RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITY OF BONN

From memory and attention to consciousness: Exploring three major aspects of cognitive brain functioning

Dissertation

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by
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A Thesis submitted to the biological department of the faculty of mathematics and sciences in complete fulfilment of the requirements to obtain the graduation of *Doctor rerum naturalium* (Dr. rer. nat.).

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Cover figure: The illustration shows a 3-D reconstruction of the authors brain, with a cut-out at the level of the interhemispheric fissure. The fMRI activation reveals a conflict network processing two interfering stimuli. The background shows regularly surface EEG activity under eyes-closed resting conditions.

„Man muss wissen, dass es der gesamten Natur unmöglich ist, irgendetwas zu zerbrechen, zu verderben oder auch nur in Gang zu setzen, ohne dass sie damit für das, was sie in Gang setzt, nicht etwas Besseres anstrebt.“

Meister Eckhart
(Buch der göttlichen Tröstungen, Predigt 9)

Contents

Chaper 1

Introduction

Historical overview – Anatomical overview – The present work

„The brain is not, like the liver, heart and other internal organs, capable from the moment of birth of all the functions which it ever discharges; for while in common with them, it has certain duties for the exercise of which it is especially intended, its high character in man, as the organ of conscious life, the supreme instrument of his relations with the rest of nature, is developed only by a long and patient training."

R.V. Pierce
(The People's Common Sense Medical Advisor in Plain English, 1917)

1.1 The long way of brain research

Cognitive brain research aims to understand how we perceive and interact with the external world using our mind. Technically, this approach in studying the brain is a part of neuroscience, because neuroscience includes all scientific studies involving the nervous system. However, from a historical point of view it is a product of classical medicine and psychology. Especially the medical investigations of the brain go back to more than 5000 years. Medicine has a long history of examining and investigating the human brain in every advanced culture of mankind, in an attempt to provide pain relief and to gain knowledge to treat the diseases of the mind. The oldest scientific description of the brain and its function known to us is the famous Egyptian "Edwin Smith Papyrus", an ancient textbook on trauma surgery which was written 1700 BC and contains knowledge pointing back to writings from 3000 BC (Wilkins, 1969). This papyrus contains the earliest recorded historical mentioning of the brain (see Fig 1.1) and the first descriptions of the cranial sutures, the meninges, the external surface of the brain, as well as the detailed descriptions of its differentiation into gyri and sulci. Interestingly the work mentions the word "nerve" at no point. Apparently the concept of nerves (or more specifically, the neurons), being the functional unit of the nervous system, was unknown to the Egyptians (Feldmann, 1999).

Fig. 1.1: Egyptian hieroglyph *ayis* ("brain"). The earliest recorded historical mentioning of the brain. From the Edwin Smith Papyrus.

From studying ancient cultures, such as Egypt, we know that thousands of years before western medicine, men gained the knowledge of the anatomical basis of the brain, but were at the same time restricted to the anatomy. They studied the structure and form of the body, respectively the physiology, meaning the study of the body's functions, but had no possibility of locating something abstract such as the mind. Without the technological equipment to investigate the physical processes underlying the mind's processes, scientists failed in conquering a fundamental problem. Our thoughts, or consciousness itself, does not seem to fit easily into the world of physical nature. The mental world seems to be different from the physical, which means that there appear to be two realities or substances in the world, namely minds and bodies, separated but interacting. The question behind this is the so called “mind-body problem” (Kim, 1995). Philosophers addressed this problem through the centuries by contemplating on the nature of the mind and its relationship to the physical body on theoretical bases. The number of theories is countless and the following paragraph provides only a very brief overview.

Philosophers such as Alkmaion of Kroton (500 BC) believed that the healthy body houses the mind and considered the brain to be the central organ for processes of the mind (Irby-Massie, 2002). Plato (400 BC) on the other hand found the relationship between mind and body not to be an ideal one; in fact, he considered the body to be the "prisoner" of the mind or (or soul), which contains the mind in order to evolve into a “true person” (Irby-Massie, 2002). During the early modern history the dualistic view prevailed with great medieval thinkers like Augustine (400 AC), who held that man is neither a body nor a soul alone, but rather a being composed of both, with the body as the inferior part (Dods, 1872). Christianity, for the most part, adopted a form of Platonic dualism as its official view and passed it on to the present era, where the radical separation between the mental and the physical world found its strongest representative in the modern philosophy of René Descartes in the seventeenth century. He concluded, that since he was unable to distinguish any parts within himself, but could not think of anything in his thoughts that he cannot easily divide into parts, the mind had to be completely different from the body (Cottingham, 1966).

For a long time the philosophers had no reason to expect help from other areas of science such as biology and physics in their consideration of the mind-body problem. Natural sciences can only accept what can be measured, and in 1844 the famous physiologist and anatomist Johannes Müller still claimed, that the nerve impulse was an example of a vital function that could never be measured experimentally (Finger et al. 2002). This changed radically with the ground-breaking work of his student Hermann von Helmholtz (1821-1894) and Emil du Bois-Reymond (1818-1896). They showed for the first time that the activity of nerves could indeed be studied with physical methods. With the discovery of the resting currents seen in excised nerves and muscles, as well as the first measurements of the speed of nerve impulses they were able to reduce physiology to applied physics and chemistry, a trend that has dominated physiology and medicine ever since (Eckart, 1994; Finkelstein, 1996). Physicists and scientific theoreticians such as Ernst Mach or Gustav Theodor Fechner as well as brain scientists such as Karl Ewald Hering among others used this groundwork to developed a new neuroscientific view of the world, that remains valid to this day.

1.2 Neuroscience today

In the recent years brain research has shown rapid technological progress. The local and global neural activity of the brain can be systematically associated with its anatomy, using advanced methods of electroencephalography (EEG) and functional imaging. In this way, empirical questions considering the neural basis of human cognitive capacities can be addressed. Nowadays, it is possible to reveal when and where in the brain certain neuronal events take place and how they are related to the specific form and procedure of the cognitive process underlying them. Modern imaging systems thereby take advantage of the fact that cognitively demanding tasks are always accompanied by increased blood circulation, metabolic and neuroelectric activity. All these findings strongly suggest a strict parallelism of mental and neural events.

Today the cognitive neuroscience is the sum of the fields such as medicine, biology, psychology, artificial intelligence, linguistics, anthropology, and philosophy. It is understood that the best way to grasp the real complexity of human thinking is to use multiple methods, especially psychological and neurological experiments and computational models. Neuroscience today understands the brain as an endless number of complex self-organizing non-linear systems, which above all interact in numerous ways. The level of complexity increases permanently, thus interdisciplinary work becomes necessary, even if the way to theoretical and experimental convergence on conclusions about the nature of the mind takes more time.

1.3 Brief anatomical overview

For purposes of clarity and orientation figure 1.2 provides a brief overview of the anatomical regions that will be the subject of discussion in the following chapters. It shows the differentiation of each of these hemispheres into lobes or sections: the frontal lobe, the parietal lobe, the occipital lobe and the temporal lobe (Fig. 1.2 A). Furthermore the main anatomical structures of the brain at the level of the interhemispheric fissure are shown, including the anterior cingulate cortex (ACC) (Fig. 1.2 B, see Chap. 4), as well as the position of the hippocampal cortex in the medial temporal lobe (MTL) (Fig. 1.2 C, see Chap. 3).

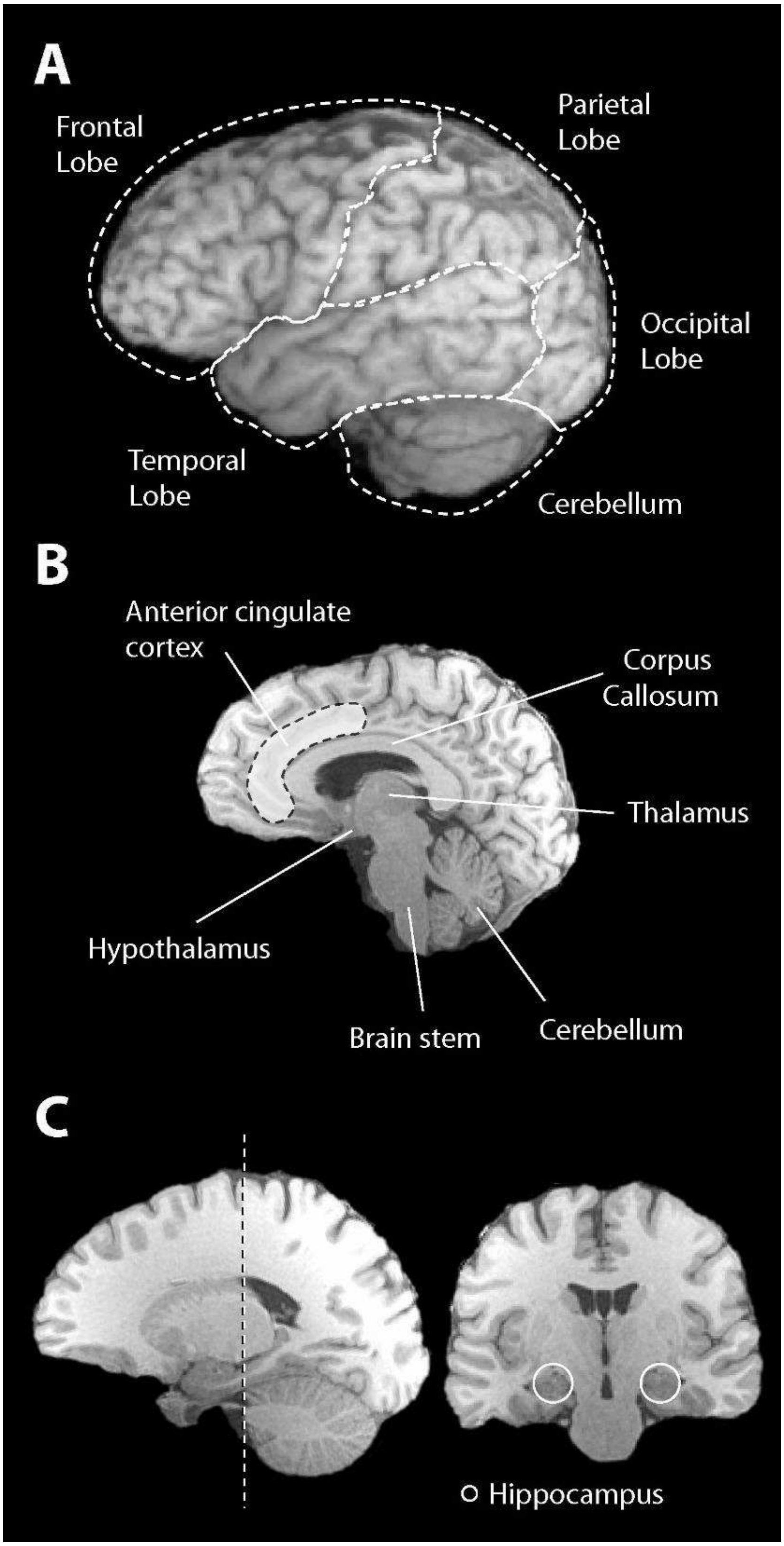


Fig. 1.2: Anatomical overview of the brain structures relevant for the present work.
(A) 3-D-reconstruction of an antaomical magnetic resonance imaging (MRI) sequence showing the lobes of the human cerebral cortex and the cerebellum. **(B)** Sagittal slice on the level of the interhemispheric fissure, showing prominent brain regions, including the anterior cingulum (see Chap. 4). **(C)** Sagittal and coronal slice on the hippocampal level.

1.4 The present work

One of the greatest advantages of current neuroscience research is the wide diversity of fields it attends to. The present work gives overview and insight into three different areas of cognitive neuroscience, representing exemplary aspects of the diverse spectrum of research areas: Memory, attention and consciousness. The following sections provide a brief overview of each of the following chapters, which will additionally be preceded by an own detailed introduction.

1.4.1 Chapter three – Memory

The third chapter focuses on a classical area of fundamental research: The human memory.

Research on memory processes distinguishes between working memory (WM) and long-term memory (LTM). A common way to seperate these two memory systems is the use of time and capacity (Thompson, 1996). The short-term memory is thereby limited to the duration of storage to about 30 seconds and can only hold about five to nine pieces of information. Memory that exceeds short-term memory duration limits is known as long-term memory. The long-term memory (LTM) system enables to permanently store, manage, and retrieve information for extended periods of time. LTM allows retrieval of information decades after it is stored, and the limits of its capacity are not known. The time-dependent process of stabilization, whereby the information achieves a permanent record in our memory, is referred to as "consolidation". The challenge for neuroscience today is to reveal where theses memory stystems are localized in the brain and how they interact.

The first attempts to localize these specific memory systems were based on lesion studies in patients and animals. The importance of the hippocampus in long-term memory formation for example, was brought to the attention of researchers by the famous patient HM (Scoville and Milner, 1957). For the relieve from frequent epileptic seizures he underwent a bilateral hippocampal removal and was henceforth unable to form long-term memories of new events or a new semantic knowledge. These findings indicated, that medial temporal lobe (MTL) regions support declarative long-term memory (LTM) encoding and retrieval (Scoville and Milner, 1957; Penfield and Milner, 1958), but are not required for WM maintenance over a short time interval (Cave and Squire, 1992). Brain imaging studies, on the other hand, have revealed high activity in the frontal lobes during WM processes (for review see Baddeley, 2003). Therefore, according to the classical view, the LTM encoding relies on structures in the MTL including the hippocampus and WM processes rely on the prefrontal and parietal cortices.

In contrast to this simple dichotomy, however, recent studies have shown that some WM tasks, e.g. those involving novel stimuli, also activate MTL structures (Axmacher et al., 2007; Ranganath and D'Esposito, 2005; Ranganath et al., 2005; Schon et al., 2004; Stern et al., 2001). In this study the question of whether the maintenance of several items in WM, which activates the MTL, influences the encoding of items into LTM was addressed. It is demonstrated that a simultaneous WM/LTM task results in an interference, which affects memory processing capacities in the MTL and leads to a decrease in the LTM performance when accompanied by a high WM load. Furthermore the parahippocampal cortex (PHC) is revealed as a locus of a memory processing interference between WM and LTM for the first time.

1.4.2 Chapter four – Conflict processing

The human brain encounters a continuous flow of information from our senses, of which it can process only a limited number. As a result, most information which enters sensory memory is lost before it can be further processed in short-term memory. The process of focussing which underlies this is what is called “attention”.

Successful information processing requires focusing attention on a certain stimulus property and suppressing irrelevant information. An important paradigm for investigating attentional top-down control in case of interfering stimulus properties is J. R. Stroop’s interference task (Stroop, 1935). In the control condition the subject is asked to read color words printed in black ink, establishing a response set to reading color words. In the interference condition, the subject is given color words which are printed in an incongruent ink color (like the word “green” printed in red). The subject is asked to report the ink color, and therefore has to suppress the tendency to read the color word. Subjects averaged 74% longer to name ink colors of incongruent words. The original paper has been one of the most cited papers in the history of experimental psychology. One of many theories trying to explain the reaction time increase claims, that interference effects may result from the greater automaticity of reading compared with color naming (MacLeod and Dunbar 1988). The naming of a color in the presence of printed words will fully load an attentional system with limited capacity, that assists in performance of the less automatic color-naming task.

Since the first description of the standard color Stroop task, its implementation underwent numerous variations and adjustments. One instructive example of how the original idea was adapted for imaging technology is the counting Stroop task, which was designed as an functional magnetic resonance imaging (fMRI) study, because it allowed online response time measurements without requiring speech (Bush et al., 1998) The subject was asked to report the number of words on a screen by pressing a button. During control blocks, the words were names of common animals, while during conflict blocks, the stimuli consisted of the number words, which led to stimulus interference.

Even though numerous different versions of Stroop tasks were developed over the past decades, they were all restricted to the modality of the visual sense (for review see MacLeod, 1991).

The present study aimed to investigate the neural correlates of a newly developed auditory Stroop task. Using an event-related fMRI design, sound files in a tone-pitch interference task were presented, that required subjects to focus on one stimulus property (pitch or meaning of a spoken word) while ignoring the other one. In different blocks, participants were asked to decide if either the word presented in the sound file was “high” or “low” (semantic block), or the tone pitch was “high” or “low” (phonetic block). Stimuli were classified into three categories: (a) congruent: word and tone-pitch were the same. (b) incongruent: word and tone pitch were different. (c) neutral: the word “good” was used.

Changes in the sensory modality result in alterations of the network activity, thereby activating different regions of the ACC. In contrast to visual Stroop tasks a very posterior part of the anterior cingulate cortex (ACC) was found activated in incongruent phonetic trials (as compared to the incongruent semantic trials), together with common regions such as the pre-supplementary motor area (preSMA) and the dorsolateral prefrontal cortex (DLPFC), areas associated with attentional control. In addition, the integration of these regions into a conflict processing network using functional connectivity was shown.

Furthermore the trial repetition effects and behavioral adjustments after conflict were analyzed, supporting the validity of the conflict-theory. The work demonstrates how classical psychological findings in combination with modern functional imaging can make important contributions to medical research and even clinical diagnostics, where the Stroop Color-Word task has been used both as a screening instrument and as part of a large repertoire of tests for the screening and detection of frontal/executive brain dysfunction.

1.4.3 Chapter five – Consciousness

Scientists and philosophers continuously try to understand what is meant by the word "consciousness". In the last 15 years, more than 15,000 articles have been published on that topic, basically trying to deal with the same fundamental questions (Gazzaniga et al. 2002). How can electrical signals of the physical brain cells produce non-physical sensations such as pain, dreams or the emotion of savouring the colorness of a flower? This is especially interesting, since from a strictly objective perspective, no such phenomenona as colors exist in the world. What accounts for the conscious and the inherently private state of being oneself?

As far as understood the variety of our conscious life is reflected, for instance, in the variable rates of neuron firings in different neuronal architectures. Every phenomenal, subjective state is therefore associated to a so called neuronal correlate of consciousness.

In the context of a theoretical excursus chapter 5 shows within the broad field of consciousness research, how new methods in recoding and analyzing electroencephalography (EEG) data can lead to a different understanding of the origination of different states of consciousness.

The starting point of consideration were recent findings revealing unusual and remarkable alterations in the EEG in meditation experts. Today meditation is considered to be a valuable source deepening our understanding of the neural correlates of consciousness, since meditation experts are usually trained for decades to reach altered states of consciousness. Meditation practice, however, is difficult to access due to its countless forms originating from the complexity of cultures it aims to serve. This makes a suitable categorization for scientific use quite difficult. It was suggested that different forms of meditation have similar steps of development, which should be related to similar neurophysiological correlates. Some electrophysiological alterations can be observed on the beginner/student level, which are closely related to non-meditative processes. Others appear to correspond to an advanced/expert level, and seem to be unique for meditation related states of consciousness. Meditation is one possibility of specializing brain/mind functions within the confines of the brain's neural plasticity. This plasticity is likely supported by certain meditation related EEG patterns, for instance, synchronized gamma oscillations. While it has been formerly postulated that meditation comprises mainly passive relaxation states, recent EEG findings suggest that meditation is associated with active states involving cognitive restructuring and learning.

Chapter 2

Methods

Data acquisition – Experimental procedures – fMRI analysis

"It is common sense to take a method and try it. If it fails, admit it frankly and try another. But above all, try something."

