresponding reaction times).

Table 4-2 Recognition performance (in percent) in experiment 1

	Day1-Group	Day2-Group
hits scenes$^{\text{no shock}}$ (M/SD)	56.25/13.14	45.37/8.96
hits scenes$^{\text{+shock}}$ (M/SD)	58.12/13.49	52.87/12.46
total hits (M/SD)	57.16/12.46	49.1/9.38
false alarms (M/SD)	27.29/12.09	25.6/13.48
scenes$^{\text{no shock}}$ corrected (M/SD)	28.94/11.66	19.75/13.98
scenes$^{\text{+shock}}$ corrected (M/SD)	30.81/12.85	27.25/8.64
total corrected (M/SD)	29.87/11.3	23.49/10.25
source memory corrected (M/SD)	-2.56/17.36	-0.9/13.82

scenes$^{\text{+shock}}$ = followed by shock, scenes$^{\text{no shock}}$ = not followed by shock
M = mean, SD = standard deviation,
Note: The percentage of misses is equal to 100-hits, the percentage of correct rejections is equal to 100-false alarms

Recognition performance was significantly above chance level in both conditions in both groups, indicated by corrected recognition scores, i.e. hits minus false alarms (day1-group: $t(19) = 11.78$, $p < 0.001$; day2-group: $t(19) = 10.42$, $p < 0.001$, for the overall corrected hit rate).

In the day1-group, there was no evidence for a significant difference in recognition performance between conditions (see Figure 4-2, on the left). In contrast, participants of the day2-group recognized significantly more scenes followed by arousal than scenes not followed by arousal ($t(19) = 3.06$, $p = 0.006$, see Figure 4-2, on the right).

In both groups, SCR during encoding did not differ between subsequently recognized and subsequently forgotten scenes of both conditions.

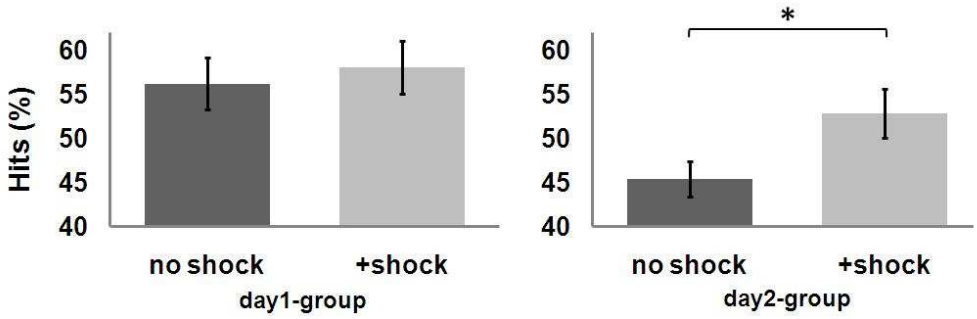

Figure 4-2 Amount of correctly recognized scenes$^{no\ shock}$ and scenes^{+shock} in experiment 1

Recognition performance for scenes followed by shock and scenes not followed by shock was different in the day2-group, only (* $p < 0.001$).

In the last step of the analysis, the confidence ratings were fitted to a dual-process model of recognition memory in order to derive estimates of recollection and familiarity (see methods section; Yonelinas, 1994; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). In the day1-group, neither R nor d' differed between conditions (see Figure 4-3, on the left). In the day2-group, d' was significantly higher for scenes followed by arousal ($t(19) = 4.04$, $p < 0.001$, see Figure 4-3, on the right), R did not differ between conditions.

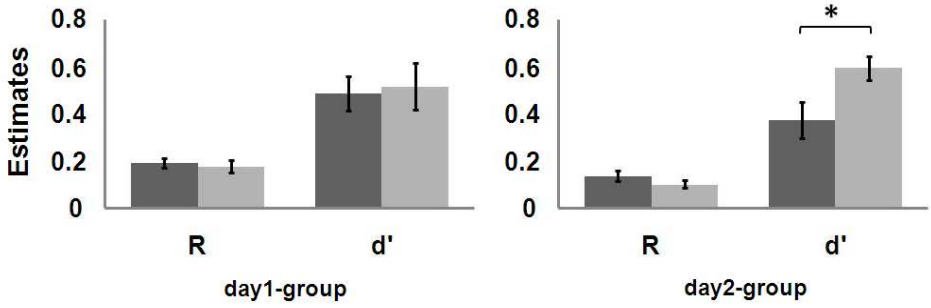

Figure 4-3 Parameter estimates for recollection and familiarity in experiment 1

For both groups, estimates for recollection (R) and familiarity (d') are depicted for scenes$^{no\ shock}$ (dark grey) and scenes^{+shock} (light grey). A familiarity-driven difference was seen for the day2-group (* $p < 0.001$).

Finally, corrected hit rates of the source memory task were at chance level for both groups indicating that recognition of scenes followed by arousal was not supported by contextual cues. In other words, participants did not acquire explicit memory for the electrical shock.

4.4 Experiment 2

4.4.1 Methods

4.4.1.1 Participants

Twenty new participants (15 males, mean age 27.5 years) were scanned, using the paradigm established in experiment 1. This group will be termed *day2-fMRI-group* in the following.

4.4.1.2 Experimental Task

Based on the results of experiment 1, the paradigm and the schedule for encoding and recognition were adopted from the day2-group of experiment 1, i.e. recognition was tested after a retention interval of 24 hours. Both encoding and recognition took place in the MR-scanner, but only the encoding data will be discussed in this thesis. Encoding was identical to experiment 1. Since recognition was scanned, timing restrictions were implemented in order to simplify later analyses. Timing was based on the median reaction times in experiment 1. Thus, during recognition, scenes were presented for 6 seconds in total. They were presented alone for 2 seconds and together with the confidence scale for additional 4 seconds. The ISI was jittered between 3 and 6 sec. The source memory task was omitted.

4.4.1.3 Questionnaires

In order to test for individual aspects which might influence the perception and the rating of an aversive stimulus, several questionnaires were implemented in experiment 2. All participants filled in self-report questionnaires estimating the presence of depression and anxiety (Allgemeine Depressions Skala (ADS), Hautzinger & Bailer, 1993; STAI, Laux, 1981). Moreover, pain-related thoughts were assessed via the *Pain Catastrophizing Scale* (PCS; Sullivan, Bishop, & Pivik, 1995) and the *Pain Vigilance and Awareness Questionnaire* (PVAQ; McCracken, 1997). Scores of the questionnaires were correlated with the intensity of the electrical shock, the VAS rating and the difference between recognized scenes^{+shock} and scenes$^{no\ shock}$.

