Tracking the mind's image in the brain

Combining evidence from fMRI and rTMS

a multi-methodological approach to the experimental investigation of functional brain-behavior-relationships in the domain of visuospatial processing and visual mental imagery

Dissertation zur Erlangung des Doktorgrades
der Naturwissenschaften

vorgelegt beim Fachbereich Psychologie und
Sportwissenschaften
der Johann Wolfgang Goethe-Universität
in Frankfurt am Main

von
Alexander Sack
aus Frankfurt am Main

Frankfurt am Main (2002)

(D F 1)

vom Fachbereich Psychologie und Sportwissenschaften der Johann Wolfgang Goethe-Universität als Dissertation angenommen.

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Datum der Disputation: 16. Januar 2003

Table of Contents

Preface

Cognitive neuroscience is an entirely new research field that originally emerged from a combination of traditional sciences such as philosophy, psychology, medicine and biology that all investigate the principles of perception, behavior and cognition from different perspectives. As technical developments of different methods and tools in the field of cognitive neuroscience came forth, and as theoretical application of different mathematical and computer science-based models were used to explain neuronal functioning, additional disciplines, such as physics, mathematics, bioengineering and computer science materialized as an important part of this research field. Subsequently, an effective research project in cognitive neuroscience requires an interdisciplinary cooperation, in which each scientific discipline contributes its respective genuine theories, models, techniques and tools for the mutual investigation of the neuronal principles of behavior, perception and cognition.

This dissertation project was conducted as a multi-methodological approach. The conceptual models are provided by cognitive psychology, and the methodological and empirical fundamentals of experimental psychology are combined with the new technical developments in functional neuroimaging in order to explore the organization and functional structure of visuospatial processing and visuospatial imagery. The empirical part of this dissertation consists of two studies. The pilot study, *The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex in visuospatial functions*, was mainly conducted in order to investigate the suitably of the intended methodology approach, and was accepted for publication by *Cognitive Brain Research* in 2002. After the empirical research method proved accurate,

the main study of the dissertation, *Tracking the mind´s image in the brain: Differential effects of repetitive transcranial magnetic stimulation of the right and left parietal lobe*, was conducted, which entailed a more complex design and testing of more cognitive paradigms. This study was presented at the ISNIP 2001 conference in Bern.

The realization of this dissertation was only possible because of the technical and personal support of a number of different people. I would like to thank Professor Ruxandra Sireteanu, who served as my internal advisor and who recognized the importance of the project and helped me to get on the initial course that would become this project two years later. Professor Rainer Goebel of Maastricht University kindly agreed to be the external advisor. The TMS experiments were conducted in the laboratory for Neurophysiology and Neuroimaging of the Department of Psychiatry and Psychotherapy I at Johann-Wolfgang-Goethe-University Frankfurt - Medical School (Head: Prof. Konrad Maurer), and the fMRI experiments at the Department of Neuroradiology (Head: Prof. Friedrich Zanella). I am very grateful to Professor Maurer and Professor Zanella for this unique opportunity. Central to the success of my project was the support of Professor Thomas Dierks, who was the head of the Laboratory when I began as an intern, and who gave constant support and advice.

Also during my internship, I had the pleasure of knowing and working with Dr. Daniela Hubl, co-first author with me on the pilot study, who introduced me to everything in the lab and trained me on the fMRI scanner. Elia Formisano helped me with statistical analysis and visualization of fMRI data. Our projects took a similar set of data and eventually merged with one another, allowing us to combine our respective research and to submit our papers as a back-to-back

project. It is also my pleasure to thank Julia Sperling, who volunteered a great deal of time collecting fMRI data for the main study. I would also like to thank all members of the research lab, currently twelve people of various backgrounds, whose company and feedback I have enjoyed thoroughly in my day-to-day workings. I would additionally like to thank Kimberly Taylor, Abigail Paul and Katrin Linser who helped me with proofreading and editing the finished product. And I would like to give a very special token of gratitude to Dr. Dr. David EJ Linden, who has been a mentor and confidant to me throughout the entire project. He helped to get me interested in the subject, got me started on both studies, and served as senior author on the main study.

Finally, I wish to thank my parents, Friedrich and Gisela Sack and, last but not least Heather Drewett for her unending patience and support.

1 Introduction

1.1 The principle of functional localization

In the early 19th century Franz Josef Gall (Gall and Spurzheim, 1810), the founder of phrenology, speculated that all functions of the mind could be attributed directly to a biological structure. He postulated a variety of discrete cognitive and behavioral functions that directly correspond to discrete areas of the brain. Gall assumed that these brain areas could potentially increase in their structure as a result of the frequency with which the corresponding functions were used. This growth of the brain tissue would induce corresponding local growth of the skull. Hence, according to Gall, it would be possible to conclude from the special anatomical form of the individual skull and its individual cranial bumps, which regions and subsequently which functions are especially pronounced. Phrenology, the science founded on these assumptions, correlated the measurements of behavioral or cognitive functions as well as different personality traits with the individual form of the skull.

The phrenologists were the first to introduce the idea of functional localization of the brain. However, the extremity of their view that each region of the brain can be considered an independent representative of a distinct function, although correct as a general idea, was wrong in its detailed assumptions and not based on any valid experimental evidence. Ironically the phrenological concept of functional organization thus led many scientists to doubt the whole concept and to initiate different attempts of a scientific rebuttal that resulted in a general renunciation of the principle of functional localization (Flourens, 1824; Lashley, 1929).

Among these antagonists of functional localization was Pierre Flourens (1824). He investigated the functional contribution of different brain areas to behavior by inducing localized lesions in animals. The results of his experimental approach led him to the conclusion that individual functions are not carried out by specific brain areas, but that any part of the cerebral cortex participate in all kinds of mental functions. The wide acceptance of his aggregate field theory reflected the desideratum of a counter model to the strict materialistically based postulates of the phrenologists.

In an experimental approach comparable to Flourens (1824), Lashley (1929) studied the consequences of experimentally induced lesions in different regions of rat brains. On the basis of his results Lashley (1929) assumed that the severity of learning deficits does not depend on the precise location of the induced lesion, but on the mere extent of the induced brain damage. Similar to Flourens (1824), he concluded that learning and other cognitive functions could not be localized in one particular region of the brain. Lashley (1924) advanced the view of the aggregate field theory to the theory of mass action, which denied even more clearly the idea that behavior or cognition could be related to individual neurons, particular networks of interconnected neurons or any functionally specific brain regions in general.

The first neuropsychological studies in humans were also based on lesions or brain damages. In these studies scientists like Broca (1865) examined the brain of a patient post mortem and made inferences about the relationships between the observed brain pathology and behavioral or cognitive deficits.

The German neurologist Carl Wernicke (1908) established a theory of brain function that is known as cellular connectionism. He revealed the existence of single individual neurons which represent a generally independent signaling unit and which connect in a very precise and organized manner into different functional groups. In this theory, different functions can also be mediated by different functional groups in different brain areas that are interconnected via neuronal pathways. Wernicke (1908) acknowledged the fact that a complex cognitive function consists of different components that are carried out at different regions of the brain, interconnected to an organized activation network. This view widened the idea of localized functions in the brain by incorporating this principle into a more complex interconnected localized functional network.

Based on this principle of distributed processing Brodman (1909) tried to identify different functional regions in the brain on the basis of their cytoarchitectonical structure. This approach categorized the functional regions based on the distribution of particular nerve cells with distinct structures as well as the characteristic organization of these cells into layers. By following this approach Brodman was able to distinguish 52 different structurally distinct areas of the brain, the so-called Brodman areas (Brodman, 1909).

With the advent of cognitive psychology in the last decades of the 20th century, a systematic approach to the development of sophisticated models of cognitive functions and the possible segmentation into different subfunctions was introduced. Cognitive psychology provided the theoretical and empirical background for the realization that every cognitive function is composed of

several independent components within an information processing model that requires the coordinated serial and parallel activation of different brain regions.

Cognitive psychology combined with the recently developed neuroimaging techniques provided the opportunity to actually visualize the functional fractionization of mental operations into simpler operations proposed by cognitive psychology. This enabled the in vivo localization of the respective regional neuronal substrates that are activated within a specific interconnected cortical network during the execution of these functions.

Today, in a multi- and interdisciplinary approach, the conceptual models of cognitive functioning and information processing provided by cognitive and general psychology in conjunction with the methodological and empirical fundamentals of experimental psychology are combined with the new technical developments in functional neuroimaging in order to explore the organization and functional structure of cognitive constructs in the human brain. Researchers representing different scientific disciplines such as psychology, medicine, physics, biology, mathematics or computer science are now working together in the new emerging field of cognitive neuroscience, in which each of these scientific disciplines contribute its respective genuine theories, models, techniques and tools for the mutual investigation of the neuronal principles of behavior, perception and cognition.

Cognitive neuroscience is based on the principle that every behavior, perception, and cognition reflects an organized neuronal activation in the brain.

Among the list of main objectives in cognitive neuroscience are questions concerning the location, function and temporal sequence of cortical activities in relation to behavior and cognition. A great amount of neuropsychological studies, and especially those using techniques of functional imaging, have provided information on the location of different perceptual and cognitive functions in the brain.

A key objective of cognitive neuroscience is to elucidate causal relationships between brain activations and perception, behavior or cognition.
Cognitive neuroscientists recognize that, besides the mere localization of brain functions, an understanding of the performance of even the simplest task requires the analysis of the different components of its execution, its functional connectivity and interactions in different regions of the brain.

Several neuroimaging studies have been conducted to investigate these functional neuronal correlates of human elementary perceptual processing, motor control, emotions and cognitive functions in vivo. The application of imaging techniques to the investigation of brain areas activated during ever more and more elaborate experimental paradigms has increased extensively in the last ten years. Since its final application to cognitive science, functional imaging has opened the door to the observation of functional brain organization.

1.2 Functional Imaging

1.2.1 Brief history of functional imaging

Several researchers of the 19th century contributed to the physiologically based investigation of functional brain organization (for review see Raichle, 1998). In 1881, the Italian physiologist Mosso (1881) was the first to recognize that neuronal activity corresponds to a regional increase of cerebral blood flow (rCBF) in humans. Similar effects were observed in animals some years later by Roy and Sherrington (1890). However, the absence of appropriate experimental techniques to validate these assumptions as well as the theoretical disagreement of several other researchers of that time (Hill, 1896) prevented a continuation of these pioneering projects (reviewed in Raichle, 1998) and resulted in a period of almost fifty years in which no attempts were made to reactivate these approaches.

The introduction of an autoradiographic method in 1955 (Landau et al., 1955; Lassen et al., 1963) marked the beginning of a series of technical developments, which enabled the actual measurement of cerebral blood flow in humans. Two important landmarks in this development to measure cerebral blood flow as well as metabolical changes in the living brain were the introduction of Positron Emission Tomography (PET) (Ter-Pogossian et al., 1975) and Nuclear Magnetic Resonance Imaging (MRI) (Lauterbur, 1973). However, for the first ten to twenty years these techniques were almost exclusively used for mere neuroanatomical and neuropathological studies.

Hence, despite these technical achievements, the actual use of these neuroimaging methods by cognitive scientists in order to measure physiological

changes corresponding to neuronal activation during the execution of different cognitive tasks did not occur until the early 1980s. One motivation for the final realization of functional neuroimaging studies in cognitive neuroscience was the adaptability of these techniques to the experimental designs of cognitive psychologists and their strategies of “cognitive dissection“ of mental processes (Raichle, 1998).

The first attempt to apply MRI to the experimental study of brain functions was realized in 1991. This approach was based on the determination of the cerebral blood volume (CBV) quantified by the signal decrease due to the dephasing effects induced by the first passage of an intravascular contrast medium (Gd-DTPA) in non-refocused (T2* weighted) MR images (Rosen et al., 1991).

In the next step it was possible to measure CBV changes determined by local brain activity. In 1991 this development led to the first functional mapping results in the visual cortex obtained during visual stimulation (Belliveau et al., 1991).

In the following years the application of MRI to functional brain imaging increased extensively. Yet, the first of these studies still used an external contrast medium in order to obtain the functional images.

Already in 1990, Ogawa and colleagues (Ogawa et al., 1990) had reported that MRI was sensitive enough to show “blood oxygenation level-dependent“ (BOLD) signal changes *in vivo*. The utilization of this physiological contrast effect of activity-related MR changes was based on the earlier observation that

changes in the oxygenation level of hemoglobin result in changes of its magnetic properties (Pauling and Coryell, 1936).

Since neuronal activity is accompanied by increases in regional cerebral blood flow and hence by local changes of the blood oxygenation level (Fox and Raichle, 1986), it was appreciated that imaging the signal changes due to the blood oxygenation level (BOLD) was a suitable technique to investigate neuronal activity without the need for an external contrast medium.

In 1992, several groups applied this BOLD-based fMRI to the functional investigation of the human brain (Ogawa et al., 1992; Kwong et al., 1992; Bandettini et al., 1992), marking the beginning of a qualitatively new era of functional imaging techniques (for review see Kim and Urgubil, 1997).

Today a variety of different imaging techniques are applied to the study of the activation of neuronal networks during the exposure to different perceptual stimulation paradigms or during the performance of different behavioral and cognitive tasks. Among these neuroimaging techniques are Magneto-Encephalography (MEG) and Electroencephalography (EEG), Near-Infrared Spectroscopy (NIRS), Single-Photon Emission Computed Tomography (SPECT), and the aforementioned Positron Emission Tomography (PET).

However, functional Magnetic Resonance Imaging (fMRI) represents the latest development of these neuroimaging techniques and takes a special place within this area due to its excellent spatial and good temporal resolution.

1.2.2 Magnetic resonance imaging (MRI)

Since its development in the early 1980´s MRI has proven to be a very powerful tool for structural imaging. In direct comparison to other available imaging techniques, like PET or SPECT, MRI uses a signal that is intrinsic to the tissue, and a signal contrast that is solely based on biochemical tissue properties. Since MRI operates on the radio frequency (rf) energy band and since most biological tissue is transparent at this energy level, the resolution quality does not decrease with tissue depth. Moreover the radiation in MRI is completely nonionizing and has no destructive effect on the tissue.

The physical principles underlying MRI are based on a phenomenon called nuclear magnetic resonance, which refers to the distinct behavior of nuclei with odd numbers of protons that are exposed to a static magnetic field. The physical term of magnetic resonance refers to the reciprocity between the spins of protons and externally applied magnetic fields. Protons that are exposed to a strong static homogeneous magnetic field physically behave like small spinning bar magnets and orientate themselves parallel to this magnetic field by developing a net alignment of their spin axes along the direction of the applied magnetic field. This equilibrium state of the protons can be disturbed by applying a brief magnetic pulse with a radio frequency (rf) exactly equivalent to the energy difference between parallel and antiparallel alignment of the protons to the static magnetic field. This applied pulse of radio waves provides the energy to flip the spinning protons away from their equilibrium state into a different alignment angle that in turn depends on the duration of the applied radio frequency pulse. Usually the aspired alignment is 90 degree from the

alignment parallel to the static field because at this angle the observable output signal is at its maximum.

This ability of the protons to absorb the energy provided by externally applied radio frequency pulses is called nuclear magnetic resonance. After the rf pulse is turned off, the protons return to their equilibrium state, which represents a lower-energy state, and in turn release this energy as a signal in the form of radio waves. In physical terms, the nuclear spins of the protons reemit the energy following the applied rf pulse in a rf magnetic field that decays with time as a function of the spin system returning to its equilibrium state. This magnetic field produces an induced voltage in a respective coil. The magnitude of this induced voltage in the receiving coil changes over time in dependence of the different chemical and physical properties of the local tissue surrounding the protons, enabling the inference about the anatomical structure of the imaged tissue. These principles are the basis of the so-called free induction decay (FID) signal in MRI.

Prevalently, a second rf pulse with a duration that leads to a flip angle of 180 degrees is applied after the initial rf pulse. This refocusing pulse reverses the dephasing of the spins and thus creates a so-called spin echo at a time that equals twice the time between the two applied rf pulses. Sequences using this technique are called gradient echo sequences and are more robust against possible static magnetic field inhomogeneity.

The frequency of the FID depends on the distinct magnetic field from spins in the different tissues, and thus enables an analysis of the voltage output based

on these frequency differences, resulting in an image of the proton density at any point in space. The main contrast for this image generation is the density of protons, and since most protons are part of the H_2O molecules, this contrast mainly represents the tissue water content. Nonetheless, there are two other contrast parameters that can be extracted in MRI. These contrast parameters are based on the fact that the rate with which protons return to a lower-energy level, their so-called relaxation, can be characteristically described by distinct time constants. There are two types of relaxation times important for MRI. One is called the longitudinal relaxation time (T1), representing the time the spin system needs to recover to its thermal equilibrium, and the second one is called the transverse relaxation time (T2), representing the time needed by the excited spins to develop a phase incoherence before relaxing back to the equilibrium state. Both of these times depend on certain properties of the tissue surrounding the protons and thus represent contrast parameters that can be visualized in the obtained images as different image intensities. This technique allows the discrimination of different components of the tissue.

However, although all of the described contrast parameters in MRI are very useful in imaging the anatomical structure of the brain tissue, none of them is affected by electrical activation in the neuronal structures or modulated by metabolic processes accompanying neuronal activity. The application of MRI for the imaging of functional processes in the brain thus requires a different approach, or rather a different signal contrast, to be imaged.

1.2.3 Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) utilizes the technique of magnetic resonance imaging (MRI) in order to visualize brain signal dynamics that represent indirect measurements of neural activation.

The general principle of BOLD fMRI is based on the characteristic relationships between blood flow and oxygen consumption, which are both associated with neuronal activity. As already described by Pauling and Coryell (1936), oxyhemoglobin and deoxyhemoglobin differ in their magnetic susceptibility. Ogawa et al. (1990) could demonstrate that the level of cortical blood oxygenation influences the signal decay rate in MR images by revealing that the visualization of cortical blood vessels can be improved by decreasing the blood oxygen level. The authors postulated that this phenomenon was brought about by local magnetic field inhomogeneities produced by different blood oxygenation levels and thus termed it the blood oxygenation level dependent (BOLD) signal. Turner et al. (1991) were able to visualize the actual time courses of these oxygenation changes while an animal breathed a nitrogen, oxygen-deprived, atmosphere. Similar oxygenation changes were revealed in humans when holding their breath (Kwong et al., 1992).

Several following studies demonstrated the applicability of this BOLD contrast signal for functional imaging in humans (Kwong et al., 1992; Ogawa et al., 1992; Bandettini et al., 1992; Frahm et al., 1992).

The idea of using the BOLD signal as an indirect measurement of neuronal activity is based on the observation that neuronal activity results in regional

cerebral blood flow (rCBF) that is uncoupled from the actual regional oxygen consumption (Fox and Raichle, 1986) and thus leads to a decrease of deoxyhemoglobin.

Using Near Infrared Spectroscopy (NIRS), Grinvald et al. (1991) were able to demonstrate that visual stimulation first leads to an increase of the deoxyhemoglobin level in the occipital cortex, due to the local increase of oxygen demand that is not yet compensated by an increased rCBF. The following increase of CBF and oxygen supply exceeds the actual oxygen consumption and hence leads to a net decrease of the local deoxyhemoglobin level. The decrease of deoxyhemoglobin partly spreads out to the surrounding areas (Kim and Ugubil, 1997; Grinwald et al., 1991). Similar observations of a focal uncoupling of CBF and oxygen consumption during neuronal activity had been made using PET (Fox and Raichle, 1986).

Due to the presence of iron in hemoglobin molecules, deoxygenated hemoglobin is paramagnetic and thus acts like a little magnet when exposed to a static magnetic field. The signal changes detected with BOLD fMRI are thus mainly determined by these paramagnetic properties of deoxyhemoglobin (Kim and Ugubil, 1997). Concretely, deoxyhemoglobin enhances the spin phase dispersion and thereby affects the transverse relaxation (T2) and especially the non-refocused transverse relaxation time (T2*). The strength of this effect depends directly on the absolute local concentration of deoxyhemoglobin and is especially pronounced in red blood cells or blood vessels because of the compartmentalization of deoxyhemoglobin. The T1 relaxation time remains unaffected by the deoxygenation level because the relaxation enhancing group

of the globin molecule is located inside a hydrophobic region (Kim and Ugubil, 1997).

Speaking in terms of BOLD fMRI, the initial increase of the deoxyhemoglobin level decreases the T2* MR signal, while the later decrease of the deoxyhemoglobin level results in a respective increase of the MR signal. Deoxyhemoglobin thus represents an intrinsic contrast parameter that dephases the spins of the protons in the surrounding tissue. Physically this dephasing of the spins results in a MR signal loss which in turn depends on the absolute concentration of deoxyhemoglobin. Since oxygen neutralizes the effect of the iron, oxygenated hemoglobin is diamagnetic and has no such paramagnetic properties. An increase of cerebral blood flow decreases the concentration of deoxyhemoglobin which in turn increases the rate of signal decay and the corresponding MR signal intensity, building the foundation of the so-called blood oxygenation level dependent (BOLD) contrast signal. The regional cerebral blood flow (rCBF) associated with neural activity surpasses the actual oxygen utilization (Fox and Raichle, 1986) leading to an increase of the oxygen level in active brain regions. This hyperoxygenation is caused by an increased cerebral blood flow that does not match the actual oxidative metabolism. Due to the diamagnetic properties of oxygenated blood, the magnetic susceptibility gradient and subsequently the extent of the T2* spin dephasing is reduced, leading to an increase of the MR signal intensity in these regions.

In sum, an increase of rCBF associated with neural activity decreases the regional concentration of deoxyhemoglobin, resulting in a signal change

detectable by the MR scanner. This method thus uses the blood oxygenation level as an endogenous contrast agent for the BOLD signal based fMRI, which enables the noninvasive observation of the hemodynamic changes associated with neuronal activity without the necessity of an exogenous contrast agent.

1.2.4 Echo-Planar imaging

MR sequences that are most efficient for imaging of functional brain activities have to be fast as well as sensitive to changes of the oxygenation level in the tissue. Sequences that best fulfill these requirements are gradient-echo imaging techniques with extended echo times and high-speed echo-planar imaging (EPI) (Cohen and Weisskoff, 1991; Stehling et al., 1991). Gradient echo and EPI mainly differ in their spatial resolution and data acquisition time. Gradient echo represents a multiexcitation sequence and has a higher spatial resolution than EPI (Frahm et al., 1993), but at the same time requires a much longer scanning time (Xiong et al., 1999).

Due to its short scanning time the EPI sequence is considered to be the method of choice in fMRI experiments (Kwong, 1995; Edelman et al., 1994), providing the opportunity to conduct fMRI experiments with high temporal resolution (event-related fMRI). EPI sequences provide a signal-to-noise ratio suitable for functional imaging studies and simultaneously offer a high temporal sampling rate on the basis of an image acquisition time of approximately 100 ms.

The difference between conventional MRI sequences and EPI lies mainly in the different relationships between the space of sampled MRI data, the so-called k-space, and the actual image space. In conventional MR sequences a concrete

series of rf pulses is used to scan the tissue representation in k-space. Following each of these rf pulses, a constant number of data samples is acquired at equal time intervals corresponding to equal intervals in the k-space. The time between the scanning volumes (TR) allows the excited protons to recover before the next line of the k-space is targeted. This technique thus requires a time equaling the number of rf pulses minus TR in order to obtain the information needed to reconstruct a complete image of the sampled data. In single-shot EPI all required k-space data necessary for the image reconstruction is completely acquired after a single rf pulse. Because the MR signal following a rf pulse decays rapidly, this data sampling has to be done in less than 100ms. EPI sequences therefore are characterized by a very high sampling rate and a very rapid scanning of the complete k-space. These requirements are achieved by applying rapidly alternating magnetic field gradients.