Franklin D. Roosevelt

2.1 fMRI – basic principle

Functional magnetic resonance imaging (fMRI) is a technique for measuring brain activity. It works by detecting the changes in blood oxygenation and flow that occur in response to neural activity. The magnetic field of a scanner affects the spins of nuclei of atoms. Normally atomic nuclei are randomly oriented but under the influence of a magnetic field the spins become aligned with the direction of the magnetic field. The stronger the field the greater the degree of alignment. A typical research scanner (such as the Siemens Magnetom Avanto) has a field strength of 1.5 teslas, which is about 30,000 times greater than the Earth's field. When pointing in the same direction, high-frequency pulses are used to change the spins and thereby the energy state of the hydrogen atoms. When the radio signal is turned off, the hydrogen atoms will, after a period of time, return to their original energy state. The excitation energy, which they had gained, will be released in the form of radio waves, which are registred by the detection coils of the MRI machine.

Oxygen is delivered to neurons by haemoglobin in capillary red blood cells. When neuronal activity increases, it results in increased demand for oxygen and the local response is an increase in blood flow to regions of increased neural activity. Haemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated, which results in a change of the magnetic susceptibility of blood. This again leads to a slight change in the local magnetic field and hence in the MR signal intensity. Since blood oxygenation varies according to the levels of neural activity these differences can be used to detect brain activity. This form of MRI is known as blood oxygenation level dependent (BOLD) imaging.

And important aspect of measuring the BOLD response is the effect, that blood oxygenation actually increases following neural activation. The blood flow peaks after around six seconds and then falls back to baseline, often accompanied by a "post-stimulus undershoot". This means, that although responses to stimuli presented as close together as one or two seconds can theoretically be distinguished from one another (using a method known as event-related fMRI), the full time course of a BOLD response to a briefly presented stimulus lasts about 12 seconds for the positive response.

Furthermore the high-frequency pulses of the magnetic stimulation fields generate detailed images of the brain by detecting differences in the distributions of molecules throughout the brain. In a structural image, the distribution of water in different tissues of the brain is detected. For example, the amount of water in blood vessels, and in the bone of the skull is different. This difference allows MRI to generate a contrast image. In the same way that blood and bone have different water concentrations, all types of tissue in the brain have different concentrations of substances that allow the production of images of their distribution. These discrete differences in concentration throughout the brain allow the fine anatomy of the brain to be resolved.

2.2 MRI Data acquisition (both studies)

Sixteen axial slices were collected at 1.5T (Avanto, Siemens, Erlangen, Germany). 1560 T2*-weighted, gradient echo (EPI) scans (slice thickness: 3mm; interslice gap: 0.3 mm; matrix size: 64x64; field of view: 192 mm; echo time: 40 ms; repetition time: 3200 ms) were collected. Thereafter, a sagittal T1-weighted MPRAGE sequence for each subject for anatomical localization (number of slices: 160; slice thickness: 1 mm; inter-slice gap: 0.5 mm; matrix size: 256x256; field of view: 256 mm; echo time: 3.93 ms; repetition time: 1660 ms) was acquired.

2.2 Memory study

2.2.1 Participants

A total of 30 healthy subjects (16 women; age 19-35, mean age ± s.d.: 25.0 ± 3.8 years; handedness: 27 right, 3 left) participated in the study. They were recruited from the University of Bonn as well as via newspaper. The study was approved by the local medical ethics committee, and all subjects provided written informed consent.

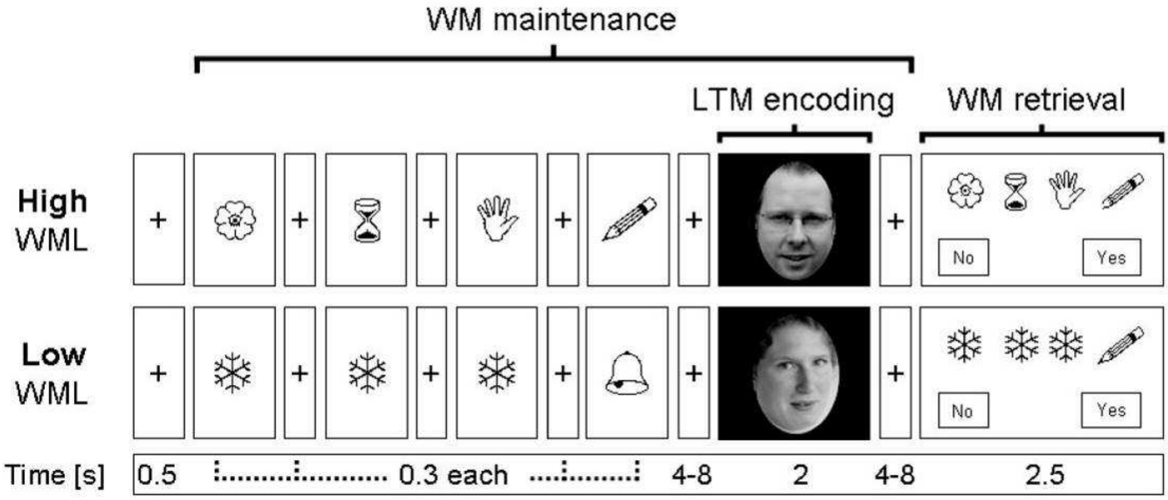


Fig. 2.1: Overview of the fMRI encoding paradigm.

2.2.2 Experimental procedures

In a newly developed experimental design, the working memory (WM) load during the encoding of black and white photographs of unknown male or female faces into long-term memory (LTM) was manipulated. An overview of the paradigm is depicted in figure 2.1. To create a sufficient WM load, a version of the Sternberg item recognition test (Sternberg, 1975) was used, in which at the beginning of each trial 4 abstract symbols were consecutively presented. At the end of each trial, subjects had to decide whether a sequence of symbols matched the one presented before. WM load was either high (with four different symbols) or low (three equal symbols plus one different, i.e. visual features for both conditions were similar). Both tasks had to produce both a sufficient memory load and a demanding task difficulty (e.g. Eng et al. 2005), without overstraining the subjects abilities, especially considering the high individual differences in WM capacities and interference susceptibility (Mecklinger et al., 2003). Since recent studies suggested a stronger MTL involvement in WM for complex and trial-unique stimuli, the symbols were generated using the Windows font “Wingdings” (Microsoft Office 2003, Microsoft Corp., Seattle, WA) to create trial-unique sequences of stimuli rather than using simple, highly familiar stimuli, such as letters or numbers. To test the influence of WM load on LTM encoding, the subjects simultaneously memorized one black and white photograph of an unknown male or female face (total of 150 male and 150 female faces) in each trial. The picture was presented during maintenance of WM items. The faces were previously rated by a large independent group of subjects as neutral with respect to facial expression. To guarantee attentive processing of faces, subjects were asked to perform a simple sex-discrimination task during the encoding. Subjects were instructed that both the Sternberg and the sex-discrimination task are equally important. Only trials with correct responses in both the Sternberg and the sex discrimination task were taken into account for the fMRI analyses.

2.2.3 Behavioral exclusion criteria

The concept of the experiment assumes that both WM processing and LTM encoding are accomplished with some amount of attention. If attention of the subjects was directed mainly towards only one of the tasks, this would result in an increased number of errors in the other task and hence to a biased outcome. Therefore subjects were only included in the analysis if the behavioral performance for three criteria was within a range of two standard deviations around the average performance.

The first criterion was the number of errors in the Sternberg task in the low WM load condition. Since the subjects had only to maintain a single symbol in these trials, this criterion provides a good control for the attention in this task. The second criterion was the number of errors in the sex-discrimination task. An exceptional number of wrong discriminations in one gender over the other was used as a third criterion to exclude a possible attentional bias towards a certain gender. In total, 7 out of 30 subjects did not meet the behavioral inclusion criteria.

2.2.4 Encoding session (during scanning)

Subjects completed a total of 200 trials while they were being scanned in fMRI. These trials were subdivided into 4 runs of 50 trials each to ascertain a stable level of attention during the entire length of the paradigm. Trials were administered in a randomized, counterbalanced order across subjects. Subjects were allowed to leave the scanner between the sessions. Trials began with a fixation cross (500 ms), followed by 4 sequentially presented WM stimuli (300 ms), each separated by a fixation cross for 300 ms. Stimulus presentation in the WM task was followed by a pause of 4000-8000 ms length during which a fixation cross was shown, before the LTM face stimulus was presented for 2000 ms. After another pause of 4000-8000 ms, the WM retrieval cue was presented for 2500 ms. Trials were separated by an inter-trial interval of 500 ms duration. Stimuli were presented using Presentation® software (Version 0.71; Neurobehavioral Systems, Inc.; Albany, California) via MRI–compatible liquid-crystal display (LCD) goggles, and responses obtained through a fiber optic magnetic resonance–compatible control pad.

2.2.5 Test session (without fMRI)

Participants were given a surprise recognition memory test 15 minutes after the scanning session to assess LTM of all 200 faces previously shown, plus 100 novel faces. During recognition, participants were shown each face individually on a computer screen and were instructed to judge on a scale from one to four whether each face was presented during the scanning session (one: sure old; two: unsure old; three: unsure new; four: sure new).

2.2.6 fMRI analysis

Analysis was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.63, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) using standard procedures. The following pre-statistics processing was applied: motion correction using MCFLIRT

(Motion Correction using FMRIB's Linear Image Registration Tool; Jenkinson, 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Brain Extraction Tool; Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 6mm; mean-based intensity normalisation of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model; Woolrich, 2001). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$ (Worsley 1992). Registration to high resolution and/or standard images was carried out using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson, 2002). Pre-processed data were fitted by the convolution of multiple regressors with a canonical hemodynamic response function to obtain parameter estimates for each condition covariate. “Sure” and “unsure” events were combined in all GLM analyses to increase statistical power.

The following set of regressors was used: 2 regressors of 2500 ms length at the onset of the Sternberg-task (high and low WM load); 2 regressors of 1000 ms length at the onset of the face stimuli (high and low WM load); 2 regressors of 2500 ms length at the retrieval of the Sternberg-task (high and low WM load), and 1 regressor of 16 s length for the collapsed encoding (WM and LTM) and retrieval phase (WM) in trials with incorrect responses. The regressors for WM maintenance were defined at the beginning of the maintenance period in order to avoid collinearity with the LTM regressors. Baseline was defined by all periods that were not explicitly modeled. Then, the following contrasts were defined: Three for the working memory maintenance: one contrast for high WM load greater than low WM load, respectively both loads compared to baseline. Correspondingly, another three contrasts were used for the WM retrieval, and three contrasts for encoding of faces into LTM. All activations are overlaid onto the average T1-weighted anatomical scans of all subjects (n = 23). Peri-stimulus time-courses were extracted as trial-averaged responses scaled to a percentage signal change value relative to trial onset.

For the regions of interest (hippocampus and PHC) a sphere with 4mm diameter centered around the peak voxel was used. Time-courses were additionally smoothed by using a moving average filter with a width of 2500 ms (one TR). Error bars denote standard error of the mean (s.e.m.) across participants.

P-values in the ANOVAs were Huynh-Feldt corrected for inhomogeneities of covariance when necessary (Huynh and Feldt, 1976). Images are displayed in neurological convention, with left side corresponding to left hemisphere.

Functional connectivity for the PHC was calculated by using the activity from the left parahippocampal region (Fig. 4A) as regressor. The analysis was conducted using the "psychophysiological interaction" method (Friston et al., 1997). The method relies on correlations in the BOLD time series data, and makes no assumptions about the nature of the neural activity that may have contributed to the BOLD signal. The entire time-course of activity of each individual subject was extracted and multiplied with a condition vector that was ones for 5 TRs following each trial type, and zeros otherwise. These resulting vectors were then used as covariates in a separate regression. Analyses were performed for each subject individually and were subsequently entered into a group-level analysis.

2.3 Conflict study

2.3.1 Participants

A total of 29 healthy subjects (14 women; age 18-34, mean age ± s.d.: 27.0 ± 7.4 years; handedness: 22 right, 7 left) participated in the study. They were recruited from the University of Bonn as well as via newspaper. The study was approved by the local medical ethics committee, and all subjects provided written informed consent.

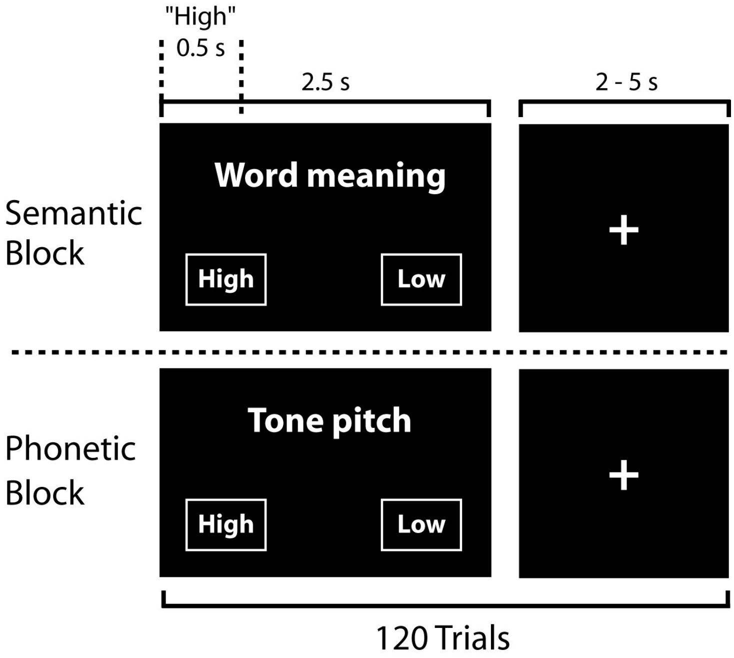


Fig. 2.2: Overview of the paradigm.

2.3.2 Experimental procedures

An auditory version of the Stroop task (Stroop, 1935) was used, in which subjects were presented the words “High” and “Low” in either a high or low tone pitch. In each of two separate parts of the paradigm, the subjects performed first a semantic block, were they indicated by a button press whether the word “high” or “low” was presented, regardless of tone pitch. In the second “phonetic” block, subjects were asked to decide if the word was presented in a high or low tone pitch, regardless of word meaning. As an additional control condition, the word “good” was used, which was presented in a either high or low tone pitch as well. Only trials with correct responses were taken into account for the fMRI analyses. An overview of the paradigm is depicted in figure 2.2.

The sound files were spoken and digitalized by one of the experimenters, and transposed to a high or low tone pitch, respectively aligned in frequency using the Entropic Timescale Modification (ETSM^{TM}) as included in the Goldwave audio editing software (http://www.goldwave.com/).

2.3.3 Test session

Subjects completed a total of 480 trials while they were being scanned in fMRI. Prior to the start of the experiment, patients went through at least 10 practice trials, or until they indicated that they understood the task. These trials were subdivided into 2 runs of 250 trials each to ascertain a stable level of attention during the entire length of the paradigm. Subjects were allowed to leave the scanner between the sessions. Every block contained all three sound files (“high”, “low” and “good”) in either a high or low tone pitch. Each of these six conditions was presented in 20 trials. The words “word meaning”, respectively “tone pitch” were presented on the screen in all trials for clarity’s sake. Words were presented for 500 ms. The subjects were asked to answer as fast as possible during the following 2000 ms. All trials with response delays greater than 2500 ms were discarded. Trials were administered in a randomized, counterbalanced order across subjects. The trial was followed by a pause of 2000-5000 ms length, during which a fixation cross was shown. Stimuli were presented using Presentation® software (Version 0.71; Neurobehavioral Systems, Inc.; Albany, California) via MRI–compatible liquid-crystal display (LCD) goggles, and responses obtained through a fiber optic magnetic resonance–compatible control pad.

2.3.4 fMRI analysis

Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.63, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) using standard procedures. The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith 2002); spatial smoothing using a Gaussian kernel of FWHM 6mm; mean-based intensity normalisation of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Time-series statistical analysis was carried out using FILM (Woolrich 2001). Registration to high resolution and/or standard images was carried out using FLIRT (Jenkinson 2002). Pre-processed data were fitted by the convolution of multiple regressors with a canonical hemodynamic response function to obtain parameter estimates for each condition covariate. The fMRI-analysis used a set of seven regressors, each with a length of 1000 ms. Four regressors were used for the congruent ("high/high" and "low/low"), respectively incongruent ("high/low" and "low/high") trials in the semantic and phonetic blocks of the paradigm (i.e.: (1) congruent semantic; (2) incongruent semantic; (3) congruent phonetic; (4) incongruent phonetic). Two regressors were used for the control-condition ("good") in the semantic and phonetic block, and one regressor for the trials with incorrect responses. The fMRI-analysis was carried out a second time with the same set of regressors, with the only exception that each repetition of a trial in the same category (congruent – congruent or incongruent – incongruent) was modeled within the same regressor as the incorrect trials. A third analysis was carried out, were instead of excluding repeating trials for every subject, the same amount of randomly chosen trials was excluded from the Stroop analysis, by moving them to the regressor for incorrect trials.

The comparison of activations was carried out by extracting activation values from the "incongruent phonetic > incongruent semantic" contrast for all three analysis. A mask containing the activated regions for the first analysis on significance level was used ($Z = 3.1$; $p = 0.001$) and a mean over the activation values for all voxels and subjects was build.

P-values in the ANOVAs were Huynh-Feldt corrected for inhomogenities of covariance when necessary (Huynh and Feldt, 1976). Images are displayed in neurological convention, with left side corresponding to left hemisphere. Effects are significant at $p < 0.001$ and a cluster size of ten or more contiguous voxels. Mean parameter estimates for the different conditions are shown for the contrasts (ordinate in arbitrary units). Error bars represent s.e.m..

The locations of 112 ACC activations were added to the contrast in figure 3A-2 using coordinates from a review by Barch and colleagues (Barch et al., 2001). The activations were collected from tasks falling under the categories of response inhibition, underdetermined responding, and commission of errors (e.g. Stroop, Go/No-Go, Flanker-tasks). The stereotactic coordinates referring to the Talairach coordinate system were transformed to MNI coordinates using the tal2mni.m script available from M. Brett (http://eeg.sourceforge.net/doc_m2html/bioelectromagnetism/tal2mni.html). The result is shown in figure 3B. The corresponding coordinates are listed in table 3. For greater clarity the perpendicular line on the intersection of the bicommissural line (AC-PC) through the anterior commissure as an additional orientation border was used.

Functional connectivity with the ACC was calculated by using activity within the functional region of interest (ROI) in the posterior ACC region (Fig. 2A-2) resulting from the “Phonetic > Semantic”-contrast, thereby identifying brain regions showing significant covariation or functional connectivity with this seed location. A sphere with 6 mm diameter centered on the peak voxel as a seed region was used. The functional connectivity analysis was conducted using the “psychophysiological interaction” method (Friston et al., 1997). The method relies on correlations in the BOLD time series data, and makes no assumptions about the nature of the neural activity that may have contributed to the BOLD signal. The entire time-course of activity of each individual subject was extracted and multiplied with a condition vector that was ones for 5 TRs following each trial type, and zeros otherwise. These resulting vectors were then used as covariates in a separate regression. Analyses were performed for each subject individually and were subsequently entered into a group-level analysis.

Chapter 3

Memory

Interference of working memory load with long-term memory formation

"The difference between false memories and true ones is the same as for jewels: It is always the false ones that look the most real, the most brilliant."

Salvador Dalí

“God gave us memory so that we might have roses in December.”

James Matthew Barrie
(Scottish novelist and dramatist)

3.1 Introduction

Life in modern societies requires the simultaneous processing of an increasing amount of information in decreasing time (Rosa, 2003). Multi-task processing is especially difficult if the simultaneously performed actions are supported by similar processes, each with limited capacity. The ability to maintain and manipulate information over a short time interval is termed working memory (WM) and has been distinguished from the encoding of information into long-term memory (LTM) (Baddeley, 1992). Traditionally, the neural mechanisms underlying WM and LTM have been considered separate: While LTM crucially relies on structures in the medial temporal lobe (MTL) such as the hippocampus (Scoville and Milner, 1957; Penfield and Milner, 1958), these regions have been considered of only minor importance for WM maintenance (Scoville and Milner, 1957). In addition, studies using fMRI found WM to be localized predominantly in extra-medial temporal regions such as the prefrontal and parietal cortices (Cohen et al., 1997; Owen et al., 1998; Owen et al., 1998). Characteristic for these studies was the use of stimuli including highly familiar information, such as numbers, letters or words.