4.4.1.4 FMRI: Data acquisition and analysis

Functional MRI was performed on a 3T system (Siemens Trio) with an EPI T2* sensitive sequence in 40 contiguous axial slices (2 mm thickness with 1 mm

gap, TR 2.38 sec, TE 25 ms, flip angle 70°, field of view 192 x 192 mm², matrix 64 x 64).

The image series was analyzed using SPM8 according to the workflow described in the general introduction to fMRI. All images were corrected for differences in time of acquisition, corrected for motion artifacts by realignment to the first volume and corrected for the interaction of motion and distortion using the *unwarp* toolbox of SPM8. They were spatially normalized into standard anatomical MNI space, and smoothed with a Gaussian kernel of 8 mm full width at half maximum.

Two event-related analyses were conducted on the first level for each participant on a voxel-by-voxel basis. The encoding-events were divided post-hoc according to subsequent recognition performance, i.e. into subsequent hits and misses. This was done separately for scenes^{+shock} and scenes$^{no\ shock}$. The resulting four event categories were modeled as separate regressors by convolving a delta function at the time of picture onset (model 1) and picture offset (model 2) with the canonical HRF. In addition, the temporal and dispersion derivatives were included as separate regressors to both models. Model 1 aimed at identifying activity related to successful memory formation irrespective of condition. This contrast is called *subsequent memory effect* or *difference due to memory (DM-) effect* since it demonstrates activity which is predictive for later recognition success by contrasting activity during encoding between items that are later remembered vs. forgotten (Brewer et al., 1998; Paller et al., 1987; Wagner et al., 1998). Accordingly, hits and misses across conditions were contrasted. Model 2 was set up in order to depict effects of arousal. First, in order to prove that the electrical shock was a potent arousing agent, scenes followed by arousal were contrasted with scenes not followed by arousal irrespective of memory performance. This contrast depicts the *main effect of arousal*. Finally, the critical analysis was conducted in model 2 by contrasting successful encoding in both conditions, i.e. by contrasting the subsequent memory effects in both conditions (by depicting the interaction of the factors condition and subsequent memory performance). This contrast will be termed *differential DM-effect* in the following.

On the second level, the contrast images of the first-level analyses were tested with one-sample t-tests. Results were considered significant at $p = 0.05$ corrected for multiple comparisons at the entire scan volume and a reduced search volume. Application of anatomical MRI masks (Amunts et al., 2005;

Tzourio-Mazoyer et al., 2002) was based on the pivotal role of the medial temporal lobe for memory and the amygdala for emotional processing (LaBar & Cabeza, 2006; McGaugh, 2004; Murty et al., 2010).

To test for differences in latency and width of the HRF between scenes followed by shock and scenes not followed by shock, the parameter estimates for the temporal and dispersion derivatives were extracted at the peak voxel of the critical analysis and contrasted in a repeated measures ANOVA outside of SPM.

4.4.2 Results

4.4.2.1 Behavioral results

The day2-fMRI-group did not differ to the equivalent behavioral group according to demographic aspects, intensity of the electrical shock or VAS ratings (see Table A- 2 for details). VAS ratings were constant across scanning. Moreover, shock intensity and VAS ratings did not correlate with mood or pain-related thoughts (all r < 0.2; see appendix Table A- 4 for descriptive results).

Performance during encoding is listed in Table 4-3.

Table 4-3 Performance during encoding in experiment 2

	Day2-fMRI-Group
Classification task	
Percent correct	
$scenes^{no\ shock}$ (M/SD)	93.2/17.77
$scenes^{+shock}$ (M/SD)	94.2/19.6
Classification task	
Reaction times (ms)	
$scenes^{no\ shock}$ (MD/SD)	616.54/75.59
$scenes^{+shock}$ (MD/SD)	629.95/94.78
Distraction task	
% correct (M/SD)	99/1.44

$scenes^{+shock}$ = followed by shock, $scenes^{no\ shock}$ = not followed by shock
M = mean, SD = standard deviation, ms = milliseconds, MD = median, % = percent

Performance in the encoding and arrow-pointing tasks was highly correct and within the presentation of images; neither accuracy nor latency was influenced by the electrical shock.

Recognition performance is summarized in Table 4-4.

Table 4-4 Recognition performance (in percent) in experiment 2

	Day2-fMRI-Group
hits scenes$^{no\ shock}$ (M/SD)	53.06/13.20
hits scenes^{+shock} (M/SD)	54.2/12.49
total hits (M/SD)	53.62/11.74
false alarms (M/SD)	33.43/11.71
scenes$^{no\ shock}$ corrected (M/SD)	19.59/10.22
scenes^{+shock} corrected (M/SD)	20.73/11.70
total corrected (M/SD)	20.15/10.85

scenes^{+shock} = followed by shock, scenes$^{no\ shock}$ = not followed by shock
M = mean, SD = standard deviation

The corrected hit rate was significantly above chance level (for the overall hit rate: $t(19) = 10.24$, $p < 0.001$, see Figure 4-4 on the left). Recognition performance for scenes not followed by shock did not significantly differ from scenes followed by shock. Moreover, R and d' did not show a significant difference between conditions (see Figure 4-4 on the right).

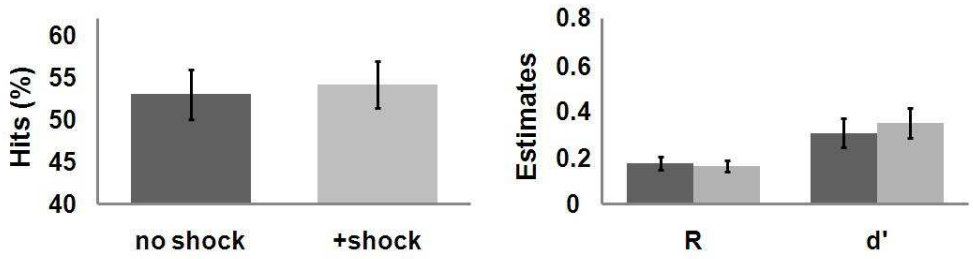

Figure 4-4 Recognition performance in experiment 2
On the left) Amount of correctly recognized scenes in both conditions; **on the right**) Estimates for recollection (R) and familiarity (d'), depicted for scenes$^{no\ shock}$ (dark grey) and scenes^{+shock} (light grey).

Memory performance was not correlated with test scores from the questionnaires (all $r < 0.3$; see appendix Table A- 4 for descriptive results).

4.4.2.2 Functional results

For the entire scan volume, the main effect of arousal was associated with activity in the right secondary somatosensory (SII, xyz = 38,-16,18, $Z = 6.13$, $p < 0.001$, see Figure 4-5, upper panel), bilateral insular (xyz = -38,-4,-6, $Z = 5.91$; xyz = 40,2,-8, $Z = 5.6$, $p < 0.001$), and bilateral parietal and occipital cortices (maximum -54,-54,18, $Z = 5.56$, $p = 0.002$; see appendix Table A- 5

for all activated clusters). Within the reduced search volume, arousal lead to bilateral activation of the amygdala (xyz = 28,2,-28, Z = 4.39, p = 0.001 small volume corrected (svc); xyz = -22,-6,-14, Z = 3.34, p = 0.025 svc, see Figure 4-5, lower panel).