The actual data acquisition in EPI sequences occurs during the MR signal decay (T2*). The time between the rf pulse excitation and the data acquisition is called the echo time (TE), which determines the sensitivity of the image acquired by EPI sequences for the rate of MR signal decay. Besides the covering of k-space through rectilinear trajectories performed by most EPI sequences, a spiral imaging of the k-space involving an intrinsic flow compensation by using curved trajectories is also possible (Edelman et al., 1994).

1.2.5 The role of fMRI in cognitive neuroscience

The development that led to the application of MRI in visualizing and mapping functional neuronal processes of the human brain represents a landmark in cognitive neuroscience. In comparison to other neuroimaging techniques, like PET or SPECT, fMRI offers a variety of unique advantages that underpin its inimitable position within the techniques of functional imaging. Among these advantages are the noninvasive character of fMRI, the possibility to frequently repeat studies of individual subjects, the high spatial and satisfying temporal resolution and the suitability of fMRI for a variety of experimental designs provided by cognitive psychology.

As a result, functional magnetic resonance imaging has been used extensively in the last 5 – 10 years in order to investigate *in vivo* the functional localization and organization of higher visual and cognitive functions like visuospatial processing and mental imagery.

1.3 Functional imaging studies

1.3.1 Functional imaging of visuospatial processing

The first applications of functional magnetic resonance imaging (fMRI) focused on investigations of basic perceptual (Rosen et al., 1991; Belliveau et al., 1991; Ogawa et al., 1992; Kwong et al., 1992) and motor (Kim et al., 1993) functions.

Recently the scientific focus shifted towards a detailed analysis of ever more specialized components of higher perceptual as well as more complex cognitive processes. Unlike basic visual processing tasks in which specific visual features like color, size or texture can easily be manipulated, the execution of more complex cognitive functions generally requires the recruitment of multiple brain areas which process multiple abstract features of stimuli or subserve operations with unknown dimensional scales. Thus, in comparison to basic perceptual and motor processes, knowledge of the functional organization of higher perceptual or cognitive functions is still limited.

When fMRI was applied to study the cerebral mechanisms of visuospatial processing, partly overlapping fronto-parietal networks were identified during the performance of tasks dependent on spatial location matching (Haxby et al., 1991; 1994), mirror reading (Goebel et al., 1998; Poldrack et al., 1998), and the discrimination of angle differences on visually presented analogue clocks (Dierks et al., 1999). Other studies also revealed activation of the superior parietal lobe during different visuospatial tasks like spatial attention (Posner and Peterson, 1990), visual attention and eye movements (Corbetta et al, 1998), visuospatial transformations (Cohen et al., 1996; Carpenter et al., 1999), visual search (Leonards et al., 2000), and spatial memory (Diwadkar et al., 2000).

Parametric variation of the demand on specific visuospatial functions revealed a differential modulation of the intraparietal sulcus (IPS) regions bilaterally in response to increased difficulty of visuospatial transformations (Carpenter et al., 1999) and a separation of the visuospatial transformation and oculomotor systems in the parietal lobes (Goebel et al., 1998).

Shikata et al. (2001) investigated which areas of the human parietal cortex are involved in the perception of surface orientation. In their event related fMRI study, the authors presented stimuli with texture gradients as monocular depth cues. In comparison to a color discrimination task, subjects showed an increased activation in the intraparietal sulcus during surface orientation discrimination. Moreover, the signal changes in the posterior intraparietal sulcus were more closely related to the performance than those in the anterior intraparietal sulcus.

Ng et al. (2000) showed that fMRI combined with human lesion studies can clarify hemispheric differences in visuospatial functioning. Using fMRI the authors revealed a significant activation in the superior parietal lobe bilaterally during the performance of a modified version of the Benton Judgment of Line Orientation (JLO) test. This result of bilateral activation of parietal regions during visuospatial tasks was supported by lesion data in which significant JLO deficits occurred after right and left parietal damage. However, right parietal damage resulted in a more severe visuospatial deficit and a detailed wavelet analysis of the fMRI time courses revealed a dominant role of the right parietal lobe in initiating the task execution.

However, evidence to a potential lateralization of parietal activation during visuospatial tasks is contradictory. While Kosslyn et al. (1994) found activation during the performance of visuospatial tasks in the right inferior parietal lobe, Alivisatos and Petrides (1997) observed visuospatial task dependent activation in the left parietal cortex. Goebel et al. (1998) report no specific lateralization of parietal activation during visuospatial tasks, although their results showed a tendency towards a stronger and more consistent activation in the left hemisphere.

1.3.2 Functional imaging of visuospatial imagery

Several imaging studies revealed the involvement of the so-called dorsal pathway (Ungerleider and Mishkin, 1982) in different imagery tasks which included a spatial processing component, suggesting that the dorsal pathway also underlies spatial processing of visual mental images (Cohen et al., 1996; Kawashima et al., 1995; Kosslyn et al., 1993; 1998; Mellet et al., 1995; 1996; Tagaris et al., 1997).

The phenomenon of visual mental imagery has for a long time been an issue of controversal debate in cognitive psychology (Kosslyn, 1980). With the advent of functional imaging techniques, mental imagery has been investigated in several imaging studies revealing that the frontoparietal networks activated during perceptual visuospatial tasks, also seem to be involved in visuospatial imagery (Trojano et al., 2000; Lamm et al., 2001; Mellet et al., 1996).

However, the question whether visual imagery and visual perception functionally share the same cortical areas is still under debate in neuropsychology. The two most important issues within this debate are the question whether mental imagery involves activation of primary visual cortex and whether there is a hemispheric asymmetry in mental imagery.

While the extent of the involvement of occipital areas is still a matter of debate (Klein et al., 2000; Mellet et al., 2000; Mellet et al., 1998; Roland and Gulyás, 1994; Kosslyn et al., 1994), bilateral intraparietal sulcus was found to be activated in visual imagery when spatial comparison between imagined objects had to be performed in the mental clock task (Trojano et al., 2000). These

activated areas in the posterior parietal lobe showed a high overlap between visual matching of perceived and imagined clocks, which was interpreted as evidence for a common neural basis for the analysis of visual space in perception and imagery (Trojano et al., 2000). A single-trial fMRI study of the mental clock task revealed different components of the fronto-parietal network, according to their place in the temporal sequence of activation (Formisano et al., submitted).

Several studies showed a left hemispheric dominance for image generation (Farah et al., 1985; D´Esposito et al., 1997), while other studies found a right hemispheric dominance or no hemispheric asymmetry (Kosslyn et al., 1996; Le Bihan et al., 1993; Mellet et al., 1995).

In a critical clinical review on visual mental imagery Trojano and Grossi (1994) present a number of single cases as well as group studies which demonstrate a dominant role of left posterior parietal areas for mental imagery. Nonetheless, the authors also report evidence of the role of the right hemisphere in visuospatial imagery as well as in perceptual visuospatial processing. Right brain damaged patients with neglect also show neglect symptoms in imagery tasks, and non-neglect right hemisphere patients show visuospatial deficits in perceptual visuospatial processing and during imagery tasks. While the left hemisphere seems to have a specific role for mental imagery, the right hemisphere seems to be of a more general relevance for visuospatial functions (Trojano and Grossi, 1994).

Mellet et al. (2000) investigated mental imagery tasks based on verbal descriptions and visual presentation. The authors revealed a similar pattern of activation in both imagery tasks, including inferior temporal, prefrontal and parietal areas, and could thus show that imagery based on verbal instructions result in activations of higher visual processing areas. The structures within the dorsal pathway which are known to be crucial for visuospatial processing of perceived visual stimuli can thus also be activated by mentally constructed images based on auditory verbal stimuli. The bilateral parietal activation found in this study could be a result of the required spatial processing of the generated images and reveal the modality-independent involvement of the dorsal stream in spatial operations based on visually as well as verbally presented stimuli. The authors also found activation in ventral stream regions including the right inferior temporal area. This association of the ventral pathway with visual object or visual shape imagery has been shown in a variety of other studies on mental imagery (D'Esposito et al., 1997; Kosslyn et al., 1993; Mellet et al., 1996; 1998a; Roland & Gulyas, 1995) and suggests the specific involvement of this region for object shape processing in visual perception as well as visual imagery.

Trojano et al. (2000) used fMRI to explore the neuronal substrate of visuospatial mental imagery and to investigate whether the parietal regions activated during perceptual visuospatial tasks are also activated during the execution of spatial judgments based on mentally imagined stimuli. Trojano et al. (2000) used a behaviorally controlled imagery task which enabled them to verify the actual execution of the imagery task online. The authors found a bilateral posterior parietal activation during the execution of the mental clock task and could thus

reveal a similarity of parietal lobe activations between perceptual visuospatial processing and visuospatial mental imagery.

Despite this large body of neuropsychological and functional imaging studies on different aspects of visual mental imagery, no currently available model of mental imagery is able to explain the inconsistent imaging and neuropsychological data.

One methodological approach to reveal deeper insights into the specific functional relevance and lateralization of activation networks underlying visuospatial processing and visuospatial imagery has been the experimental combination of evidence from lesion and imaging studies (e.g. Ng et al., 2000). Yet, the scientific value of these combinations is restricted due to a variety of methodological limitations of functional imaging and lesion studies for the investigation of brain-behavior-relationships.

1.4 Limitations of functional imaging for the investigation of brain-behavior-relationships

The different techniques of functional imaging are capable of demonstrating on-line an association between different behavioral or cognitive functions and patterns of neuronal activity.

Within strict and carefully designed functional imaging studies it seems possible to conclude with a certain reasonability that the observed correlation between the applied behavioral or cognitive tasks and the measured brain activations can be attributed to a respective causal relationship.

However, despite the prominent advances and possibilities provided by functional imaging, the functional relationship between the passively measured brain activity and the investigated cognitive functions still has to be inferred. When making this inference one has to consider that the observed changes in neuronal activation, measured by indirect parameters of biochemical changes associated with this increased neuronal activity, and the execution of a particular cognitive function do not automatically have to be causally related. A brain region that shows increased metabolic activity during the execution of a certain function might as well reflect the attempt of this area to stop or inhibit the execution of this function or to inhibit other functions that are competing with the successful execution of the respective function. The activated brain area could theoretically also just be accidentally activated or the activation could be merely epiphenomenal in reference to the cognitive function in question. The methods of functional neuroimaging thus provide evidence for transient local increases in neuronal activity, but they reveal little about the nature of this activity, e.g.,

whether it is inhibitory or excitatory (Raichle, 1998) or whether the task-correlated activation in one brain area might be a non-functional by-product of activation in other areas. Furthermore, in the case of an identified distributed network of cortical activity during the execution of a complex cognitive task, functional imaging is not capable of distinguishing the different contributions of different brain areas within a complex task execution that consists of multiple components.

In sum, the mere computation of a correlation between neuronal activity and certain stimulation paradigms or cognitive tasks does not allow any assumptions about the causal relationship or functional relevance of the measured neuronal activation patterns for the actual performance in these tasks.

This methodological limitation of causal interpretations is brought about by the experimental designs used in neuroimaging studies. In these studies brain activity is measured while subjects execute different cognitive tasks. The different operationalizations of neuronal activity are the dependent variables whose variance is analyzed with regard to the chosen stimulation protocol (the cognitive task). The experimenter can only control and manipulate these stimulation protocols as independent variables and analyze the influence of the execution of the different tasks on brain activity. Functional neuroimaging can thus establish associations but not causal relationships between task performance and patterns of cortical activation.

Speaking in terms of causality, a brain region can only be considered functionally relevant for a certain behavior or cognitive performance if this region is a) activated during the performance of the particular task (showing a temporal association revealed by e.g. fMRI), and b) if a controlled manipulation of this regional activity results in a modulation of task performance.

As a result, the experimental investigation of causal brain-behavior-relationships would require a combination of studies in which brain activation patterns during the execution of different cognitive tasks would first be measured as a dependent variable and afterwards these identified activated brain areas would have to be turned into independent variables that can actually be controlled and manipulated by the experimenter within an experimental design.

Besides the possibilities provided by functional imaging, such a methodological approach requires a technique that enables the local manipulation of neuronal activity.

The following chapter describes a recently developed technique called Transcranial Magnetic Stimulation (TMS) that provides exactly this possibility due to its capacity to manipulate brain activity as an independent variable and to investigate its influence on the performance of different cognitive tasks. TMS thus can be regarded as a tool for the investigation of causal relationships between the physiological parameters measured as operationalizations of brain activity and the behavioral task performances.

1.5 Transcranial Magnetic Stimulation (TMS)

1.5.1 History and development of TMS

In 1831 Faraday discovered the principle of mutual induction which addresses the physical phenomenon that electrical fields can be converted into magnetic fields, and magnetic fields can be converted into electrical energy. Based on this principle, Faraday described the so-called electromagnetic induction, which refers to the possibility to produce a current in a conductive medium by either moving the conductive object through a static magnetic field, or by placing the conductive object into a time-varying magnetic field.

The technique of TMS depends on these basic principles of mutual and electromagnetic induction. The first systematic experiments with magnetic stimulation were conducted by d'Arsonval in 1896. He was able to produce phosphenes (flickering lights in the visual field), vertigo, and even syncope after placing a subject's head inside a powerful magnetic coil. Nonetheless, several scientists speculated later that these phosphenes were mere magnetophosphenes, the result of a direct stimulation of the retina rather than of the visual cortex (Barlow et al., 1947; Dunlap, 1911; Magnusson and Stevens, 1911; Thompson, 1910; Walsh, 1946).

In 1902, Beer replicated this finding and reported that phosphenes could also be produced by applying an oscillating strong magnetic field to the head (Beer, 1902).

Since that time several researchers have attempted to construct different magnetic stimulation devices in order to produce and investigate phosphenes

systematically (Dunlap, 1911; Magnusson and Stevens, 1911; Thompson, 1910). Unfortunately these devices were very slow to recharge and thus very restricted in their intensity and frequency capabilities. Nonetheless, the development of more precise and more powerful magnetic stimulators continued and still continues until the present day.

Magnetic stimulation of isolated nerves was accomplished only several decades later, first in the frog by Kolin et al. in 1959 and then in the human peripheral nerve by Bickford and Fremming who, in 1965, demonstrated the non-invasive magnetic stimulation of facial nerves. In 1982 Polson et al. produced and described a magnetic stimulator for peripheral nerve stimulation. Using pulses of 2 ms duration they recorded the first motor evoked potentials (MEP´s).

An important landmark and maybe the beginning of modern TMS was the development of the first modern TMS device by Barker et al. in 1985. By stimulating the human motor cortex and inducing the respective motor contractions they measured the connectivity and excitability of the motor cortex in healthy subjects. Moreover Barker et al. (1985) realized the first clinical examinations by comparing conduction times of motor response in healthy subjects and patients with different neurological diseases (Barker et al., 1985; 1986).

1.5.2 Basic physical principles of TMS

Faraday (1831) was the first to describe a relationship between time-varying electric and magnetic fields. He could show that an induced electrical current in a receptive circuit occurs either as a result of a) the current in a nearby curcuit

being switched on and off in an oscilating manner, b) a nearby circuit with a steady current moving with respect to the first circuit or c) a permanent magnet moving into or out of the circuit. He explained the temporally induced current by a changing magnetic flux connected through the circuit, which induces a surrounding electric field. The integral of this electric field around the circuit is called the electromotive force, which is proportional to the change rate over time of the magnetic flux connecting the circuit.

Transcranial magnetic stimulation (TMS) is based on these principles of electromagnetic induction. A large and brief pulse of current is discharged into an electromagnetic coil held above a subject's head. This current produces a time-varying magnetic field perpendicular to the current lasting for approximately 100 to 200 microseconds. This magnetic field passes into the tissue and induces a perpendicular electric field. The strength of the induced electric field mainly depends on the rate of change of the magnetic field. Due to the electrical conductivity of the living tissue, the electric field leads to an electrical current in the cortex parallel but opposite in direction to the current in the coil (Lenz´s law), and subsequently to a depolarization of the underlying neurons (Hallett, 2000).

Physically the change rate of the electrical current in the coil determines the strength of the induced electrical field. Therefore the electrical field has its maximum at the instant of the switching on of the electrical current since this point marks the maximum rate of change of the current. With increasing current strength this change rate decreases and consequently the induced electrical field strength decreases as well, reaching zero at the current`s maximum value.

With current decrease the change rate increases again exponentially to another change rate maximum creating another peak in the induced electrical field. Consequently, the induced electrical field has two pulses, the first approximately 100 µs long, and the second about 150 µs long and slightly less intense.

1.5.3 TMS hardware

The TMS apparatus itself consists of two major devices: a main power pulse generation unit that charges a bank of capacitors capable of producing high discharge currents, and an electromagnetic stimulating coil to apply magnetic pulses of 1 to 2.5 Tesla. The capacitors are rapidly discharged through the coil which is connected to the stimulator by a strong copper cable carrying the high and rapidly changing currents (approximately 2000 volt; 10.000 ampere) in order to create the very short magnetic field pulses (approximately 250 µs). The main unit also allows the setting of stimulation frequency and intensity either directly at the unit or externally via a special triggering software.

The two types of coils most widely used are the circular coil and the figure-eight coil, both coated by characteristically shaped plastic covers. Both coils can achieve peak magnetic field strengths of 1.5 to 2.5 Tesla at the surface of the coil.

Inside the circular coil a low-resistance copper is wound in one or several turns into a ring-shaped configuration. This coil type has no single magnetic field focus but a maximum current in the entire outer winding, forming a ring shaped magnetic field around the coil. Therefore, the site of stimulation in a circular coil is not well defined.

Inside a figure-eight coil are two circular ring-shaped coils mounted next to each other and coated by the characteristic butterfly-shaped coil mantle. The copper wire inside these two inner circular coils are wound in such a manner that the currents in these two loops circulate in opposite directions. The magnetic fields of these two coil loops add up at the coils` intersection resulting in a more focussed magnetic field distribution of the figure-eight coil. A great advantage of the figure-eight coil over circular coils is the localisation of the maximum induced current directly under the centre of the coil. The field of a figure-eight coil is thus stronger and more focal than that of a circular coil (Cohen et al., 1990) and hence more appropriate for TMS based functional mapping of the brain.

1.5.4 Repetitive TMS versus single pulse TMS

Due to technical developments of TMS in the last decade, it is now possible to apply the magnetic pulses either in single pulses (spTMS), or in trains of pulses with the so-called repetitive TMS (rTMS). The number of repetitive stimuli per second, the stimulation frequency, as well as the stimulus intensity, the duration of the stimulation train, the inter-train interval, and finally the total number of trains and total number of stimuli represent the stimulation parameters of TMS.

While with spTMS a single magnetic pulse is delivered at a precise point in time during a task, rTMS applies a repetitive train of pulses of rates up to 50 Hz. Moreover, rTMS is capable of modulating the excitability of the stimulated area even beyond the duration of the TMS application itself. The precise neuronal mechanisms of effects that last beyond the stimulation itself are not clear but similarities to neurophysiological electrical stimulation studies in animals are

apparent. In these studies direct high-frequency electrical stimulation resulted in long term increases of intersynaptic transmission efficiency, termed long-term potentiation (LTP), while low-frequency electrical stimulation led to a long-term decrease of intersynaptic transmission efficiency, called long-term depression (LTD) (Stanton and Sejnowsky, 1989; Artola et al., 1990; Sil'kis et al., 1994).

TMS can thus have excitatory as well as inhibitory effects, depending on the stimulation frequencies used. Generally speaking, low-frequency rTMS (<= 5Hz) tends to have inhibitory effects, while high-frequency rTMS (>5Hz) increases cortical excitability.

Only a few studies have systematically looked at these different frequency-dependent excitatory and inhibitory effects of rTMS (e.g. Pascual-Leone et al., 1994a; Chen at al., 1997a; Maeda et al., 2000).

In the case of higher perceptual or cognitive functions rTMS acts more as a “disruptor” of the normal pattern of cortical processing leading to an impaired or delayed task performance. In these cases the TMS induced neuronal activity operates as “neural noise”, which adds random activity to the original temporally and spatially organized network of cortical activity. This neural noise can overwhelm this organized neural communication and hence produce transient “functional lesions” without any actual damage to the neuronal structures.

1.5.5 The principle of TMS effects on neuronal tissue

The magnetic stimulation indirectly creates a transmembrane potential by moving a charge across the cellular membrane which can lead to membrane depolarization and hence to an action potential of the respective axon.

An electric field parallel to the axon causes current flow inside and outside, but does not lead to a change of the transmembrane potential of the axon. But if this current inside the axon changes along the nerve, a current similar in strength to this change has to pass through the membrane of the axon leading to a respective change of the transmembrane potential. If this membrane potential passes a crucial threshold, it can result in an action potential of the axon.

The temporal-spatial characteristics of the magnetic pulse depend on the physical parameters of the magnetic field such as rise time and spatial field distribution, which underlie the electrical characteristics of the stimulator and the coil. The temporal-spatial characteristics of the induced electric field, and thus the actually stimulated area, depend on several additional factors such as scalp shape, scalp-cortex-distance, coil shape, stimulation intensity, monophasic vs. biphasic pulse application and so forth. The magnetic field strength decreases logarithmically with distance from the coil, which limits the area of depolarization. Generally speaking, the spatial distribution of the cortical area affected by current TMS devices has approximately a diameter of 3 cm long, 2 cm wide and 3 cm deep, measured from the center of the coil (Epstein et al., 1990; Rudiak and Marg, 1994). However, several blood flow studies demonstrated that TMS may affect remote cortical and subcortical areas via transsynaptical connections (Dressler et al., 1990; Paus et al., 1997).

Although the magnetic field distribution can be investigated directly in vivo (Bohning et al., 1997) and the distribution of the induced electric field can be at least theoretically modeled, the precise extent of the actual TMS induced neuronal activation remains speculative.