In contrast to the ”classical” view, recent fMRI and intracranial EEG studies showed that structures in the medial temporal lobe (MTL) are involved in WM processes if trial-unique novel stimuli are used (Axmacher et al., 2007; Ranganath and D'Esposito, 2005; Ranganath et al., 2005; Schon et al., 2004; Stern et al., 2001). These findings provide growing evidence that the criterion whether the MTL is involved in a specific memory task lies beyond the classical distinction between WM and LTM. Alternative theories suggest that the MTL is recruited whenever relations among items are encoded (Cohen and Eichenbaum, 1993; Eichenbaum, 2004; Henke et al., 1999), sequences of items are processed (Eichenbaum et al., 1999; Schendan, et al., 2003; Jensen and Lisman et al., 2005; Kumaran and Maguire, 2006), or when novel stimuli are encoded (Hasselmo and Stern, 2006). Importantly, the endurance of memory contents is only a secondary criterion for the involvement of the MTL. Considering this wide field of functions for the MTL, it remains unclear how information in the MTL is transferred from one memory system to the other, and how structures involved in both memory systems interact. Previous findings from Schon et al. (Schon et al., 2004) and Ranganath et al. (Ranganath and D'Esposito, 2005; Ranganath et al., 2005) indicate that WM maintenance facilitates simultaneous LTM encoding of items maintained in WM, suggesting that partly the same neural mechanism is underlying WM and LTM processes. Put differently, these results emphasize that WM processes play a role in successful LTM encoding as well. This hypothesis can be directly tested in a dual-task paradigm involving simultaneous WM and LTM processing.

In this study, the question was addressed of how LTM encoding is affected by a simultaneously performed WM task with a high information load. It was predicted that a WM task with trial-unique stimuli, for which the subjects had no prior LTM representation, would recruit MTL structures and thereby suppress simultaneous LTM encoding. Finally, a functional connectivity analysis using the “psychophysiological interaction” approach (Friston et al., 1997) was performed, to identify networks involved in WM versus LTM processing.

3.2 Results

3.2.1 Behavioral results

In the Sternberg task correct response rate was 95 % (9 %, s.e.m.) in the low WM load condition and 80 % (10 %, s.e.m.) in the high WM load condition ($t_{22} = 4.991$, $p < 0.001$; two-tailed t-test). Reaction times were significantly higher for the high WM load condition (mean: 1402 ms, s.e.m.: 24 ms) as compared to the low load condition (mean: 843 ms, s.e.m.: 26 ms, $t_{22} = 20.44$, $p < 0.001$; two-tailed t-test).

As predicted by our hypothesis, maintenance of a high WM load caused a decrease in LTM performance: LTM recognition of faces presented during the low WM load condition was significantly better as compared to LTM recognition during the high WM load condition (Fig. 3.1; $p < 0.005$, $t_{22} = -3.196$; two-tailed t-test).

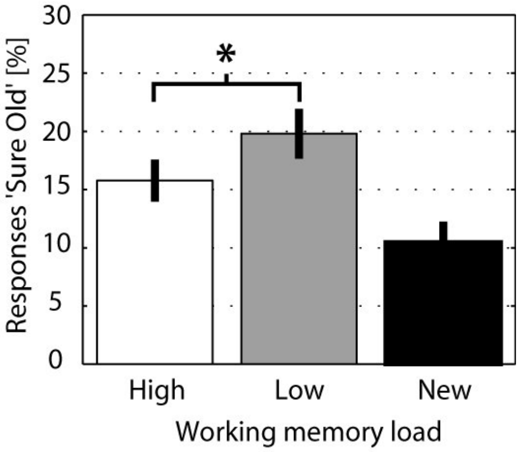


Fig. 3.1: Behavioral results. Memory effect for the picture stimuli. The memory performance for items encoded during the low WM load condition is significantly higher than for items encoded during high WM load condition ($p < 0.01$; $t_{22} = 4.342$ two-tailed t-test).

3.2.2 fMRI - working memory

Firstly, it was investigated which brain regions were recruited due to increased memory load in the WM task. The results for the contrast “high WM load > low WM load” are shown in the figure 3.2, and table 1 provides an overview of all significantly activated regions for this contrast. The “high WM load > low WM load” contrast revealed bilateral activations in the superior parietal and dorso-/ventro-lateral prefrontal cortices, as well as in the thalamus and caudate nucleus. The network was focused around a strong medial frontal activation, involving the dorsal anterior cingulate cortex. All of these regions are known to be involved in the maintenance of items in WM.

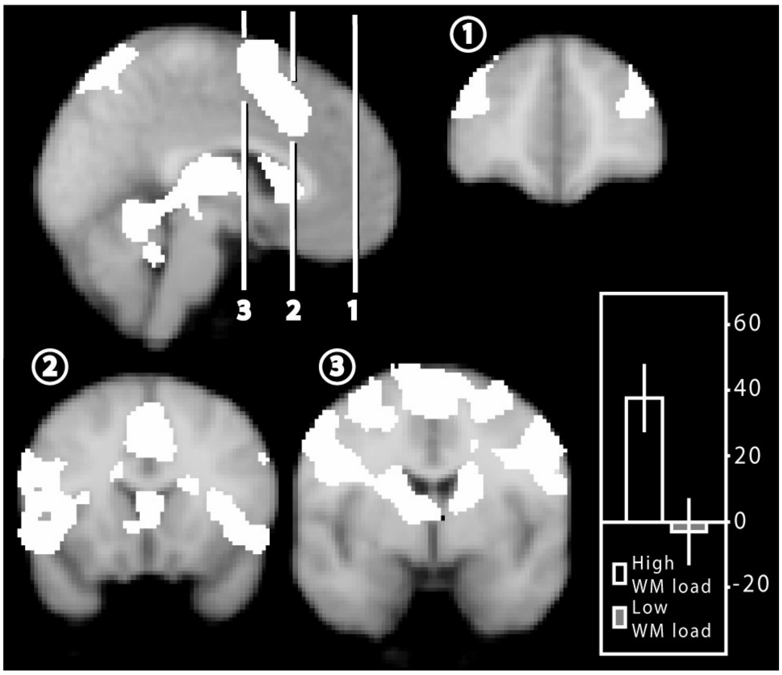


Fig. 3.2: Working memory networks. Regions with increased activation in the high WM load condition as compared to the low WM load condition during presentation of items in the Sternberg task. Mean parameter estimates for the different memory loads are shown for the contrasts (ordinate in arbitrary units, with a negative value representing a value lower than the global mean of the parameter estimates). Error bars represent s.e.m. Effects are significant at $p < 0.05$, corrected for multiple comparisons; cluster size of ten or more contigous voxels.

According to our hypothesis, the maintenance of trial-unique sequences of abstract symbols should also lead to a recruitment of regions in the MTL. However, the contrast between the two WM load conditions did not show any MTL activation. To explore this question in further detail, the processing of items for both WM load conditions against baseline was analyzed. All significantly activated regions are listed in table 1. Indeed, peak activations for both high and low WM load against baseline bilaterally in the hippocampus were observed (Fig. 3.3 A,B).

To investigate whether the hippocampus may have exhibited transient load-dependent effects, time courses of WM related activation in bilateral hippocampal regions of interest were extracted (Fig. 3, C). A two-way ANOVA with “time” (8 time points) and “load” as repeated measures revealed main effects of each factor (“time”: $F_{7,147} = 9.67$, $p < 0.001$, $\varepsilon = 0.324$; “load”: $F_{1,22} = 4.57$, $p = 0.05$) and a significant “load” × “time” interaction ($F_{1,22} = 6.23$; $p = 0.004$; $\varepsilon = 0.29$). The time-courses of activation show that the BOLD response for the high WM load is significantly larger than for the low WM load starting around the peak time points (5-8 s, for each time point: $t_{21} > 2.5$, $p < 0.05$; two-tailed t-test).

3.2.3 fMRI - long-term memory

Because MTL activations for LTM encoding in both WM load conditions were expected, firstly activation contrasts during presentation of faces in the high and low load condition against baseline were build (Fig. 3.3, D,E). Bilateral peak activations within the hippocampus were observed (Fig. 3.3, A,B; the results are presented at a Z score threshold of 5). The time courses of activations within a sphere with 4 mm diameter around the peak voxels (left and right voxel collapsed) are shown in figure 3.3 F for the high and low WM load condition. The time courses demonstrate an inverse effect for LTM encoding of face stimuli, as compared to WM maintenance. While hippocampal activation during WM was clearly enhanced in the high load condition, hippocampal activation during LTM encoding was significantly larger for the low WM condition. A three-way ANOVA with “load”, “subsequent memory” and “time” as repeated measures did reveal a main effect of "load” ($F_{1,22} = 4.852$; $p = 0.04$), but no main effect of “subsequent memory” ($F_{1,22} = 2.010$; $p = 0.174$) and no “load”/”time” × “subsequent memory” interaction ($F_{1,22} = 0.535$; $p = 0.474$). Again, load effects were significant around the peak time points (6-7s, for each time point: $t_{22} > 2.1$; $p < 0.05$; two-tailed t-test between load conditions, collapsed across subsequent memory).

Because of the lack of a significant subsequent memory effect within the hippocampus, it was hypothesized, that LTM encoding in the low and high WM load condition may rely on activations in other mediotemporal brain regions. Regions were preselected by computing the contrast between the two WM load conditions to reveal regions exhibiting also a WM load effect. While the “high WM load > low WM load” contrast yielded no significant activation, the reverse contrast (“low WM load > high WM load”) indeed revealed, besides bilateral activations in the right superior parietal cortex and the orbitofrontal cortex, an activation in the left parahippocampal cortex (PHC) (Fig. 3.4 A; all significantly activated regions of this figure are listed in table 1).

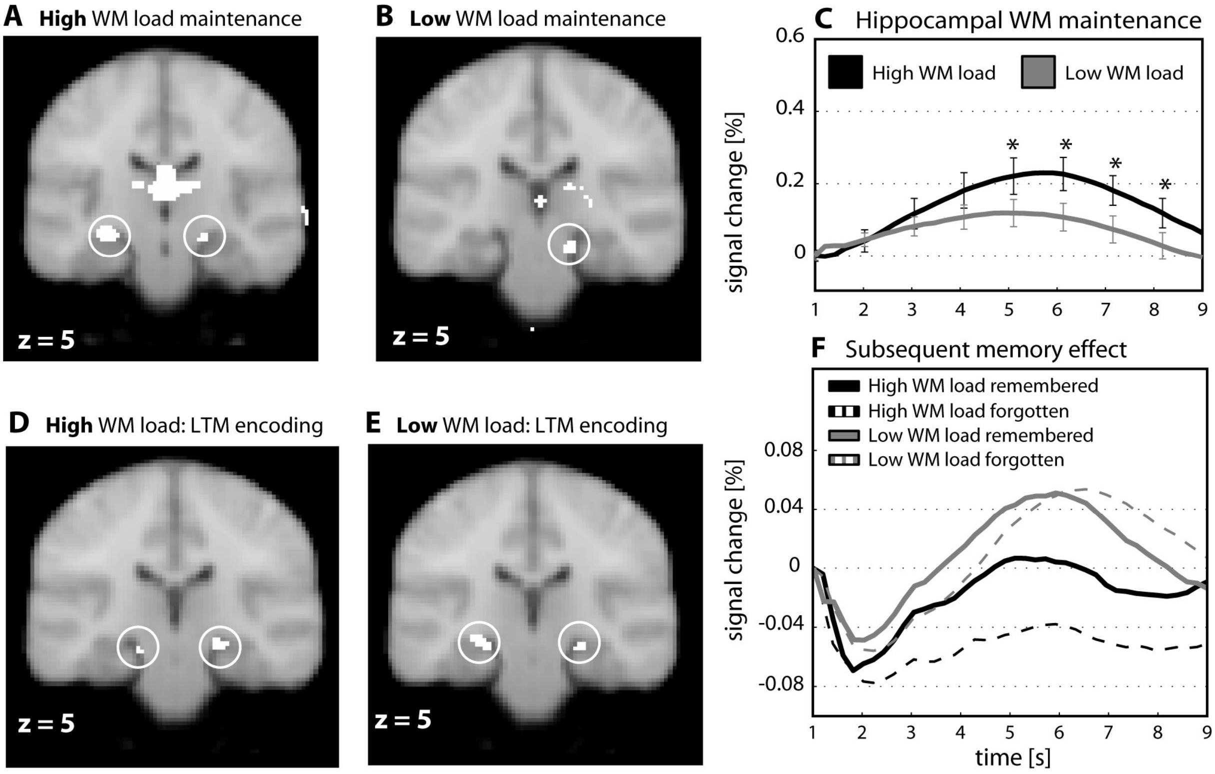


Fig. 3.3: Working memory maintenance of multiple items interferes with hippocampal long-term memory encoding. Regions of sigificant activation during WM and LTM encoding relative to fixation baseline. A, B, D, E “high WM load: WM maintenance with high load; High WM load (LTM): encoding of face stimuli with high WM load” show peak activations in the hippocampus (Z score of 5 for graphical depiction). (C) shows time courses of hippocampal activity in the high and low WM load condition. Graphs depict the time course of activation during encoding of WM. (F) shows time courses of hippocampal activity during LTM encoding for high and low WM load trials. Graphs depict the time course of activation during encoding of the faces and are further subcategorized due to subsequent memory performance. Asterisks in (C) denote time points in which significant differences were observed between high and low WM load trials ($p < 0.05$; two-tailed t-test).

To investigate subsequent memory effects separately for the two WM load conditions, time courses from the PHC activation were extracted. A three-way ANOVA with “load”, “subsequent memory” and “time” as repeated measures revealed a significant main effect for “subsequent memory” ($F_{1,22} = 4.186$; $p = 0.05$), and a trend for a “load” × “subsequent memory” interaction ($F_{1,22} = 3.29$; $p = 0.08$). Since WM load dependent subsequent memory was of special interest, memory effects separately for the low and high load condition were further analysed. A subsequent memory effect for faces encoded during high WM load (two-way ANOVA, “subsequent memory”, $F_{1,22} = 5.86$; $p = 0.02$, Fig. 3.4, B) was found. Statistical tests for the low WM load were not significant. To investigate which other brain regions support LTM formation, ANOVAs on the time courses derived from the neocortical clusters of activation resulting from the “low WM load > high WM load” contrast were calculated.

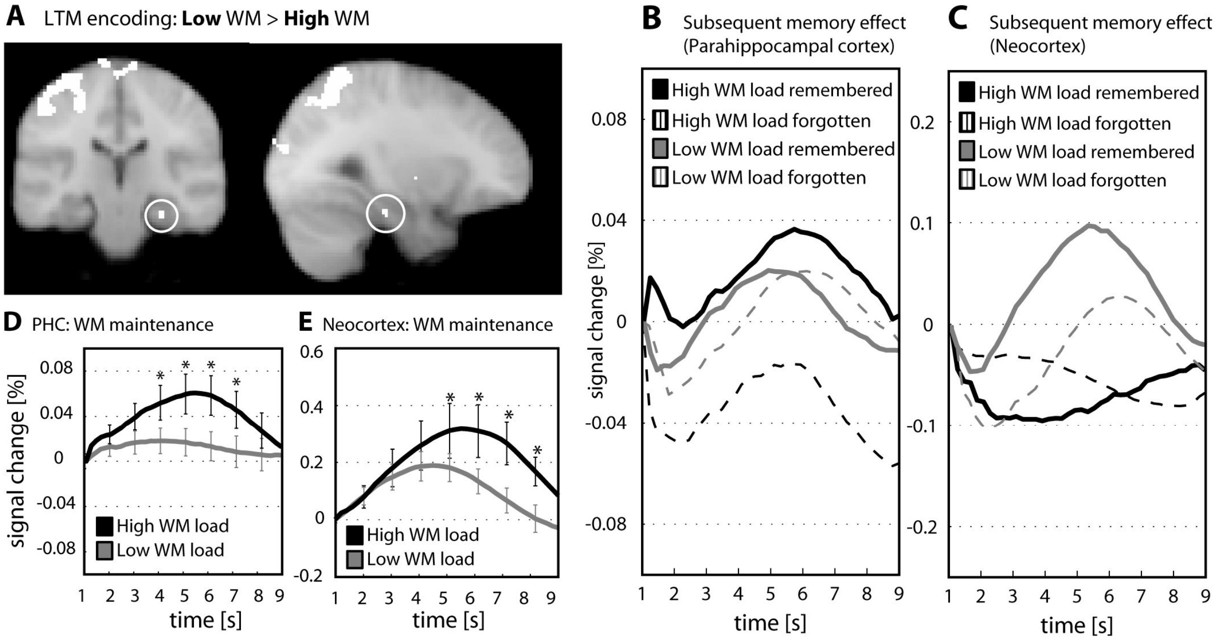
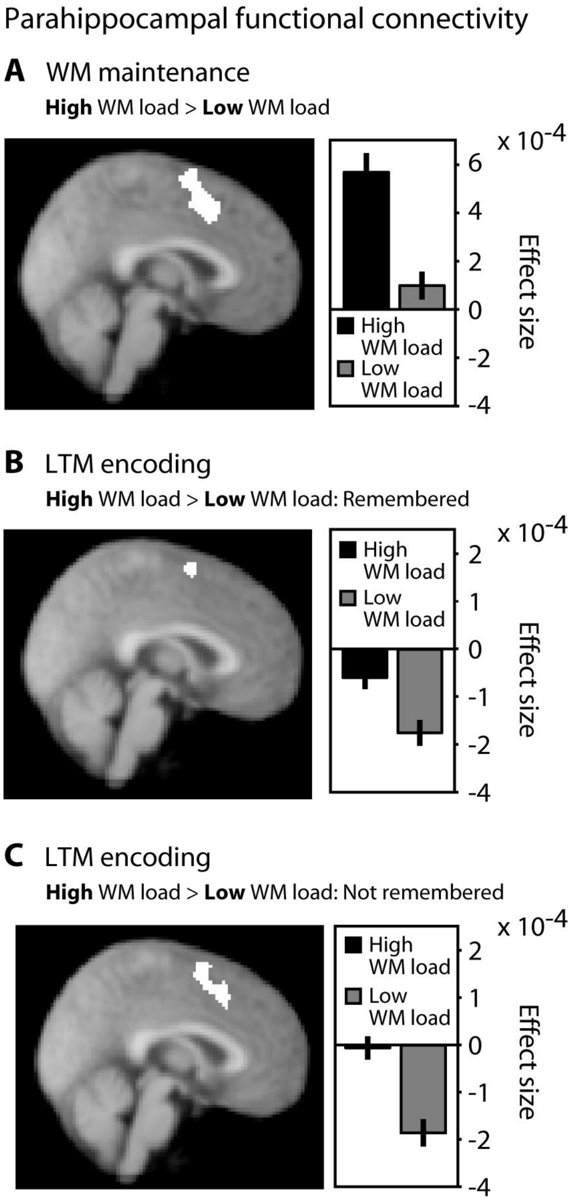


Fig. 3.4: Parahippocampal long-term memory encoding. The contrast (A) shows fMRI regions of significant activation during LTM encoding for “low WM load > WM load”, including the parahippocampal cortex (circled). Effects are significant at $p < 0.001$, uncorrected; cluster size of ten or more contignous voxels. Time courses of parahippocampal activity during high and low LTM encoding are shown in (B), the time courses for the cortical activity in the same contrast are shown in C. Both graphs depict the time course of activation during encoding of the faces and are further subdivided dependent on subsequent memory performance. The parahippocampal activity during high and low WM load encoding is shown in (D), the corresponding cortical activity in (E). Asterisks denote time points in which significant differences were observed between high and low WM load trials ($p < 0.05$; two-tailed t-test).