No significant activation was found for the reverse contrast, i.e. scenes$^{no\ shock}$ > scenes^{+shock}, after correction for multiple comparisons.

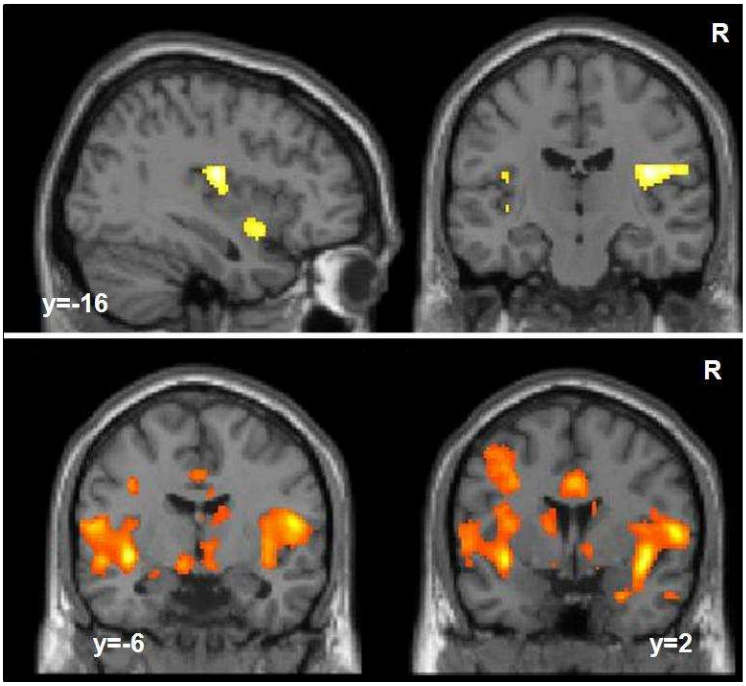

Figure 4-5 Main effect of arousal
Activity associated with nociceptive stimulation: **Upper Panel**) Enhanced activity of SII and insula (whole-brain corrected), **Lower Panel**) activity of the left amygdala (on the left), and the right amygdala (on the right; small volume corrected; for visualization purposes a threshold of p<0.001 uncorrected was applied).

The DM-effect, i.e. successful memory formation across encoding conditions was correlated with enhanced activity in the right hippocampus (xyz = 24,-14,-10, Z = 4.4, p = 0.004 svc, see Figure 4-6).

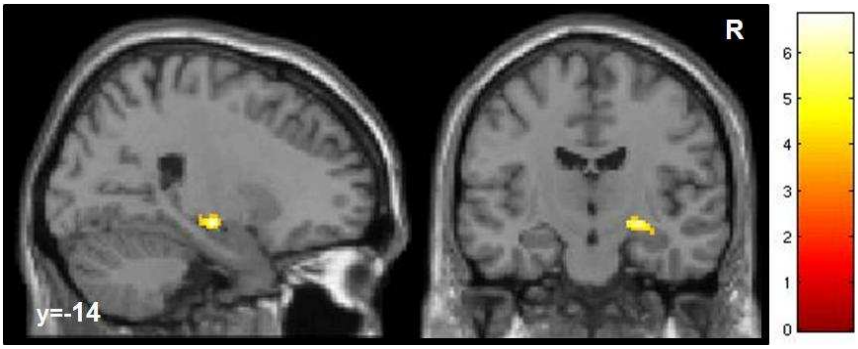

Figure 4-6 Main effect of memory
Subsequent memory performance across conditions was associated with activity in the right hippocampus (small volume corrected, for visualization purposes a threshold of p<0.001 uncorrected was applied).

The differential DM-effect, i.e. successful memory formation for scenes followed by shock compared to scenes not followed by shock, was represented by enhanced activation of the right posterior parahippocampus (xyz = 22,-34,-12, Z = 3.75, p = 0.019 svc, Figure 4-7).

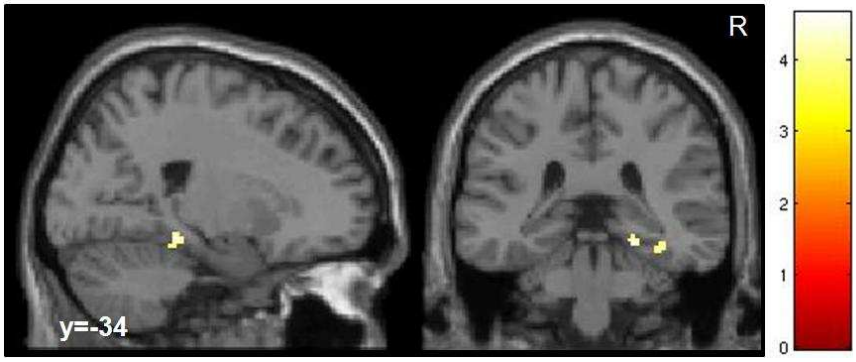

Figure 4-7 Arousal-dependent (differential) DM-effect
Activation of the right parahippocampal gyrus was associated with a subsequent memory effect for scenes^{+shock} compared to scenes$^{no\ shock}$ (for visualization purposes a threshold of p<0.001 uncorrected was applied).

The temporal and dispersion derivative in the peak voxel did not differ significantly, indicating that neither the latency nor the width of the HRF were affected by the electric shock after stimulus offset.

4.5 Discussion

Experiment 1 revealed that memory was not affected by arousal when it was tested immediately after encoding but after a 24 hours retention interval only: Scenes followed by shock were better recognized than scenes not followed by shock. As proposed in hypothesis 1, this delayed impact of arousal is consistent with an effect on consolidation. These results are in line with effects described by the modulation hypothesis (McGaugh, 2000, 2004) and the multifactor theory of emotion (Talmi, Luk, et al., 2007; Talmi, Schimmack, et al., 2007). However, the present data also differ from standard studies of the EEM using emotional stimuli. Superior memory for scenes followed by nociceptive arousal was solely driven by familiarity, which is in contrast to the typical increase in recollection for emotional stimuli (Sharot & Yonelinas, 2008). Another difference to studies of the EEM is the finding that SCR (experiment 1) and amygdala activity (experiment 2) are correlated with the nociceptive stimulation but not with successful memory formation. Thus, hypothesis 2 cannot be accepted completely. Experiment 2 showed that nociceptive arousal modulated MTL but not amygdala activity during successful encoding. Memory for scenes^{+shock} compared to scenes$^{no\ shock}$ was mediated by activity in the right parahippocampal cortex.
In the following, these results will be discussed in more detail.