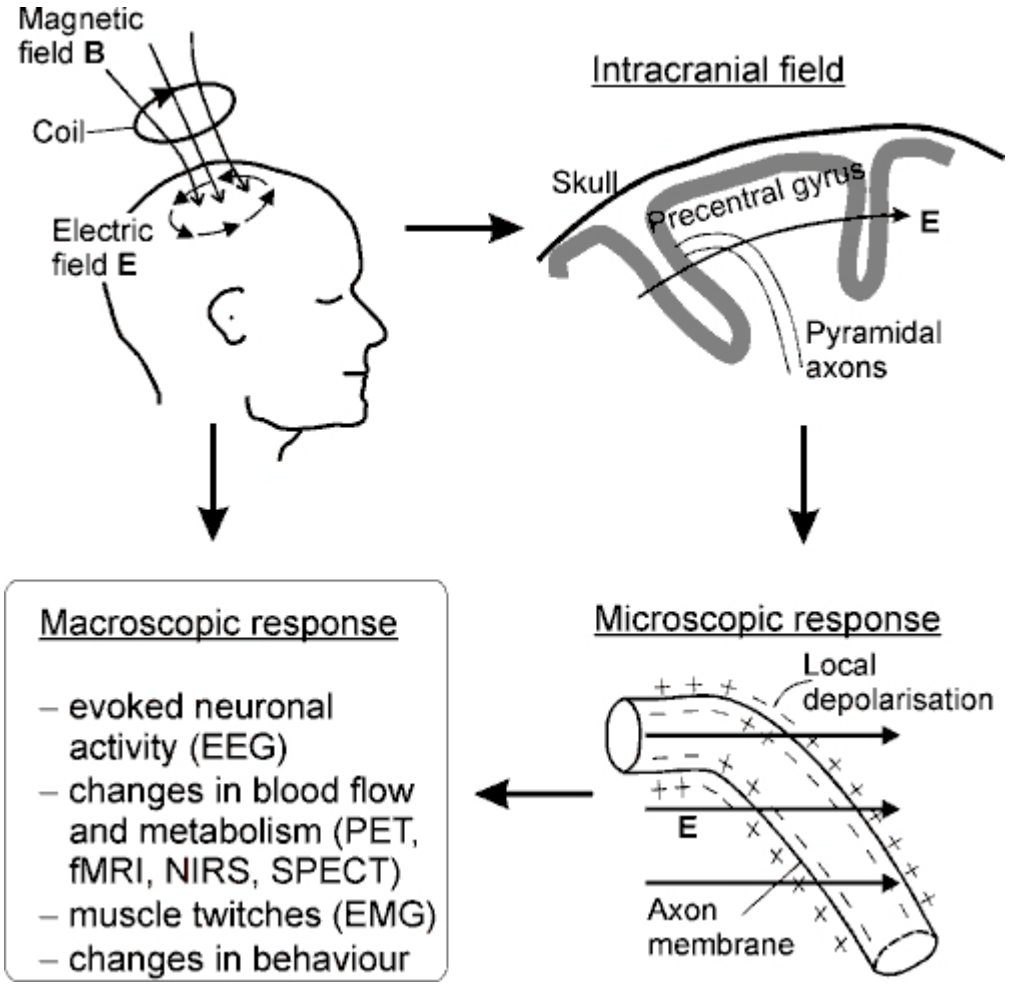

Figure 1: Current in the coil generates a magnetic field B that induces an electric field E. The lines of B go through the coil; the lines of E form closed circles. The upper-right drawing illustrates schematically a lateral view of the precentral gyrus in the right hemisphere. Two pyramidal axons are shown, together with a typical orientation of the intracranial E. The electric field affects the transmembrane potential, which may lead to local membrane depolarisation and firing of the neurone. Pyramidal axons are likely stimulated near bends, as illustrated here, but also other mechanisms exist and other neurones may be stimulated. Macroscopic responses can be detected with functional imaging tools (EEG, PET, fMRI, NIRS and SPECT = single photon emission computed tomography), with surface EMG, or as behavioral changes.

(source: www.biomag.helsinki.fi/tms/thesis/dt.html)

1.5.6 Safety of TMS

For the safety of TMS, possible immediate, short-term or long-term side effects of the magnetic stimulation have to be considered.

Generally, due to the application of strong magnetic pulses, TMS may lead to heating or moving of any metallic objects near the stimulation sites. Therefore the same precautions should be taken as in the case of clinical magnetic resonance imaging. This includes the general absence of magnetic objects like pacemakers, medication pumps, cochlear prostheses, or other implanted metallic objects, magnetic media and watches.

The group that should generally be excluded from TMS studies involves patients with focal or generalized encephalopathies, a history of severe head trauma, untreated epilepsy, first-degree relatives of patients with idiopathic epilepsy (Pascual-Leone et al., 1993), and patients with severe heart diseases. Furthermore, any subject or patient receiving medication or abusing substances that might lower the subject's seizure threshold should also be excluded from stimulation with TMS.

The most severe and critical immediate side effect of repetitive TMS is its potential to induce epileptic seizures if applied at high frequencies and intensities.

The risk of causing a seizure with rTMS depends on the stimulation parameters used. Particularly the stimulation frequency seems to be crucial in this context since high-frequency rTMS (> 5 Hz) has caused eight reported seizures in

healthy subjects while no seizure has been induced by spTMS or low-frequency TMS until today (Wassermann, 1998).

Therefore, a safety guideline restricting the safe use of rTMS to different stimulation frequencies and other stimulation parameter combinations has been published. Within these safety guidelines, no cases of TMS induced seizures or other negative side effects are reported and thus rTMS application within these limitations is considered safe (Wassermann, 1998; Chen et al., 1997b).

A very important stimulation parameter, besides the frequency, is the stimulation intensity. Due to a wide interindividual variability vulnerability to cortical excitation as well as seizure thresholds, the stimulation intensity should always be defined relatively for the individual and not in absolute intensity values. This relative individual sensitivity reference was defined as the subject's individual intensity threshold for a motor evoked potential (MEP) or muscle twitch induced by TMS over the primary motor cortex. This individual motor threshold varies widely across individuals (Cicinelli et al., 1997; Mills and Nithi, 1997), thereby confirming the demand for an individual relative sensitivity index, but is highly consistent over time as measured by a comparably small intraindividual variance (Ziemann et al., 1996a; Cicinelli et al., 1997). The precise statistical definition of the motor threshold is usually the lowest stimulation intensity capable of producing MEP´s of 50µV or more in the abductor pollicis brevis muscle in at least 50% of the applied pulses (Rossini et al., 1994). As reported by Pridmore (1999) the visible muscle twitch produced by TM stimulation of the primary motor area can be also used as a measure for the individual motor threshold since it proved to be as reliable as the MEP´s.

In recent updates of the rTMS safety guidlines, other stimulation parameters and especially combinations of different parameters, including train duration and in particular the intervals between stimulation trains, were included to further restrict the safety limits (Chen et al., 1997b; Pascual-Leone et al., 1993; Wassermann, 1998).

It should be mentioned that TMS has also been shown to temporarily increase the hearing threshold due to the generated “click” sound of the coil (Pascual-Leone et al., 1992; 1993). Yet, these side effects can be prevented by using appropriate ear plugs during stimulation (Counter and Borg, 1992; Pascual-Leone et al., 1993).

As a consequence of the local stimulation of scalp or facial muscles during suprathreshold stimulation, TMS can potentially lead to a slight headache, reported by approximately 10%-20% of the stimulated subjects during the time of stimulation (George et al., 1996; 1999).

1.5.7 The persistency of TMS induced effects

A description of the potential side effects of TMS needs to take into consideration that rTMS can disrupt cognitive processing that lasts beyond the stimulation period itself.

For spTMS no lasting effects on cognitive functions have been found (Bridgers and Delaney, 1989; Bridgers, 1991; Chokroverty et al., 1995).

Many studies used the potential of rTMS to explicitly produce transient functional disruptions of a wide variety of cognitive functions that lasted for a short time beyond the stimulation period itself. In these studies, transient short-term effects on cognitive processing were explicitly desired by the experiment. In the context of the safety of TMS and the persistency of its effects, the question arose if there were any undesired irreversible long-term effects of rTMS on cognitive processing.

Several studies investigated possible irreversible long-term effects of high intensity rTMS with different frequencies applied to several scalp positions on a wide test battery of different cognitive functions, as well as on basic neurological measures. These studies revealed no significant effect of rTMS on any of these tests (Pascual-Leone et al., 1993; Jahanshahi et al., 1997, Wassermann, 1998). Previous studies systematically investigated long-term effects of rTMS on different cognitive functions measured by a psychological test battery and revealed only mild and reversible effects on cognitive processing (Triggs et al., 1999; Little et al., 2000)

However, concerning the temporal window of revealed transient effects of rTMS, few studies demonstrated changes in cognitive processes such as short-term memory that lasted for up to one hour following the rTMS in healthy subjects (Flitman et al., 1998).

1.5.8 TMS and functional imaging

The combination of functional imaging and focal TMS provides an opportunity to investigate the local responses of TMS at a neurophysiological level, thus helping to determine *in vivo* which brain areas are either directly or transsynaptically affected by the magnetic stimulation.

The functional imaging techniques can be applied either before, during or after the magnetic stimulation. Functional imaging before TMS can be used to localize precisely the cortical area of activation during the performance of a certain task and thus optimize the exact coil positioning for TMS of this identified area. This methodological approach enables the experimental investigation of the functional relevance of a local cerebral activation for the execution of a certain task by transiently disrupting the identified cortical area and subsequently measuring the behavioral effect of this TMS induced transient functional lesion on task performance. Functional imaging during TMS is capable of registering the actual effects of TMS on cortical activities, revealing *in vivo* information about regional cortical excitability as well as intracerebral functional connectivity of the stimulated areas (Paus et al., 1997; Bohning et al., 1997; 1999; 2000a; 2000b). Functional imaging after TMS finally could be used to investigate the possible functional long-term effects of TMS on brain activation, leading to empirical insights into functional cortical plasticity (Siebner et al., 2001).

TMS combined with functional neuroimaging techniques therefore enables the precise positioning and focusing of the TMS coil and provides information on

the magnetic field distribution inside the cortex as well as the TMS-induced brain alterations in cortical physiology.

TMS has been combined with functional neuroimaging techniques such as positron emission tomography (PET) (Paus et al., 1997; 1998), single photon emission computed tomography (SPECT) (Stallings et al., 1997), electroencephalography (EEG) (Ilmoniemi et al 1997), as well as functional magnetic resonance imaging (fMRI) (Bohning et al., 1997; 1998; 1999; 2000a; 2000b) in order to simultaneously stimulate and record brain activity.

By combing TMS with PET, Paus et al. (1997) revealed a dose-dependent (number of TMS pulses) increase of cerebral blood flow after a 10 Hz stimulation over the frontal eye fields at the stimulation site and, paradoxically, a dose dependent decrease of regional cerebral blood flow (rCBF) after identical TM stimulation over motor cortex (Paus et al., 1998). These results suggest that TMS not only has different neurophysiological effects that depend on the chosen stimulation parameter, but that these different effects (e.g. excitatory versus inhibitory) might differ between different regions of the brain.

Some studies combined TMS with simultaneous fMRI in order to stimulate and image the brain at the same time and to obtain 3D maps of the magnetic field created by TMS coils (Bohning et al., 1997). Bohning et al (1997) were the first to demonstrate the technical feasibility of combined TMS and fMRI. By using a purpose-built non magnetic TMS coil simultaneously with MRI phase imaging, Bohning et al. (1997) were able to image in vivo 3D maps of the magnetic field distribution in the brain. While most computational models of the magnetic field

distribution inside the brain had simply assumed that the brain is an isotropic homogenous conductor of spherical shape, this pioneering study showed the actual magnetic field distribution in the living brain.

Bohning et al. were also able to produce changes of the BOLD signal measured with fMRI in local and remote brain areas by varying the intensity of TMS (Bohning et al., 1999). In this study the left motor cortex of seven healthy subjects was stimulated with a figure-eight-coil at two different stimulation intensities (110% motor threshold versus 80% motor threshold) while simultaneously acquiring BOLD sensitive EPI images. The higher intensity of TMS led to a greater activation in comparison to the lower intensity, both at the local stimulation sites as well as at the transsynaptically connected brain areas. The blood flow changes induced by rTMS as well as single-pulse TMS were comparable to those induced by voluntarily executed behavioral tasks (Bohning et al., 1999; 2000a; 2000b). By comparing TMS induced finger movements to voluntary movements, Bohning et al. (2000b) revealed a clear comparability of the measured neuronal changes. These data suggest that TMS acts on a neurophysiological level very comparable to normal physiology.

The combination of TMS and fMRI promises to be of especially great value for cognitive neuroscience since it offers the possibility to stimulate brain circuits while simultaneously monitoring changes in brain activity and behavior with a very high spatial and satisfying temporal resolution.

1.6 Studies with TMS

The precise timing and duration of TM stimulation has been used intensively in the last 10 - 15 years for a precise motor output mapping and the investigation of basic perceptual processes. With increasing technical developments of high intensity and high frequency rTMS, more spatially focal coils as well as the observation that rTMS can induce transient functional lesions in different cortical areas beyond the stimulation itself, rTMS has also been used increasingly as a research tool for the investigation of higher cognitive functions.

Most of these studies used rTMS to interfere temporarily with neuronal functioning in order to reveal information about the functional contribution of the stimulated area to the execution of a particular task (e.g. Kosslyn et al., 1999; Walsh et al., 1999)

Single pulse TMS, on the other hand, disrupts activity only for a very brief period of time. This enables the investigation of the precise time point, at which the contribution of a certain area is critical to the task performance (e.g. Ashbridge et al., 1997; Ganis et al., 2000; van Donkelaar et al., 2000).

SpTMS and rTMS have been used in a variety of studies investigating different perceptual and cognitive functions such as visual shape-processing (Amassian et al., 1993a), hemispheric asymmetry in visual perception (Amassian et al., 1993b) and attentional processes (Pascual-Leone et al., 1994b; Ashbridge et al., 1997; Walsh et al., 1998), as well as to study the hemispheric lateralization and anatomical localization of object-related visual working memory tasks (Hong et al., 2000), the involvement of parietal cortex in novel (Ashbridge et al.,

1997) and learned (Walsh et al., 1998; 1999) visual search tasks, the anatomic and physiologic localization of speech arrest (Epstein et al., 1999), the functional relevance of primary motor cortex activation for mental rotation (Ganis et al., 2000), the contribution of posterior parietal cortex (PPC) to eye-hand coordination processes (van Donkelaar et al., 2000), the contribution of visual cortex to tactile discrimination (Zangaladze et al., 1999), the processing of visual information (Amassian et al., 1989), and the execution of hand (Desmurget et al., 1999) and eye movements (Ro et al., 1999).

Nonetheless, the great majority of TMS studies are still conducted on the timing, excitability and conductivity of the primary motor cortex and the respective motor responses because of the unique opportunity to quantify easily and on-line the TMS-induced effects via electromagnetic measurements of the motor evoked potentials or the observation of evoked muscle twitches.

1.6.1 Studies on motor cortex

Due to the unique possibility to measure the perceptual effects of the neural responses in the primary motor cortex as a physiological validation of induced neuronal effects, several TMS studies were conducted to investigate the concrete effects of rTMS at different frequencies on the neuronal activity in the stimulated motor areas.

The nature of this effect, inhibitory or excitatory, has been found to be dependent on the frequency used in rTMS (Maeda et al., 2000; Hallett, 2000). Chen et al. (1997a) revealed that rTMS with a low-frequency stimulation (1 Hz or less) decreases the cortical excitability of motor cortex as measured by a

long-lasting depression of possible motor-evoked potentials, while stimulation with high-frequency rTMS (5 Hz and more) led to increases in cortical excitability (Pascual-Leone et al., 1998). This frequency dependent rTMS effect has been demonstrated during (Pascual-Leone et al., 1994a; Jennum et al. 1995), as well as for minutes following the TMS stimulation (Chen at al., 1997a; Kosslyn et al., 1999; Pascual-Leone et al., 1994a; 1998).

This frequency dependent effect of rTMS on the excitability of the motor cortex was replicated by several other studies in all of which a suprathreshold (> 100% MT) slow-frequency (< 1 Hz) rTMS resulted in a decreased excitability, especially in the measured MEP amplitude (Chen et al., 1997a; Siebner et al., 1999; Tergau et al., 1997; Wassermann et al., 1996) lasting up to 15 minutes beyond the stimulation period itself (Pascual-Leone et al. 1998; Tergau et al., 1997), whereas a high-frequency (5 – 20 Hz) suprathreshold rTMS led to an increased MEP amplitude (Jahanshahi et al., 1997; Jennum et al., 1995; Pascual-Leone et al., 1994a; Tergau et al., 1997) and decreased intracortical inhibitory mechanisms (Pascual-Leone et al. 1998; Tergau et al., 1997).

A large corps of studies systematically investigated the motor thresholds differences of different muscles, reflecting different densities of the corticomotoneuronal projections for these different muscles (Brouwer and Ashby, 1990; Macdonell et al., 1991; Chen et al., 1998).

Other studies investigated the change of motor threshold when tested during tonic muscle activation and observed a threshold decrease in comparison to conditions of muscle relaxation (Chen et al., 1998; Ziemann et al., 1996a).

TMS has also been used to interfere with different aspects of behavioral motor responses and motor control. By applying a brief and strong single TMS pulse directly before the behavioral motor response, Day et al. (1989) increased the response reaction time to the signal without modulating other characteristics of the motor response.

Generally TMS and rTMS has been used to map the cortical location of motor control in order to outline the motor homunculus (Brasil-Neto et al., 1992a; Kiers et al., 1993; Mortifee et al., 1994) as had previous been done by direct electrical stimulation.

Another TMS study investigated the timing of pre-motor and primary motor cortex activity in a simple choice reaction time task (Schluter et al., 1998). The authors applied spTMS over the posterior and anterior pre-motor cortex as well as over the sensorimotor cortex while subjects performed a cued movement task. By varying the time interval of the spTMS after the visual cue presentation, the authors revealed a temporal sequence of cortical processing following the visual cue presentation from the anterior pre-motor area (140 ms), over the posterior pre-motor area (180ms) to the sensorimotor cortex (220 ms and later). This temporal sequence represents the cortical processing underlying the events from receiving the initial signal to performing the actual movement. In a separate study (Schluter et al., 1999) the authors implemented a cue that *a priori* informed the subjects about the required movement, followed by a second cue, which prompted them to execute the movement. Under these circumstances the time interval of spTMS for impairing reaction times was equal between the three stimulation sites. The authors interpret these results as an

indication for the equal involvement of pre-motor and motor cortices in set-related processing.

However, the majority of TMS studies on motor cortex also revealed a great interindividual variability of motor cortex responses to rTMS (Pascual-Leone et al. 1998; Tergau et al., 1997). It should hence be considered in future TMS studies that this objectively measurable interindividual variance of respondence to motor cortex TMS might similarly occur in other "silent" cortical areas, resulting in a general interindividual variability of TMS induced effects.

1.6.2 Studies on basic perceptual processes

TMS has been used extensively to study basic perceptual processes, especially in the visual system. Several studies produced phosphenes by stimulating the occipital cortex (Amassian et al., 1989; Kastner et al., 1998; Meyer et al., 1991) and paraesthesia by stimulating the sensorimotor cortex with high intensity spTMS (Amassian et al., 1991; Cohen et al., 1991a; 1991b). By stimulating with a lower stimulus intensity, Amassian et al. (1989) were able to induce a temporal scotoma when TMS was applied 80 – 100 ms after the visually presented stimulus. In following studies different authors tried more precisely to reveal the critical time interval for this TMS induced interruption of basic visual processing and revealed an even earlier suppression period, probably representing the arrival of the raw visual information in the occipital cortex. By systematically varying the latency between visual stimulus presentation and the application of the spTMS as well as the exact position of the coil over the occipital cortex, the authors revealed at least two distinct time periods when

visual cortex activity is essential for the perception of visually presented stimuli (Corthout et al., 1999).

A variety of other studies also observed that TMS to the visual cortex could selectively impair or disrupt different visual processes depending on the precise location and stimulation parameters (Amassian et al., 1998; Beckers and Homberg, 1991; Marzi et al., 1998; Masur et al., 1993; Ray et al., 1998). Takayama and Sugishita (1994) demonstrated an inhibition of stereoscopic perception when stimulating with rTMS over the occipital cortex.

This visual cortical suppression was attributed to the IPSP lasting for a few milliseconds that is induced by TMS in the targeted area initially processing or temporarily storing the visual stimuli (Amassian et al., 1989).

However, Amassian et al. (1993c) could show that stimulating with an ineffective pulse intensity during visual stimulus presentation can also lead to a significant visual suppression effect when a second pulse, that alone is equally ineffective, is delivered 50 ms after the first magnetic pulse, probably due to a subcortical conditioning mechanism (Amassian et al., 1993c)

Due to the possibility of exactly setting different time intervals between visual presentation and spTMS, appropriately designed TMS studies were able to reveal information about the neuronal representation of visual masking (Amassian et al., 1993b: 1993c).

By using rTMS over the lateral occipital cortex Pascual-Leone et al. (1994b) were able to impair visual detection of a single target stimulus presented in the contralateral visual field of the subjects. Unilateral TMS to the parietal cortex did not impair visual detection of a single visual target in the contralateral field, but led to a contralateral extinction of the visual stimulus when a second stimulus was simultaneously presented in the ipsilateral field. This later phenomenon was attributed to a TMS-induced disruption of visual attentional processes, comparable to the clinical symptoms in hemineglect.

A similar result was observed with tactile instead of visual stimuli (Seyal et al., 1995). In this study TMS over the parietal lobe induced a tactile extinction of the contralateral side while the ipsilateral side showed an even increased sensitivity to tactile stimulation.

Epstein and Zangaladze (1996) used spTMS to time the interference latency of impaired visual target detection, while other studies (Elkington et al., 1992; Oyachi and Ohtsuka, 1995) used spTMS over left and right parietal cortex to disrupt eye movements.

TMS has also been used to temporarily impair visual motion detection (Beckers and Homberg, 1992). The authors stimulated an area of the occipitotemporal cortex that was claimed to represent a visual motion processing area (V5). The authors displaced a random dot pattern with the dots moving in a certain direction and observed a modulation of motion detection when stimulating the targeted area within a time window of 10 ms before and 10 ms after stimulus

onset. The TM stimulation over V5 had no significant effect on color vision revealing the specificity of the induced TMS effect.

A similar study replicated the general result but found a stimulation time that was most effective in impairing motion detection at about 100 – 150 ms after stimulus onset (Hotson et al., 1994). However, the authors in this study stimulated over parietolateral occipital cortex and the extra delay time could either represent a later component of the stimulus itself or correspond to a different component within the temporal sequence of a cortical pathway for processing visual motion.

On the basis of these contradictory results, as well as on their own studies on the temporal aspects of effective TMS in visual processing, Beckers and Zeki (1995) suggested two different visual pathways to area V5. In the one pathway information would flow to V5 via V1, resulting in a relatively slower information processing (approximately 100 – 150 ms), and in a second pathway, bypassing V1 and directly transferring the visual information to V5 in a relatively faster way (below 20 ms). In the study of Beckers and Zeki (1995), TMS of area V5 selectively impaired motion perception without interfering with basic recognition of the stimuli. These studies replicate results of different imaging studies, which claimed that V5 represent the motion perception region in the brain and furthermore differentiate them by revealing the actual information processing time of the different visual pathways.

Particularly studies like the latter are of high scientific value since they are capable of charting the exact timing of visual processing following stimulus

onset. TMS is thus capable of identifying the temporal order in which specific visual processes are activated. In this respect, TMS can be used to fractionize specialized processing components in cortical association areas.

1.6.3 Studies on higher perceptual functions

Several TMS studies revealed a differential involvement of the parietal cortex in visual search and visual conjunction tasks. By stimulating the right parietal lobe with spTMS 100 ms after stimulus onset Ashbridge et al. (1997) significantly affected the performance of a conjunction visual search task. Tasks that did not require actual visual search, but simply required the detection of so-called "pop-out" stimuli, were not affected by TMS. The parietal cortex thus seems to be involved in an attentional process for combining different aspects of a visual search task, while the attentional process of mere target detection seems to be carried out at a temporally earlier stage in the information processing chain. However, in trials where the subjects had to decide whether a target was present in the display or not, performance was also impaired with TMS, but only when applied 160 ms after stimulus onset. In comparison to the mentioned TMS induced impairment of visual search for conjunction tasks, this result suggests that the decision to terminate a visual search for an absent target takes a longer processing time, probably due to the involvement of a more distributed frontoparietal activation network.

Even though several other studies had been able to produce attentional deficits with high-frequency rTMS at similar stimulation sites (e.g. Pascual-Leone et al., 1994b), this study revealed explicit information on the timing of these processes by using spTMS.