While there were no significant effects when each cluster was analyzed differently, there was a significant “subsequent memory” × “time” interaction ($F_{7,147} = 3.460$; $p = 0.04$; $\varepsilon = 0.31$) when it was collapsed over all neocortical clusters (Fig. 3.4 C). This interaction probably arises from the increase of the time-courses for the low WM load condition, which differ significantly for the memory condition, while at the same time the time-courses for the high WM load show a deactivation after stimulus onset.



Parahippocampal functional connectivity

A WM maintenance

High WM load > **Low** WM load

B LTM encoding

High WM load > **Low** WM load: Remembered

C LTM encoding

High WM load > **Low** WM load: Not remembered

Fig. 3.5: Group level differences in parahippocampal functional connectivity. Regions showing significantly greater functional connectivity with the PHC in the high WM load condition as compared to the low WM load condition in the medial frontal cortex for the onset of the WM load (A) and the encoding of items into LTM. The latter were further subdivided as a function of subsequent recognition (B,C). Histogram ordinate is in arbitrary units, with a negative value representing a value lower than the global mean of the parameter of interest estimates. Error bars represent s.e.m. Effects are significant at $p < 0.05$, corrected for multiple comparisons; cluster size of ten or more contignous voxels.

These results suggest that LTM encoding is supported by neural processes in multiple neocortical regions during low WM load, but crucially depends on the PHC during high WM load, i.e. when the MTL is recruited by simultaneous WM maintenance of multiple items. Stated differently, the PHC appears to be the locus of interaction between WM and LTM. To test this hypothesis more directly, additional time courses for the PHC and the neocortical clusters triggered to the onset of WM maintenance in both WM load conditions were extracted. The findings were similar to the results for the hippocampus: The PHC and the neocortical clusters were strongly activated in the high vs. low WM load condition during WM maintenance. A two-way ANOVA with “time” and “load” as repeated measures revealed a main effects of “load” for both the PHC ($F_{1,22} = 5.04$; $p = 0.04$) and the neocortical clusters ($F_{1,22} = 7.73$; $p = 0.01$). Time-courses differed significantly for the peak time points (4-7 s for WM PHC; 5-8 s WM neocortex; for each time point: $F_{22} > 2.2$; $p < 0.05$; two-tailed t-test).

Finally, it was aimed at elucidating the mechanism by which the PHC was recruited for LTM encoding.

Interaction of one region with another is reflected by correlated activation in both regions. A functional connectivity analysis using the “psychophysiological interaction” method (Friston et al., 1997) was performed, with a seed region in the left PHC. It was found that functional connectivity was significantly enhanced during high as compared to low WM load in the medial frontal cortex during both WM maintenance and LTM encoding. Furthermore, the analysis of connectivity between the PHC and the medial frontal cortex during memory encoding revealed a higher “high WM load > low WM” load difference for later forgotten than for later remembered faces (Fig. 3.5 B,C). This suggests that the influence of the medial frontal cortex over this region may influence LTM encoding. The “high WM load > low WM load” difference in functional coupling during LTM encoding is thereby driven by a pronounced decrease in correlation in the low WM load condition. During WM maintenance the contrast was driven by a strong increase in correlation for the high WM load condition.

3.3 Discussion

In the present study, it was investigated whether maintenance of multiple items in WM interfered with LTM encoding. Based on findings that the MTL is not only crucial for LTM encoding, but supports WM for multiple items as well (Aggleton et al., 1992; Axmacher et al., 2007), it was hypothesized that a high WM load would impair encoding of items into LTM. This interference might be due to a resource conflict between the maintenance of a high WM load and the demand of simultaneous LTM formation. It was hypothesized that such a conflict could be explained by neural processes underlying LTM and multi-item WM, which are partially localized in the same anatomical structure. This structure would then represent the locus of conflict between WM and LTM. This question was addressed in a dual-task paradigm where subjects performed a WM task with trial-unique stimuli (designed to activate structures in the MTL such as the hippocampus) and an embedded LTM encoding task, forcing the subjects to access the same structures for memory formation in both tasks.

3.3.1 Behavioral results

The combined WM and LTM recognition task manipulated the LTM encoding of faces by a WM load in a modified version of the Sternberg item recognition test. The behavioral performance of the subjects during the modified Sternberg task met the expectations in creating a sufficiently high WM load without overstraining the subjects capacities (e.g. Eng et al. 2005). The 80% hit rate in the (more demanding) high WM load condition showed a good balance between minimizing the number of incorrect trials while maximizing memory load.

LTM recognition of faces that were encoded during maintenance of a high WM load was significantly reduced as compared to LTM recognition of faces learned in the low WM load condition. Thus, consistent with the predictions, the amount of information being held in WM indeed influenced LTM recognition, indicating that these processes were not independent but required similar resources. Several precautions to guarantee a sustained level of high attention during these relatively demanding tasks were established. First, the encoding (fMRI) part of the paradigm was performed in multiple blocks with breaks in between, where subjects had the possibility to briefly leave the scanner. Second, subjects were excluded from further analysis if their behavior suggested that they were not attentively pursuing both tasks.

3.3.2 fMRI - Working memory

Extensive research on WM load manipulation has shown that various brain regions are directly affected by WM load, including the bilateral praefrontal cortex (PFC) and the bilateral parietal cortex (Postle, 2006). This is consistent with our findings of WM load-dependent activation patterns in a network similar to that found in other working memory studies, involving bilateral superior parietal and bilateral dorsolateral prefrontal areas, as well as the bilateral thalamus and caudate nucleus (Tomasi et al., 2007; Altamura et al., 2007; Feredoes and Postle, 2007; Eldreth et al., 2006; Cairo et al., 2004; Jansma et al., 2000; Postle et al., 1999).

The WM network comprised activation in the medial frontal cortex, in particular, in the pre-supplementary motor area (preSMA), and the dorsal anterior cingulate cortex (dACC). The ACC is known to be activated in a large variety of experimental conditions such as reward processing, target detection, novelty detection, error detection, response selection, response competition, or task difficulty in general (see Devinsky et al.,1995 for review). However, especially the dorsal ACC is often described in the role of mediating cognitive functions (Bush et al., 2000; Devinsky et al., 1995; Whalen et al., 1998). Imaging studies have shown activation of dACC in demanding WM tasks requiring rapidly paced manual responses (see Paus et al., 1998, for review). Some authors speculate that the activation of the dACC signals an increasing demand of cognitive control when WM load is high (Gray, et al., 2002). This fits well with the findings described in this study. The activation of the preSMA region exclusively in the high WM load condition may appear surprising, as activations of both the SMA and preSMA regions are more commonly reported in studies involving complex motor control tasks (see Picard et al.,1996, for review). However, a recent fMRI-study showed a load dependent activation of a common frontoparietal network, including bilateral dorsolateral prefrontal cortex (DLPFC), the SMA in combination with the anterior cingulate cortex (ACC) and bilateral parietal areas in an n-back task (Zhu et al., 2006). It thus appears that the combination of a high WM load represented in a novel sequence of information is likely to activate preSMA. In tapping and rhythmic tasks, for example, lateral premotor activation (e.g. preSMA activation) has been attributed to a memory function, reflecting a process where the visual or auditory rhythm input is transformed into a motor sequence, providing a reference structure for a mnemonic representation (Kawashima et al., 1999; Schubotz and von Cramon, 2001). This is also in line with findings in monkeys, where individual pre-SMA neurons are more active during learning of sequences when the task is internally guided (Halsband, 1994). Finally, an fMRI study focusing on the role played by medial wall areas in humans during WM also identified activation in preSMA and dACC regions during both spatial and face WM tasks (Petit, 1998).

The main WM network activations were consistent with previous research. Furthermore, a highly significant activation in the MTL when activity was found during both WM load condition was contrasted with activity during baseline (cross-hair fixation breaks). Indeed, the bilateral hippocampi were among the most strongly activated regions in this contrast, together with occipital visual areas and medial parietal regions. This result strengthens the theory established by recent studies, that novel stimuli, like the trial unique combinations of abstract symbols used in this study, need structures in the MTL (e.g. the hippocampus) for WM maintenance (Schon et al. 2004; Ranganath and D'Esposito, 2001; Nichols, 2006). Furthermore, there is evidence for an involvement of MTL structures whenever novel sequences of items are processed (Henke et al., 1999; Eichenbaum et al. 1999; Schendan et al., 2003; Jensen and Lisman, 2005; Kumaran and Maguire, 2006). However, no activations in the MTL in the contrast between the two memory load conditions was found. To investigate in greater detail, whether the hippocampus, in addition to its general role in our WM task, may have exhibited transient load-dependent effects, the time-courses of hippocampal activation in the two conditions were analyzed. This analysis showed that the hippocampus was indeed significantly more activated in the high WM load than in the low WM load activation, but that this difference only reached significance close to the peak of the time courses, i.e. 6-7 s after the beginning of WM processing.

It may be argued that some WM stimuli also underwent obligatory encoding into LTM. The functional activations observed for WM maintenance described above, however, revealed a network typically found to be involved in WM tasks. Although a contribution of LTM to the WM task cannot be excluded, these findings suggests that the paradigm indeed mainly monitored the interaction between WM and LTM and not the interaction between two LTM processes.

3.3.3 fMRI - Long term memory

To identify activation due to LTM-encoding per se, BOLD responses related to the presentation of the faces under high WM load and low WM load against baseline were analyzed. This analysis revealed a network similar to that engaged in WM processing. The memory network for the long-term encoding of faces also comprised a strong bilateral hippocampal activation. MTL regions are well known to support declarative LTM encoding and retrieval (Scoville and Milner, 1957; Penfield and Milner, 1958). However, in contrast to WM maintenance, where hippocampal activity was more pronounced for the high WM load, the time-courses at the onset of LTM encoding showed the opposite pattern. The following interpretation of this finding is proposed: Resulting from the conflict of processing resources, LTM encoding in the high WM load condition cannot recruit a similar level of hippocampal activity as in the low WM load condition. Therefore, LTM encoding-related hippocampal activation was diminished in the high compared to the low WM load condition. This effect could be related to the reduced LTM performance in the high WM load condition: as the hippocampus is the most crucial region supporting LTM encoding, a reduced activation likely corresponds to a worse performance.

But which region actually represents the locus of conflict between WM and LTM? To answer this question LTM encoding-related activity in the two WM load conditions were contrasted. There was no significant additional activation in the high WM load as compared to the low WM load condition (triggered to the onset of the LTM face stimuli). On the other hand, the inverse contrast (low WM load versus high WM load) revealed a network (Figure 3.4 A) including medial parietal cortex, superior parietal cortex, postcentral gyrus and posterior cingulate, respectively medial parietal cortex (precuneus). It is likely that these regions are related to the better LTM performance in this condition: The role of the parietal lobe in episodic memory is well known (Wagner et al., 2005). In combination with activity in the posterior cingulate/precuneus, the parietal lobe was reported in various fMRI investigations involving face processing. Several studies showed similar activations, e.g. comparing familiar with famous faces (Gobbini et al., 2004), comparing the own face with other faces (Kirchner et al., 2000), or during visual imagery of famous faces (Ishai, et al. 2002). In addition, bilateral activation in the orbitofrontal cortex and the left PHC for the low versus high WM load contrast were found. These findings are related to results from recent studies indicating that greater activity in the orbitofrontal cortex, which is massively connected to the MTL, is part of a network underlying LTM formation (Frey and Petrides, 2002; Frey and Petrides, 2003). The role of the PHC in LTM formation is similarly well described. Several studies showed increased activity in the PHC during LTM encoding e.g. of complex novel scenes (Schon et al., 2004), novel pictures (Stern et al., 1996) or complex scenes and line drawings (Gabrieli et al., 1997). Furthermore, subsequent memory effects in the PHC was demonstrated during encoding of complex color photographs (Brewer et al., 1998), complex color pictures of indoor or outdoor scenes (Kirchhoff, et al., 2000) and during semantic processing (Wagner et al., 1998).

The extracted time-courses for the PHC show a significant subsequent memory effect for the high WM load condition, thereby demonstrating the key role of the PHC in the encoding of faces within the resource-demanding high load condition. During WM processing (Fig. 3.4 D) the time-courses exhibited a significantly stronger activation of the PHC in the high vs. low load condition. These results suggest that the PHC represents the bottleneck for LTM processing in case of a simultaneous high WM load. Only if encoding related activity in the PHC surpasses a certain level, the face will be remembered. Interestingly, the neocortical network activated for low WM > high WM showed a significant subsequent memory effect for the low WM load condition (Fig. 3.4 C), suggesting that LTM face encoding during low WM load is controlled by neocortical preprocessing and does not crucially depend on the PHC.

3.3.4 Functional connectivity

The results from the univariate analyses demonstrate that encoding of LTM items during simultaneous maintenance of multiple items in WM is possible, but at the expense of a decreasing memory performance as compared to a low WM load. To further support the hypothesis of the PHC as a locus of memory processing conflict, a functional connectivity analysis with the PHC as a seed region was performed. The results show a strong connectivity with the medial frontal cortex (anterior ACC and preSMA) during WM processing (Fig. 3.5 A). This region represented the peak activation during WM maintenance in the high load condition, but was inactive in the low load condition (Fig. 3.2). This suggests that maintaining the high WM load with novel, trial-unique stimulus combinations requires the interaction between the medial frontal cortex and the PHC.

In the context of the paradigm, this interaction results in a processing conflict between LTM encoding and simultaneous WM maintenance. One would therefore expect that the coupling between the medial frontal cortex and the PHC has to be dissolved to the same extent, that the PHC will get involved in LTM encoding. According to this hypothesis, successful LTM encoding should be accompanied by a reduced interaction between PHC and medial frontal cortex. For subsequently forgotten items, the connectivity should be stronger. Indeed, the results for functional connectivity during LTM encoding support this theory.

Taken together, the results support the idea that the hippocampus is recruited by WM tasks involving for trial-unique item sequences. Furthermore, it was demonstrate that the PHC is the locus of processing interference between WM maintenance and LTM formation. Probably as a consequence of this interference, the subsequent memory performance was significantly decreased due to the maintenance of a high WM load. In contrast to classical theories claiming that the MTL is only involved in LTM, but not in WM tasks, these results demonstrate that both memory processes recruit this region, leading to conflicting demands in dual-task situations.

Table 1: Significantly activated regions in the different experimental conditions.
The table displays the coordinates of the maximally activated voxel in each activation cluster.

Region	L/R	BA	MNI coordinates			z-score
			x	y	z	
High WM load > low WM load. Bold entries identify retrieval network.						
Dorsal Anterior Cingulum	**M**	**24**	**0**	**16**	**46**	**7.5**
Precentral Gyrus	R	6	52	-2	42	7.3
Superior Frontal Gyrus	R	6	2	4	56	7.1
preSMA	M	6	0	6	54	6.8
Thalamus	R	-	2	-20	12	6.5
Precuneus	R	7	14	-76	56	6.4
Declive	**R**	**-**	**44**	**-58**	**-20**	**6.2**
Middle Frontal Gyrus	L	10	-40	42	24	6.2
Culmen	**R**	**-**	**36**	**-48**	**-26**	**6.2**
Precentral Gyrus	**R**	**6**	**48**	**0**	**26**	**6.1**
Inferior Parietal Lobule	R	40	32	-48	44	5.7
Precuneus	**L**	**7**	**28**	**-64**	**30**	**5.6**
Middle Temporal Gyrus	R	21	60	-30	-2	5.5
Inferior Frontal Gyrus	L	45	-34	26	4	5.5
Precentral Gyrus	**L**	**6**	**-56**	**0**	**38**	**5.4**
Superior Parietal Lobule	**L**	**7**	**-22**	**-66**	**54**	**5.4**
Superior Temporal Gyrus	R	38	48	16	-8	5.3
Caudate	L	-	0	16	8	5.2
Middle Frontal Gyrus	L	6	-28	0	60	5.2
Superior Temporal Gyrus	L	38	-48	14	-6	5.2
Inferior Parietal Lobule	L	40	-36	-40	40	5.2
Middle Frontal Gyrus	R	9	50	28	28	5.0
Precentral Gyrus	**L**	**6**	**-44**	**0**	**34**	**4.9**
Superior Frontal Gyrus	R	9	40	46	30	4.9
Posterior Cingulate	R	29	2	-46	10	4.8
Middle Frontal Gyrus	R	6	28	6	52	4.7
Inferior Frontal Gyrus	L	9	-50	2	24	4.6
Sub-Gyral	R	6	22	-2	50	4.3
Cerebellar Tonsil	L	-	-20	-34	-32	3.9
LTM encoding > baseline (high WM load). Bold entries identify WM > baseline network.						
Culmen	R	-	36	-48	-30	7.1
Hippocampus	R	28	24	-20	-14	6.9
Culmen	L	-	-40	-50	-28	6.6
Hippocampus	L	35	-20	-22	-14	6.1
Lingual Gyrus	R	19	12	-62	-2	5.8
Cerebellar Tonsil	R	-	34	-36	-34	5.8
Medial frontal gyrus	**M**	**6**	**0**	**0**	**58**	**5.3**
Inferior Frontal Gyrus	L	47	-18	32	0	5
Angular Gyrus	**L**	**39**	**30**	**-64**	**30**	**4.9**
Supramarginal Gyrus	**R**	**40**	**-38**	**-44**	**34**	**4.7**
Inferior Frontal Gyrus	L	47	-22	26	-8	4.3
Precentral Gyrus	**L**	**6**	**-50**	**-8**	**40**	**4.3**
Cingulate Gyrus	**M**	**32**	**2**	**18**	**38**	**4.2**
Inf. Frontal Gyrus	L	47	-26	32	-6	4
DLPFC	**L**	**46**	**-36**	**40**	**18**	**3.9**
Putamen	L	-	-20	20	-8	3.9
Caudate Body	L	-	-18	4	20	3.9
Cingulate Gyrus	L	32	-20	10	30	3.6
Postcentral Gyrus	R	2	38	-26	30	4.7
Caudate Body	R	-	22	-6	22	4.3

Insula	R	13	38	4	14	4.2
Caudate Body	R	-	18	-8	32	4
Insula	R	13	40	-6	20	4
Caudate Body	R	-	20	8	18	3.8

LTM encoding > baseline (low WM load) Bold entries identify WM > baseline network.