4.5.1 Behavioral results

As denoted in the introduction, effects of emotional stimuli on memory are confounded by effects during the initial processing of memoranda, i.e. cognitive characteristics of emotional stimuli and effects of attention (e.g. Talmi, Luk, et al., 2007; Talmi, Schimmack, et al., 2007). In the present study, arousal was separated from stimuli probed for memory by subsequent presentation, similar to animal and human studies using post-training stress or pharmacological interventions (see van Stegeren, 2008). Accuracy and latency during encoding confirmed that the initial processing of visual stimuli was indeed completed when the electrical shock was administered. In summary, its occurrence cannot have influenced selective attention to specific scenes during encoding, but only processes afterwards. Moreover, stimuli probed for memory in the present study did not differ according to cognitive characteristics. In other words, scenes were equal by the time of presentation.

The delayed memory enhancement found in the present study was exclusively driven by familiarity. In studies of the EEM, attention during encoding has been linked to subsequently enhanced recollection (Kensinger, Clarke, & Corkin, 2003; Yonelinas, 2001). In particular, the increase in recollection rather than familiarity for emotional arousing items is consistent with the attraction of attention during encoding by emotional items (Anderson, Yamaguchi, Grabski, & Lacka, 2006; Kensinger & Corkin, 2003; Sharot & Yonelinas, 2008; Sharot et al., 2007). Thus, on the contrary, the effect of familiarity in the present study can be attributed to unaffected initial processing. This interpretation is supported by the familiarity-driven EEM for neutral stimuli that was observed in studies inducing arousal by cold pressor stress or skydiving after a blocked encoding phase (McCullough & Yonelinas, 2011; Yonelinas, Parks, Koen, Jorgenson, & Mendoza, 2011). The absence of recollection was emphasized by the observation that participants were not aware of the context of an image when explicitly asked for it. In other words, recognition of items followed by shock was not supported by contextual cues.

Taken together, the absence of an immediate effect and the absence of an increase in recollection in the present study suggest that both characteristics of the EEM for emotional stimuli rather result from differences in the initial processing than from pure arousal.

Since cognitive factors were excluded in the present study, increased efficiency of consolidation can be explained by arousal. Post-learning stress induced by a nociceptive stimulus has been shown to activate the noradrenergic system across species (Andreano & Cahill, 2006; Cahill et al., 2003; van Stegeren, 2008); electrical shocks are one possibility to trigger arousal mediated by the noradrenergic system (Berridge & Waterhouse, 2003; Delaney et al., 2007; Sara, 2009). Importantly, the reported effects are assumed to rely on the central release of NA and not on adrenal stress hormones. This assumption is based on the time scale of the intervention. The release of adrenal stress hormones due to arousal as proposed by the modulation hypothesis can account for findings of blocked post-learning arousal (Andreano & Cahill, 2006; Cahill et al., 2003). However, it cannot account for the present results, since electrical shocks were applied in an event-related fashion. Event-related studies of the EEM using emotional stimuli have shown rapid effects (Anderson, Wais, et al., 2006; Strange et al., 2003). The short time course of the EEM in these studies and pharmacological

interventions indicated that emotional arousal might initiate neurochemical processes directly in the brain, i.e. modulate the central release of NA (Strange & Dolan, 2004; Strange et al., 2003). The primary source of NA in the brain is the LC which can be activated directly by various salient stimuli, including electrical shocks (Berridge & Waterhouse, 2003; Sara, 2009).
Taken together, the effect of arousal in experiment 1 was presumably driven by NA centrally released from the LC, since the systemic response of adrenal stress would be too slow to account for an event-related effect.

Contrary to the results in experiment 1 and at first glance surprising, the day2-fMRI-group did not show an effect of arousal on memory performance. In particular, encoding and retrieving in the scanner had a beneficial effect on memory for all scenes, but did not lead to a further increase in memory for scenes^{+shock}. Since questionnaire scores did not correlate with the electrical shocks or memory performance, this observation cannot be explained by effects of mood, anxiety or pain-related thoughts.
On the one hand, this observation could be plausibly explained by differences in the experimental setting. Participants are likely more motivated and focused on the task in an fMRI experiment since the extensive set-up emphasizes the importance of the experiment and visual distraction is low inside the scanner. The scanner also constitutes a highly distinct and congruent context during encoding and retrieval which results in greater context-dependent memory (Smith & Vela, 2001; Törnqvist, Mansson, Larsson, & Hallström, 2006).
On the other hand, the finding could be due to an interaction of adrenal and central stress hormones. The scanning situation has been associated with the systemic secretion of adrenal stress hormones (Eatough, Shirtcliff, Hanson, & Pollak, 2009; Peters, Cleare, Papadopoulos, & Fu, 2010; Tessner, Walker, Hochman, & Hamann, 2006). In the present sample, a release of adrenal stress hormones seems plausible because most participants had very limited scanning experience. Studies using neutral material consistently report improved memory performance due to cortisol (Andreano & Cahill, 2006; Kukolja, Thiel, Wolf, & Fink, 2008). Moreover, when NA levels are elevated in addition to cortisol, there is no additive effect on memory performance compared to cortisol alone (Kukolja, Klingmüller, Maier, Fink, & Hurlemann, 2011; van Stegeren et al., 2010).

In summary, the beneficial effects of the fMRI set-up on memory performance for all scenes and the potential release of adrenal stress hormones might have masked the more subtle effects of post-stimulus arousal.

Obviously, the effects of neurotransmitters cannot be clarified with the present study but with a pharmacological experiment, a heterogeneous group for scanning or different scan times in order to reduce effects of levels of stress hormones. According to the existing literature, arousal was most likely due to noradrenergic innervations (Andreano & Cahill, 2006; Berridge & Waterhouse, 2003; Strange et al., 2003; van Stegeren, 2008). But, non-noradrenergically mediated mechanisms might occur in addition. This thought stems from studies of the EEM. For example, although a positive correlation of increase of salivary alpha-amylase (indicating noradrenergic activity) and recall of emotional information exists, the EEM can also be detected in participants without elevated salivary alpha-amylase response (Segal & Cahill, 2009).