The results of Ashbridge et al. (1997) were further differentiated by the studies of Walsh et al. (1998; 1999), who were able to show that the mentioned impairment in visual conjunction search after right parietal TMS only occurs when the stimuli were novel to the subjects. In this study, right parietal TMS did not impair the performance of a trained visual conjunction task. The authors speculated that with increasing training or familiarity of the subjects with the conjunction tasks, they were able to use parallel information processing comparable to simple visual detection tasks. These parallel visual processes do not necessarily involve parietal cortex activation and hence remain unaffected by parietal lobe TMS. However, in a series of psychophysical studies, specifically conducted to investigate the role of practice in visual search tasks, Sireteanu and Rettenbach (2000) clearly revealed that visual conjunction search remains serial even after extensive training.

Hilgetag et al. (2001) stimulated subjects with low-frequency rTMS over the right or left parietal cortex. The precise locations for the TMS coil positioning were obtained by marking the coordinates of the 10-20 EEG system with vitamin E capsules on the scalp of each subject, and measuring the respective areas of brain activities via MRI (for details on this procedure see chapter 3.1.2.3). While the visual detection of presented stimuli contralateral to the stimulated hemisphere was significantly impaired when a stimulus was simultaneously presented in the ipsilateral field, the attention to the ipsilateral visual targets was significantly enhanced. Besides the mere extinction phenomenon comparable to spatial hemineglect, this study supports the idea of interhemispheric competition and interhemispheric suppression within a

distributed cortical network underlying spatial attention. Despite the general effect of rTMS over right and left parietal cortex, the improved attention to ipsilateral stimuli was descriptively larger for the left hemifield after right parietal stimulation, suggesting a right parietal dominance for spatial attentional processes.

These TMS studies replicate findings from lesion and neuroimaging studies that also revealed the importance of the parietal lobes for attentional processes (Corbetta et al., 1998; Robertson, 1998). However, these studies rather identified a fronto-parietal network to be involved in the controlled mediation of different attentional processes.

As another TMS based replication of these findings, Sabatino et al. (1996) revealed that TMS over the prefrontal cortex significantly improved subjects` performance in several verbal and visuospatial tasks. This improvement mainly affected the accurate performance of these tasks, probably due to an improved controlled attention during task execution. TMS over the temporal cortex had no effect on task performance and accuracy.

1.6.4 Studies on higher cognitive functions

By stimulating the occipital cortex with rTMS centered over the striate cortex, Cohen et al. (1997) were able to disrupt Braille reading in blind patients while their performance in simple tactile control tasks remained unaffected by the stimulation. The occipital rTMS stimulation resulted in an increased reading error rate in the blind patients, both compared to control subjects and compared to other stimulation sites. The authors interpreted the results as an indication

that the occipital cortex in blind patients can be recruited for other sensory modalities than vision. The mere imaging results of visual cortex activation during Braille reading and other tactile discrimination tasks (Sadato et al., 1996) reveal no information about the functional relevance of this activation for the particular spatial discrimination ability of blind subjects. Only the TMS results provided experimental evidence that the occipital activity is a functionally essential component for Braille reading in blind patients.

High-frequency rTMS has also been shown to produce transient speech arrests (Pascual-Leone et al., 1991; Jennum et al., 1994; Michelucci et al., 1994; Epstein et al., 1996; 1999). Pascual-Leone (1991) induced a lateralized speech arrest when stimulating with high-frequency rTMS over the left inferior frontal region, while Epstein et al. (1996) could show that speech arrest also occurs when stimulating with 4 Hz suprathreshold rTMS over the individual region representing the area of TMS induced motor responses of facial muscles. Epstein et al. (1999) revealed in a second study that rTMS to the left inferior frontal area led to an arrest of spontaneous speech and reading aloud while the general generation of language like writing, comprehension, singing etc. remained unaffected.

Several TMS studies investiagted the influence of spTMS and rTMS of different brain areas on the performance of different short-term memory tasks. The results of these TMS studies are partly conflicting with a few studies that revealed no effect of TMS on short-term memory (Ferbert et al., 1991; Hufnagel et al., 1993) and several other studies demonstrating an effect on different memory tasks (Grafman et al., 1994; Pascual-Leone and Hallett, 1994).

Ferbert et al. (1991) investigated whether TMS with different stimulation intensities over the motor cortex influences the performance in a free recall nonsense word memory task. The TMS pulses were applied with either 60%, 80% or 100% intensity of the 2 Tesla stimulator unit and administered immediately after the visually presented nonsense word. In comparison to a control group subjects showed a significant impairment in the free recall short-term memory task only when stimulated with 100% stimulation intensity. However, after controlling for the immense noise artefact in the 100% intensity condition, by comparing the performance of these subjects to a control group that received TMS with 100% stimulation intensity over the cervical spine, no significant differences in task performance were detected.

Hufnagel et al. (1993) systematically investigated the effect of rTMS on the performance of standardized verbal and visuospatial memory tasks. Subjects had to either immediately reproduce a memorized number series or the spatial positions of geometrical objects. During stimulus presentation, subjects were stimulated with high-frequency rTMS over left or right anterior lateral parietal lobe or over superior and posterior temporal areas, respectively. Statistically compared to their own baseline performance within a cross-over design, no rTMS-induced significant changes of performances were observed in any of the short-term memory tasks.

In another TMS study, Pascual-Leone and Hallett (1994) investigated the involvement of the dorsolateral frontal cortex in the performance of short-term memory tasks. The authors used a delayed response task, in which subjects

had to recall the position of a filled square in a row with three distractors after a 5 seconds delay period. Compared to sham stimulation, as well as compared to stimulation over motor cortex, the unilateral rTMS over left and right prefrontal cortex during the delay period led to a significantly impaired task performance, revealing the functional contribution of these cortices to the execution of short-term memory tasks.

Grafman et al. (1994) investigated the influence of rTMS on the recall of a list of learned words. After stimulating the left midtemporal as well as bilateral dorsofrontal cortex, subjects` performance on this working memory task was significantly impaired. Similar studies also revealed TMS induced deficits in picture-word matching tasks following left anterior rTMS (Flitman et al., 1998) or increased reaction times in picture naming after delivering TMS to the left occipito-temporal cortex (Stewart et al., 2001).

One of the few studies revealing a hemispheric asymmetry in the response to unilateral rTMS during short-term memory tasks was the study by Hong et al. (2000). The authors investigated a visual working memory task while stimulating over different sites separately for both hemispheres. The performance in visual working memory was significantly impaired by rTMS over right inferior frontal (F8), right inferior temporal (T8) as well as right parietal areas (P4), while rTMS over the respective areas in the left hemisphere had no effect on the task performance. This study thus revealed a lateralization of visual working memory to the right hemisphere and further indicated the concrete anatomical localizations for the task performance.

Oliveri et al. (2001) investigated the specific effect of TMS on visual object versus visual spatial short-term memory tasks. Subjects had to perform an n-back task that either required them to memorize abstract objects or spatial locations. Unilateral and bilateral TMS was delivered to several stimulation sites and at several time intervals during task performance. A bilateral temporal stimulation led to a significantly impaired performance in the object memory task, while bilateral parietal as well as superior frontal gyrus stimulation selectively increased the reaction time in the spatial memory task. Bilateral stimulation over the dorsolateral prefrontal cortex significantly increased reaction times in both memory tasks. Temporarily these effects occurred at a delay of 300 ms in the posterior stimulation sites, and at a delay of 600 ms in the frontal regions. These results thus reveal separate neural information processes for visual spatial and visual object working memory as well as a temporal sequence within a fronto-parietal activation network underlying both short-term memory processes.

Studies particularly stressing the capability of rTMS to induce transient lesions in stimulated cortical areas systematically investigated the functional relevance of certain cortical regions for certain cognitive functions. In this respect rTMS has been used to study the contribution of the primary visual cortex to visual imagery (Kosslyn et al., 1999). In this study, subjects had to compare different features of a mentally visualized pattern of stripes. Kosslyn first used PET in order to localize the activated brain areas during task execution. This functional imaging study revealed activation of area 17 during visual mental imagery. Based on these results Kosslyn et al (1999) applied rTMS over the medial occipital cortex and were able to reveal a significant impairment of task

performance in comparison to a sham condition. This experimental setup enabled the authors to conclude that the primary visual cortex is not only activated during the execution of visual imagery tasks, but that a disruption of neural activation in this area significantly impairs the performance in this task.

Zangaladze et al. (1999) used TMS to investigate the exact timing of the contribution of visual cortex to orientation discrimination. The authors could disrupt the performance in tactile discrimination of grating orientation by stimulating the peristriate visual cortex 180 ms after stimulus presentation. The tactile discrimination of grating texture was unaffected by peristriate TMS. TMS to the somatosensory cortex on the other hand impaired tactile discrimination of grating orientation as well as texture indicating the specific involvement of visual cortex in tactile discrimination of orientation.

Ganis et al. (2000) applied spTMS to the primary motor cortex in order to investigate its causal role for mental rotation tasks. Single-pulseTMS to the representation of the hand in the left primary motor cortex 650 ms after stimulus onset led to an impairment of a mental rotation task in which pictures of hands and feet had to be rotated. No such effect was observed if TMS was applied 400ms after stimulus onset indicating a relatively late involvement of primary motor cortex in the mental rotation process. The disruptive effect of single-pulse TMS 650 ms after stimulus onset was larger for the mental rotation of hands than for feet suggesting a stimulus-specificity of primary motor cortex activation in mental rotation.

Jahanshahi et al. (1998; 1999) used TMS to reveal information about the functional relevance of frontal cortex activity in the generation of a random number series.

Terao et al. (1998) applied spTMS with different latencies after stimulus presentation to different stimulation sites in order to investigate the contribution of the frontal cortex (frontal eye fields) and the parietal cortex (posterior parietal cortex) to the performance of an anti-saccade task systematically. Saccade onset was significantly delayed by parietal TMS when applied 80 ms after stimulus presentation, while frontal TMS significantly delayed the saccade onset only when applied 100 ms after stimulus presentation, suggesting that information was first processed in parietal regions before being transferred to the frontal regions of the cortex.

Single-pulse TMS to the posterior parietal cortex was used to investigate the contribution of this area to eye-hand coordination processes. By comparing the effects of single-pulse TMS to the relation between saccades and manual motor output at different time intervals, the study revealed that posterior parietal cortex integrates signals related to saccade amplitude with limb movement information just prior to the onset of the saccade (van Donkelaar et al., 2000)

Brasil-Neto et al. (1992b) stimulated subjects over the left or right motor cortex, respectively, while they had to freely decide to either move their left or right index finger. Compared to other stimulation sites and sham stimulation, TMS over left or right motor cortex significantly increased the probability of subjects choosing to move their contralateral finger. Interviews conducted after the

actual experiment revealed that subjects were subjectively not aware of this TMS induced movement bias and expressed their opinion of a complete random and voluntary finger movement choice. The authors claim to have shown a possible TMS induced modulation of motor responses without interfering with the conscious perception of volition.

Evers et al. (2001) systematically investigated a possible improving effect of rTMS on cognitive processing operationalized by a behavioral and neurophysiological measurement. High-frequency rTMS over the left prefrontal cortex significantly decreased reaction times as well as the P 300 component in a visually evoked event-related potential choice reaction time task. Sham TMS, rTMS over the right prefrontal cortex as well as spTMS had no significant effect on behavioral and physiological measures. TMS induced improvement of performances has also been shown after stimulation of Wernicke´s area for tasks involving analogic reasoning (Boroojerdi et al., 2001) and recall of picture naming (Topper et al., 1998).

In general, the performance improving or performance impairing nature of the TMS induced effects potentially last up to hours beyond the stimulation itself and depend in nature and persistence on the stimulation location and stimulation parameter used in the respective TMS study (Grafman and Wassermann, 1999; Jahanshahi and Rothwell, 2000).

1.7 Objective and methodological approach of this dissertation

This study attempts to combine evidence from functional Magnetic Resonance Imaging (fMRI) and repetitive Transcranial Magnetic Stimulation (rTMS) for the investigation of the functional relevance of parietal activation in visuospatial information processing and visuospatial mental imagery.

One of the major contributions of combined TMS and functional imaging studies to cognitive neuroscience is the possibility to take functional brain mapping one step further by investigating causal relationships between brain activity and behavioral measurements.

This possibility was attributed to the fact that TMS enables the manipulation of the excitability of certain brain areas and the investigation of the effect of this manipulation on behavioral or cognitive performances.

It could be argued that this methodological approach merely equals the insights that could already be obtained on the basis of combining evidence from functional imaging with neuropsychological deficits occurring in structural brain damage. In these lesion studies the exact location of brain damage can be specified by high resolution structural imaging and the respective clinical deficits of the patients can be systematically observed. Combining structural imaging and lesion studies thus represents a methodological approach that provides the same advantages as combined functional imaging and TMS studies. This view was further supported by the technical developments in structural imaging that have made it possible to obtain ever more detailed images of the human brain and hence ever more detailed information about the precise extent of lesions

and brain damages in patients. The combination of this knowledge with an exact observation and registration of the affected behavior and cognitive deficits of these patients thus reveals information about the original functional relevance of the injured brain area.

On the basis of such a lesion study, it has been claimed recently, that spatial awareness is represented in the right superior temporal rather than the parietal cortex (Karnath et al., 2001). It proved to be considerably difficult to reconcile this observation that was based on a particular large lesion study with most of the functional neuroimaging literature.

However, such a lesion study approach does not meet the methodological criteria of an experimental investigation of causal brain-behavior-relationships as described above, since the affected brain areas in these studies represent an organism variable rather than an independent variable, and their relevance for particular cognitive functions can therefore only be analyzed within an *ex-post facto* design with all its possible methodologically confounding factors. Above all, lesion studies are specifically limited by the pronounced effects of cortical compensatory plasticity and intracortical functional connectivity that might result in a functional deficit that can be more or less widespread than the structural lesion itself. Lesion studies that are based exclusively on structural imaging data have to be interpreted with caution because of the effects of functional reorganization (Jenkins et al., 1990) or the functional impairment of remote areas (diaschisis) (Seitz et al., 1999).

This study aimed to overcome this difficulty by combining evidence from transient functional lesions induced by rTMS with that from functional imaging in order to address the question of the functional relevance of parietal activation during visuospatial processing and visuospatial mental imagery.

This study thus consists of two parts: In the first part fMRI is used to exactly identify the brain areas activated during the performance of visuospatial processing and visuospatial imagery tasks. In the second part, rTMS is used to induce temporary regional deactivations in these identified brain areas and to investigate its influence on the performance of these visuospatial tasks within a controlled experimental design (Hallett, 2000).

Compared to studies that combine functional imaging with neuropsychological deficits occurring in structural brain damage (Price et al., 1999), the functional deficits induced by TMS are far more transient, and therefore its effect is unlikely to bring about the mentioned effects of functional reorganization (Walsh and Rushworth, 1999) or diaschisis (Seitz et al., 1999).

In the main study of this dissertation, spatial operations on visually presented as well as mentally imaged stimuli were investigated. In the angle and color discrimination task, a series of analogue clocks was presented, each shown for 400 ms with an ISI of 900 ms. Subjects had to press a button whenever a target stimulus appeared. Targets were defined as clocks with angles of 60° or 30° (angle discrimination task) or clocks with white hands (color discrimination task). In the mental clock task subjects were asked to imagine two analogue clock faces based on acoustically presented times, and to judge at which of the two

times the clock hands form the greater angle. Subjects were asked to press the left mouse button if the hands of the first clock formed the greater angle, or the right mouse button for the second. Subjects‘ responses were registered by an optic fiber answer box and analyzed for reaction time and accuracy.

For the fMRI study, six healthy subjects were recruited. The two visually presented tasks (angle + color discrimination) were performed in one session following the classical block design. The mental clock task was performed in one session on the basis of an event related design. Vitamin E capsules were used to mark the positions P3 and P4 of the international 10-20 EEG system on the scalp of each subject for coregistration with TMS (for details see 3.1.2.3). MRI data were acquired with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) using the standard head coil.

FMRI data analysis and visualization was performed using the BrainVoyager 4.4 software package. The statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). For significantly activated voxels (smallest 3D-spatial units containing information on MR signal change over time), the relative contribution *RC* between two selected sets of conditions in explaining the variance of a voxel time course were computed. An *RC* value of 1 (red) indicates that a voxel time course is solely explained with predictor 1, whereas an RC value of –1 (green) indicates that a voxel time course is explained solely with predictor *2* (Trojano et al., 2000).

In the rTMS-experiment, 60 subjects were randomly assigned into 3 groups (stimulation for 12 minutes at 1 Hz and 130% of motor threshold over P3 and P4, and sham). A custom TMS stimulator (MagPro, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. Magnetic pulses were delivered with a figure-eight-coil (Magnetic Coil Transducer MC-B70, Medtronic). Performance was measured at four different times: as a pretest, during TMS (stimulation), immediately after TMS (posttest 1) and 12 minutes after TMS (posttest 2). In order to control for possible effects of rTMS on motor response a finger tapping task for both hands was included at all four times of measurement. The used rTMS protocol has been shown to suppress transiently cortical excitability during as well as for several minutes beyond the rTMS stimulation period (Chen et al., 1997; Kosslyn et al., 1999; Pascual-Leone et al., 1994a).

The methodological approach of this study provided the possibility of investigating the causal relationship between unilateral parietal activation and the execution of visuospatial tasks, based on physically presented as well as mentally imaged stimuli, and presents the first systematic experimental investigation of potential functional hemispheric asymmetry of parietal activation for visuospatial processing and visuospatial imagery.

Prior to this main study of the dissertation, a pilot study was conducted in order to investigate if rTMS is physically capable of reaching the targeted brain structures within the parietal lobe as well as to test the suitability of the created stimulation paradigms to actually result in a task-correlated increase of neuronal activity in these parietal areas.

Due to this preparatory character of the conducted pilot study, the cognitive functions investigated were limited to visuospatial processing based on visually presented tasks. Moreover the rTMS stimulation was restricted to one stimulation site of the parietal cortex since the main objective of this pilot study was to reveal the principal capability of parietal rTMS to manipulate the respective task performance.

In this pilot study, subjects saw sequences of colored clocks and performed a task that required them to discriminate angles, colors or conjunctions of both. The study consists of two experiments. In the first experiment, subjects had to perform the tasks during fMRI in order to localize the areas of activation during the execution of the different tasks. In the second experiment, a different set of subjects performed the same tasks before (pre-test) and after (post-test) having received real or sham rTMS at 1 Hz to the activated sites. The color discrimination task served as a control task for the specificity of the TMS effect on visuospatial tasks. A differential effect of real rTMS on reaction times of the angle discrimination and color task conditions was assumed to support the hypothesis that parietal activation not only accompanies, but subserves, the performance of visuospatial tasks, and that rTMS as an experimental tool has the potential to influence higher cognitive functions such as visuospatial information processing.

The empirical part of this dissertation starts with a brief description of the methods and results of this pilot study. Because some of the methods and statistical analyses of the pilot study are equal or similar to those in the main

study, a more detailed methodological and statistical description can be found in the methods and results part of the main study of this dissertation, following the pilot study chapter.

2 Pilot study

2.1 Methods

2.1.1 FMRI and rTMS experiments

2.1.1.1 Cognitive tasks

The stimuli consisted of analogue clocks with a yellow face and two white or yellow hands. The angle between the hands varied in steps of 30 degrees. Subjects had to press a button whenever a target stimulus appeared. Targets were defined as clocks with angles of 60° or 30° (angle discrimination task), clocks with white hands (color discrimination task), or both (conjunction task). Stimuli were generated using the STIM software package (Neuroscan Inc. Hernon, USA). Stimuli were shown for 800 ms with an interstimulus interval of 1.2 seconds. In each condition, 20 % of the presented stimuli were target stimuli. Note that only the target-defining cue varied between conditions, while the stimuli were physically identical.

Both experiments were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. All subjects gave their informed consent to participate in the respective study and reported being in good health and free of any psycho-active medication. There had been no incident of prior neurological disorder, including seizures, in any of the subjects.

2.1.2 fMRI-experiment

2.1.2.1 Subjects

Six healthy subjects were recruited (mean age 27.5 years, range: 26 - 31 years; all male). Volunteers were naive within the limits of informed consent.

2.1.2.2 Apparatus and procedure

MRI data were acquired with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) using the standard head coil. For functional imaging a gradient echo EPI sequence was used (1 volume = 15 axial slices parallel to the plane crossing the anterior and posterior commissure, repetition time/echo time [TR/TE] = 4000ms/69 ms, flip angle [FA] = 90°, field of view [FoV] = 210x210 mm^2, voxel size = 1.6x1.6x5.0 mm^3). Functional time-series consisted of 128 volumes and lasted 512 s. A T1-weighted 3D MP-RAGE (magnetization-prepared rapid gradient echo) scan was recorded in the same session (voxel size = 1x1x1mm^3). Subjects were asked to keep their eyes steady during scanning. Offline electrooculography recordings showed absence of differences in saccade rate between conditions.

2.1.2.3 Design

The three different conditions (angle, conjunction, color) were tested in one session following the classical block design (4 separate blocks in a pseudorandom order, each lasted 20 seconds and contained 10 stimuli, altogether 12 blocks). Stimuli were delivered to a high luminance LCD projector (EIKI LC-6000). The images were back-projected onto a frosted screen positioned at the foot end of the scanner and viewed by the subjects through a mirror placed on the head coil.

2.1.2.4 Statistical analyses

FMRI-data analysis and visualisation was performed using the BrainVoyager 3.7 software package. Spatial and temporal smoothing, removal of linear trends, motion correction, Talairach transformation of 3D anatomical data sets and

generation of 3D functional data sets (volume time courses) followed procedures published elsewhere (Goebel et al., 1998; Linden et al., 1999).

The statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). The general linear model (GLM) of the experiment was computed from the six (one for each subject) z-normalized volume time courses. Z-normalization of the BOLD signal was performed subject by subject for each voxel time course. The signal values during the angle detection, color detection and conjunction task conditions were considered the effects of interest. The corresponding predictors, obtained by convolution of an ideal box-car response (a graphical display, representing an *a priori* defined model of the hemodynamic response, obtained by assuming the value 1 for the time-points of task presentation and the value 0 for the remaining time points) with a linear model of the hemodynamic response (Boynton et al., 1996), were used to build the design matrix of the experiment. The global level of the signal time-courses in each session was considered to be a confounding effect. To analyse the effects of each separate condition compared to baseline, 3D group statistical maps were generated by associating each voxel with the *F* value corresponding to the specified set of predictors and calculated on the basis of the least mean squares solution of the GLM. Voxels were only accepted as activated when the associated p-value was $< 3.591 \times 10^{-13}$ (uncorrected, corresponding to a multiple regression coefficient $R > 0.3$) and they formed part of a cluster of 200 mm^3 or more (Table 2). Furthermore, in areas that were significantly activated during more than one condition, statistical comparisons were performed on the basis of the mean time course of all voxels of an analysed area. Values of percent signal change averaged over subjects

were computed on the basis of the difference between the mean values of the fMRI signal in each experimental condition and the mean fMRI signal in the baseline periods for each individual subject (Goebel et al., 1998). These values were analysed using ANOVA and a *post hoc* pairwise comparison with stimulus condition as a within-group factor and correction of p-values for multiple comparisons (Table 2, contrasts).

2.1.3 r-TMS-experiment

2.1.3.1 Subjects

Twenty subjects volunteered to participate (mean age: 28 years, range: 19 - 44 years; nine males, eleven females).