Superior Frontal Gyrus	R	11	38	-48	-30	7.1
Superior Frontal Gyrus	L	11	-32	-52	-26	6.6
Hippocampus	R	28	20	-20	-14	6.5
Superior Frontal Gyrus	L	11	-36	-46	-26	6.4
Hippocampus	L	35	-20	-26	-14	6.2
Culmen	L	-	-40	-50	-28	6.2
Supramarginal Gyrus	**L**	**40**	**-40**	**-50**	**32**	**4.7**
Anterior Cingulate	R	24	6	26	-2	4.5
Anterior Cingulate	R	24	10	28	-2	4.5
Inferior Frontal Gyrus	L	47	-20	28	-4	4.2
Caudate Body	R	-	2	18	12	4.1
Precentral Gyrus	**L**	**10**	**-34**	**-16**	**48**	**4**
Sub-Gyral	L	-	-22	32	6	3.8
Putamen	L	-	-18	20	-6	3.3

LTM encoding for low WM load > high WM load

Orbitofrontal Cortex	R	11	18	40	-22	5.2
Precuneus	L	7	-28	-58	50	4.7
Medial Parietal Cortex	M	-	0	-52	62	4.6
Postcentral Gyrus	R	3	42	-26	66	4.5
Occipital Cortex	L	19	-56	-68	-2	4.4
Superior Parietal Lobule	L	7	-26	-56	62	4.4
Medial Parietal Cortex	L	-	-6	-18	76	4.3
Temporal Pole	L	38	36	10	-32	4.1
Praecuneus	R	23	6	-56	16	3.9
Subcallosal Gyrus	R	-	20	8	-14	3.8
Thalamus	L	-	-2	0	4	3.8
Parahippocampal cortex	L	36	-28	-24	-22	3.3

Functional connectivity with parahippocampal cortex. Activations for forgotten faces. Italic: only WM load encoding Bold: only LTM encoding remembered

preSMA	***M***	***6***	***0***	***4***	***60***	***4.3***
anterior Cingulate Gyrus	M	32	2	16	48	4.3
DLPFC	L	46	28	48	20	4.3
Sub-Gyral	L	40	34	-42	34	4.2
Precentral Gyrus	**L**	**6**	**54**	**-6**	**44**	**4.2**
DLPFC	R	46	-38	40	18	4.0
Precentral Gyrus	**R**	**6**	**-52**	**-4**	**40**	**4.0**
Posterior Caudate Body	R	-	-18	0	20	3.7
Posterior Caudate Body	L	-	20	-6	22	3.5
Anterior Cingulate Gyrus	R	32	-10	20	34	3.5

Chapter 4

Conflict processing

Auditory Stroop interference activates a modality specific network including the posterior part of the anterior cingulate cortex

"Conflict is the beginning of consciousness."

M. Esther Harding
(American psychoanalyst)

"Managing conflict enables us to approach the upheaval of chaos and find invigorating new solutions."

John Ford

4.1 Introduction

Since the Stroop effect was first described more than seventy years ago (Stroop, 1935), it became one of the most intensively studied phenomena in cognitive neuroscience and still has a key role in the study of attentional top-down mechanisms (for reviews see Dyer, 1973; MacLeod, 1991). In spite of many variations of the Stroop task, the basic principle of word reading and color detection has not changed over the decades and is still widely used. In the standard Stroop task, subjects are asked to name the colors of compatible and incompatible color-words and of control patches, e.g. solid color squares. Stroop interference corresponds to the difference between the reaction times in the incongruent and the control condition. The interference effect and significant reaction time increase during the incongruent trials is accompanied by a facilitation effect for the congruent trials, reflected by a decrease in reaction times, although facilitation is considered to be a somewhat weaker phenomenon than interference (MacLeod, 1991).

During the last two decades, the Stroop task was implemented using neuroimaging techniques such as PET and fMRI, and revealed functional neural networks involved in the control of Stroop interference (e.g. Carter et al., 1995; Leung et al., 2000; Pardo et al., 1990; Peterson et al., 1999). The Stroop interference task seems to principally rely on the activity of a limited number of key regions, in spite of the fact that the experimental designs evolved to numerous specializations. According to the standard theory, the anterior cingulate cortex (ACC) signals frontal regions, such as the dorsolateral prefrontal cortex (DLPFC), to further increase the attentional bias toward task-relevant processing when distracting stimulus properties cause a task-related conflict. Consequently, recent studies showed a major interest in the ACC and DLPFC, which emerged as the two anatomical regions playing the most important role in the control of conflict management (e.g. Milham et al., 2001; Banich et al., 2001; MacDonald et al., 2000).

Several studies have addressed theories of ACC functions related to different cognitive abilities, such as for example conflict monitoring (MacDonald et al., 2000, Botvinick et al., 1999, 2001; Carter et al., 2000; Kerns et al., 2004), error detection (see reviews by Bush et al., 2002; Gehring and Knight, 2000) and response selection (Erickson et al., 2004; Milham et al., 2003; Paus, 2001). In addition, the DLPFC has been shown to contribute to cognitive control function (MacDonald et al., 2000; Miller and Cohen, 2001).

In the present study, an auditory Stroop interference task using fMRI was implemented. Two studies demonstrated the applicability of the Stroop interference task in the auditory domain behaviourally (Leboe et al., 2007; Shor, 1975). The motivation for implementing the auditory Stroop approach with functional imaging was threefold:

(1) Selective attention might be different in the auditory as compared to the visual domain. Most applications of the Stroop interference task were designed using visual stimuli and revealed variations of activity in the anterior ACC and DLPFC. The question of whether the functional network activated by conflict processing represents a common system or whether there are specific alterations regarding the sensory modality was addressed. It was expected that the behavioral results and the conflict network activations generally follow the common Stroop findings, but prominent differences due to the new sensory modality were hypothesized for two reasons. Firstly, because the visual and the auditory pathways include fundamentally different processing steps for sensory input (Hendee and Wells, 1997; Handel, 1989). Secondly, because alterations of activations in ACC due to different cognitive processes are well described in the fMRI literature, e.g. in the context of conflict processing and movement execution (Picard and Strick 2001), attention and stimulus detection (Posner and Petersen 1990) and emotional processing (Devinsky et al. 1995; Bush et al. 2000). To further investigate the integration of activity within the conflict network and to reveal its adjustments due to the auditory modality, a functional connectivity analysis using the “psychophysiological interaction” approach (Friston et al., 1997) was performed.

(2) There is an ongoing discussion regarding the role of priming in the Stroop task. A center of debate in recent studies involving conflict-adaptation is the controversy of the conflict theory versus priming-effects. It is still unclear if reaction time decreases related to repetitions of equal stimuli during a conflict task are actually caused by the greater recruitment of top-down conflict monitoring or should rather be attributed to episodic memory or stimulus-specific repetition priming as shown for Flanker-tasks (Mayr et al., 2003, Nieuwenhuis et al., 2006).

(3) An auditory Stroop approach could be useful for clinical purposes. Abnormal conflict management was evidenced for several brain disorders, e.g. attention-deficit/hyperactivity disorder (for review see Lansbergen et al., 2007) or in paranoid schizophrenia (Nordahl et al., 2001). An auditory approach to the common Stroop interference task seems of particular interest since the auditory sense is especially affected in psychiatric disorders such as schizophrenia (Veuillet et al., 2001)

4.2 Results

4.2.1 Behavioral results

The auditory Stroop design created a robust Stroop interference effect. A two-way ANOVA with “congruency” and “semantic-phonetic” as repeated measures revealed main effects of each factor (“congruency”: $F_{1,28} = 10.15$, $p = 0.004$; “semantic-phonetic”: $F_{1,28} = 43.31$, $p < 0.001$) and a significant “congruency” × “semantic-phonetic” interaction ($F_{1,28} = 107.38$; $p < 0.001$). As expected, the incongruent phonetic trials turned out to be the critical condition of top-down conflict processing in this Stroop task, producing significantly longer reaction times compared to the other conditions (incongruent phonetic trials: 906 ms (s.e.m. 52 ms), other conditions: < 800 ms (s.e.m. < 45 ms), each $p < 0.001$, each $t_{28} < 6.14$; two-tailed t-tests; for detailed behavioral data, see Tab. 2, Fig. 4.1 A). In the phonetic control condition using the word “good”, subjects had a reaction time of 854 ms (s.e.m. 48 ms), which differed significantly from the other conditions (each $p < 0.001$, each $t_{28} < 6.2$; two-tailed t-tests) and was almost at the exact half between the reaction times of the condition of highest conflict (incongruent phonetic) and the others.

The error rates confirmed the results of the reaction times. Again, Stroop interference was maximal in the incongruent-phonetic condition, as the error rate was significantly higher (11%, s.e.m. 3%) as compared to the other conditions (<5%; Fig. 4.1 B). A two-way ANOVA with “congruency” and “semantic-phonetic” as repeated measures revealed main effects of each factor (“congruency”: $F_{1,28} = 10.72$, $p = 0.003$; “semantic-phonetic”: $F_{1,28} = 12.23$, $p = 0.002$) and a significant “congruency” × “semantic-phonetic” interaction ($F_{1,28} = 10.01$; $p = 0.004$). Pair-wise t-tests showed that error rates in the “incongruent-phonetic” condition were larger than in any other condition ($p < 0.05$, $t_{28} > 4.82$; two-tailed t-tests).

A common observation during the Stroop task is that processing of incongruent stimuli is facilitated by previous processing of incongruent stimuli, which has been explained by behavioral adjustments (Botvinick et al., 2001). Thus, an incongruent trial following an incongruent trial (iI) should result in faster reaction times than on incongruent trials following congruent (cI) trials. Similarly, reaction times should be slower on iC than on cC trials. The reaction times for each of the four conditions were calculated; the results are shown in figure 4.1 C.

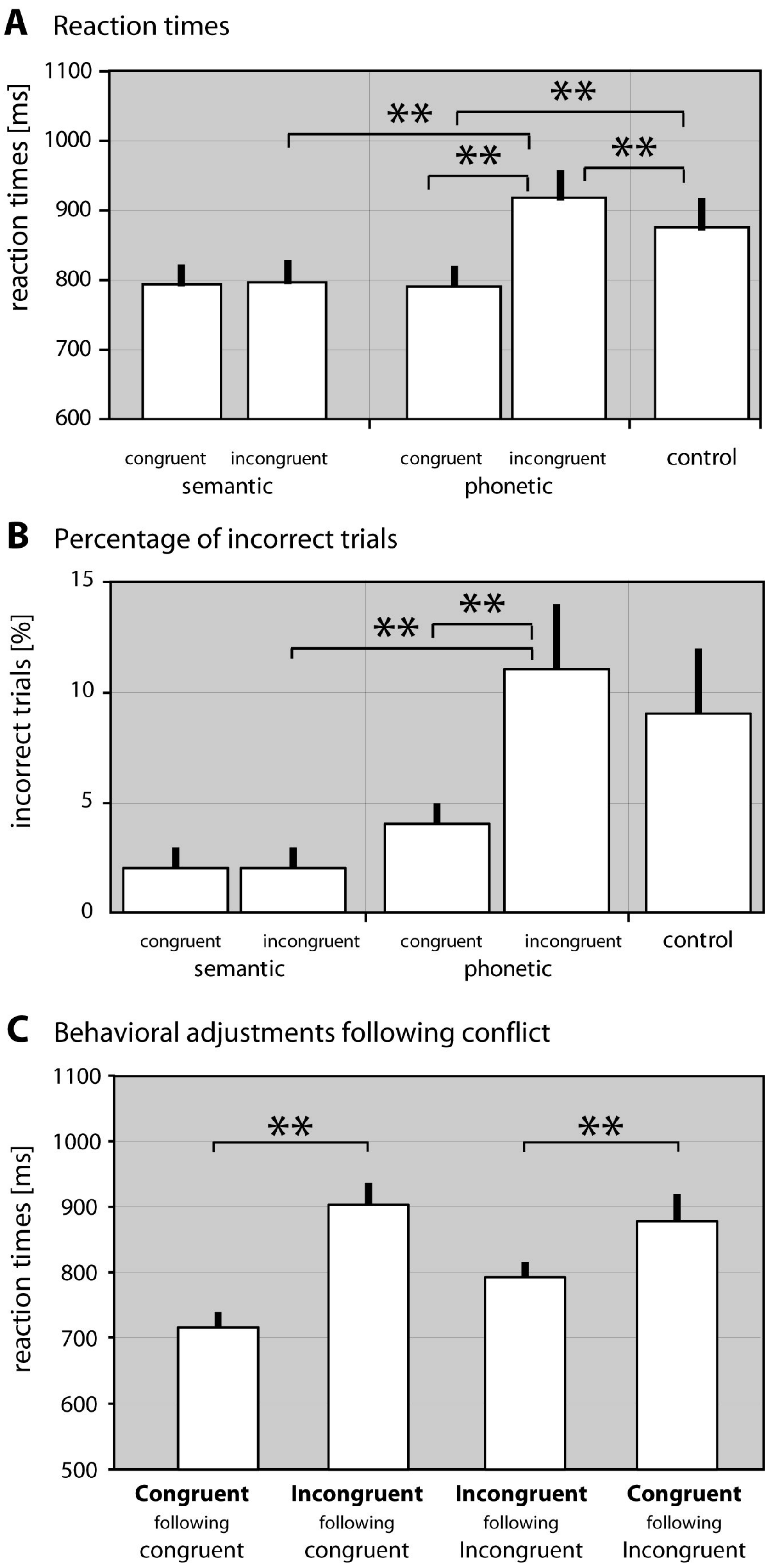


Fig. 4.1: Behavioral results. **(A)** Reaction times. **(B)** Percentage of incorrect trials **(C)** Behavioral adjustments following conflict. Previous trial (congruent versus incongruent) by current trial (Congruent versus Incongruent) interaction.

Consistent with previous data, it was found that reactions for iI-trials were significantly faster than for cI trials ($p < 0.001$, $t_{28} > 5.9$; two-tailed t-tests), and were also faster for cC-trials than for iC trials ($p < 0.001$, $t_{28} > 5.49$; two-tailed t-tests). A two-way ANOVA with “Position1 (congruent/incongruent)” and “Position2 (congruent/incongruent)” as repeated measures revealed a main effect for “Position2” ($F_{1,28} = 18.68$, $p < 0.001$) and a significant “Position1” × “Position2” interaction ($F_{1,28} = 11.95$; $p = 0.002$).

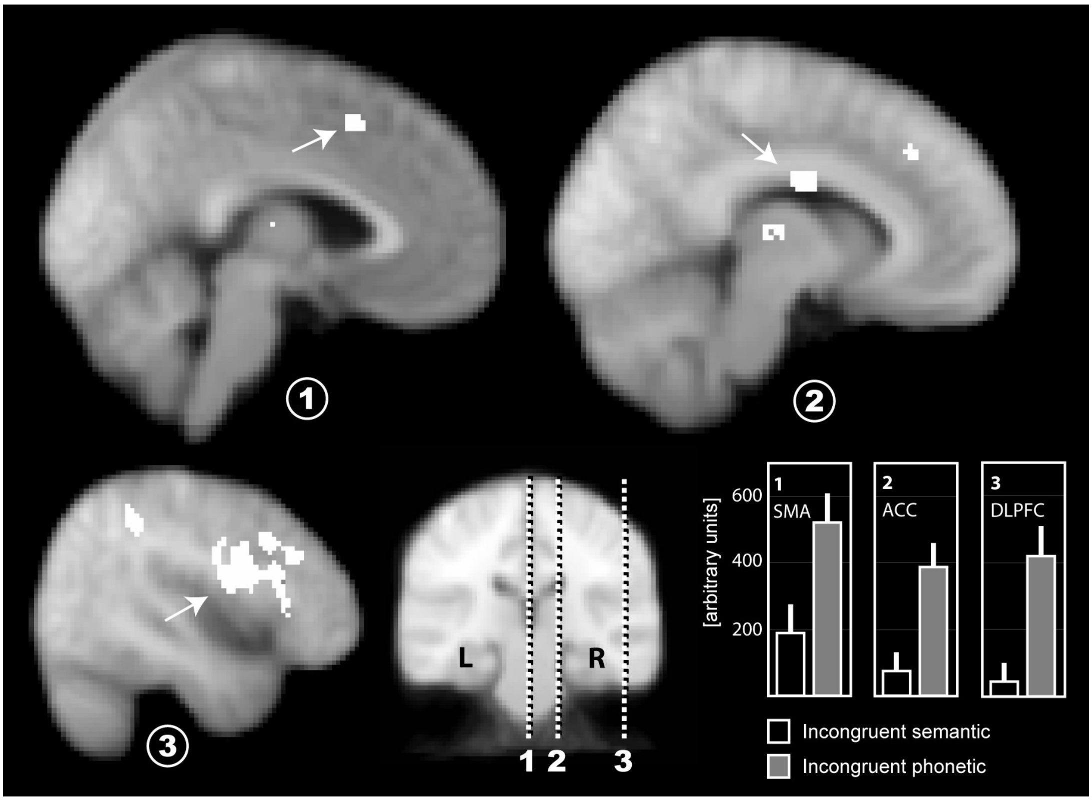
To control for repetition priming effects and their contribution to the Stroop effect, at first the reaction times for every condition without repeating trials, i.e. trials with exact the same stimulus, were calculated. A significant increase in reaction times (mean: +13.6 ms, std: 2.6 ms; not shown) for the trials excluding direct repetitions was found. A three-way ANOVA with “congruency”, “semantic-phonetic”, and “repetition” (repeated trials vs. excluded) as repeated measures revealed main effects of each factor (“congruency”: $F_{1,28} = 9.74$, $p < 0.001$; “semantic-phonetic”: $F_{1,28} = 50.93$, $p < 0.001$; “repetition”: $F_{1,28} = 55.96$, $p < 0.001$) and a significant “congruency” × “semantic-phonetic” interaction ($F_{1,28} = 115.50$, $p < 0.001$).

Further, the effect of excluding all repeated trials from the statistics of the behavioral adjustments following conflict was tested. It was again found that reaction times were increased as compared to the analysis including repeated trials (Cc:+29ms; Ic:+1ms; Ii:+2ms; Ci:+59ms). The increase in reaction times did not change the significance of the different condition interactions. A three-way ANOVA with “repetition”, “position1” and “position2” as repeated measures revealed main effect for “repetition” ($F_{1,28} = 38.98$, $p < 0.001$) and significant “position1” x “position2” interaction ($F_{1,28} = 59.54$, $p < 0.001$).

4.2.2 fMRI results

The behavioral findings indicated that interference was highest in the incongruent phonetic condition. To investigate the neural basis for modality-specific interference effects, the incongruent phonetic condition was contrasted with the incongruent semantic condition. In this condition subjects had the identical auditory input, but the opposite decision was correct (e.g., if they were presented the word ‘High’ in a low pitch, they had to press ‘High’ in the semantic condition, but ‘Low’ in the phonetic condition). Activations in the posterior part of the ACC, the medial frontal cortex, left and right dorsolateral prefrontal cortex (DLPFC), thalamus, and the pre-supplementary motor area (pre-SMA) were observed. The results for the contrast “incongruent phonetic > incongruent semantic” are shown in the figure 4.2 A, and table 3 provides an overview of all significantly activated regions for all contrasts. The parameter estimates shown in figure 4.2 demonstrate that the activations are clearly driven by the conflict processing originating from the incongruent phonetic condition.

A Incongruent phonetic > Incongruent semantic



B Plot of ACC activations associated with different response modalities (in MNI space)

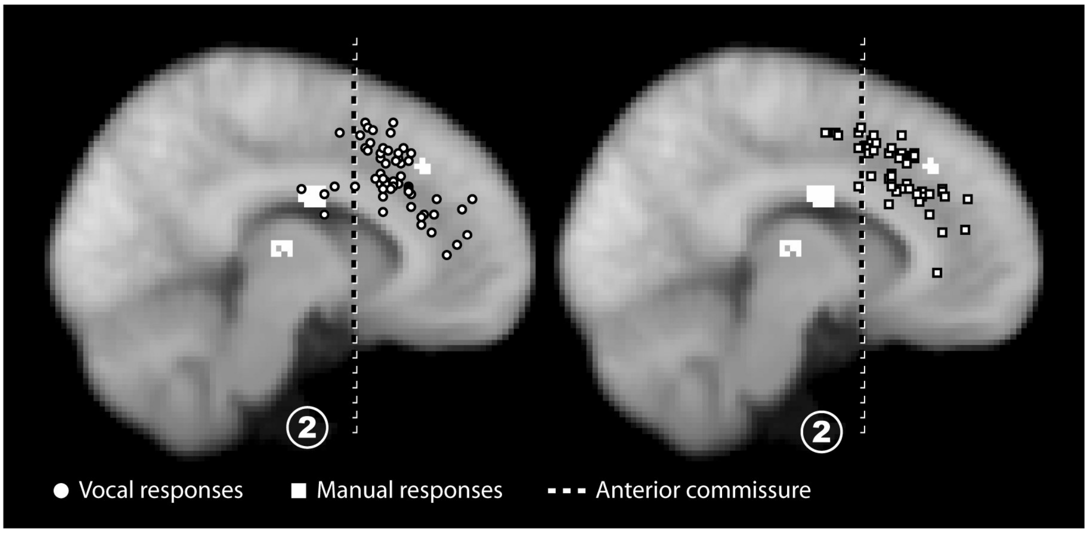


Fig. 4.2: **(A)** fMRI-activations. incongruent phonetic > incongruent semantic. **(B)** Plot reviewing 112 ACC activations associated with vocal and manual responses. Coordinates were collected and reviewed by Barch and colleagues (Barch et al., 2001) and transferred to MNI space.