4.5.2 Functional MRI

The main effect of arousal proved that arousal was induced by a nociceptive stimulus: Activity associated with electrical stimulation was found in the somatosensory and insular cortices. These regions are part of a network termed *pain matrix*. This pain matrix is not an entity but a dynamic network of regions which are active during the perception of pain. It usually comprises primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices (Apkarian, Bushnell, Treede, & Zubieta, 2005; Schnitzler & Ploner, 2000; Tracey & Mantyh, 2007). While the more lateral regions are thought to be involved in sensory-discriminative processes, the medial regions are associated with cognitive-emotional aspects of processing. Thus, as in the present study, the amygdala can be part of the pain matrix. It is a target for stress-responsive and pain-responsive nuclei of the brain stem and a target for central nociceptive actions of NA (Sara, 2009). On the other hand, as has been stressed before, it is a central structure involved in emotional memory (LaBar & Cabeza, 2006). FMRI studies using emotional stimuli or contexts consistently report a greater activity of the amygdala and amygdala-hippocampal coupling during encoding of subsequently remembered arousing stimuli and contexts (Dolcos, LaBar, & Cabeza, 2004; Erk, Martin, & Walter, 2005; Murty et al., 2010). Also autonomic measures, i.e. SCR and heart rate, are usually correlated with successful memory formation for emotional

arousing stimuli (Abercrombie, Chambers, Greischar, & Monticelli, 2008; Anderson, Yamaguchi, et al., 2006; Buchanan et al., 2006). In the present experiment, bilateral amygdala activity and SCR were correlated with the electrical shock but did not show a systematic relationship with subsequent memory performance. This could be due to the following fact. Emotional stimuli are characterized by a great variability in subjective arousal which correlates with memory performance, amygdala activity and SCR (Lang et al., 1993; Phan et al., 2004; van Stegeren et al., 2005). On the contrary, the nociceptive stimulation in the present experiment was physically and subjectively relatively constant throughout the experiment. The small fluctuations in the sensory processing and affective appraisal of the shock did not lead to significant differences in SCR and amygdala activity.

However, notwithstanding the constancy of arousal, activity in the right parahippocampal cortex correlated with successful memory formation for scenes^{+shock}. This area has previously been described as parahippocampal place area which is involved in perceptual processing and successful memory formation of scenes (Epstein & Kanwisher, 1998; Epstein, Graham, & Downing, 2003; Epstein, Harris, Stanley, & Kanwisher, 1999; Litman, Awipi, & Davachi, 2009). Recently, it has been suggested that the parahippocampal cortex is also involved in the encoding of contexts (Diana et al., 2007). However, due to the scenic stimulus material and the exclusive increase in familiarity-driven, acontextual recognition in the present setting, parahippocampal activity in the present study presumably reflects scene processing (Doeller & Kaplan, 2011). An activity increase in the parahippocampus has also been reported for successful encoding of emotionally arousing information (Murty et al., 2010). Therefore, the increased activity might reflect a common process which is induced by arousal and does not depend on the initial processing based on the cognitive characteristics of emotional stimuli. An open question is whether the lateralization, i.e. activity in the right but not left parahippocampus, represents a true effect in line with studies on emotional stimuli or a threshold effect (Kensinger & Schacter, 2005; Vuilleumier, Armony, Driver, & Dolan, 2001).

It is important to note that the differential activity in the parahippocampal cortex was not accompanied by more efficient consolidation in the day2-fMRI-group. However, it reflects processing differences that are probably related to the performance differences outside of the scanner environment.

As argued above, electrical shocks are assumed to directly activate the noradrenergic system. In general, nociceptive stimuli activate the central noradrenergic system in the LC directly and also indirectly via the centromedial amygdala that allocates attention to relevant stimuli (Gao, Ren, Zhang, & Zhao, 2004; Mosher, Zimmerman, & Gothard, 2010; Van Bockstaele, Bajic, Proudfit, & Valentino, 2001). This results in the release of NA in the projection areas of the LC, e.g. the amygdala, the hippocampus, and also the parahippocampus where β-adrenoceptors are abundantly expressed (Berridge & Waterhouse, 2003; Joyce et al., 1992). NA mediates an increase in cortical neuronal responsiveness and in cortical synaptic plasticity (Flores et al., 2010; Mondaca et al., 2004; Tully & Bolshakov, 2010). Therefore, the activation of the central noradrenergic system could affect processing in the parahippocampal cortex directly via afferents from the LC and/or indirectly via afferents from the amygdala (Suzuki, 1996).

Since the pattern of the BOLD response does not indicate a later or prolonged processing, the modulatory input from the LC reaches the parahippocampal cortex during the initial neural processing of the stimuli and may directly interact with stimulus-specific variability in the neural processing. This increases the likelihood that activity or synaptic efficacy reaches a level that supports subsequent consolidation, e.g. by the conversion from early in late LTPs as formulated by the synaptic tagging hypothesis (Redondo & Morris, 2010). Animal studies have shown that various ways of enhancing NA augment cell signalling mechanisms which enhance the durability of LTP (Korol & Gold, 2008; Sara, 2009) Whether the amygdala is involved in modulating parahippocampal activity or whether its constant activity merely reflects the affective aspect of the nociceptive stimuli cannot be decided based on the data.

4.5.3 Conflicting results from studies on nociception

As indicated above, the arousing stimulus is nociceptive, i.e. painful. This fact is also reflected by the enhanced activity in areas related to pain. Previous studies investigating effects of acute pain on short-term and long-term memory have found diminished memory performance due to pain (Bingel, Rose, Glascher, & Buchel, 2007; Kuhajda, Thorn, Klinger, & Rubin, 2002; Lorenz & Bromm, 1997). In all studies, memory distortions were attributed to an *interruptive function of pain* (Eccleston & Crombez, 1999). This theory is based on the assumption that pain achieves salience by demanding attention

in order to direct action. Because, in this framework, attention is seen as a limited capacity, decreased cognitive performance is attributed to deficits of attentional resources. The present study clearly differs from these results. As for studies of the EEM, the most obvious explanation for this difference is based on the experimental design. In the cited studies, pain was present either throughout the whole experiment or at least during an experimental block. Thus, effects on memory processes cannot be disentangled from effects on initial processes of perception. Therefore, it is most likely that effects of pain reported by previous studies are mediated by processes prior to memory. Support for this assumption derives from studies which suggest a general theory of load on the basis of similar patterns of interference for different stimuli (e.g. Klemen, Buchel, Buhler, Menz, & Rose, 2009). Thus, any high load of a relevant task reduces the resources available for a concurrent irrelevant task.

In summary, the theory of an interruptive function of pain is challenged by the present and other findings of enhanced memory when nociceptive arousal is induced after initial processing (compare Andreano & Cahill, 2006; McCullough & Yonelinas, 2011).

4.5.4 Limitations

The present study intended to investigate effects of arousal on memory. As stated before, arousal is assumed to result from actions of the noradrenergic system. This assumption is based on an extensive literature on noradrenergic effects of nociceptive stimuli (Andreano & Cahill, 2006; Berridge & Waterhouse, 2003; Cahill et al., 2003; Sara, 2009; van Stegeren, 2008). However, it would be desirable to directly test the involvement of NA in the present effect. Since salivary samples are not suitable in event-related design, it would be necessary to conduct pharmacological interventions.