2.1.3.2 Apparatus and procedure

A custom TMS stimulator (MagPro, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. Magnetic pulses were delivered with a figure-eight-coil (Magnetic Coil Transducer MC-B70, Medtronic) with an outer radius of 50 mm. Individual motor thresholds were identified by stimulating the motor cortex with single TMS pulses until a movement of the contralateral thumb was detected in relaxed muscle state. For real rTMS, the centre of the coil was held tangentially to the skull over parietal cortex (Pz). For sham rTMS, the coil was moved downwards from Pz by 3 cm and rotated so that the edge of the two wings of the coil rested at 90 degrees on the scalp. In this sham rTMS condition, the induced magnetic field did not enter the brain, although the touch on the scalp and the sound of the coil being activated are comparable to those in the real rTMS condition (Kosslyn et al., 1999).

During the experiment the coil was fixed in position and subjects were asked to keep their eyes steady throughout the experiment. Repetitive TMS was delivered at 80% of the subject's motor threshold, a field intensity sufficient to influence cortical activity (Ziemann et al., 1996b), at 1-Hz stimulation frequency, in a single train of 10 minutes duration, in accordance with international safety standards of rTMS experimentation (Wassermann et al., 1998). Overall each subject received 600 stimuli. These stimulation parameters produce effects that last after the stimulation period (Hallett, 2000; Kosslyn et al., 1999).

2.1.3.3 Design

Every clock reading task (angle, conjunction, color) consisted of 3 blocks, each containing 20 stimuli (60 stimuli). Therefore, the whole sequence consisted of 180 stimuli. Before every block the target-defining cue was presented. The trial sequence of the blocks as well as the sequence within each block was randomized.

Subjects were randomly assigned to one of two groups. One group was stimulated with real rTMS (stimulation-group), while the other group received sham rTMS stimulation (control-group).

Subject's performance in the three different tasks was measured repeatedly, before and after the stimulation or before and after the sham condition, respectively, in order to compare possible differences in the change of the task performances from pre-test to post-test between the two groups (Table 1).

2.1.3.4 Statistical analyses

Mean reaction times for correctly detected target stimuli were computed by task condition and subject. Mean reaction times in the pre-test were compared to mean reaction times in the post-test for each group and task condition by calculating the difference between the two test times. A two-way ANOVA for repeated measurements was computed to test for a significant interaction of the two factors of the experimental design (Table 1).

Table 1: Multivariate two-factorial design. Randomly assigned group comparison factor (two levels: real rTMS, sham rTMS); factor of repeated measurement (two levels: pre-test, post-test)

	pre-test	treatment (IV)	post-test
stimulation group	**visuospatial tasks:** angle, conjunction **non-visuospatial task:** color	**real rTMS**	**visuospatial tasks:** angle, conjunction **non-visuospatial task:** color
control group	**visuospatial tasks:** angle, conjunction **non-visuospatial task:** color	**sham rTMS**	**visuospatial tasks:** angle, conjunction **non-visuospatial task:** color

Notes:
Angle: Angle discrimination in the clock reading task (targets = hands with angles of 30 or 60 degrees)
Color: Color discrimination in the clock reading task (targets = white hands)
Conjunction: Combined angle and color discrimination in the clock reading task (targets = white hands with 30 or 60 degrees)

2.2 Results

2.2.1 fMRI experiment

All three task conditions (angle, conjunction, and color), compared to baseline, were accompanied by an increase in the BOLD signal in striate and extrastriate visual cortex (Figure 2), inferior parietal lobule (IPL), primary motor cortex (PMC), the frontal eye fields (FEF) and the supplementary motor area (SMA). The angle and conjunction detection tasks showed additional activation of regions in SPL bilaterally (Table 2).

The comparison between BOLD signal changes for the different conditions in visual cortical areas revealed that the overall activation level tended to be higher during the angle and conjunction than during the color condition (Table 2, contrasts). This effect was particularly pronounced in the left intraparietal sulcus (IPS), an area of SPL where signal changes were consistently highest for the angle condition, followed by the conjunction and color conditions (Figures 2 & 3) and was also observed in the FEF bilaterally (Table 2). Other parietal areas, including the IPL bilaterally, did not show a significant difference between the angle and conjunction conditions. On the other hand, the activation of the fusiform gyrus in the occipitotemporal ventral stream were roughly equal for all conditions (Table 2, contrasts). PMC and SMA did not show task specific differences.

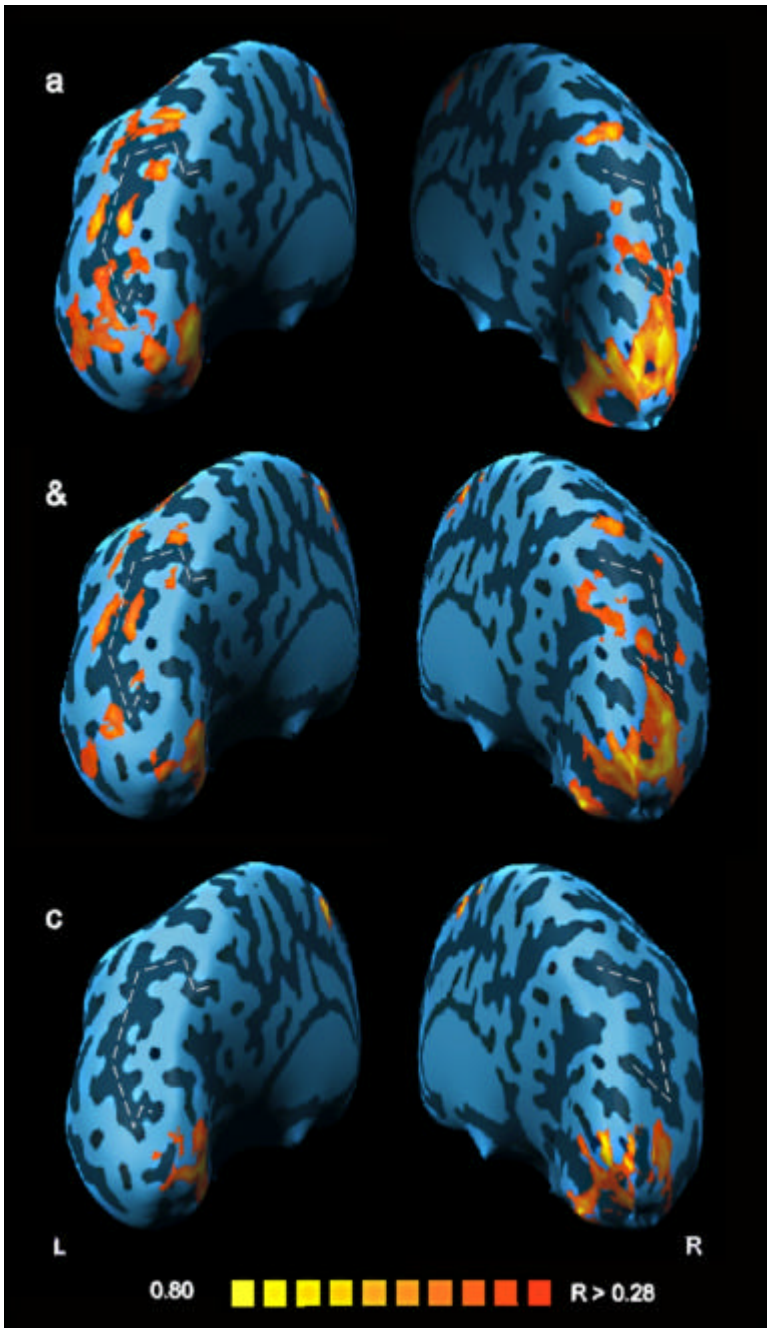

Figure 2: Group analysis (GLM) for 6 subjects at F(6,743)=10.95 ($p=10^{-11}$, uncorrected). Color coded group statistical maps (see Methods) of BOLD signal increase for task vs. baseline (predictors: a = angle, & = conjunction, c = color) superimposed on the inflated hemispheres of a single subject. View from the occipital pole. The white lines indicate the descending portions of the intraparietal sulci.

Table 2: Talairach coordinates†

Anatomical area	BA	Color vs Baseline			Angle vs Baseline			Conjunction vs Baseline			Contrast		
		X	Y	Z	X	Y	Z	X	Y	Z	1	2	3
Left posterior parietal cortex	7	-	-	-	-19	-74	47	-26	-75	46	A	A	-
					-29	-74	22	-32	-75	23	A		
Right posterior parietal cortex	7	-	-	-	26	-69	48	29	-67	53	A	-	-
					29	-78	21	26	-75	23	A		
Left inferior parietal lobule	40	-40	-43	53	-38	-49	56	-42	-46	54	-	-	&
					-34	-45	44	-34	-45	44	-	-	
Right inferior parietal lobule	40	-	-	-	37	-50	47	-	-	-	-	-	&
Left superior frontal gyrus	6/8	-3	-8	52	-1	-8	53	-2	-6	55	-	-	-
(SMA)								-1	6	47	-	-	-
Right superior frontal gyrus (SMA)	6/8	4	-8	51	4	-9	52	6	-5	51	-	-	-
Left precentral sulcus (FEF)	6	-59	2	24	-56	0	32	-58	2	30	A	-	-
Right precentral sulcus (FEF)	6	56	2	31	48	2	35	49	4	34	A	A	-
Left middle frontal gyrus	44	-	-	-	-	-	-	-50	25	29	-	-	-
Left precentral gyrus (PMC)	4	-39	-20	55	-38	-19	55	-36	-17	55	-	-	-
Right precentral gyrus (PMC)	4	36	-13	60	32	-16	55	35	-13	57	-	-	-
Left occipital lobe	17/18	-11	-75	-9	-7	-88	-5	-17	-71	-13	A	-	-
Right occipital lobe	17/18	9	-73	-9	5	-81	-3	5	-80	-7	A	A	-
Left occipitotemporal cortex	37/19	-	-	-	-46	-73	-6	-46	-73	-5	A	-	-
Right occipitotemporal cortex	37/19	-	-	-	37	-77	-2	35	-76	-5	A	-	-
Left middle occipital gyrus	19	-	-	-	-26	-91	9	-23	-90	11	A	-	&
Right middle occipital gyrus	19	24	-90	11	21	-91	12	27	-89	6	A	A	-
Left fusiform gyrus	37	-30	-51	-18	-30	-52	-18	-28	-58	-18	-	-	-
Right fusiform gyrus	37	21	-53	-18	20	-50	-15	24	-54	-18	-	-	-

†Talairach coordinates of centres of mass of activated clusters > 200 mm³ (at F = 12.25, R > 0.3; 6 subjects) of the Condition vs. Baseline maps. *Contrast*: Comparison of signal change from baseline for 1) Angle (A) vs. Color (C); 2) Angle vs. Conjunction (&); 3) Conjunction vs. Color. A, C, & indicate the larger value. $p<0.05$ post hoc paired t-tests. Empty fields indicate that differences in signal change from baseline between experimental conditions did not reach significance. BA = Brodmann Area.

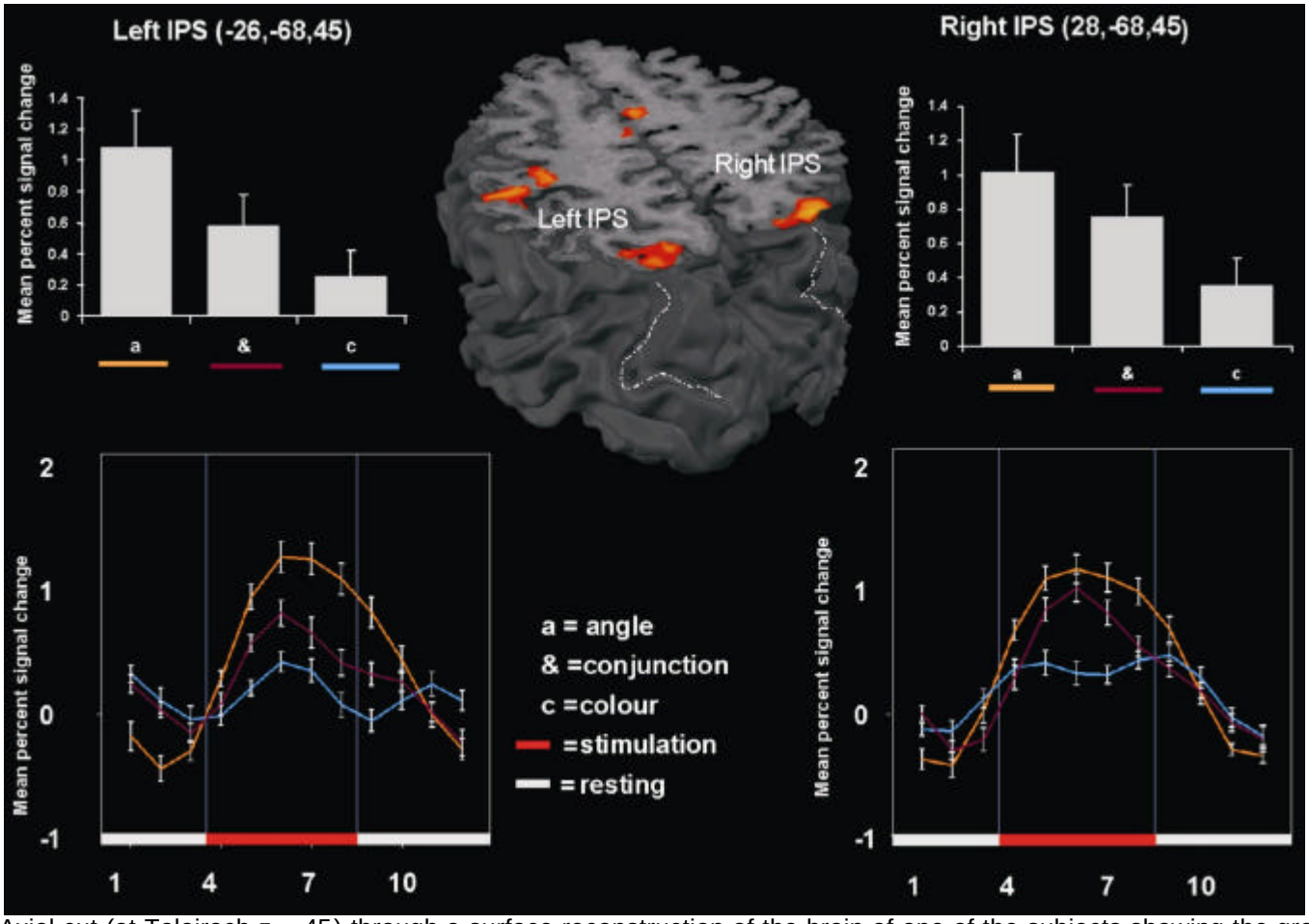

Figure 3: Centre: Axial cut (at Talairach z = 45) through a surface reconstruction of the brain of one of the subjects showing the group activation map (thresholded at R = 0.3, corresponding to an uncorrected p-value = 3.591×10^{-13}) for angle condition versus baseline.

Left and right: BOLD signal time courses in the left and right IPS averaged over 6 subjects (bottom) and box plots (top) of mean activation levels during the angle, conjunction, and color conditions in the IPS areas. Mean percent signal change and standard deviation are displayed on the y-axis for each condition.

2.2.2 rTMS-experiment

In order to analyse the change of the reaction time from pre-test to post-test in the rTMS-experiment, the mean reaction time in the post-test was subtracted from the mean reaction time in the pre-test for every task independently for both groups. A negative difference means an increase of the reaction time in the post-test while a positive difference means a decrease of reaction time in the post-test (Figure 4a).

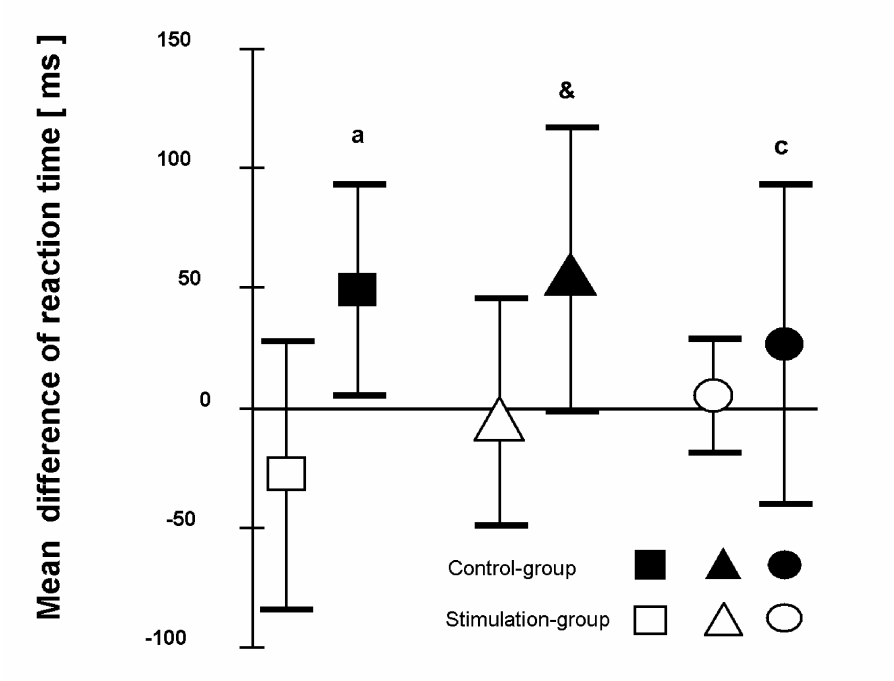

Figure 4a: Comparison of the mean differences between the reaction times in the pre-test and in the post-test calculated for both groups and each test. Negative differences mean increases in reaction time and vice versa. As a reference, the line of no difference (pre-test minus post-test = 0) is drawn in the figure. Error bars denote standard deviation.

As seen in Figure 4a the stimulation group showed virtually no change in reaction time from pre-test to post-test in the color discrimination (+ 5.3 ms) and the conjunction task (- 1.6 ms) and even an increased reaction time in the post-test in the angle discrimination task (- 28.1 ms). The control group, on the other hand, showed a decrease in reaction time in all three tasks (+ 49.4 ms in the

angle discrimination task; + 26.8 ms in the color discrimination task; + 57.9 ms in the conjunction task). This decrease in reaction time was probably due to a familiarization effect. The difference in the change from pre-test to post-test between stimulation and control-group was highest in the angle discrimination task (77.5 ms), followed by the conjunction task (59.4 ms), while the color discrimination task showed almost no difference between the two groups (21.4 ms). These results suggest a difference in the change from pre-test to post-test between the two groups as expected by the hypotheses.

Figure 4b shows the change of the mean reaction time from pre-test to post-test of the three tasks for both groups.

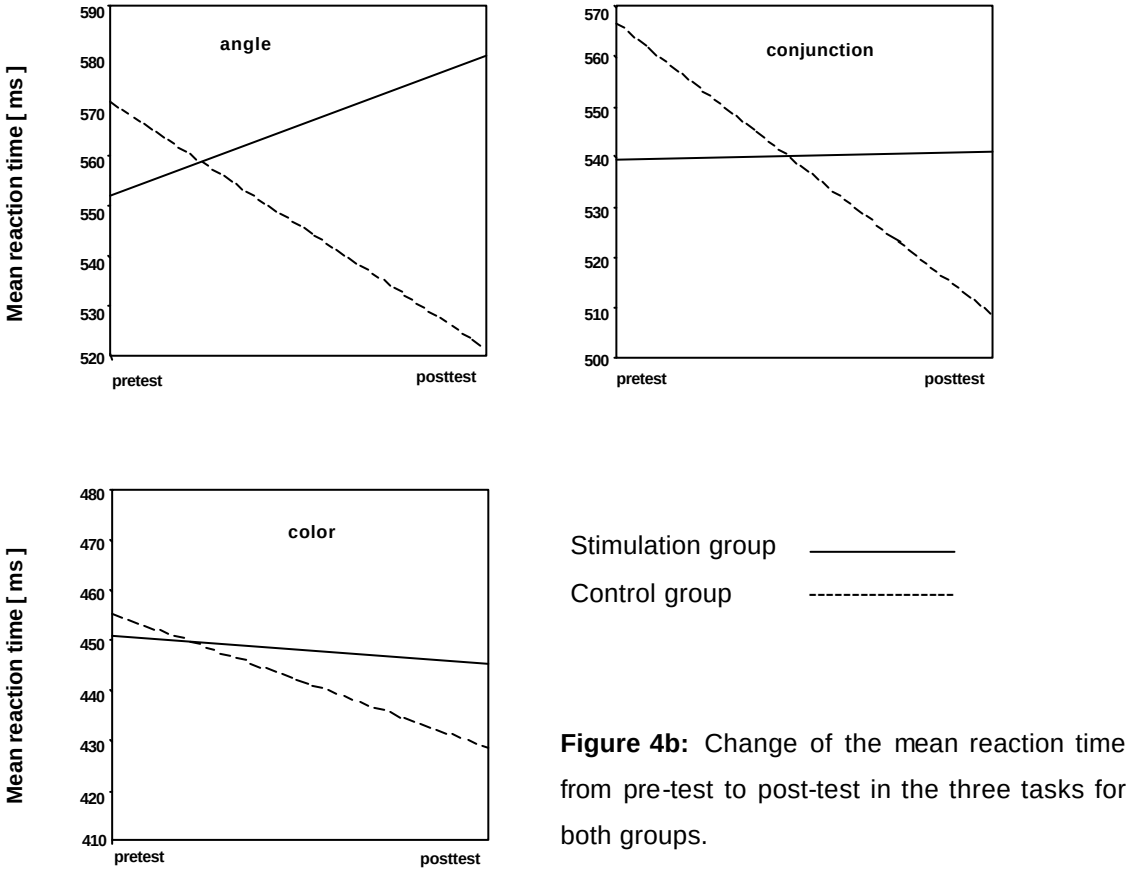

Figure 4b: Change of the mean reaction time from pre-test to post-test in the three tasks for both groups.

The stimulated subjects showed an increased reaction time in the angle discrimination task from pre-test (552 ms, SD = 67 ms) to post-test (580 ms, SD = 77 ms), while the non-stimulated subjects showed a decreased reaction time from pre-test (571 ms, SD = 69 ms) to post-test (521 ms, SD = 76 ms). In the conjunction task the stimulated subjects showed almost no difference between reaction time in the pre-test (539 ms, SD = 74 ms) and post-test (541 ms, SD = 78 ms), while the non-stimulated subjects again decreased in their reaction time from pre-test (567 ms, SD = 62 ms) to post-test (509 ms, SD = 76 ms). In the color condition, both groups showed a slight improvement in the post-test (control group: from 455 ms [SD = 80 ms] in the pre-test to 429 ms [SD = 81 ms] in the post-test; stimulation group: from 451 ms [SD = 76 ms] in the pre-test to 446 ms [SD = 70 ms] in the post-test).

The two-way ANOVA for repeated measurements revealed that the differences between the stimulation and control groups in the change of reaction time from pre-test to post-test were only significant for the angle discrimination task ($F(1,18) = 11.8$; $p = 0.003$; $?^2 = 0.396$) and the conjunction task ($F(1,18) = 6.1$; $p = 0.024$; $?^2 = 0.251$), while the color discrimination task ($F(1,18) = 0.92$; $p = 0.35$; $?^2 = 0.049$) showed no significant statistical difference between the groups.