Regarding the discussion about conflict-adaptation versus priming-effects, it was tested how an analysis excluding all repeating trials influences the Stroop-interference activation network. For the second analysis every event containing a direct repetition of a trial from the regressors of the first analysis was removed. This way an average of 16 % of the trials (from an average of 152 events to 127) were excluded. The results revealed activations corresponding to the areas shown in figure 4.2 A, while the number of activated voxels decreased (ACC 58 to 3; DLPFC 135 to 19; not shown). A comparison of the activation-values for the voxels of the ACC region in the analysis with repetitions and without repetitions across all subjects revealed that the ACC activation without repetitions is significantly smaller ($p = 0.003$, $t_{28} > 3.29$; two-tailed t-tests). A critical objection to this result could be the fact that the number of trials for the two analyses did not match. To test this idea, the first analysis was repeated, while randomly removing 16 % of the trials to match the number of events. Indeed, this revealed a significantly decreased number of activated voxels (ACC 58 to 3; DLPFC 135 to 42; $p < 0.001$, $t_{28} > 3.93$; two-tailed t-tests; not shown). Interestingly, the activation-values for the analysis without repetitions and the trial-matched analysis did not significantly differ ($p = 0.163$, $t_{28} > 1.43$; two-tailed t-tests).

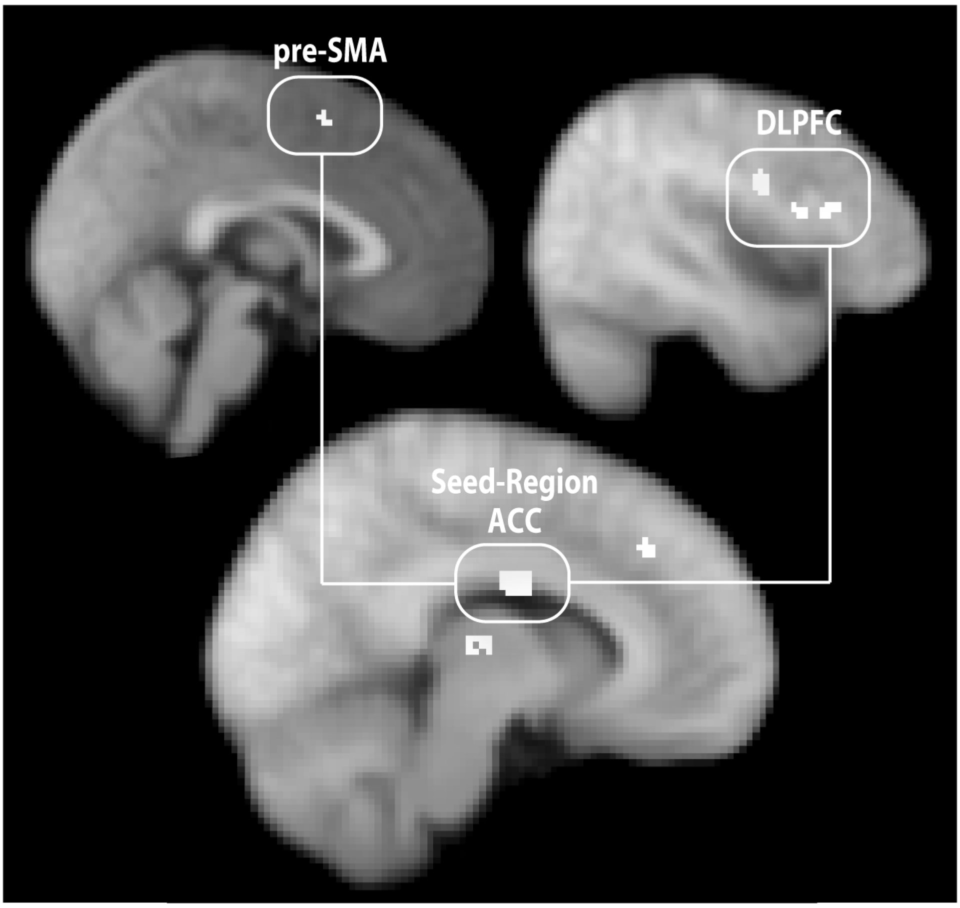


Fig. 4.3: Connectivity analysis contrast “Phonetic > semantic” using the ACC activation (Fig. 4.3 A-2) as seed region. Activity is shown at p = 0.001.

Finally, it was aimed to reveal the mechanism by which the activated clusters participate in a conflict processing network. Interaction of one region with another is reflected in correlated activations in both regions. A functional connectivity analyses using the “psychophysiological interaction” approach (Friston et al., 1997) was performed, with a seed region located in the activated posterior part of the ACC (see arrow in figure 4.2 A-2). The results show a strong connectivity with the left DLPFC and the pre-SMA (Fig. 4.3).

4.3 Discussion

The motivation for implementing the auditory Stroop approach via functional imaging was threefold: (1) Conflict processing might be different in the auditory as compared to the visual domain. The question was, whether the neural basis underlying Stroop interference shows modality specific alterations. (2) The ongoing discussion regarding the role of priming in the Stroop task motivated investigations on the influence of repeating trials on the activity of the conflict processing network. (3) Since the auditory domain is especially affected by certain psychiatric disorders, the usefulness of an auditory Stroop approach in clinical research is discussed.

4.3.1 Conflict processing in the auditory as compared to the visual domain

The major interest in this study was to find out if the use of a different sensory modality in a Stroop interference task would reproduce the common conflict effect in general, or if the auditory stimuli per se would result in a different behavioral outcome. While visual input undergoes a large amount of filtering and reconstruction on the way from the retina to the cortex, auditory information performs exact measurements of the sound frequencies (Hendee and Wells, 1997; Handel, 1989). This led to the hypothesis that a classical Stroop task used with auditory stimuli should result in a robust conflict effect, while at the same time recruiting a network of well-known conflict-related regions, but with adjustments to the different sensory modality.

The results confirm the hypothesis by showing a robust behavioral effect, with a highly significant reaction time difference of about 100 ms between the conflict condition and the other conditions. This behavioral effect remains significant even after exclusion of all repetition trials. The activated network meets the expectations by demonstrating areas well known for conflict management, including the ACC, the DLPFC, the pre-SMA, the medial frontal cortex, the parietal cortex and the thalamus.

4.3.2 ACC

Interestingly, the ACC region activated in this study is located at the very posterior/caudal part of the ACC. This was in contrast to the vast majority of previous studies investigating Stroop interference, conflict, and error detection, which reported activation of more anterior regions of the ACC (Barch et al., 2001). This even led Barch and colleagues to hypothesize that especially this anterior part of the ACC is more strongly associated with monitoring conflict.

On the other hand, different response modalities in conflict tasks using oculomotor, manual, and speech responses, activate slightly different ACC regions (Paus et al., 1993; Picard et al. 1996), indicating a functional heterogeneity of the ACC supporting different aspects of cognitive processing. Unfortunately, the general findings related to functional subdivisions of the ACC are heterogeneous. Whereas activation of the caudal region of the ACC is associated with cognitive functions such as attention, for instance detection of an increasing number of stimuli (Posner and Petersen 1990), the rostral regions of the ACC appear to support the regulation of emotional processing (Devinsky et al. 1995; Bush et al. 2000). Furthermore it was proposed that conflict processing and response selection are associated with the activity of the rostral cingulate cortex, while the actual movement execution is linked to the caudal cingulate zone of the ACC (Picard and Strick, 2001). Interestingly, a recent study using dynamic causal modeling claimed that the intrinsic connectivity between different subregions of the ACC (e.g. the medial cingulate zone and the caudal cingulate zone) is increased during conflict processing to facilitate selection and response execution (Fan et al., 2007).

To visualize the spectrum of conflict-related activations and to further investigate the degree to which the network found in the study differs from previous findings related to conflict processing, the locations of another 112 ACC activations using coordinates as they were reviewed by Barch and colleagues (2001) were added to the contrast (see Fig. 4.2 B). It is striking that of 112 activations, only 14 (12.5 %) are located posterior to the anterior commissure line. Especially the very posterior and inferior parts of the ACC were exclusively found to be activated in four studies investigating Stroop interference using vocal responses. It was hypothesized that increasing integration of the auditory sense in conflict processing results in a posterior/caudal and inferior/ventral shift of ACC activity due to the different sensory modality. Auditory responses alone are probably not sufficient to reliably alter the network activity, considering that within 24 reviewed Stroop tasks with vocal responses only 4 activated the posterior ACC.

Additional evidence for this hypothesis comes from a study not directly related to Stroop interference, but involving auditory stimuli and responses. A PET study from Paus and colleagues (1993) use a speech task instructing the subjects to verbally respond to the auditory word stimuli in a way that conflicted with a former conditioning. The activated regions correspond to the findings including posterior ACC, medial frontal cortex and pre-SMA.

4.3.3 DLPFC

Together with the ACC, the dorsolateral prefrontal cortex (DLPFC) is the most commonly reported region in Stroop interference tasks. It has been suggested that if a conflict is detected by the ACC, a cognitive control system located in the DLPFC is alerted, which is responsible for reducing conflict by biasing information processing toward successful task completion (Botvinick et al., 2001). Accordingly, neuroimaging studies have shown the engagement of the left and right DLPFC in executive functioning, and more specifically during selective attention (Durston et al., 2003; Kerns et al., 2004; MacDonald et al., 2000; Milham et al., 2003) and attention-related and conflict-related activity (Weismann et al., 2004). While the DLPFC is a critical component of the decision-making network recruited for the Stroop interference task, its activation seems to be independent of response modality (Heekeren et al. 2006). A modality specific adjustment of activity of the DLPFC is not described for conflict interference, but greater activation of the same DLPFC area was observed during an auditory compared to the visual working memory task (Crottaz-Herbette et al., 2004). Results from a divided attention task (involving competing auditory and visual stimuli) have revealed, that the activity of the DLPFC is more strongly modulated by the performance of the subjects (poor performers recruit more DLPFC in an attempt to improve performance), than by the actual sensory modality (Johnson and Zatorre, 2006).

4.3.4 pre-SMA

The activation of the pre-SMA, as it was found for the incongruent condition is unusual, since the SMA and pre-SMA regions are more commonly reported from studies involving complex motor control tasks (for review see Picard et al., 1996). Nevertheless, activation of the pre-SMA has been reported in numerous studies involving cognitive control (Barch et al., 2001; Ikeda et al., 1999; Zysset et al., 2001), and also appears frequently in Stroop interference tasks, without being always clearly characterized. One reason for that may lie in the fact that the terminology in this historically old research field is often not compelling. The pre-SMA is sometimes reported as rostral/anterior dorsal ACC (e.g. Critchley et al. 2005; Bush et al. 2002), or in combination with the rostral/anterior dorsal ACC (Holroyd et al., 2004; Braver et al., 2001; Milham et al., 2002; Ruff et al., 2001).

4.3.5 Connectivity

The power in the "incongruent phonetic > incongruent semantic" contrast was not high enough to show a significant functional connectivity, however it was possible to show the connectivity-network for the more general "phonetic > semantic" contrast. The connectivity analysis demonstrated that a network including the ACC, the pre-SMA and the DLPFC is recruited for control and adjustment of the behavior during conflict processing. Several recent studies using functional connectivity are in accordance with the results of the connectivity analysis.

Functional connectivity of the ACC with the pre-SMA and the DLPFC was shown for the "interference-related" condition of a Stroop color-word paradigm (Harrison et al., 2005), for a counting Stroop paradigm (Zheng et al. 2006), respectively supported by recent findings in a study of ACC resting-state functional connectivity (Marguilies et al., 2007).

The strong correlation between the activity of the caudal ACC and the lateral prefrontal cortex as well as medial frontal gyrus, particularly the region of the pre-SMA, is also consistent the meta-analysis of functional connectivity of the ACC within the human frontal lobe (Koski and Paus 2000). These findings are further supported by the results of several studies in monkeys. Using neuronal tracers, it has been demonstrated that both the primary (Morecraft and Van Hoesen 1992) and supplementary (Bates and Goldman-Rakic 1993) motor areas are densely interconnected with the caudal ACC.

4.3.6 Influence of stimulus repetition

An exclusion of repeating trials results in significantly increased reaction times for all conditions but did not eliminate the Stroop effect. The results for the behavioral adjustment following conflict are only slightly influenced by the exclusion of repeating trials and do not change their significance. This result could be explained by both the conflict theory and a stimulus-specific repetition priming. The recruitment of frontal cognitive control would as well result in faster reactions as the utilization of priming related memories. Using the data from fMRI, it was shown that an analysis without trial repetitions resulted in significantly lower activations of the conflict areas than an analysis with all trials. An additional analysis with the same number of trials as the actual stimulus repetitions randomly removed confirmed that this effect was rather due to the reduced trial number, than a trial repetition effect. Both trial-reduced analyses were significantly different from the original analysis, but their activation values did not differ significantly from each other.

This demonstrates that processing of the repeating trials cannot be related to priming effects, because events related to priming activity should not reduce power in an area assigned to conflict monitoring in the same way as randomized chosen events do. The conclusion from this fact is, that first occurring trials and repeating trials activate conflict monitoring areas similarly. Since this is contradictory to the priming theory, the results support the conflict adjustment theory.

4.3.7 The auditory Stroop approach for clinical purposes

It has been shown that the ability to perform tasks related to conflict management is altered in bipolar patients (Kronhaus et al. 2006), patients with e.g. attention-deficit/hyperactivity disorder (Lansbergen et al., 2007), or in paranoid schizophrenia (Henik et al., 2004; Nordahl et al., 2001; Strauss et al., 1993). Among the different sensory modalities, the auditory modality is of particular interest for schizophrenia (Veuillet et al., 2001), because schizophrenia particularly affects auditory processing (Bentaleb et al., 2002). While processing deficits of the visual domain are typically evoked by structural brain damages (Prigatano and Wong, 1999), auditory verbal hallucinations are one of the most characteristic symptoms of schizophrenia (David, 1999). Furthermore, recent studies have shown that patients with schizophrenia, who frequently experience auditory hallucinations, exhibit dysfunctions of the ACC and bilateral temporal lobe (Cleghorn et al., 1992; Shergill et al., 2000), respectively do not show activation of the ACC during Stroop task performance (Carter et al. 1997). Many studies also reported abnormalities in the generation of pre-attentive automatic processing of auditory stimuli (e.g. mismatch negativity) in schizophrenia (for overview see Umbricht et al., 2005). Furthermore a recent study has shown that patients with schizophrenia performed worse on an auditory emotional perception task than participants from other groups (Vaskinn et al., 2007). Since the Stroop-task in this study showed a very robust behavioral effect for the auditory modality, the suggested version of the Stroop interference task may be particularly useful for clinical investigations.

Table 2: Descriptive statistics of behavioral data.

Condition	**Reaction time [ms]**	**s.e.m [ms]**	**errors [%]**	**s.e.m [%]**
Semantic-congruent	793	38	2	1
Semantic-incongruent	794	46	2	1
Phonetic-congruent	789	40	4	1
Phonetic-incongruent	906	52	11	3
Control	854	48	9	3

Table 3: Significantly activated regions in the different conditions. The table displays the coordinates of the maximally activated voxel in each activation cluster for the “incong. phonetic > incong. semantric“ contrast. Bold entries identify connectivity network.

Region	**L/R**	**BA**	**MNI coordinates**			**z-score**
			x	**y**	**z**	
Left DLPFC	**L**	**9**	**-44**	**4**	**20**	**4,9**
White Matter	L	-	-28	8	28	4,3
Insula	L	13	-34	16	14	3,9
Cingulate Gyrus	**L**	**24**	**-6**	**-6**	**26**	**3,9**
Lentiform Nucleus	L	-	-18	12	0	3,8
Medial Frontal Gyrus	L	9	-6	32	38	3,8
Right DLPFC	R	9	48	14	30	3,7
Thalamus	L	-	-6	-16	8	3,7
Anterior Cingulate	L	24	-2	32	18	3,7
Cingulate Gyrus	L	24	-18	-6	46	3,6
PreSMA	**M**	**6**	**0**	**14**	**48**	**3,6**
Thalamus	L	-	-18	-8	16	3,5
Sub-Gyral	L	6	-18	-8	62	3,5
Superior Frontal Gyrus	M	8	0	30	48	3,4

Chapter 5

Consciousness

Neural correlates of meditation related states of consciousness

“How can technicolor phenomenology arise from soggy gray matter?"

Colin McGinn (British philosopher)

“It is on the whole probably that we continually dream, but that consciousness makes such a noise that we do not hear it.”

Carl Gustav Jung

5.1 Introduction

The investigation of neural correlates of meditation practice has recently attracted the attention of the neuroscience community (e.g. Barinaga, 2003). Meditation practice is usually associated with a large amount of ritual and esoteric qualities. These associations mostly arise from influences and adaptations of the Eastern cultures, but also from those of Western faiths such as the Christian Contemplation practice. Various meditation practices exist in almost every religion or esoteric belief. Throughout the human history people had dedicated their lives to meditation and attained mastery in reaching the goals of meditation by realizing certain so-called altered states of consciousness. These special mental abilities attracted the attention of neuroscientists during the past decades. They aimed to reveal not only the mechanisms behind these voluntary alterations of mental states and the possible gains of extraordinary skills. Furthermore, they tried to assess measurable physiological differences, that characterize the highly experienced meditator compared to the untrained individual. Many respectable studies were released throughout the past years, which contributed to a new perspective of meditation practice. Research on meditation is no longer stigmatized as a dubious esoteric and non-scientific concept, associated with vague terms of spiritual ecstasy, enlightenment, or supernatural miracles. Today the unique abilities of meditators, trained for decades to reach altered states of consciousness, are considered a valuable source deepening our understanding of the neural correlates of consciousness.

By the use of magnetic resonance imaging (MRI), magnetoencephalography (MEG) and electroencephalography (EEG) our knowledge on the effects of meditation has changed rapidly over the recent years. Scientific research has discovered several basic effects, which show the influence of meditation practice on a wide range of autonomic parameters such as breathing patterns, heart rate, skin conductance, blood volume pulse, and even neurophysiologic processes (e.g. Arambula et al., 2001; Delmonte, 1984; Lee et al., 2000). For scientific purposes it is necessary to disburden the meditative practice from any kind of cultural pathos and ritual embellishment. Under a scientific approach, meditation can be understood as a method for training and developing the mind by altering mental states and thereby producing deep relaxation and at the same time an increased internalized attention. Understood in this way, meditation practice does not necessarily need a religious background and does not have to be connected with mystical experiences. This chapter will concentrate on the neurophysiologic side of meditation research pointing directly to the related mental states, which of course are more difficult to access quantitatively. One of the early approaches of investigating the effects of meditation practice from the 1960s was EEG recordings, on which the main emphasis will be placed. The basic idea behind these studies is the premise that an altered state of consciousness is always accompanied by an analogue altered neurophysiologic state (so-called psychophysical isomorphism, e.g. Fell, 2004). If meditation is used as a repetitive influence on consciousness, certain measurable qualitative and quantitative neurophysiological effects should develop. This refers to transient effects, as well as supposed lasting effects, e.g. in terms of permanent changing baselines.