In order to examine the proposed effects of arousal mediated by NA, a series of experiments was conducted. Participants were randomly assigned to one experiment. However, some participants were not willing to take part in an experiment at two consecutive days. Moreover, group composition was affected by exclusion criteria for MRI scanning. Therefore, it was not possible to perfectly randomize the groups. This issue also affected the distribution of the sexes: The behavioral groups in experiment 1 were not matched. Therefore, analyses of covariance were used for between-group comparisons.

An effect of sex was not detected: The groups did not differ according to real or perceived pain intensity. Previous studies on effects of arousal, which have not controlled for the duration and intensity of the aversive stimulus, are inconsistent regarding effects of sex (Andreano & Cahill, 2006; Cahill et al., 2003).

The day2-groups of both experiments did not differ with respect to any demographic aspects. Nevertheless, the distribution of the sexes could have influenced the fMRI data. Previous studies have shown different patterns of activity for emotional material in men and women (Cahill, 2006; Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004). Moreover, these studies propose structural differences, i.e. sex differences in receptor affinity (Cahill, 2006; Strange et al., 2003). However, pain has been shown to activate the same brain areas in men and women, but with different strength (Kong et al., 2010).

In summary, an effect of sex seems unlikely, but cannot be ruled out. Therefore, data were reanalyzed including sex as a covariate in all analyses. The results did not change. However, it would be useful to replicate the findings in larger groups of men and women which allow for direct group comparisons.

4.5.5 Conclusion and future directions

In conclusion, the present data show that event-related, arousal- induced enhancement of consolidation can occur independently of the initial processing of stimuli. Even though the behavioral effect was masked due to the MR-scanner environment, this effect may be based on centrally released NA modulating the responsiveness or synaptic efficacy in cortical areas involved in the processing of stimuli. The observed memory enhancement was exclusively based on an increase in familiarity but not recollection. Thus, the findings differ from studies using emotional material. In summary, the present data imply that the immediate EEM and the increase in recollection in studies using emotional stimuli might rely on enhanced initial processing which is triggered by evaluative processes in the amygdala (Liddell et al., 2005; Vuilleumier, 2005).

Regarding enhancing effects on consolidation, an open question relates to the critical window in which arousal must occur (compare Anderson, Wais, et al., 2006). Moreover, it would be interesting to implement tests at different retention intervals in order to examine whether sleep is really necessary or whether more efficient consolidation might already be seen during

wakefulness (see Peigneux et al., 2006). As stated before, the proposed effect of the noradrenergic system needs confirmation by pharmacological studies. In addition, it is not clear whether a certain level of noradrenaline mediates the efficiency of consolidation (compare Andreano & Cahill, 2006). Furthermore, it would be interesting to test whether the pattern of activity changes due to changes of the modality of memoranda, i.e. to test for effects of arousal on verbal material. Last, further studies should test different aversive procedures since novelty of an aversive stimulus might be relevant for enhancing effects (compare Eccleston & Crombez, 1999).

5 General discussion

The present thesis comprised two studies aimed at investigating different factors modulating the efficiency of memory formation. To simplify matters, potential modulators were classified into constant and temporary factors. Within this reference frame, the class of constant factors was represented by temporal lobe epilepsy which affects the integrity of the medial temporal lobe and thereby influences memory processing on a sustained basis. Study I of the present thesis revealed a reduction in encoding efficiency due to TLE of unknown cause. Given a sensitive test, patients' memory performance was reduced compared to controls, even in the absence of overt grey matter damage. In particular, an associative memory task and fMRI data suggest that enhanced hippocampal activity during successful encoding in light of reduced memory performance reflects a compensational process. In other words, the efficiency of hippocampal cell assemblies is impaired due to epilepsy. Thus, more neural activity is necessary in cryptogenic TLE patients for successful encoding. However, the compensational process fails and results in diminished memory performance if the higher activity threshold is reached less frequently.

In contrast, Study II focused on transient factors which do not affect the integrity of the underlying anatomy, but the functional processes of encoding and/or consolidation. The present study showed that arousal due to event-related nociceptive stimulation enhances the efficiency of memory consolidation, but not the efficiency of encoding. Most likely, enhanced consolidation was mediated by the central release of noradrenaline triggered by the electrical shocks. The effect occurred in the absence of cognitive factors, e.g. the attraction of selective attention, which are known to influence enhanced memory in the case of emotional stimuli. Moreover, the subsequent memory effect was not associated with amygdala or hippocampal activity during encoding as consistently reported for emotional stimuli, but based on enhanced activity of the parahippocampus which is involved in the processing of the presented scenes.

Although examples of constant and temporary factors were investigated in two separate studies, this does not imply a mutually exclusive relationship. On the one hand, temporary factors might boost memory processing which is altered due to morphological damage (or reduce memory even more; for example by

hippocampal electrical stimulation during encoding (Coleshill et al., 2004)). On the other hand, lesions of certain key structures might prevent effects of temporary modulators. These interactions can also be illustrated using the example of TLE.

Memory performance in epilepsy is influenced by a variety of factors, as shown in chapter 3.1.2. Although constant factors, e.g. brain lesions, might be prior-ranking factors, transient factors can additionally modulate memory performance (Dodrill & Ojemann, 2007; Elger et al., 2004; Jokeit et al., 2005). However, transient factors might be ineffective, if anatomical substrates of memory formation are damaged. For example, given the pivotal role of the amygdala and MTL in emotional memory, accordant lesions in TLE are proposed to influence the impact of emotional arousal on memory formation (LaBar & Phelps, 1998).

This assumption has been confirmed by studies probing memory for emotional and neutral stimuli in TLE patients: Memory for emotional (and neutral) stimuli is impaired in the case of pronounced amygdala and MTL damage (LaBar & Phelps, 1998; Richardson, Strange, & Dolan, 2004; Richardson et al., 2003). However, the results are inconsistent regarding enhanced memory for emotional compared to neutral words, i.e. the EEM. In a series of studies in temporal-lobectomy patients, an immediate EEM was found (LaBar & Phelps, 1998; Phelps, LaBar, & Spencer, 1997). But, whereas memory for emotional words was increased in healthy controls after a 1 hour delay, forgetting rates for emotional stimuli did not deviate from neutral stimuli in patients with left and right temporal resections (LaBar & Phelps, 1998). Therefore, the authors concluded that the large lesion of the MTL comprising the amygdala, the hippocampus and adjacent cortices preclude consolidation processes, irrespective of the side of the lesion or stimulus material. Yet, while the study focused on the relevance of MTL structures for consolidation, possible explanations for the observed immediate EEM were only briefly touched upon. Effects were ascribed to arousal as indicated by enhanced SCR; it was not explained how arousal could operate on encoding, but not on consolidation in the case of amygdala damage. In a previous study, the authors had shown that an immediate EEM in TLE patients likely resulted from enhancing effects of semantic cohesion of emotional stimuli and categorical processing (Phelps et al., 1997). Moreover, other studies have shown that enhanced SCR in patients with damage to the amygdala does not reflect arousal, but rather

orienting responses towards distinct stimuli (Knight, Nguyen, & Bandettini, 2005; Tranel & Damasio, 1989). Since infrequent taboo words were used, the immediate EEM in the cited study is most likely based on cognitive factors rather than arousal.