2.3 Discussion

2.3.1 fMRI study

The analysis of the BOLD signal changes associated with the different conditions of the cognitive paradigm reveals that a significant activation of SPL occurred only during the conditions involving a visuospatial judgement (angle and conjunction), in accordance with prior results (Cohen et al., 1996; Goebel et al., 1998; Haxby et al., 1994; Poldrack et al., 1998), while brain areas subserving elementary visual processing (striate and extrastriate visual cortex), and motor responses (PMC) were activated in all conditions. The higher activation level in the FEF during the angle condition compared to the color (bilaterally) and conjunction (only right FEF) conditions might reflect differences in spatial attention or maintenance of spatial information between the tasks (Goebel et al., 1998; Zarahn et al., 2000). In the IPS, both contrast effects and signal amplitude were highest during the angle discrimination task, followed by the conjunction task, where visuospatial features contributed only part of the task-relevant information. These different activation patterns cannot be attributed to changes in the composition of the visual stimulus, because stimuli were kept physically identical across conditions and only the cue and the task given to the subjects varied. Therefore the BOLD activation levels in SPL reflect a modulation of cortical activity that is related to the visuospatial component, which is a specific task-relevant feature of only two of the used conditions.

2.3.2 rTMS experiment

Corresponding results were obtained by rTMS of PPC at a field intensity sufficient to induce cortical inhibition (Ziemann et al., 1996b).

By using low-frequency rTMS we were able to inhibit the excitability (Chen et al., 1997a; Kosslyn et al., 1999) of the parietal cortex as an independent variable and examine the influence of this experimenter-made manipulation of cortical excitability on the performance in two visuospatial tasks as dependent variables. To control the specific effect of the manipulation on visuospatial tasks, a non-visuospatial task was included in the experimental design.

The control group (sham rTMS) performed faster in all tasks after the stimulation session (post-test), which is an effect attributable to familiarization with the tasks. The stimulation group, whose SPL had been exposed to real rTMS, performed more slowly in both the angle and conjunction task. The color discrimination task was unaffected by rTMS over PPC.

The significant two-factor interaction in the ANOVA could thus show that decreased excitability of SPL reduces the performance of visuospatial tasks (angle, conjunction), but not that of visual tasks which do not require the analysis of the spatial features of the stimulus (color discrimination).

2.3.3 Conclusion

In sum, the pilot study was able to show that real, compared with sham, rTMS applied to the parietal cortex led to a significantly impaired performance in both visuospatial tasks, while the performance in the non-visuospatial task showed no significant change, providing strong evidence for a causal relationship of parietal cortex activation and visuospatial abilities.

These findings not only show that the parietal cortex is activated when healthy volunteers perform visuospatial tasks, but also suggest that performance of these tasks is impaired when neural activity in this region of cortex is disrupted by rTMS. This provides strong evidence for a causal relationship of parietal cortex activation and visuospatial abilities.

Conventional functional imaging by, e.g., PET or fMRI, provides information about transient local changes in neuronal activation, but not about the functional role of this activation (irrelevant, necessary, or sufficient for the performance of the task). By combining fMRI of three different cognitive tasks that were performed on the same visual material and differed in the demand on visuospatial functions with rTMS-induced temporary underexcitability of PPC, this study demonstrated that areas in PPC, notably the IPS region, do subserve the execution of spatial judgements on visually presented material. The present series of fMRI and rTMS experiments confirms that areas in human PPC are necessary for the extraction of spatial information from visual stimuli.

By combining fMRI and rTMS within one experimental design this study thus reveals that rTMS has the potential of taking functional neuroimaging one step further by elucidating causal relationships between neural activation and cognitive function (Hallett, 2000).

As mentioned in the introductory part of this dissertation, one aim of this pilot study was to investigate whether the used perceptual visuospatial paradigm is suitable to induce a task-dependent visuospatial demand resulting in a task-correlated increase of neuronal activity in parietal structures. However, the main

objective of this pilot study was to test the intended methodological approach of an experimental combination of fMRI and rTMS by investigating whether rTMS is physically capable of reaching the targeted brain structures within the parietal lobe and of inducing respective behavioral effects in the visuospatial domain.

Encouraged by the presented results of this pilot study, the main study of this dissertation included an additional visuosptial imagery paradigm in order to systematically investigate and compare the neuronal activation patterns associated with perceptual visuospatial functions and visuospatial mental imagery.

The experimental approach to investigate functional brain-behavior-relationships was further differentiated by inducing unilateral transient functional lesions with rTMS to both parietal lobes separately. This enables an investigation of potential functional hemispheric differences of parietal activation for perceptual visuospatial functioning and visuospatial mental imagery.

3 Main study

3.1 Methods

3.1.1 FMRI and rTMS experiments

3.1.1.1 Cognitive tasks

The cognitive tasks used in both the fMRI and rTMS experiment included a visual and mental visuospatial paradigm.

In the visual paradigm the stimuli consisted of visually presented analogue clocks with a yellow face and two white or yellow hands. The angle between the hands varied in steps of 30 degrees. Subjects had to press a button whenever a target stimulus appeared whereas targets were either defined as clocks with angles of 60° or 30° (angle discrimination task), or as clocks with white hands (color discrimination task). In the rTMS experiment, stimuli were shown for 400 ms with an interstimulus interval of 900 ms. Stimuli were generated using the STIM software package (Neuroscan Inc. Hernon, USA). In the fMRI study, stimuli were presented using a custom visual stimulation software provided by Professor Rainer Goebel. Note that only the target-defining cue (angle versus color task) varied between conditions, while the stimuli were physically identical.

In the mental paradigm subjects were asked to imagine two analogue clock faces based on acoustically presented times (e.g. 9.30 and 10.00), and to judge at which of the two times the clock hands form the greater angle (mental clock task). This task thus requires the subjects to compare the acoustically presented digital times by generating visual mental images of two analogue clocks to the numerical cues and then mentally comparing the angles of their hands. Subjects were asked to press the left mouse button if the hands of the

first imagined clock formed the greater angle, or the right mouse button for the second. Stimuli involved only half-hours or hours intervals and were balanced for the spatial side of the clock the hands had to be imagined on, as well as the numerical greatness of the corresponding digital time. Subjects‘ responses were registered by an optic fiber answer box and analyzed for reaction times and accuracy.

In order to estimate the psychometric reliability of the used visuospatial paradigms, subjects` mean performances in five independent trials with twenty-one stimuli, each measured within a separate pretest session, were used to calculate the Cronbach´s alpha of all three tasks. This estimation of the internal consistency suggested all tasks to be of high reliability (cronbach alpha = 0.887 for the visual angle discrimination, alpha = 0.914 for the visual color discrimination and alpha = 0.881 for the mental clock task). The calculated retest reliability (rr), measured on the basis of the mean performance of a subsample, revealed similar results (rr = 0.89 for visual angle discrimination; rr = 0.938 for visual color discrimination and rr = 0.722 for the mental clock task).

In the rTMS experiment, an additional finger tapping task for both hands was included. In this task subjects were asked to use their left or right index finger, respectively, to repeatedly tap the left or right mouse button, respectively. The frequency of achieved finger taps within a certain time interval was measured independenty for both hands. This task was included at all four times of measurement in order to control for possible effects of rTMS on motor response as a confounding effect on the performance in the visuospatial tasks.

Both experiments (fMRI and rTMS) were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. All subjects gave their informed consent to participate in the respective study and reported being in good health and free of any psycho-active medication. There had been no incident of prior neurological disorder, including seizures, in any of the subjects.

3.1.2 fMRI-experiment

3.1.2.1 Subjects

Six healthy subjects were recruited (mean age 27.8 years, SD = 5.7). Subjects were balanced for gender (3 males, 3 females). All subjects were right handed. Half of the subjects were asked to use their left hand for the button response. Volunteers were naive within the limits of informed consent.

3.1.2.2 Apparatus and procedure

MRI data were acquired with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) using the standard head coil.

For functional imaging of the visual paradigm, a gradient echo EPI sequence was used (1 volume = 16 axial slices parallel to the plane crossing the anterior and posterior commissure, repetition time/echo time [TR/TE] = 2000ms/60ms, flip angle [FA] = 90°, field of view [FoV] = 200x200 mm^2, voxel size = 3.13x3.13.x5.0 mm^3). Functional time-series consisted of 240 volumes and lasted 480 s.

For functional imaging of the mental paradigm a gradient echo EPI sequence was used (1 volume = 10 axial slices parallel to the plane crossing the anterior and posterior commissure, repetition time/echo time [TR/TE] = 1300ms/60ms, flip angle [FA] = 90°, field of view [FoV] = 200x200 mm^2, voxel size = 3.13x3.13x5.0 mm^3). Functional time-series consisted of 400 volumes and lasted 520 s.

A 3D T1 weighted FLASH (Fast Low-Angle Shot) scan was recorded in the same session for each subject (voxel size = 1x1x1mm^3).

Subjects were asked to keep their eyes steady during scanning. In order to control for differences in eye movements between conditions, a subsample performed the tasks offline while electrooculography (EOG) was recorded using NeuroScan equipment with a Synamps amplifier (Neuroscan, Inc.). Two bipolar pairs of electrodes were placed to record horizontal and vertical EOG. The EOG recordings showed absence of differences in saccade rate between conditions.

3.1.2.3 Design

During an fMRI experiment different stimuli or tasks are presented in a controlled way by the experimenter in order to evoke neuronal activations. The spatial and temporal distribution of this task or stimulation induced neuronal activation is recorded by the MR scanner and hence represents the dependent physiological variable in fMRI studies.

The concrete design of a stimulation or task protocol requires the mutual consideration of constraints from cognitive psychology and the physical constraints of MR sequence engineering.

Two classical strategies in designing appropriate stimulation protocols in fMRI are block and event-related designs. While block designs are characterized by the presentation of homogeneous stimulation blocks with alternating conditions assuming the linear additivity of neuronal task-related activation, event-related designs present single trials with an appropriate interstimulus-interval in order to describe the tempo-spatial sequence of single trial induced neuronal activation patterns.

In this study the two different conditions of the visual paradigm (visual angle and visual color discrimination) were tested in one session following the classical block design (4 separate blocks in a pseudorandom order, each lasted 38 seconds and contained 18 stimuli, altogether 8 blocks, inter-block-interval 10 scans (20 seconds)). Stimuli were delivered to a high luminance LCD projector (EIKI LC-6000). The images were back-projected onto a frosted screen positioned at the foot end of the scanner and viewed by the subjects through a mirror placed on the head coil.

The imagery condition of the mental clock task was presented in one session during an fMRI run of 520s (400 scans) on the basis of an event related design. The session consisted of 23 tasks with a resting period between the tasks of 16 scans (20.8 seconds). The presentation of the different stimuli of the mental clock task within an event-related design enables the spatial and temporal

discrimination of a potential sequence of activated brain regions during this more complex multicomponent cognitive task. Stimuli were digitized and presented in pseudorandom order using a custom-made MR-compatible auditory stimulation device.

Prior to the fMRI scanning sessions, Vitamin E capsules were used to mark the positions of the international 10-20 EEG system on the scalp of each subject for coregistration with TMS. These capsules produce MR signals detectable by the scanner, which do not interfere with functional imaging. The capsule-induced MR signals enable the localization of cortical activation in reference to standardized positions on the surface of the scalp. The capsules thus served as a reference for the TMS coil positioning in the second part of the study.

3.1.2.4 Statistical analyses

FMRI-data analysis and visualization was performed using the BrainVoyager 4.4 software package. Spatial and temporal smoothing, removal of linear trends, motion correction, Talairach transformation of 3D anatomical data sets and generation of 3D functional data sets (volume time courses) followed procedures published elsewhere (Goebel et al., 1998; Linden et al., 1999).

Statistically the physiological time-course of the measured BOLD signal changes of each voxel represents the dependent variable, whose variance is analyzed in dependence to the stimulation protocol, which thus contributes the set of predictors to explain the BOLD signal variance. In simple correlation maps, each voxel time course of BOLD signal changes is correlated with a respective reference time course (rtc). Correlation maps thus measure the

similarity between physiological time series and *a priori* conducted reference functions, based on the chosen stimulation protocol. Classically, a theoretical reference time course is defined as a so-called ideal box car time course, which represents a simple ON/OFF response function in correspondence to the alternating stimulation conditions. In order to consider for the hemodynamic properties of the measured BOLD signal changes, these ideal box car response functions are typically shifted on the basis of a linear model for hemodynamic responses (Boynton et al., 1996).

This general principle of computing linear correlations between a set of hypothesis driven reference function predictors and physiological signal changes represents a special case of the General Linear Model (GLM). The application of GLM and respective statistical analyses in fMRI was introduced by Friston et al. (1995). As already proven in other statistical contexts the GLM provides a great flexibility in analyzing multi factorial designs by determining the specific contribution of a defined predictor or set of predictors to the explanation of the BOLD signal variance in a multiple context. Within multiple regression analyses for time series the calculated ß value of a certain predictor thus represents the partial correlation of this predictor with the actually measured neuronal activation and can hence be interpreted in comparison and in contrast to another predictor or set of predictors of the factorial design.

In this study the statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). The general linear model (GLM) of the experiment was computed from the six (one for each subject) z-

normalized volume time courses. Z-normalization of the BOLD signal was performed subject by subject for each voxel time course.

For the visual paradigm the signal values during the angle and color discrimination task were considered the effects of interest. The corresponding predictors, obtained by convolution of an ideal box-car response (assuming the value 1 for the time-points of task presentation and the value 0 for the remaining time points) with a linear model of the hemodynamic response (Boynton et al., 1996), were used to build the design matrix of the visual paradigm.

During the mental paradigm the mental processes following the acoustic presentation of the clock times were the effects of interest. Based on the individual response time of each subject, an appropriate set of predictors were created starting with stimulus onset as predictor 1, followed by a separate predictor for every following scanning volume (every 1.3 s), ending with the volume/predictor corresponding to the time point of the subject`s button press. The ideal box-car response function was shifted on the basis of a linear model of the hemodynamic response (Boynton et al., 1996). The global level of the signal time-courses in each session was considered to be a confounding effect.

To analyze the effects of each separate condition, 3D group statistical maps were generated by associating each voxel with the *F* value corresponding to the specified set of predictors and calculated on the basis of the least mean squares solution of the GLM.

For significantly activated voxels, the relative contribution *RC* of the two visual paradigm conditions in explaining the variance of a voxel time course were computed as $RC = \frac{R^{(2)}_{extra} - R^{(1)}_{extra}}{R^{(2)}_{extra} + R^{(1)}_{extra}}$, where $R^{(2)}_{extra}$ is the contribution of the angle discrimination task predictor to the model and $R^{(1)}_{extra}$ is the contribution of the color discrimination predictor. The contribution of a (set of) predictor(s) to a model is computed as an incremental multiple correlation coefficient, R_{extra}, according to the "extra sum of squares principle" (Draper and Smith, 1998). The formula ensures that the parameter *RC* lies in the interval [-1,1]. An RC value of 1 (color coded red) indicates that a voxel time course is solely explained with predictor *1* (angle discrimination) whereas an RC value of –1 (color coded green) indicates that a voxel time course is explained solely with predictor *2* (color discrimination). In the contrast maps of the visual paradigm, only RC values greater than 0.7 were visualized.

In the mental paradigm RC maps were generated by contrasting the predictor of stimulus onset to the predictor corresponding to the individual motor response of each subject. By defining the temporal beginning and ending points of the task execution and contrasting the predictors representing these time points within a statistical RC map, a color coded visualization of the temporal sequence of activated brain areas during the mental clock task with a temporal resolution of 1300 ms was obtained.

Statistical results were then visualized through projecting 3D statistical maps on axial cuts of the anatomical data sets that show the position of the vitamin E capsules indicating P3 and P4.

3.1.3 r-TMS-experiment

3.1.3.1 The optimal sample size

The conception of classical significance tests provide the opportunity to determine the probability of an empirical result under the assumption of a valid null hypothesis (H0). An empirical result is conventionally labeled as statistically significant if the probability of this observed empirical result, in case of a valid H0, is five percent or less. The incompatibility of the empirical result with the H0 leads to a rejection of the H0 on the basis of the principle of falsification *sensu* Popper (1989) and results in the assumption of the alternative hypothesis (H1), which simply represents all possible results deviating from the H0.

Mathematically, the statistical significance of an empirical effect depends on the size of the tested sample, and the assumption of the H0, as a theoretical model that hardly ever represents reality, has no chance not to be statistically falsified. A statistically significant result *per se* therefore reveals nothing about the practical meaning or textual significance of the results. Tested on a large sample, even the smallest empirical effect becomes statistically significant, and tested on a small sample, even a practically meaningful empirical effect will be statistically insignificant.

The optimal sample size of an experiment is defined as the exact number of subjects within the experimental design that is nesessary to reveal an *a priori* as meaningful determined empirical effect of a certain size, or any greater size, as statistically significant. This implies that any smaller empirical effect, even though potentially statistically significant at a greater sample size, will not reach statistical significance under these circumstances.

This methodological approach of a so-called statistical power analysis thus addresses the potential limitations of conventional statistical analyses which reveal even the smallest empirical effect as statistically significant with increasing sample size (Cohen, 1988). This limitation can be overcome by *a priori* specifying the H1 parameter and therefore simultaneously controlling for the alpha (a)- and beta (ß)-error-probability of the statistical analysis.

Assuming a constant population variance, the sample size determines the standard error of mean differences. Statistically the sample size therefore should be chosen to result in a standard error that leads to a standardized mean difference of z = 1.65. Chosing the optimal sample size only on the basis of these statistical assumptions has nonetheless one major disadvantage: Under the assumption that the true difference of means in the population equals the *a priori* determined empirical effect, a H1 distribution can result in which the pre-determined empirical effect represents the mean of this H1 distribution. In this case the probability of a significant result in the case of a valid H1 equals exactly 50%. The idea to solely choose the optimal sample size so that a pre-determined empirical effect but no smaller effects are statistically significant, leads to a test with very low test power. This can be prevented by statistically controlling for the ß-error-probability.

The ß-error represents the probability with which one wrongly rejects a valid H1 because of a statistically non-significant result. 1-ß thus represents the probability with which one statistically rejects the H0 and thus accepts the H1 in case of a valid H1 (test power). Speaking in statistical terms, the exact pre-

determination of a H0 and a H1 parameter enables one to calculate the probability of an empirical effect (and all higher effects) in case of a valid H0 (a-error-probability), as well as to calculate the probability of an empirical effect (and all smaller effects) in case of a valid H1 (ß-error-probability).

According to Cohen (1988) the consequences of an a-error are conventionally four times as severe as the consequences of a ß-error and therefore a higher ß-error-probability can be tolerated. Cohen (1988) suggests an a/ß-error ratio of one to four resulting in a reduction of the optimal sample size.

The significance level (a), the test power (1 – ß), the experimental effect ($?^2$) and the sample size (n) are interdependenty connected. After fixating three of these parameters, it is possible to calculate the respective fourth one.

The significance level in empirical sciences is conventionally at a = 5% (or 1%). It has been suggested that an agreement be made on a conventional standardization of empirical effects. Cohen (1988) standardizes the experimental effect revealed by ANOVA´s as $f = \frac{s_m}{s}$ in which *f* equals the deviation of population means expected according to the H1 distribution (s_μ), divided by the deviation of the variable within the population (s). The result can then be categorized as a small, middle or high experimental effect (Cohen, 1988).

Regarding the test power the “scientific community” conventionally suggests 1 – ß = .80 as a value appropriate for most empirical studies and moreover as a value in accordance with the claimed 1:4 ratio of a/ß error.

Three of the mentioned parameters are thus conventionally defined which enables the mathematical calculation of the sample size. This calculated sample size is called the optimal sample size.

In this main experiment the a-error-probability was conventionally set at 5% and the ß-probability at 20% (a/ß-ratio 1:4). The estimation of the expected experimental effect was mainly based on our results in the pilot study. The eta-squared of the two found significant effects were $?^2$ = 0.396 for the angle discrimination and $?^2$ = 0.251 for the conjunction task (see results of the pilot study). Eta-squared represents the correlation equivalent of multifactorial ANOVA´s and equals the variance of the dependent variable that can be explained by the independent variable in relation to the total variance of the dependent variable: $h = \sqrt{\frac{QS_{IV}}{QS_{tot}}}$ or $h = \sqrt{\frac{df_{IV} \times F}{df_{IV} \times F + df_{error}}}$.

The standardized experimental effect *f* can mathematically also be expressed in terms of eta-squared: $h^2 = \frac{f^2}{1+f^2}$ and can thus be calculated by $f = \sqrt{\frac{h^2}{1-h^2}}$.

The resulting standardized experimental effects of the pilot study are *f* = 0.8 (angle discrimination task) and *f* = 0.59 (conjunction task) which, according to the mentioned conventional categorization, represent high experimental effects (Cohen, 1988).

Since this main experiment includes a variety of additional and cognitively more complex tasks than the pilot study, the estimation of the expected experimental effect was “downgraded” from a high to a middle effect (Cohen, 1988). Since a TMS-induced modulation of the dependent variables within the times of measurement was explicitely intended by the experiment, a non-correlation between the different measurements was assumed (see design).

On the basis of the chosen experimental design, the optimal sample size to reveal a middle (or higher) standardized experimental effect of $f = 0.25$ as statistically significant is nineteen subjects per condition (Bortz and Döring, 1995). Based on these assumptions and calculations, twenty subjects were randomly assigned to each of three different groups (see design) resulting in an optimal sample size of sixty subjects.

3.1.3.2 Subjects

Sixty subjects volunteered to participate (mean age: 28.4 years, SD = 7.3; 23 males, 37 females). The subjects were randomly assigned to one of three groups (see Design). Twenty subjects were assigned to stimulation group “stim P4” (mean age: 28.3 years, SD = 8.3; 6 males, 14 females), twenty to stimulation group “stim P3” (mean age: 27.7 years, SD = 5.7; 12 males, 8 females) and twenty to the control group “sham” (mean age: 29.2 years, SD = 8; 5 males, 15 females).

3.1.3.3 Apparatus and procedure

A custom TMS stimulator (MagPro, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic

pulses. Magnetic pulses were delivered with a figure-eight-coil (Magnetic Coil Transducer MC-B70, Medtronic) with an outer radius of 50 mm. Individual motor thresholds were identified by stimulating the motor cortex with single TMS pulses until a movement of the contralateral thumb was detected in relaxed muscle state. For real rTMS, the center of the coil was held tangentially to the skull over P3 or P4, respectively (corresponding to left and right superior IPS, as revealed by the MRmeasurements). For sham rTMS, the coil was moved downwards from Pz by 3 cm and rotated so that the edge of the two wings of the coil rested at 90 degrees on the scalp. In this sham rTMS condition, the induced magnetic field did not enter the brain, although the touch on the scalp and the sound of the coil being activated are comparable to those in the real rTMS condition (Kosslyn et al., 1999).

During the experiment the coil was fixed in position and subjects were asked to keep their eyes steady throughout the experiment. Repetitive TMS was delivered at 130% of the subject's motor threshold, a field intensity sufficient to influence cortical activity (Ziemann et al., 1996), at 1-Hz stimulation frequency, in a single train of 12 minutes duration, in accordance with international safety standards of rTMS experimentation (Wassermann et al., 1998). Overall each subject received 720 stimuli. These stimulation parameters produce effects that last beyond the stimulation period (Hallett, 2000; Kosslyn et al., 1999).

3.1.3.4 Design

Each of the two conditions in the visual paradigm (angle and color discrimination) consisted of 5 blocks, each containing 21 stimuli with 8 of the presented clocks being target stimuli.