A large number of studies aimed at classifying and categorizing observed effects but were only able to assess certain general changes in the EEG, which are hardly related to the meditation style, performance, or experience (for a review see Cahn et al., 2006). The major reason for this is that the access to every state of consciousness is restricted to the subjective reports of the subject. Because of the constraints of meditation practice it is difficult to collect reliable behavioural data. Moreover, the enormous bandwidth of non-clearly circumscribed meditation styles and the fact that there is no commonly accepted phenomenal classification of waking states of consciousness, only allow conclusions about general findings and rough tendencies. Thus, even though meditation research has produced a large number of studies during the past years, there is still a strong need for clear and standardized definitions in terms of meditative techniques as well as in terms of the involved states of consciousness.

At first there will be a close look at the term ‘meditation’, explain the difficulties that arise from the need for clear definitions, and point out why has the large field of meditation research never undergone a clear and practical categorization. With regard to these problems the perspective will then be changed by trying to describe meditation practice from a more general point of view. A hypotheses will be presented that will allow not only to arrange the electrophysiological findings in order, but also to predict how certain meditation related states of consciousness may be reached. In the following sections a close look at the results of meditation research in terms of the EEG recordings will be taken and these results will be discussed with respect to the hypotheses. It will be asked how, according to the present knowledge, meditation practice is manifested in EEG activity and more importantly: how can these observations be understood with respect to the latest findings on neural oscillations and their major role in the processing and integration of information?

By doing this no specific meditation style will be justified by pointing out the conclusiveness of the related EEG findings. Rather, it will be explained how these findings and contexts contribute to the present picture of the brain as a dynamic and highly variable system, which comes along with a mind able to adapt to almost any necessary requirements.

5.2 What is meditation?

The word ‘meditation’ can be derived from the Latin word ‘meditatio’, which refers to an exercise originally not predefined by intellectual or physical domain. In both domains it points to the center (lat. ‘medium’ = ‘center’) of either the body or the mind. The word ‘medium’ again is rooted in the Indo-Germanic stem ‘*me(d)’, meaning ‘to ambulate’ or ‘to measure’. Today ‘meditation’ is related to various practices aiming to alter the state of consciousness, hence belonging to a more spiritual context closer associated with the term ‘contemplation’.

‘Meditation’ as used in a modern sense, does not refer to a specific spiritual practice, but involves various meanings depending on the tradition in which it is used. In Christian spirituality a form of meditation can be found in for instance, the “contemplation on the suffering of Christ”, although nowadays the term is in most cases associated with Eastern traditions. Hinduism, Buddhism, and Taoism, found their way to Europe in the late nineteenth century and brought along a large amount of terminology that highly influenced our parlance. In the case of these Eastern traditions meditation only refers to a pure religious purpose, but a closer look illustrates that implications of meditation can reach far beyond this purpose. A number of so-called, ‘religious movements’ such as the Hatha Yoga employs meditation, as well as in a more secular context most of the Eastern martial arts. Furthermore, seemingly non-spiritual activities, such as dancing (e.g. the whirling dance, which is the spiritual practice of the Moulavi-Order of the Sufi tradition in Turkey), singing such as the Christian chorales or Buddhist chanting can be used as a meditative technique. In some traditions, such as the ‘red tantra’ the sexual impulses and activities are also a part of the meditative spectrum. There are certainly rather unlimited variations of the same topic in regard to the complexity of cultures it has to serve. Thus, one could try to achieve a definition of meditation through its effects on the meditator, but that also will not completely clarify the picture.

Depending on the tradition we study, meditation is a way to relax and deepen a sense of calmness and serenity; a method to concentrate and focus on a single point, to stop the continuous verbal thinking, to relax the mind, relieve stress, alleviate depression, and a way to reduce anxiety and build up self-esteem. Perhaps it is only used to benefit the health, such as to stabilize the cardio-vascular system or to the other extreme, it seeks ways to get in contact with God, or to reach hard-to-define ‘peak experiences’ such as ‘samadhi’, ‘nirvana’, or ‘oneness’. Unfortunately the term ‘meditation’ in research is sometimes used to describe diametrical contents. An instructive example is that of comparing studies from

Indian Yogis and Japanese Buddhist monks. In the early 1960s a couple of studies showed, that Yogi masters, while in meditation, exhibited no response to external stimuli (e.g. to pain when their hand was placed in cold water). Even auditory stimuli showed no effect on the simultaneously recorded EEG as compared to control subjects (Das & Gastaut, 1955; Wenger & Bagchi, 1961). These findings are consistent with the theory of certain Yogi practices, which are meant to cut off every sensory input and reach a state of complete internalized attention with extreme reduction in body functions.

Conversely, studies from the 60s and 70s, on the meditation of Japanese Zen Monks demonstrated an EEG response of the meditators to a repetitive auditory stimuli, that did not show any habituation as would be the case in control subjects (Kasamatsu, 1966). These findings correspond nicely to the demands of Zen meditation, which seeks to achieve a state of highly concentrated mindfulness, in other words, merely witnessing whatever passes through the mind, without trying to suppress external stimuli. Both of the aforementioned studies referred to the state of their subject as ‘meditation’.

It seems that a clear definition of the field including all its variations must fail given these first approximations to the term ‘meditation’ and consequently, its high diversity. This is again something that can be expected from a number of spiritual, mystical and religious traditions. These traditions developed rather by separating from one another and by further pointing out the differences, uniqueness, and the distinctive features of their own special training. They attempt to stand out in contrast to other beliefs, rather than allowing a categorization of their techniques within a large field of similar techniques of reaching spiritual goals. Nevertheless, it is fundamental for the scientific research on meditation to use at least a basic form of categorization, which is a prerequisite for understanding the results. In most of the current studies a division that categorizes meditation techniques in two main groups is used.

The two groups of meditation technique categorization are distinguished by the way in which the meditator employs his/her attention. If the focus is directed to a single point, whether abstract (e.g. an imagined picture or a feeling about some entity) or concrete (e.g. own breathing, a mantra or a specific body part), the technique is categorized as a concentrative form of meditation. The other end of the spectrum involves a concept referred to as the mindfulness form of meditation, which is considerably more difficult to define. In a mindfulness meditation, the idea is to reach a state, in which all oncoming thoughts and emotions are passively observed, without judging, analyzing them. By reaching this state, the meditator should transcend beyond the thinking mind, quieten the automatically generated train of thoughts up to a point of being ‘one’ with his meditation without thinking about meditating.

Out of this attempt at defining meditation, which is clearly not suitable for scientific purposes, it can be understood why former reviews find an unusually large variability in the results. The very same distinction is used and commonly accepted in the meditation literature, even though there is often a conceptual confusion about what form of meditation is actually described or used. Moreover, most traditions use both mindfulness and concentrative forms of meditation equally (e.g. in a didactic order which build up on each other), because they both simply employ a different access to the same goal.

Considering all the aforementioned issues, a serious question of how can a scientist distinguish between the various forms a meditative practice is raised. It appears that even the simplest attempt at objectively differentiating between different meditation approaches can only be suggested by a highly experienced instructor, who also does not differentiate by a list of objective criteria, but rather by his own extensive experience. It is likely that the scientist cannot distinguish here at all, which is a crucial point. Since a rather non-experienced student of meditation is not expected to be able to distinguish between the subtleties of his meditative practices, the best option would be to test the highly experienced students. This would undoubtedly reduce the number of available subjects substantially. The other option would be to get a report from the teacher about what would the right practice be, however this raises the issues of subjective assessment.

The combination of the vague concepts about the content of meditation and the high variability within the results of the studies creates difficulty in approaching the neurophysiological basis of interest here. It will not allow us any further understanding of the processes that lead from the simpler forms of meditative concepts to the specific, meditation related, states of consciousness. Hence, a more general way to think about meditation will be suggested in the following chapter.

5.3 A new approach to describing meditation practice

Rather than trying to correlate the neurophysiological data with various meditation practices, it is suggested to describe meditation as a type of training that involves certain steps of brain/mind development. It is hypothesized, that long-term practice of different meditation forms is associated with comparably developments. This idea is supported by the experiences of meditation experts, who coherently report comparably states – although often with a quite different vocabulary (e.g. Kopp 1996). In neuroscientific terms, this hypothesis implies that due to continuous meditation practice similar mind/brain states are reached, i.e. states comparative to non-meditative states, located in close proximity in the mental/physiological state space (see chapter 7). It is further hypothesized, that the initial mind/brain states occurring during meditation are adjacent and overlap with "regular" states experienced outside meditation. Only after long-term meditation practice new mind/brain states, which do not overlap with regular states, may be reached.

Definition:

Through the process of meditation the brain/mind tries to apply training and alteration of mental states to itself. Starting with internalized attention a development is aspired in which neural/mental processes are changed in order to reach the goal intended by spiritual training including the permanent implementation of new, self-induced states of consciousness.

Hypothesis 1:

The main hypothesis is that every meditative training, independent from its cultural background or practiced technique, involves a comparable scheme of development. This development is carried out stepwise from the status of an average non-pathological brain. Every development has it's neural correlates. Within this theory the sequence of steps leading to certain meditation related states of consciousness is always alike and a student of meditation has to master all of these steps. High intrasubject variability should be expected, due to different investments of time and effort, depending on the individual resources and flexibility of integrating new concepts. Not every meditation style integrates all possible steps; some meditators would even restrict themselves to the first levels of meditation just to benefit the health by slowing down and calming certain body functions. The characteristics of these steps can be generally defined.

Hypothesis 2 (steps of meditative development):

The first step would mostly involve the physical demands. The beginner should get used to a new and uncomfortable posture and should concentrate mainly on the performance of the technique. His/her attention will be cursory and restless. The expected neurophysiological alterations should be very small and transient.

With increasing experience the student should be able to internalize his/her attention, focussing on a rather simple, easily accessible object such as a simple mantra, a picture, a part of the body or his own breathing. In this manner he/she would experience the aspect of meditation in the form of physical function slowing and relaxing, with all its physiological effects that are easy to measure and reproduce. Internally, the slowing of the automatically produced internal dialog, accompanied by a deep sense of calmness and serenity would be observed, which represents the basic condition for any form of meditative practice. In principle, this second step is within the reach of every beginner and thus still closely related to the non-meditative processes. For this reason, the neurophysiological changes should be reminiscent of those occurring during well-known non-meditative tasks.

The following step is characterized by the correct performance of the meditation technique, which implies that the advanced student should be able to focus his/her attention on the object of meditation. The first alterations in perception and processing of the incoming stimuli occur through which the advanced student consequently realizes a basic change in the relationship between thoughts and feelings. With the growing distance among perception of the way in which the mind handles thoughts, emotions, and observing the related processing streams,, the student experiences constantly and automatically generated brain/mind processes as temporary and transitory. The corresponding neurophysiological alterations may be less comparable to non-meditative tasks, and thus may be new but still transient.

The most advanced step of meditation practice reached by experts is associated with certain peak experiences, described with difficult-to-define terms, such as ‘samadhi’, ‘nirvana’, ‘kensho’ or the experience of ‘oneness’, all of which arise from the cultural context. These experiences come together with permanent changes of personality traits and alterations of the states of consciousness outside of the meditation practice. Due to the large amount of time necessary to reach this step (typically several decades), the availability of suitable subjects is substantially reduced. In electrophysiological recordings new and unique oscillation patterns, highly correlated only to the expert level of meditation may be observed. Alterations of electrophysiological characteristics should be detectable not only during, but also outside the meditation practice. These new EEG patterns may be accompanied by a restructuring of neural networks enabling a permanent implementation of altered neural processing.

In the following chapter the results of meditation-related EEG studies will be described followed by the discussion of the hallmarks of these findings with respect to the present hypotheses.

5.4 Oscillatory EEG correlates of meditation

5.4.1 Alpha activity

The most dominant effect in the majority of the studies on meditation is the influence of meditative practice on the EEG alpha band (8-12 Hz). Since research on meditators was established in the 60s in Japan, the most reliable meditation related finding is a state-related slowing of the alpha rhythm in combination with an increase in the alpha power (Hirai, 1974; Kasamatsu et al., 1966; Taneli et al.; 1987). These findings can be rather simply replicated, as they do not depend on either a certain meditation tradition or the experience of the meditator. Subjects experienced in various styles of meditation reportedly demonstrate increased alpha power during practice (Delmonte, 1984; Kubota et al., 2001; Travis, 2001; Woolfolk, 1975), localized mainly over frontal regions (Takahashi et al., 2005; Tassi & Muzet, 2001; Young & Taylor, 1998). In a study on advanced Qi-gong meditators the frontal alpha power increase was correlated with a simultaneous decrease over occipital regions (Zhang et al., 1988). These alterations in the alpha band illustrate a reproducible and coherent outcome of meditative practice. Since they appear in different specific forms, however independent from the technique and level of experience, it can be postulated that these effects represent the first basic change in the course of meditative development.

With regard to the present hypothesis, these first self-induced alterations correspond to a beginner/student level and should fulfil two demands: As the subject begins his training he has to use neural patterns available for the average non-pathological brain, thus the first demand is that the underlying neural pattern should be closely related to a common simple mental task related process. The second demand is that even the inexperienced student of meditation should be able to experience these first basic alterations that would actually be within the reach of our everyday experience. Known to arise from the increase of internal attention, which occurs not only due to meditation (e.g. Ray & Cole, 1985), alpha oscillations fulfill these demands. Various studies showed the increase of alpha power related to internally driven mental operations such as the imagery of tones (Cooper et al., 2003; Cooper et al., 2006; Ray & Cole, 1985) or working memory retention and scanning (Jensen et al., 2002; Klimesch et al., 1999).

Is it then realistic that an inexperienced subject can furthermore learn to control the power and duration of his alpha rhythm? First EEG biofeedback studies show that subjects could be trained to either produce or suppress alpha activity (Ancoli, 1978; Kamiya et al., 1969). The baseline activity shifts according to the instruction, which seems to be a continuous trend, as if the subjects continue beyond meditation to do what they have been trained to do. Interestingly the subjects reported increasing of alpha activity to be more difficult, however more pleasurable than decreasing of the same.

These findings provided a first scientific hint about the possible positive effect on emotional management that can arise from a training closely related to a meditative approach. Further clues concerning emotional implications and alpha activity come from studies focussing on the laterality of anterior EEG activity. A recent study by Davidson et al. (2003) using mindfulness meditation reported significant increases in brain electrical activity of the left anterior activation (corresponding to decreases in alpha power) in the meditators compared with the non-meditators. Other studies reported that the same regions are related to certain positive emotions in subjects with 'more dispositional positive affect' (Davidson, 1990). Furthermore, patterns of asymmetric frontal EEG activity have been reported in pathological processes. Subjects with currently and previously depressed showed greater left to right frontal alpha activity as well as greater right than left parietal alpha activity (Bruder et al., 1997; Debener et al., 2000) than never-depressed controls (Allen, 1993; Rosenfeld et al., 1996) The authors of these studies suggest that the resting frontal EEG-asymmetry may serve as a 'stable trait-like marker to distinguish depressed individuals from never depressed individuals', and that as a method of increasing the positive affect, meditation could effectively be applied to depressed patients (Slapin, 2005). In general the prefrontal activation asymmetries seem to be plastic and susceptible to changes, as a result of the appropriate training (Davidson et al., 1992).

5.4.2 Theta activity

The theta rhythm, with a frequency in a range between 3 Hz and 8 Hz, characterizes a transition from wakefulness to sleep, and is classified as a sleep stage I (Rechtschaffen & Kales, 1968). The increase of diffuse theta slowing in adults who are awake may indicate brain injury (Nuwer, 2005).

In meditation related contexts theta activity has been mentioned in several studies. Increased theta activity can be produced by different relaxation techniques (e.g. Jacobs & Lubar, 1989; Jacobs & Friedman, 2004). Individuals highly trained in self-hypnosis show increased theta activity not only during hypnosis, but also while they are awake (Tebekis et al., 1975). In addition to alpha, theta activity is also mentioned in neurofeedback studies, e.g. as an effective treatment of anxiety disorders (for a review, see Moore, 2000).

A general increase of theta activity during meditation has been reported in a large number of studies. These increases in theta activity were however, never convincingly associated with either a specific meditation technique or the experience level of the subjects (for a review see Cahn & Polich, 2006). On the other hand, some studies investigating certain meditation techniques, attempted to demonstrate theta activity increases as a specific outcome of meditation (e.g. in a recent study by Takahashi (2005) correlating changes in fast theta power (6-8 Hz) in frontal areas with enhanced mindfulness).

There may be several reasons for the conflicting findings of the above mentioned studies. Theta activity itself shows high variability related to different tasks. In contrast to alpha, theta activity may arise without internalizing the attentive focus, for instance, due to a relief from anxiety (Kubota 2001). Anterior theta rhythms have been reported during short-term memory tasks (reviewed in Vertes 2005) and are also densely related to the long-term memory formation. Neocortical and hippocampal theta, as well as gamma rhythms, take part and interact in the formation of declarative memories (e.g. Fell et al., 2003a; Sederberg et al., 2003). It has been speculated that theta activity might reflect a hippocampal state of readiness, in anticipation of incoming signals that need to be processed (Buszaki, 2002). These findings are supported by the results from animal studies indicating that theta activity also appears in the rodent cortex during memory encoding and retrieval (for a review see Kahana, 2001), in particular during spatial navigation (Buszaki 2005). Due to it’s clear effect on transition from wakefulness to sleep, theta activity may be simply related to tiredness and the transition to sleep. Although this interpretation is often not consistent with the subjective reports of meditators, it is difficult to exclude it in the absence of behavioural data. These different types of theta rhythms occurring throughout the brain are likely produced by different mechanisms and do not necessarily have to be functionally related.

Despite its great variability, theta activity in meditators shows some specific characteristics. Several studies describe increasing theta activity (accompanied with alpha activity) in the form of sharp burst or theta trains, which are preceded and followed by alpha rhythm (Banquet, 1973; Herbert & Lehmann, 1977; Kasamatsu et al., 1966). For some authors these findings imply a distinct theta activity found in meditators rather than those that appear during drowsiness (e.g. Austin, 1999), i.e. when the external stimuli recede and imaginations seem to take over (Brown, 1974). The separation between a deep state of meditation and a period of sleep stage I is difficult to distinguish just from the EEG recordings. Meditators may deliberately stay in a theta state over a longer time period, which resembles the deep relaxation state of sleep stage I. However, this state may not be completely equivalent to the sleep stage I, given that the subjects showed ongoing theta activity after the meditation ended with opened eyes and while alert (Hirai, 1974; Kasamatsu & Hirai, 1966).

Taken together the general findings of theta activity related to meditative processes do not provide enough evidence of correlation with a specific step of meditative development. It can be speculated that theta activity may occur after the specifically altered alpha patterns at the beginner/student level are already established in the brain (Aftanas et al., 2005; Travis et al., 1999), possibly as a correlate of increased relaxation. In line with the present hypothesis theta activity may be more closely related to the advanced level of meditative practice.