No differential memory effect was observed in a series of studies investigating memory in patients with left TLE and hippocampal sclerosis after a 90 minutes delay (Richardson, Strange, & Dolan, 2004; Richardson et al., 2003). Interestingly, this was also true for a behavioral control group. Nevertheless, activity during successful encoding differed between emotional and neutral words and thus reflected modulation of emotional arousal. Similar to Study II of the present thesis, the data suggest that temporary modulations which are evident at the neuronal level might not necessarily result in overt behavioral differences. However, the factors determining this effect, e.g. variations of the experimental set-up, are not always obvious and do need further exploration. In the cited study, pathology - i.e. the constant factor - modulated the lateralization of activity elicited by the temporary factor during encoding: Severe hippocampal sclerosis was associated with a reallocation of amygdala activity during encoding of emotional words, i.e. reduced ipsilateral and enhanced contralateral activity (Richardson, Strange, & Dolan, 2004). Since the severity of brain damage was also associated with reduced memory performance, these results emphasize the notion that reallocation goes along with reduced efficiency of both neutral and emotional memory processing (for a different interpretation see Richardson, Strange, & Dolan, 2004).

Both series of studies on emotional memory in TLE show that emotional arousal potentially influences memory formation, even in the presence of overt brain damage. While one group of authors focused on effects of emotional arousal on different memory stages (LaBar & Phelps, 1998), the other group focused on effects on neuronal activity (Richardson, Strange, & Dolan, 2004; Richardson et al., 2003). Both studies illustrate the importance of intact brain morphology for memory formation, since the degree of morphological alteration determines the range of the potential temporary modulation. However, the conclusions drawn from both studies face the problem of confounding effects.

In the case of emotional stimuli, effects of arousal are confounded by effects of cognitive factors: Distinctiveness, relatedness and the attraction of attention contribute to enhanced performance. Accordingly, amygdala activity during

encoding of emotional stimuli not only reflects arousal, but also evaluative processes (Liddell et al., 2005). By changing standard paradigms, as done in Study II, it is possible to disentangle effects of arousal from effects of cognitive factors. The results implicate that memory enhancement might not rely on the amygdala, if arousal is mediated by the noradrenergic system and cognitive factors are excluded. As said before, efficient consolidation was mediated by activity in the parahippocampus and the resultant memory enhancement was driven by familiarity. With regard to the influence of familiarity on patients' memory, the relevance of posterior MTL structures and the influence of noradrenaline in epilepsy, it would be interesting to implement the paradigm used in Study II in studies with TLE patients. The following paragraphs will explain this assumption.

In contrast to the aforementioned studies on emotional memory in TLE, another study with patients suffering from hippocampal damage found memory enhancement for emotional compared to neutral scenes (Sharot et al., 2007). Since memory was tested with a 2 hours delay, the results confirm effects of emotional arousal on consolidation. Since overall memory performance was diminished, the results also emphasize the relevance of brain integrity for consolidation. In other words, consolidation cannot be effective, if it is restricted to unilateral processing. However, the results indicate that consolidation might not be entirely ineffective. In contrast to healthy controls, emotional memory enhancement in patients was not driven by recollection, but was solely driven by familiarity. The authors concluded that the hippocampus is not necessarily involved in emotional memory, but in recollection (Sharot et al., 2007). The latter assumption is in line with theories on specialization within the MTL for recollective experience and familiarity (Diana et al., 2007; Eichenbaum et al., 2007). Therefore, given these theories, the fact of hippocampal damage, the use of scenic stimuli and the finding of familiarity-driven enhancement, it is most likely that the effect was mediated by the parahippocampus. At least, the results suggest that emotional memory enhancement can be accomplished by posterior MTL cortices. However, as also seen in Study II, the effects might be more subtle and only evident with a sensitive recognition test and a prolonged retention interval. As argued before, the modality of stimulus material might be important because posterior MTL regions have been associated with perceptual processing and encoding of scenes (Epstein & Kanwisher, 1998; Epstein et al., 1999). However, a

reallocation of encoding activity to the parahippocampus has also been shown for verbal stimuli (Richardson et al., 2003), in line with fMRI studies suggesting a role of the parahippocampus in emotional memory (Murty et al., 2010).

The remarks on emotional arousal in TLE and the findings of Study II can be summarized as follows. The reciprocity of amygdala and hippocampus mediates (immediate) effects of emotional stimuli on memory. Should these structures be damaged or should the stimulus material and the character of arousal differ from standard emotional stimuli (and therefore prevent effects of cognitive factors during initial processing), memory processing might rely on posterior regions of the MTL. However, the effects might not be immediately evident and severe damage might prevent any effect. Further studies would be needed to directly test interactions of amygdala and extrahippocampal structures during memory processing modulated by arousal. Importantly, the kind of arousal can determine the interaction. Emotional stimuli are only one possibility to induce arousal. Arousal mediated by the noradrenergic system can be triggered by various salient stimuli, including nociceptive stimuli as used in Study II (Berridge & Waterhouse, 2003). If the noradrenergic system is activated, it can influence activity in the MTL directly or indirectly via the amygdala (Gao et al., 2004; Van Bockstaele et al., 2001).

So far, electrical shocks have not been used in studies on memory in TLE. Nevertheless, effects of noradrenaline have been demonstrated. Some patients are treated by vagus nerve stimulation (VNS). As said before, the vagus nerve is part of the noradrenergic system (Berridge & Waterhouse, 2003). The release of norepinephrine as a result of VNS is assumed to be anticonvulsant (Ben-Menachem, 2002; Fitzgerald, 2010). Two studies have shown that vagal stimulation administered after learning resulted in enhanced memory compared to sham stimulation (Clark, Naritoku, Smith, Browning, & Jensen, 1999; Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006). This effect was ascribed to consolidation facilitated by NA released in the LC. However, the effect was only found at moderate levels of stimulation, but not at higher intensities (Helmstaedter, Hoppe, & Elger, 2001). This finding is in line with effects of medium arousal induced by the cold pressor stress test (Andreano & Cahill, 2006). Given these effects of NA revealed by VNS, nociceptive stimulation as implemented in Study II should not only improve consolidation in healthy participants, but also in TLE patients. In order to test for effects on consolidation, it is important to test recall or recognition at

several points in time. Otherwise, in case of impaired performance, it would be impossible to differentiate between inefficient encoding, consolidation and retrieval (compare LaBar & Phelps, 1998).