The mental clock condition also consisted of 5 blocks, each containing a series of 8 tasks (acoustical time pairs) whereas in half of the tasks the hands of the first imagined clock formed the greater angle and in the other half the hands of the second imagined clock formed the greater angle (40 stimuli in total). Therefore, the whole sequence consisted of 250 stimuli. Before every block the target-defining cue was presented. The trial sequence of the blocks as well as the sequence within each block was randomized.

Subjects were randomly assigned to one of three groups. One group was stimulated with real rTMS over P3 (stim P3), one was stimulated over P4 (stim P4) and one group received sham rTMS stimulation (sham).

Subject's performance in the three different tasks was repeatedly measured at four different times of measurement: as a pretest, during TMS (stimulation), immediately after TMS (posttest 1) and 12 minutes after TMS (posttest 2). In order to control for possible effects of rTMS on motor response a finger tapping task for both hands was included at all four times of measurement in all groups (table 3).

3.1.3.5 Statistical analyses

Mean reaction times for correctly detected target stimuli and mean error rates for undetected targets as well as falsely detected non-targets were computed by group and time of measurement separately for every task. A one-way ANOVA was computed to test for a significant difference between the groups at any of the four different times of measurement in the tasks, including a Scheffé

procedure to test for significant single contrasts within the group factor. Additionally a two-way ANOVA for repeated measurements was computed in which the time of measurement was included as a separate factor in order to test for significant interactions between the group factor and the time of measurement. In further analyses the gender as well as the handedness of the subjects were separately included as independent factors within a three-way ANOVA in order to test for possible interactions of second order (e.g. gender x group x time of measurement).

Table 3: Multivariate 2-factorial design: Randomly assigned group comparison factor: “rTMS treatment“ (three levels: real rTMS over P3, real rTMS over P4, sham rTMS); factor of repeated measurement: “Time of measurement“ (four levels: pretest, during stimulation, post-test 1, post-test 2)

group	Pretest	Stimulation	Posttest 1	Posttest 2
stimulation group P4 rTMS over P4	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping
stimulation group P3 rTMS over P3	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping
control group Sham TMS	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping	**visual angle** visual color **mental clock** finger tapping

Notes:
Visuospatial tasks are printed in bold

3.2 Results

3.2.1 fMRI-experiment

3.2.1.1 Position of vitamin E capsules

Prior to the fMRI scannings, Vitamin E capsules were placed on the positions of the 10-20 EEG system on the scalp of each subject. These capsules enabled the localization of parietal activation in reference to the standardized positions P3 and P4 of the international 10-20 EEG system. The following table reports the Talairach coordinates and anatomical areas corresponding to the capsules positioned over parietal cortex P3 and P4.

Table 4: Position of vitamin E capsulses in Talairach coordinates averaged over all subjects (Median, Mean) with respective values of dispersion (quartiles, SD)

	capsules over P3			capsules over P4				
	X	Y	Z	X	Y	Z	ANATOMICAL AREA	BA
Median	-31.0	-84.0	43.0	29.0	-84.0	43.0	Superior parietal lobule	7
Mean	-32.7	-80,3	42.0	32.0	-79. 7	42.0	Superior parietal lobule	7
1. quartile	-29.5	-76.0	41.5	28.5	-76.5	41.5	Superior parietal lobule	7
3. quartile	-35.0	-86.5	43.0	34.0	-85.5	43.0	Superior parietal lobule	7
SD	5.7	11.0	1.7	6.1	10.2	1.7	Superior parietal lobule	7

3.2.1.2 Perceptual visuospatial tasks

Both conditions of the visual paradigm, angle and color discrimination, were accompanied by a significant increase in the BOLD signal in primary visual cortex compared to baseline. The color condition, compared to baseline, additionally activated the right superior occipital gyrus and the lingual gyrus. The angle condition showed several additional significant clusters of activation, both compared to baseline as well as compared to the color discrimination condition within a statistical RC map, in the left and right superior parietal lobule

(SPL), the precuneus and the right middle frontal gyrus (Table 5). The low frequency of motor responses in both conditions explains the lack of motor cortex activity.

Table 5: Talairach coordinates† (plus BA`s) for activated clusters during the visual clock paradigm. The table shows the results of the computed angle vs. color relative contribution (left part), angle vs. baseline (middle part) and color vs. baseline (right part) map.

Anatomical area	**BA**	**Angle vs Color**			**Angle vs Baseline**			**Color vs Baseline**		
		X	Y	Z	X	Y	Z	X	Y	Z
Right superior parietal lobule	7	29	-70	41	21	-69	49	-	-	-
Right superior parietal lobule	7	14	-76	48	16	-72	48	-	-	-
Left superior parietal lobule	7	-15	-69	52	-13	-67	52	-	-	-
Precuneus	7	-8	-68	53	-1	-72	49	-	-	-
Right middle frontal gyrus	46	35	39	27	36	35	28	-	-	-
Primary visual cortex	17	-	-	-	1	-75	7	2	-77	7
Gyrus lingualis	19	-	-	-	-	-	-	19	-57	-3
Right superior occipital gyrus	19	-	-	-	-	-	-	26	-73	27

†Talairach coordinates of centres of mass of activated clusters > 400 mm^3 at R > 0.40 for a) angle vs. color relative contribution ($F = 28$ (12, 1403), $p < 0.01$ (corr.); RC index= 0.7), b) angle vs. baseline ($F = 44{,}73$ (6, 1403); $p < 0.01$(corr.)) and c) color vs. baseline ($F = 44.73$ (6, 1403); $p < 0.01$(corr.)). BA = Brodmann Area.

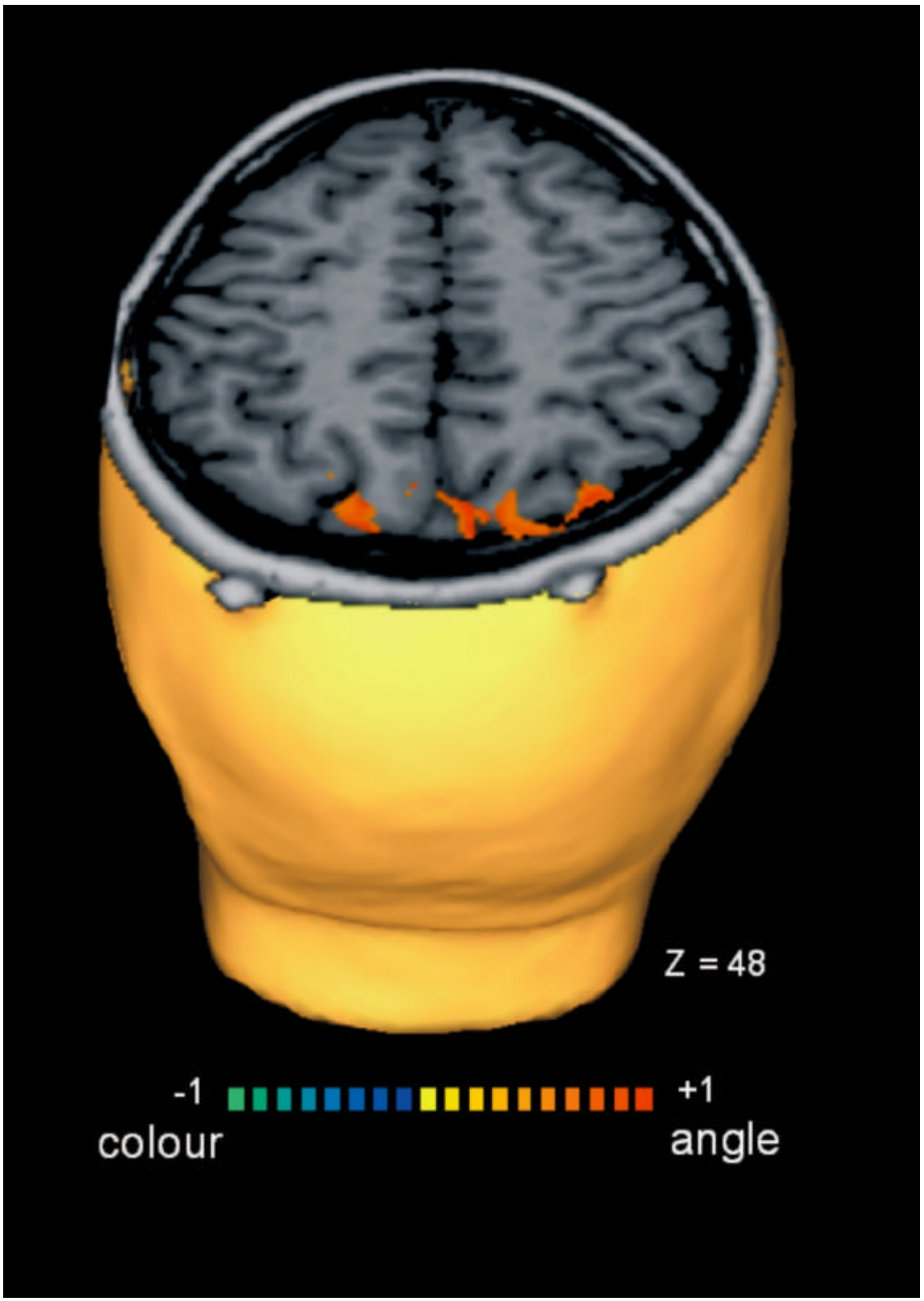

Figure 5: Cortex based parametric anaylsis of the fMRI time-series in the visual paradigm. The results of a statistical RC group analysis are color coded for both visual tasks and superimposed on an axial cut of a single subject. Z value refers to the Talairach Coordinate Sytem.

Figure 5 shows the group analysis (GLM) of the visual paradigm for all subjects at $F = 28$ (12, 1403), $p < 0.01$ (corr.); RC index = 0.7. The color coded group statistical RC maps of BOLD signal increase for angle vs. color discrimination are superimposed on an axial cut of the anatomical data set of a single subject that shows the position of the capsules over P3 and P4. Green color indicates that a voxel time-course is explained mainly with the first predictor (color discrimination); red colors indicate that a voxel time-course is explained mainly with the second predictor (angle discrimination task). Only RC values greater than 0.7 are visualized resulting in only red-coded clusters. In the presented visualization of the statistical RC map in the visual paradigm (Figure 5) only red-coded clusters appear, indicating a high RC in favor of the angle-discrimination task. These significantly activated areas in the parietal lobes that were exclusively explained by the angle discrimination task were located directly below the vitamin E capsules, marking P3 and P4 and correspond to the anatomical area of the superior IPS, bilaterally (Figure 5, Table 4).

3.2.1.3 Visuospatial imagery task

The event related design used in the mental clock task enabled to measure the temporal sequence of activation occurring between the acoustical onset of task presentation and button press. Since half of the subjects were asked to respond with their left hand, the sample was divided into subjects with left button press and right button press. This procedure revealed significant activations that correspond to the temporal sequence of mental processes during the execution of the mental clock task, starting with activity in left and right Heschl`s gyrus, followed by supplementary motor area (SMA), frontal eye fields (FEF), precuneus, left and right posterior parietal cortex (PPC) and finally primary motor cortex (PMC) of the contralateral side of button press (Table 6 & 7).

The crucial parietal clusters of activation in this mental visuospatial task were located below the vitamin E capsules, marking P3 and P4, corresponding to the anatomical areas of left and right superior IPS (Figure 6 & 7, Tables 4; 6; 7).

Table 6: Talairach coordinates† (plus BA`s) for activated clusters during the mental clock paradigm. The table shows the results of the computed stimulus onset vs. button press relative contribution map (left part) for subjects with right hand button press (multi-study GLM), and the interindividual variance in Talairach coordinates of these activated areas (middle part) as well as the number of activated voxels and the temporal delay of BOLD signal peak (right part)

Anatomical area	**BA**	**Stmulus onset vs button press**			**Interindividual variance**			**Clustersize**	**Temporal Delay**
		X	Y	Z	X	Y	Z	Voxel	delay (s)
Right Heschl`s Gyrus	41	+50	-19	+9	±3	±3	±5	8084	6.5
Left Heschl`s Gyrus	41	-52	-24	+11	±2	±5	±2	9741	6.5
Gyrus Frontalis Medialis (SMA)	6	±0	±0	+51	±0	±7	±3	2765	6.5
Left Precentral Gyrus (FEF)	6	-45	-6	+42	±2	±8	±8	2959	7.8
Left Middle Frontal Gyrus	9	-47	+18	+35	±4	±5	±1	729	7.8
Left Superior Occipital Gyrus / Left Superior Parietal Lobule	19 / 7	-29	-80	+31	±6	±8	±3	226	8.45
Right Superior Parietal Lobule	7	+34	-71	+35	±6	±4	±6	217	9.1
Right Middle Frontal Gyrus	9	+47	+18	+38	±6	±1	±4	676	9.1
Left Postcentral Gyrus	2	-46	-35	+51	±2	±14	±5	10096	9.1
Precuneus	7	±0	-77	+42	±8	±1	±1	427	10.4

†Talairach coordinates of centres of mass of activated clusters > 100 mm³ at R > 0.22 for a) stimulus onset vs. button press relative contribution ($F = 30\ (2,\ 1183)$, $p < 0.01$ (corr.)), b) interindividual variance in talairach coordinates of these clusters, c) number of activated voxels d) the temporal delay of BOLD signal peak in reference to onset of acustical stimulation. BA = Brodmann Area.

Table 7: Talairach coordinates† (plus BA`s) for activated clusters during the mental clock paradigm. The table shows the results of the computed stimulus onset vs. button press relative contribution map (left part) for subjects with left hand button press (multi-study GLM), and the interindividual variance in Talairach coordinates of these activated areas (middle part) as well as the number of activated voxels and the temporal delay of BOLD signal peak (right part)

Anatomical area	**BA**	**Stmulus onset vs button press**			**Interindividual variance**			**Clustersize**	**Temporal Delay**
		X	Y	Z	X	Y	Z	Voxel	delay (s)
Right Heschl`s Gyrus	41	58	-9	11	±7	±8	±3	597	6.5
Left Heschl`s Gyrus	41/ 42	-56	-33	15	±1	±2	±3	1127	6.5
Left Precentral Gyrus (FEF)	6	-47	0	34	±4	±3	±5	4298	7.8
Left Precuneus	7	-9	-72	48	±4	±8	±4	517	7.8
Left Superior Parietal Lobule	7	-25	-66	43	±8	±6	±3	239	7.8
Gyrus Frontalis Medialis (SMA)	6	-3	0	44	±1	±3	±5	3239	9.1
Left Inferior Parietal Lobule	7	-43	-44	54	±6	±3	±5	1630	9.1
Right Precuneus	7	8	-78	46	±2	±4	±2	1045	9.1
Left Precentral Sulcus	4	-30	-10	59	±6	±23	±9	1903	9.1
Right Precentral Gyrus	4	34	-29	56	±0	±8	±8	2188	9.1
Right Superior Parietal Lobule	7	35	-54	54	±7	±6	±11	590	10.4

†Talairach coordinates of centres of mass of activated clusters > 200 mm^3 at R > 0.34 for a) stimulus onset vs. button press relative contribution ($F = 80\ (2, 1183)$, $p < 0.01$ (corr.)), b) interindividual variance in talairach coordinates of these clusters, c) number of activated voxels d) the temporal delay of BOLD signal peak in reference to onset of acustical stimulation. BA = Brodmann Area.

Figure 6 shows the group analysis (GLM) of the mental paradigm for subjects with left hand response at $F = 80$ (2, 1183), $p < 0.01$ (corr.). The color coded group statistical RC maps of BOLD signal increase for auditory stimulation vs. button press are superimposed on axial cuts of the anatomical data set of a single subject. On one of these axial cuts (Z = 48) capsules positioned over P3 and P4 are shown. The color of significantly task-related voxels encodes the delay of BOLD activation following the auditory presentation of the stimulus. Green color indicates that a voxel time-course is explained mainly with the first predictor (auditory stimulation), blue-yellow colors indicate that a voxel time-course is explained predominantly with the second and third predictor (mental imagery), and red color indicates that a voxel time-course is explained mainly with the fourth predictor (motor response).

Figure 7 shows the respective group analysis (GLM) of the mental paradigm for subjects with right hand response at $F = 30$ (2, 1183), $p < 0.01$ (corr.). The color coded group statistical RC maps of BOLD signal increase for auditory stimulation vs. button press are superimposed on axial cuts of the anatomical data set of a single subject. On one of these axial cuts (Z = 43) capsules positioned over P3 and P4 are shown. The color of significantly task-related voxels encodes the delay of BOLD activation following the auditory presentation of the stimulus. Color coding was identical to figure 6.

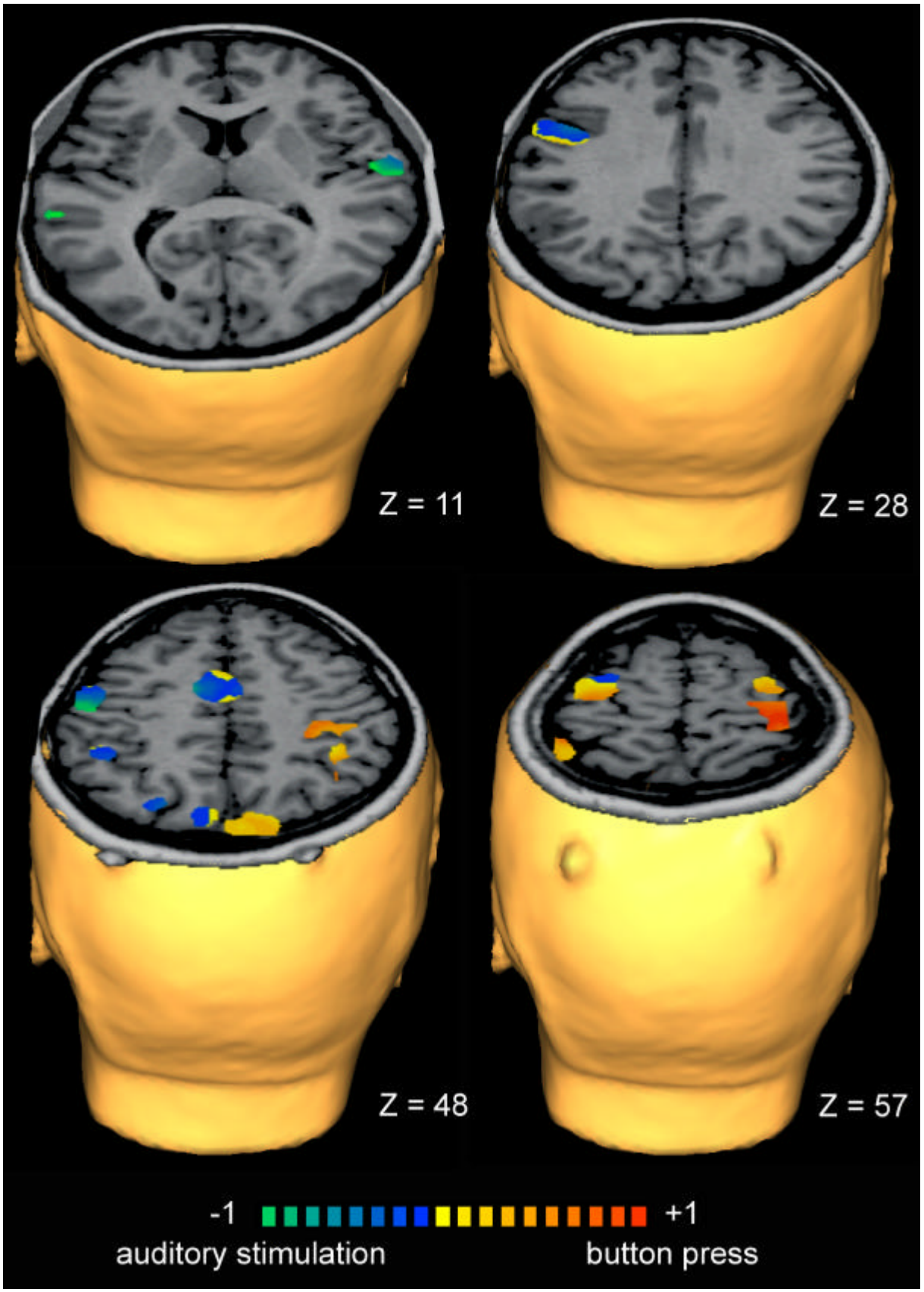

Figure 6: Cortex based parametric anaylsis of the fMRI time-series in the mental paradigm for subjects with left hand response. Z values refer to the Talairach Coordinates System.

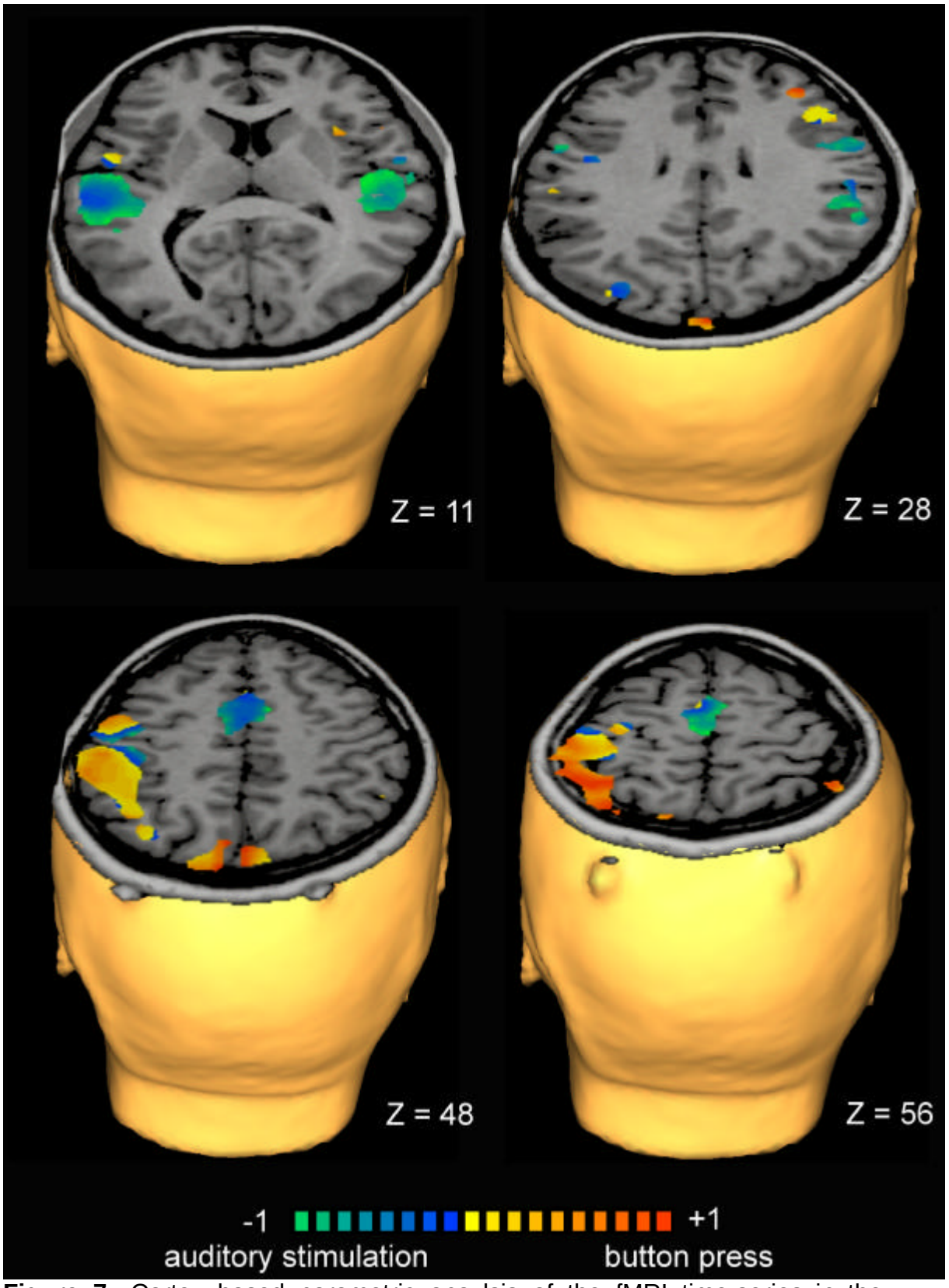

Figure 7: Cortex based parametric anaylsis of the fMRI time-series in the mental paradigm for subjects with right hand response. Z values refer to the Talairach Coordinates System.