5.4.3 Gamma activity

An oscillatory frequency of approximatelly 40 times per second (40 Hz), is referred to as gamma activity. The range can however, vary substantially from 20 Hz to 200 Hz as shown in different studies. This lack of precision exists mainly due to the focus on gamma activity of around 40 Hz in early studies on humans (Eckhorn et al., 1988; Joliot et al., 1994; Rodriguez et al., 1999), while recent studies include higher frequency ranges as well (Crone et al. 2006; Lachaux et al., 2005; Müller et al., 2004).

Activity in high frequency ranges related to meditative processes was already observed in the early studies on meditation (Banquet, 1973; Das & Gastaut, 1955). These studies aimed to investigate the EEG changes correlated with the experience of the subjects during different levels of meditation. They involved both beginners and advanced students of a certain Yoga style (Kriya-Yoga, Kundalini-Yoga) and Trancendental Meditation (TM). Both studies reported fast gamma activity with peaks around 40 Hz in both hemispheres. Interestingly, both studies describe these peak-activities only for the highly advanced meditators. These findings should however, be considered with caution due to several methodological deficits (reviewed in Ott, 2000).

Later research on meditators focused mainly on the lower gamma frequency ranges for the following twenty years. With the development of better EEG amplifiers, more efficient recording techniques, and computer-based analysing strategies, high frequency EEG activity regained the interest of neuroscientists. Consequently, more recent studies deal with the occurrence of gamma activity during meditation.

In one recent study four different forms of focused meditation were investigated in a Buddhist Lama (Lehmann et al., 2001). Functional images of the gamma band activity (Electromagnetic Tomography – LORETA) differed significantly among all four forms of meditation. The authors interpreted these findings as evidence that altered states of consciousness are associated with distinguishable patterns of brain activation.

In another study, which concentrated on a mindfulness approach (Lutz et al., 2004), the authors found self-induced gamma-band oscillations to be sustained and phase-synchronized during meditation. These patterns differed between meditators and the control subjects in particular over lateral frontal and parietal electrodes. The largest amplitude increases of synchronous activity were found for the long-term practitioners. The ratio between high (25-42 Hz) and low oscillatory activity (4-12 Hz) was already initially higher for meditators compared to the control subjects at rest baseline before meditation. These differences increased sharply during meditation. The authors describe some of the large-amplitude gamma oscillations as the most pronounced oscillations ever to be recorded in a non-pathological context. The authors further discuss that the level of meditative training can alter the spectral distribution of the EEG in terms of possible permanent baseline changes. Further studies are needed to corroborate this interpretation. In accordance to the present hypotheses these changes seem to be closely related to an expert level of meditation practice.

5.5 Synchronized gamma oscillations in sensory and cognitive processing

The phenomenon of induction and synchronization of oscillations in the gamma frequency range is well known and reported from various areas of neurophysiologic research (e.g. from the integration of sensory stimuli). Here, the findings are a part of a strong body of evidence, suggesting that synchronous cortical oscillations solve a central neuroscientific problem. This has been called the binding problem, which attempts to explain how different features of a perceived object are bound together to become one coherent representation (feature integration). A more specialized aspect of the binding problem is the question of how visual sceneries are spatially segmented into different objects (perceptual segmentation). Complementary to the binding problem is the superposition problem: how are different perceptual entities prevented from interfering with each other, i.e. how are the different features belonging to different objects grouped together and how is mixture or misattribution between them avoided?

The oldest hypothesis about the brain's solution to the binding problem proposed the model of cardinal neurons. In this model, complex information is represented in the brain by convergence of the processing stream to highly specified assemblies or even single neurons (e.g. Barlow, 1972). This model however could not explain why are the objects, perceived for the first time, processed instantaneously by the brain. Moreover, the representation explained by the cardinal neurons model would be very costly and there would not be enough neurons in the brain to account for the astronomical number of possible feature combinations. Nevertheless, it has been experimentally demonstrated that cardinal cells or networks do indeed exist for some kinds of complex representations, for example for face percepts (e.g. Young &Yamane 1992). However, these neurons seem to respond to a class of related complex patterns rather than to individual perceptual objects (e.g. Fujita et al., 1992).

Because of the shortcomings of the cardinal cell hypothesis another binding mechanism proposing a coding mechanism that relies on time based coding at the beginning of the 1980s by von der Malsburg (1994, 1986). The idea is that neurons belonging to one functional neural assembly are bound together by synchronization of their action potentials. Even neurons exhibiting the same firing rate but belonging to different assemblies, could be distinguished on the basis of the relative timing of their discharges. Since neurons could participate in different transient assemblies via slight changes in their action potential timing, this mechanism would be fast and flexible and it would enable the representation of a very large number of feature combinations. The simultaneous action potential firing of associated neurons or assemblies would correspond to phase synchronous oscillations in the domain of field potentials and EEG. Psychophysical evidence suggests that formation and dissolving of transient assemblies has to occur within the fraction of a second. Because of these timing requirements, binding related phase synchronization was expected to be effective for high frequency field potentials and EEG activity.

Experimental evidence supporting the feature binding hypothesis was first reported at the end of the 80s. Synchronization of intracranially recorded gamma activity (20-80 Hz) was observed in the visual cortex of anesthetized cats, when they were presented with coherently moving bars as compared to independently moving patterns (Gray et al., 1989; Eckhorn et al., 1988). This effect could not be attributed to local connectivity because the synchronously firing assemblies corresponded to non-overlapping receptive fields. Later, analogous findings were reported for intracranial recordings on awaken monkeys (Frien et al., 1994; Kreiter & Singer, 1996). With similar experimental paradigms, an amplitude enhancement of occipital gamma activity in human scalp EEG recordings was observed (Lutzenberger et al., 1995; Müller et al., 1996). Considering that it is not possible to separate local synchronization from amplitude effects in scalp recordings, this amplitude enhancement may have also been caused by the increased phase synchronization in the gamma range.

Stimulus-specific phase synchronization of gamma oscillations has not only been observed in the visual domain, but also within the somatosensory (e.g. Desmedt & Tomberg, 1994; Lebedev & Nelson, 1995), the olfactory (e.g. Bressler, 1987; Freeman, 1978), and the auditory system (Brosch et al., 2002). In addition, it has been shown that odour discrimination deteriorates in insects, when synchronization is pharmacologically blocked in neurons of the olfactory bulb, thus yielding a direct proof for the functional role of synchronization (Stopfer et al., 1997). Gamma synchronization was reported to be furthermore involved in learning visuotactile associations (Miltner et al., 1999), in the cognitive integration of visual face perception, task related motor responses (Rodriguez et al., 1999), visual working memory (Pesaran et al., 2002), and in mediotemporal and neocortical memory processing (Fell et al., 2001; Sederberg et al., 2003). Recently, high-frequency gamma oscillations in the range between 60 Hz and 200 Hz have been demonstrated to be relevant for sensory and cognitive processing (e.g. Crone et al., 2006; Lachaux et al., 2005; Müller et al., 2004; Trautner et al., 2005).

Today it is known that phase synchronized gamma oscillations are present at almost every level of information processing. They are crucial for integration of sensory information, cognitive processing, and learning, hence seem to represent a general mechanism enabling a transient association of cortical assemblies (for overviews see e.g. Engel & Singer, 2001; Kaiser & Lutzenberger, 2005; Keil et al., 2001; Tallon-Baudry & Bertrand, 1999; Varela et al., 2001). This mechanism appears to provide effective communication within, as well as between different subsystems of the brain (e.g. Fries, 2005). In the next chapter, the relevance of gamma activity for cortical plasticity and the formation of neural circuits, and how these functions may contribute to the goal of meditative practice, namely the development of new states of consciousness will be discussed.

5.6 Cortical plasticity and meditation related states of consciousness

Neural plasticity comprises the definition of creation of additional neurons and new synaptic connections, as well as the expansion and shift of functional areas. These modifications are most evident in people exhibiting pathologically induced plasticity, for example due to hydrocephalus (Lewin, 1980), or in people who have been trained in specific functions, for example in musicians. A musician can integrate auditory stimuli and motor responses in a way, which enables him/her to play an instrument with the extreme tactile demands in precise rhythmic coordination with other musicians. The neural changes find expression on many levels, including, for instance, the cortical representation of the motor skills (Elbert et al., 1995), or the morphological appearance of certain brain structures such as the corpus callosum (Schlaug et al., 1995). In the same way the brain can be trained to process and integrate visual stimuli fast enough to pilot a supersonic aircraft. Furthermore, the motor specialization enables an expert in gymnastics to perform a difficult choreography. Similarly, meditation training may be accompanied by alterations in neural structures. Indeed, it has been shown by magnetic resonance imaging that long-term meditation practice is associated with an increase of cortical thickness (Lazar et al., 2005).

Although the brain/mind contains and provides the general possibility to realize these changes, behaviouraly it may be restricted by multiple psychological factors such as motivation and talent. From a neuroscientific view, talent is merely a neural pre-specialization that the brain is equipped with from birth. But how may the EEG findings, reported in the last chapter, be related to meditation-induced plasticity and processing circuits?

Members of neural assemblies, phase synchronized in the gamma range, fire action potentials in a highly time locked manner with a precision of a few milliseconds (Chrobak & Buzsaki, 1998; Fries et al., 2001; Jacobs et al., 2007). When these action potentials are propagated to common target neurons they can cooperate to elevate the membrane potential above firing threshold (e.g. von der Malsburg, 1999). Such rapid depolarizations depending on synchronous excitatory synaptic inputs were shown to result from voltage-gated Na^+ and K^+ conductances (Azouz & Gray, 2000). This cooperation does not occur for incoming action potentials that are not time locked, since meanwhile the membrane potential decays depending on the membrane time constants. Thus, synchronized neural assemblies can reliably trigger activity in target neurons. This results in the firing of several target neurons with little jittering, enabling the synchronization of target assemblies (e.g. Marsalek et al., 1997). Such activity propagation has been demonstrated, for instance, from thalamic neurons to neurons in the visual and the somatosensory cortex (Alonso et al., 1996; Roy & Alloway, 2001). In the cat geniculocortical pathway the maximal delay times, for which spikes from two different presynaptic neurons cooperatively enhance postsynaptic firing probabilities, were observed to be around 7 ms (Usrey et al., 2000). Synchronized oscillations in the gamma range were shown to be associated with such precise spike timing (Buzsaki, 1998; Fries et al., 2001; Jacobs et al., 2007).

Gamma synchronization may represent a mechanism for the precise activation of target neurons, and thus for controlling the flow of neural information (Salinas & Sejnowski, 2001). If synchronization occurs between neurons belonging to different feature maps, which project to higher-order neurons in the associative cortex, these higher-order neurons could be reliably triggered (bottom-up). On the other hand, top-down influences from higher-order areas might also be propagated by synchronized gamma activity (e.g. Engel et al., 2001).

As long ago as 1949, Donald Hebb proposed a flexible mechanism for the formation of functionally associated neural assemblies. Hebb postulated an increase in synaptic efficacy in the case of correlated activity of the presynaptic and the postsynaptic neuron. In other words, he proposed that neurons that fire together are wired together. This kind of "Hebbian" synaptic plasticity has been experimentally verified and was found to depend on the interaction between postsynaptic potentials and action potentials backpropagating into the dendrite of the postsynaptic neuron (e.g. Magee & Johnston, 1997; Markram et al., 1997). The most well investigated examples for Hebbian plasticity are long-term potentiation (LTP) and depression (LTD), which provide the basis for models of learning and memory. Hebbian plasticity also represents a mechanism for the refinement of initially imprecise neural connections during ontogenetic development.

The required delay times for effective Hebbian modification of synaptic connections by correlated firing of the pre- and postsynaptic neurons are in the order of less than ± 10 ms (e.g. Abott & Nelson, 2000). Synchronized high frequency EEG rhythms such as the gamma activity could also provide an optimal condition for the establishment and modification of Hebbian neural assemblies and therefore, may be a crucial mechanism in associative learning and memory formation. This view is supported by several recent memory studies (e.g. Fell et al., 2001; Gruber et al., 2004; Herrmann et al., 2004; Miltner et al., 1999; Osipova et al., 2006; Sederberg et al., 2003).

In conclusion, these data suggest that synchronized gamma activity is highly relevant for neural plasticity and the implementation of new processing circuits (for a review see e.g. Axmacher et al., 2006). The findings of strongly increased synchronized gamma activity in meditation experts may thus be related to processes of cortical restructuring and learning. These processes may provide a permanent neural basis facilitating specific meditation-related states of consciousness, as well as altered perception and cognition outside the meditation practice.

5.7 Are meditation related brain/mind states unique?

What is actually meant by the statement that a brain/mind state is unique? A mind state, in other words a state of consciousness, may be considered to be a point or a small area in a state space describing all possible mind states (e.g. Fell et al., 2004). The variables defining the axes of the mental state space (i.e. the co-ordinate system) are then different psychological properties. For instance, Vaitl and colleagues (2005) have suggested a state space for the classification of altered states of consciousness defined by four variables: activation, awareness span, self-awareness, and sensory dynamics. In principle, such a state space should enable separation of different states of consciousness, i.e. states that are subjectively perceived as different. If such states of consciousness cannot be separated, additional psychological variables have to be added to the state space. In the same manner a neural state space may be constructed with different physiological variables. The statement that meditation related states are unique, in this description, means that those states do not overlap with other states.

The basic assumption underlying psychophysical research is that a one-to-one correspondence between mind and brain states does exist (often called psychophysiological isomorphism). This implies that if a certain state of consciousness is unique the corresponding neural state should also be unique. Conversely, for the same state of consciousness the neural characteristics should always be the same, at least with regard to the neural variables linked to the mind domain (not all neural variables are associated with consciousness).

In the present chapter, it is argued that brain/mind states related to meditation practice on the beginner/student level may overlap with brain/mind states that regularly occur outside meditation practice, such as for instance, states associated with moments of relaxation. In other words, it is proposed that there is no qualitative difference between meditation related brain/mind states of beginners and some “regular states”. But unlike the regular states, meditation related states may be prolonged and may occur more reliably. However, brain/mind states related to an advanced/expert level of meditation training are supposed to be unique. Such unique states may be reached because meditation training may not only be associated with the occurrence of certain electrophysiological signatures, but may also stimulate cortical plasticity and involve changes in neural structures (similar to other kinds of training, e.g. learning to play an instrument). In other words, the constituents of the brain, i.e. the dynamical system supporting neurophysiological processes, are modified. These modifications may supply the neural basis for unique brain/mind states associated with new electrophysiological signatures.

The above differentiation is supported by reports of meditation beginners indicating a more reliable and prolonged occurrence of psychological states sometimes perceived outside meditation. On the other hand, experts often report about states of consciousness, which they perceive as new and unique (e.g. Kopp, 1996). After these states have occurred during meditation, they may also be experienced outside meditation.

Is there evidence for the suggested differentiation on the physiological side? As described in chapter 5, meditation related brain states at the beginner/student level were often found to correspond to an increased power and synchronization of low frequency activity, in particular, alpha and theta activity. Such alterations are rather unspecific, because they are also observed during relaxation and transition to sleep, as well as during several so-called altered states of consciousness (see e.g. Vaitl et al., 2005). On the other hand, the few empirical data on meditation experts tentatively indicate that expert states may imply both, an increase of power/synchronization of low frequency oscillations, as well as an increase of power/synchronization of gamma activity. Such a combination of EEG changes is rather uncommon because increased relaxation and transition to sleep are normally associated with a decrease of gamma power/synchronization (e.g. Fell et al., 2003b, Ferri et al., 2000; Mann et al., 1993). However, it is not yet clear, whether such electrophysiological pattern is indeed unique for meditation related brain/mind states of experts or whether it may also occur during other altered states of consciousness.

Summary

The present work gives overview and insight into three different areas of cognitive neuroscience, representing exemplary aspects of the diverse spectrum of research areas: Memory, attention and consciousness.

Research on memory processes distinguishes between working memory (WM) and long term memory (LTM). According to the classical view, the LTM encoding relies on structures in the MTL including the hippocampus and WM processes rely on the prefrontal and parietal cortices. In contrast to this simple dichotomy, however, recent studies have shown that some WM tasks, e.g. those involving novel stimuli, also activate MTL structures. In the first part the question of whether the maintenance of several items in WM, which activates the MTL, influences the encoding of items into LTM is addressed. It is demonstrated that a simultaneous WM/LTM task results in an interference, which affects memory processing capacities in the MTL and leads to a decrease in the LTM performance when accompanied by a high WM load. Furthermore the parahippocampal cortex (PHC) is revealed as a locus of a memory processing interference between WM and LTM for the first time.

Successful information processing requires focusing attention on a certain stimulus property and suppressing irrelevant information. An important paradigm for investigating attentional top-down control in case of interfering stimulus properties is Stroop's interference task (Stroop, 1935). The second part the neural correlates of a newly developed auditory Stroop task are investigated. Using an event-related functional magnetic resonance imaging (fMRI) design, sound files in a tone-pitch interference task were presented, that required subjects to focus on one stimulus property (pitch or meaning of a spoken word) while ignoring the other one. In contrast to visual Stroop tasks a very posterior part of the anterior cingulate cortex (ACC) was found activated in incongruent phonetic trials (as compared to the incongruent semantic trials), together with common regions such as the pre-supplementary motor area (preSMA) and the dorsolateral prefrontal cortex (DLPFC), areas associated with attentional control. In addition, the integration of these regions into a conflict processing network using functional connectivity was shown.

In the context of a theoretical excursus the third part shows within the broad field of consciousness research, how new methods in recoding and analyzing electro-encephalography (EEG) data can lead to a different understanding of the origination of different states of consciousness. The starting point of consideration were recent findings revealing unusual and remarkable alterations in the EEG in meditation experts. Today meditation is considered to be a valuable source deepening our understanding of the neural correlates of consciousness, since meditation experts are usually trained for decades to reach altered states of consciousness. It is suggested that different forms of meditation have similar steps of development, which should be related to similar neurophysiological correlates. Some electrophysiological alterations can be observed on the beginner/student level, which are closely related to non-meditative processes. Others appear to correspond to an advanced/expert level, and seem to be unique for meditation related states of consciousness. Meditation is one possibility of specializing brain/mind functions within the confines of the brain's neural plasticity. This plasticity is likely supported by certain meditation related EEG patterns, for instance, synchronized gamma oscillations. While it has been formerly postulated that meditation comprises mainly passive relaxation states, recent EEG findings suggest that meditation is associated with active states involving cognitive restructuring and learning.

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Abbreviations

ACC	Anterior Cingulate Cortex
ANOVA	Analysis Of Variance
BA	Brodmann Area
BET	Brain Extraction Tool
BOLD	Blood Oxygen Level Dependency
DLPFC	Dorsolateral Praefrontal Cortex
EEG	Electroencephalography
EPI	Echo Planar Imaging
fMRI	Functional Magnetic Resonance Imaging
FEAT	FMRI Expert Analysis Tool
FILM	FMRIB's Improved Linear Model
FLIRT	FMRIB's Linear Image Registration Tool
FWHM	Full width at half maximum
LTM	Long Term Memory
MCFLIRT	Motion Correction using FMRIB's Linear Image Registration Tool
MEG	Magnetoencephalography
MPRAGE	Magnetization Prepared Rapid Acquired Gradient Echoes
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
PFC	Praefrontal Cortex
PHC	Parahippocampal Cortex
preSMA	Pre-Supplementary Motor Area
TR	Time Repetition
WM	Working Memory

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich für meine Promotion mit dem Titel:

**„From memory and attention to consciousness:
Exploring three major aspects of cognitive brain functioning“**

keine anderen als die angegebenen Hilfsmittel benutzt habe, und dass die inhaltlich und wörtlich aus anderen Werken entnommenen Stellen und Zitate als solche gekennzeichnet sind.

(Sven Haupt)