In conclusion, the present thesis showed that both constant and temporary factors modulate memory formation, i.e. enhance or diminish the efficiency of encoding and/or consolidation. Besides individual effects, interaction effects can occur at different parts of anatomical and functional memory circuits.

Importantly, effects of both categories can be masked by additional factors which arise from the stimulus material or experimental setting. Both paradigms implemented in the present study aimed at excluding such contributing cognitive factors. Given an appropriate memory task and different test intervals, it is possible to determine effects on encoding or consolidation. Moreover, functional MRI can be used to reveal effects of both factors on the neural substrates of encoding and thereby encoding efficiency.

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Appendix

Study I

Table A- 1 Additional results of neuropsychological assessment

Test	Patients Mean (SD)	Controls Mean (SD)
Verbal IQ		
WST	101.1 (11.05)	106.1 (11.68)
Visuospatial abilities		
ROCF drawing	33.5 (1.37)	32.61 (2.1)
Working memory		
TAP WM RT	625.66 (179.36)	773.76 (229.29)
TAP WM Errors	1.67 (1.75)	3 (3.57)
TAP WM Omissions	1.33 (1.5)	2.69 (3.03)
Attention		
TAP DA RT	681.33 (51.62)	685.38 (51.03)
TAP DA Omissions	2.16 (0.75)	1.15 (1.4)
Executive functions		
TAP F RT	791.16 (379.29)	848.07 (215.66)
TAP F Errors	3.81 (2.85)	1.23 (1.64)
RWT, lexical	18.5 (8.52)	22 (3.39)
RWT, lexical shift	20 (9.48)	25 (5.14)
RWT, semantic	35 (8.57)	41 (4.18)
RWT, sem. shift	23.5 (6.28)	24.8 (2.11)
Questionnaires		
BDI	5.16 (3.37)	3.79 (2.71)
STAI (Trait)	38.16 (5.67)	33.69 (6.63)

WST = Wortschatztest, ROCF = Rey-Osterrieth-Complex-Figure, TAP = Testbatterie zur Aufmerksamkeitsprüfung, WM = working memory, RT = reaction time in milliseconds, DA = divided attention, F = flexibility, RWT = Regensburger Wortflüssigkeitstest,
BDI = Becks Depression Inventory, STAI = State Trait Anxiety Inventory, Trait part
Note: Results = raw values for each test

Study II

Table A- 2 Demographic data, shock intensity and VAS scores of all groups included in Study II

	Day1-Group	Day2-Group	Day2-fMRI-Group
Age (M/SD)	28.5/3.7	26.05/4.94	27.5/3.37
Age range	22-38	20-40	21-35
Sex (m/f)	6/14	13/7	15/5
VAS 1/2/3	65.6/69.3/72	65.3/67.1/69	66.1/67.9/68.3
VAS (M/SD)	69/11.74	67.15/12.76	67.4/13.81
shock* (M/SD)	2.00/1.54	2.08/1.73	2.83/1.15

*intensity of the electrical shock in milliAmpere;
age in years, M = mean, SD = standard deviation, m = male, f = female, VAS = Visual Analog Rating Scale

Table A- 3 Reaction times during recognition (in seconds)

	Day1-Group	Day2-Group	Day2-fMRI-Group
Hits scenes$^{no\ shock}$			
Low conf. (MD/SD)	3.48/1.05	3.32/2.09	2.17/0.64
Medium conf. (MD/SD)	3.53/2.92	3.31/2.42	2.34/0.49
High conf. (MD/SD)	2.81/1.36	3.48/5.15	1.94/0.72
Hits scenes^{+shock}			
Low conf. (MD/SD)	3.56/2.83	3.37/2.5	2.22/0.53
Medium conf. (MD/SD)	3.41/1.98	3.64/2.77	2.39/0.45
High conf. (MD/SD)	2.82/1.97	3.49/0.41	2.07/0.56
False alarm			
Low conf. (MD/SD)	3.47/0.87	3.42/1.05	2.22/0.75
Medium conf. (MD/SD)	2.62/1.3	2.77/1.15	2.20/0.39
High conf. (MD/SD)	2.53/2.87	2.02/2.14	1.93/1.20

Scenes^{+shock} = scenes followed by shock, scenes$^{no\ shock}$ = scenes not followed by shock
MD = Median, SD = standard deviation
Note: In experiment 1, latency refers to stimulus onset. In experiment 2, latency refers to the appearance of the confidence scale

Table A- 4 Questionnaires: Descriptive results and correlation analyses

Questionnaire	score M/SD	Correlation* of questionnaire score and shock intensity	mean VAS	hits scenes$^{no\ shock}$	hits scenes^{+shock}
ADS	8.1/5.45	-0.24	-0.2	-0.26	-0.3
STAI, State	30.8/3.74	-0.17	0.3	-0.21	-0.08
STAI, Trait	30.1/4.78	-0.16	0.19	-0.2	-0.23
PVAQ	29.8/8.58	0.1	-0.08	-0.07	-0.33
PCS	11/7.11	-0.36	0.02	-0.04	0.08

* Correlation coefficient = Pearson's r
score = raw value for each questionnaire, M = mean, SD = standard deviation
ADS = Allgemeine Depressions Skala, STAI = State Trait Anxiety Inventory, PVAQ = Pain Vigilance and Awareness Questionnaire, PCS = Pain Catastrophizing Scale

Table A- 5 Brain regions activated by arousal

	XYZ (MNI coordinates)		Peak Z		
Region	**left**	**right**	**left**	**right**	**P ***
SII		38, -16, 18		6.13	<0.001
		56, 0, 10		5.51	0.003
Insula	-38, -4, -6	40, 2, -8	5.91	5.6	<0.001
		32, 10, 12		5.13	0.016
Angular gyrus	-54, -54, 18		5.56		0.002
V1/lingual gyrus	-8, -66, 4	2, -80, -4	5.11	5.08	0.018
Precuneus	-12, -44, 46	20, -62, 28	4.95	4.9	0.035

* at the entire scan volume p<0.05 was defined significant after correction for multiple comparisons
SII = secondary somatosensory cortex, V1 = primary visual cortex

Erklärung nach § 9 Abs. 1, Nr. c der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich, dass die von mir vorgelegte Dissertation nicht Gegenstand eines anderen Prüfungsverfahrens gewesen ist.

Hamburg, _____

Unterschrift

Eidesstattliche Erklärung nach § 9 Abs. 1, Nr. d der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst habe. Andere als die angegebenen Quellen und Hilfsmittel habe ich nicht benutzt und die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht.

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