The color coded visualizations of significantly activated brain areas shown in figure 6 and 7 suggest, in addition to the precise localization of task-correlated brain activities, a specific temporal sequence within the activation pattern measured during visuospatial imagery.

The temporal delay columns in table 6 and 7 attempt to quantify this temporal sequence of different brain areas by associating each significantly activated area with the respective predictor that temporarily corresponds to the peak of BOLD signal change in this area. Since the set of predictors in the visuospatial imagery task was constituted in reference to each separate fMRI scan following the stimulation onset, each predictor marks the temporal delay of the BOLD signal change following the onset of a trial.

For a better illustration of this temporal sequence, figures 8 and 9 show the actual BOLD signal time courses measured in four different significantly activated clusters during the execution of the visuospatial imagery task. These four clusters represent the auditory cortex, the left and right SPL and contralateral primary motor cortex activation.

The BOLD signal changes in the respective clusters were averaged across all trials of the mental imagery task in order to obtain the so-called event-related averaging curves. Similar to figure 6 and 7, the event-related averaging curves were separately calculated for subjects with left and right button press.

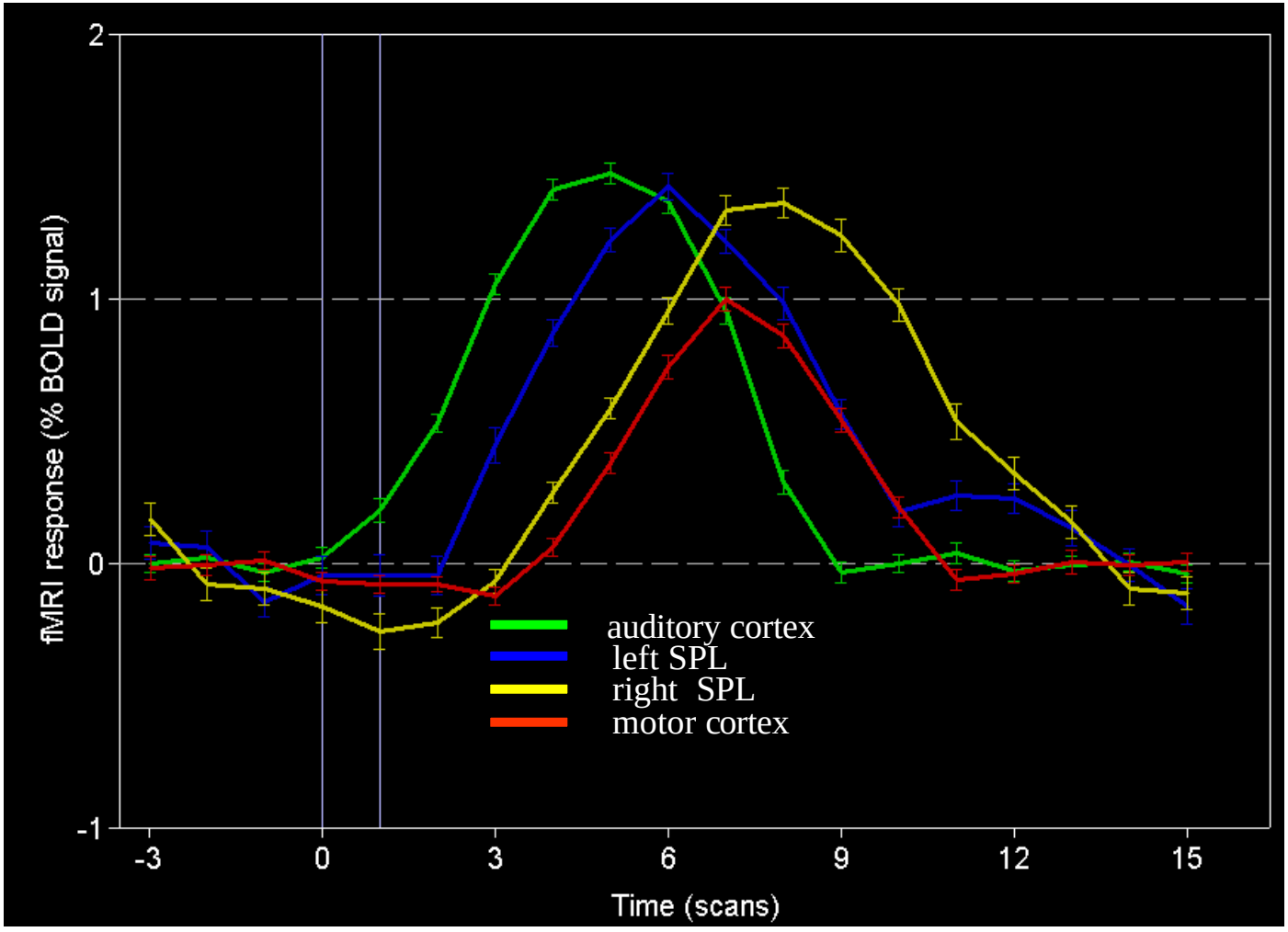

Figure 8: Event-related-averaging curves of four different activated clusters averaged over subjects with left button press and all single trials. On the x-axis three scans prior to (-3) and 15 scans following (15) the onset of the task (0) are shown. The time interval between each scan is 1.3 seconds. The y-axis shows the BOLD signal change in percent.

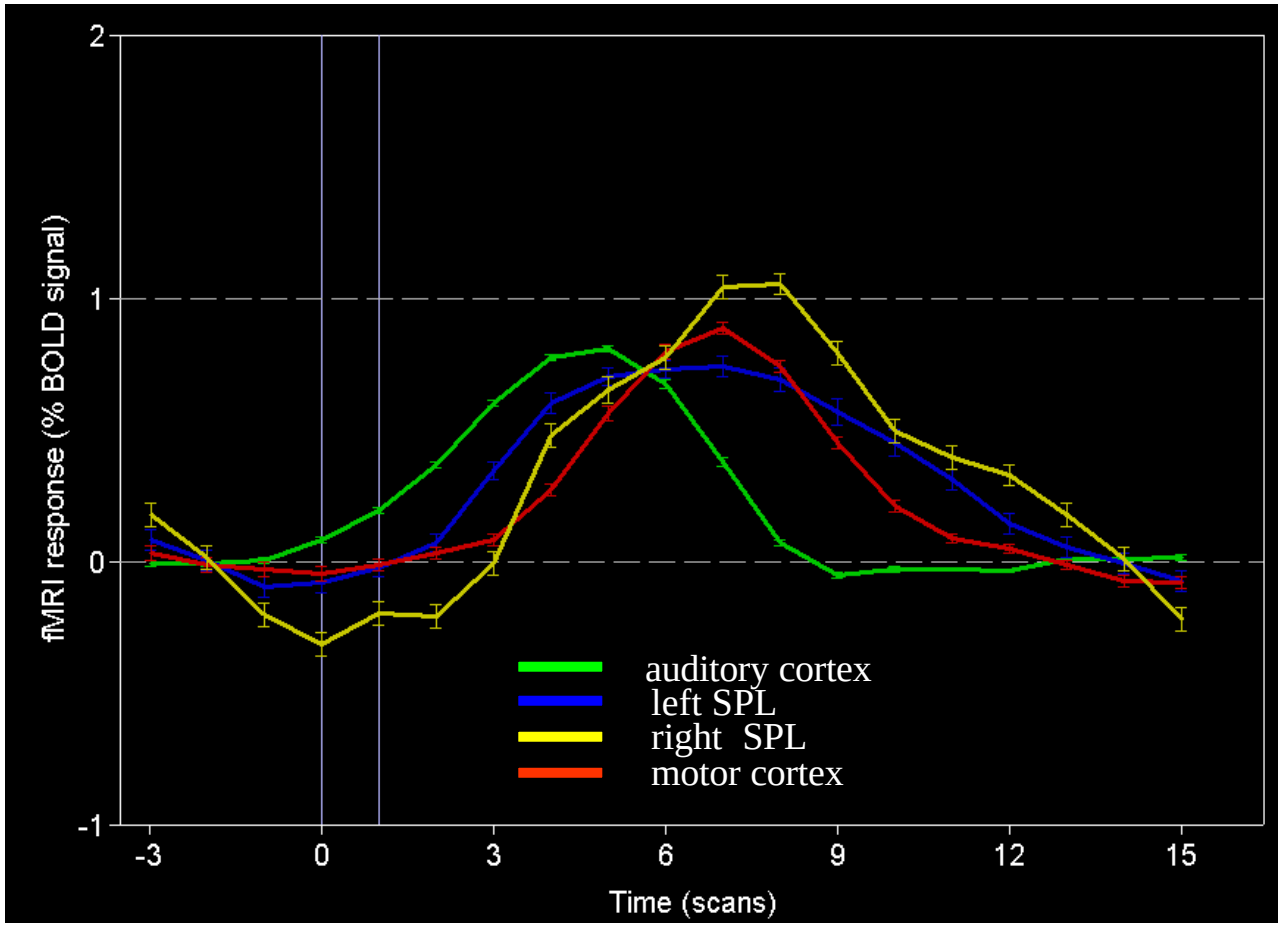

Figure 9: Event-related-averaging curves of four different activated clusters averaged over subjects with right button press and all single trials. On the x-axis three scans prior to (-3) and 15 scans following (15) the onset of the task (0) are shown. The time interval between each scan is 1.3 seconds. The y-axis shows the BOLD signal change in percent.

3.2.2 rTMS-experiment

The sham group showed a monotone decrease in mean reaction time from pretest to posttest 2 in all of the three tasks, probably due to a familiarization effect. The two stimulation groups showed a different pattern of change in mean reaction time between the times of measurement in the three tasks (Table 8).

Table 8: mean reaction times of the three groups in the three tasks in ms plus standard deviation

mean reaction time in ms (SD) of the visual angle-task

	N	Pretest	Stimulation	Posttest 1	Posttest 2
stimulation group P4	20	436.662 (34.804)	464.485 (19.338)	460.318 (20.613)	436.974 (39.447)
stimulation group P3	20	455.351 (34.929)	440.766 (34.668)	441.516 (33.414)	439.674 (34.575)
sham group	20	441.285 (33.068)	429.197 (31.382)	431.430 (32.568)	424.553 (32.278)

mean reaction time in ms (SD) of the visual color-task

	N	Pretest	Stimulation	Posttest 1	Posttest 2
stimulation group P4	20	361.553 (33.204)	367.542 (39.706)	368.605 (41.228)	367.983 (37.083)
stimulation group P3	20	356.536 (35.969)	361.553 (33.204)	361.143 (33.764)	354.723 (36.627)
sham group	20	348.615 (27.622)	347.181 (31.953)	345.369 (33.966)	343.880 (24.596)

mean reaction time in ms (SD) of the mental clock task

	N	Pretest	Stimulation	Posttest 1	Posttest 2
stimulation group P4	20	5.197 (0.630)	5.230 (0.666)	5.026 (0.570)	5.285 (0.913)
stimulation group P3	20	5.046 (0.556)	4.816 (0.494)	4.862 (0.476)	4.723 (0.432)
sham group	20	5.142 (0.457)	4.890 (0.391)	4.775 (0.364)	4.615 (0.314)

The group that was stimulated over P3 (stim P3) showed a monotone decrease in reaction time from pretest to posttest 2 in the angle discrimination and the mental clock task, and an almost unchanged reaction time in the color discrimination task. The group that was stimulated over P4 (stim P4) showed an

increase in reaction time during stimulation as well as in posttest 1 in the visual angle discrimination task. This increased reaction time decreased again in posttest 2. In the mental discrimination task the stim P4 group showed a slight increase in reaction time during stimulation as well as in posttest 2. The change in mean reaction time in the color discrimination task was comparable to the stim P3 group (Table 8).

These results suggest that a difference between real and sham TMS in the performance of the visuospatial tasks, as expected by the hypotheses, only occurred in the stim P4 group, while the stim P3 group showed no noticeable differences to the sham group.

The following figures show the influence of unilateral rTMS on mean reaction times in the angle discrimination task (Figure 10a, b).

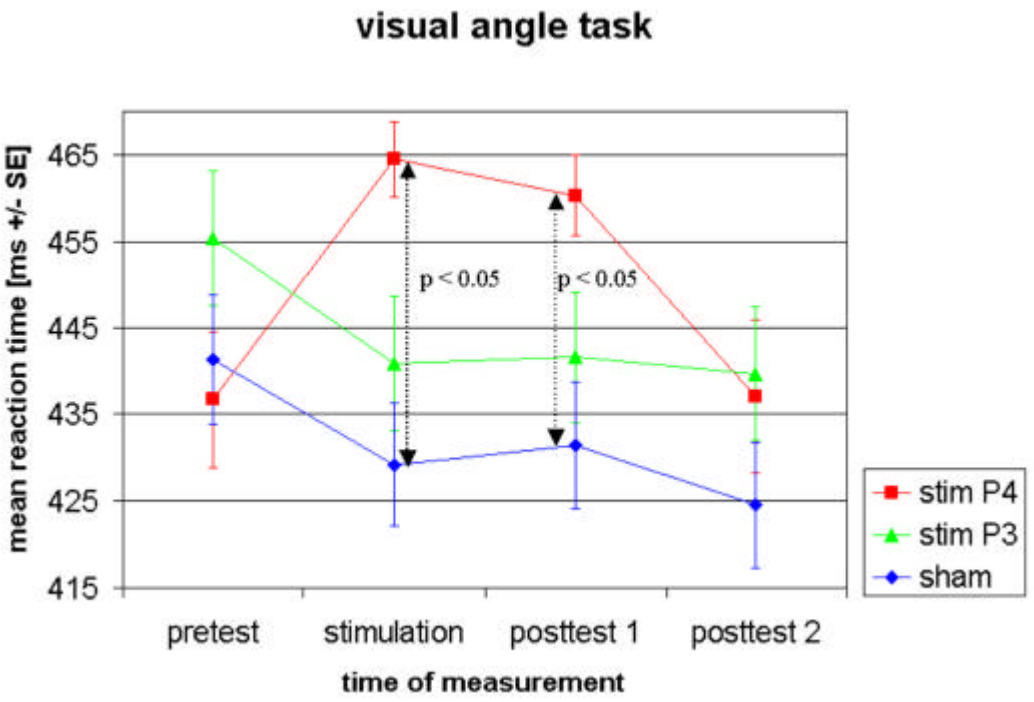

Figure 10a: Mean reaction times in the angle discrimination task at the four times of measurement (pretest, stimulation, posttest 1 and 2) for the three groups.

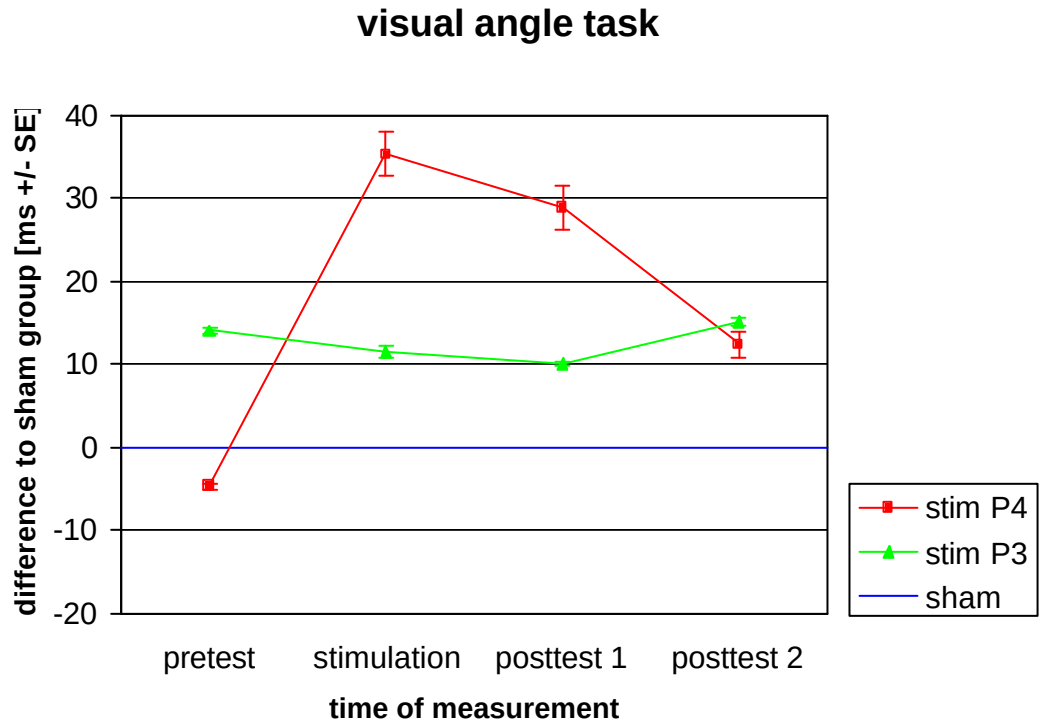

Figure 10b: Difference between the mean reaction time of the sham group (blue baseline) and both stimulation groups in the angle discrimination task at the four times of measurement.

The one-way ANOVA for the angle discrimination task revealed a significant difference in mean reaction time between the groups during the stimulation (F [2, 57] = 7.582; p = 0.001; $?^2$ = 0.210) and in posttest 1 (F [2, 57] = 4.957; p = 0.01; $?^2$ = 0.148), but not for the pretest (F [2, 57] = 1.613; p = 0.208; $?^2$ = 0.054) or posttest 2 (F [2, 57] = 1.029; p = 0.364; $?^2$ = 0.035). The computed Scheffé procedure for multiple contrasts differentiates this significant main effect as being due to a significant difference only between the stim P4 group and the sham group during stimulation and in posttest 1, while the stim P3 group showed no significant difference in comparison to the sham group at any of the times of measurement (Figure 10a, b).

Figures 11a and b show the influence of unilateral rTMS on mean reaction times in the color discrimination task.

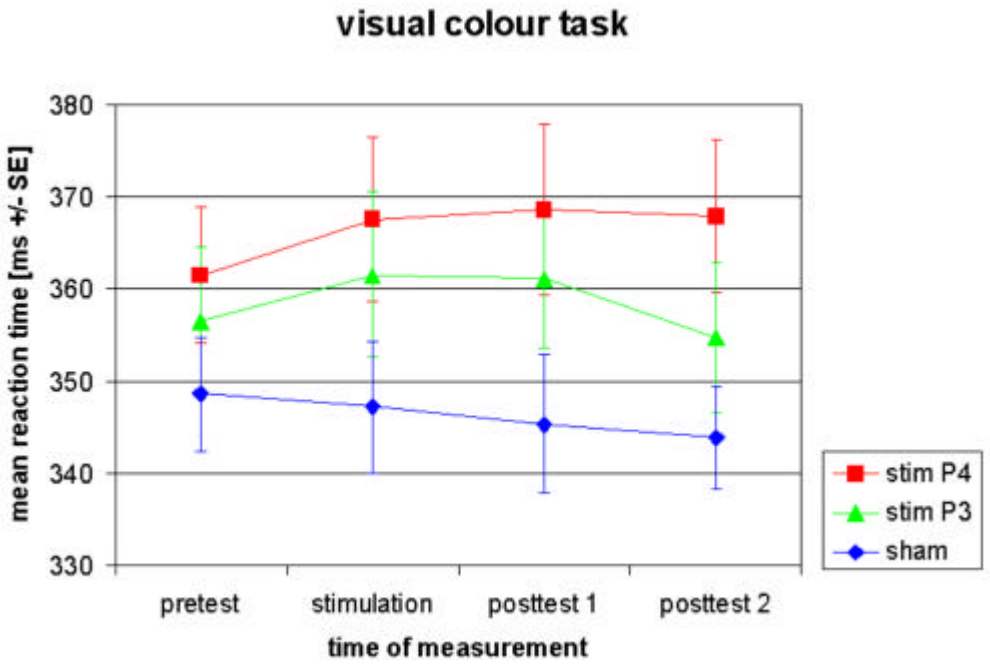

Figure 11a: Mean reaction times in the color discrimination task at the four times of measurement (pretest, stimulation, posttest 1 and 2) for the three groups.

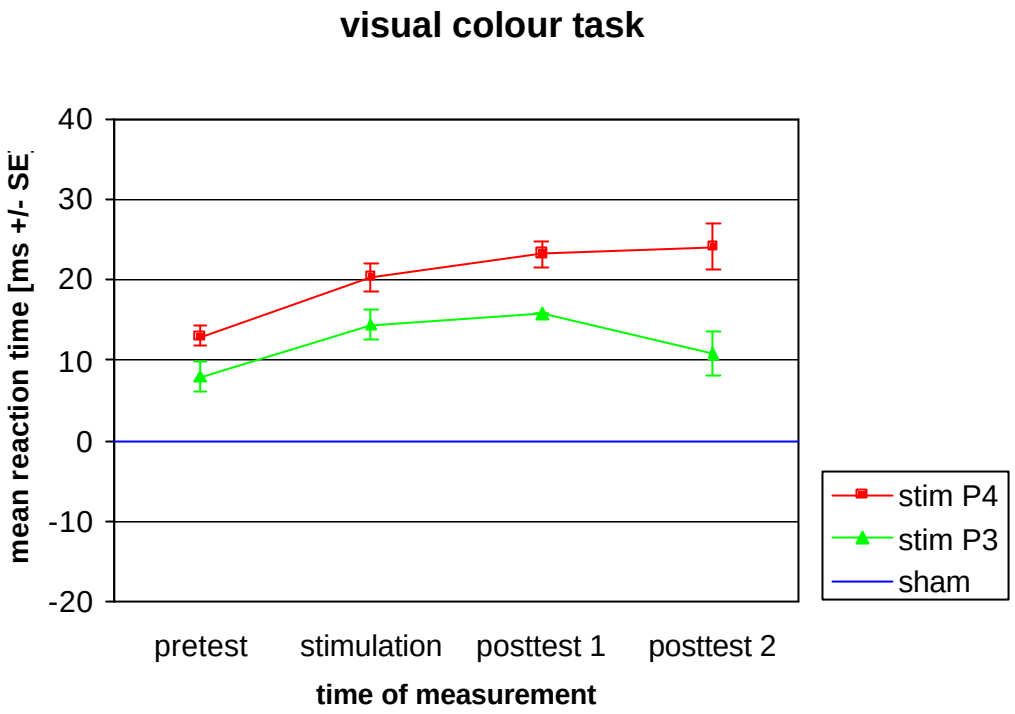

Figure 11b: Difference between the mean reaction time of the sham group (blue baseline) and both stimulation groups in the color discrimination task at the four times of measurement.

In the color discrimination task no significant differences between the groups were found at any of the times of measurement (Figure 11a, b).

The influence of unilateral rTMS on mean reaction times in the mental clock task is shown in figure 12a and b.

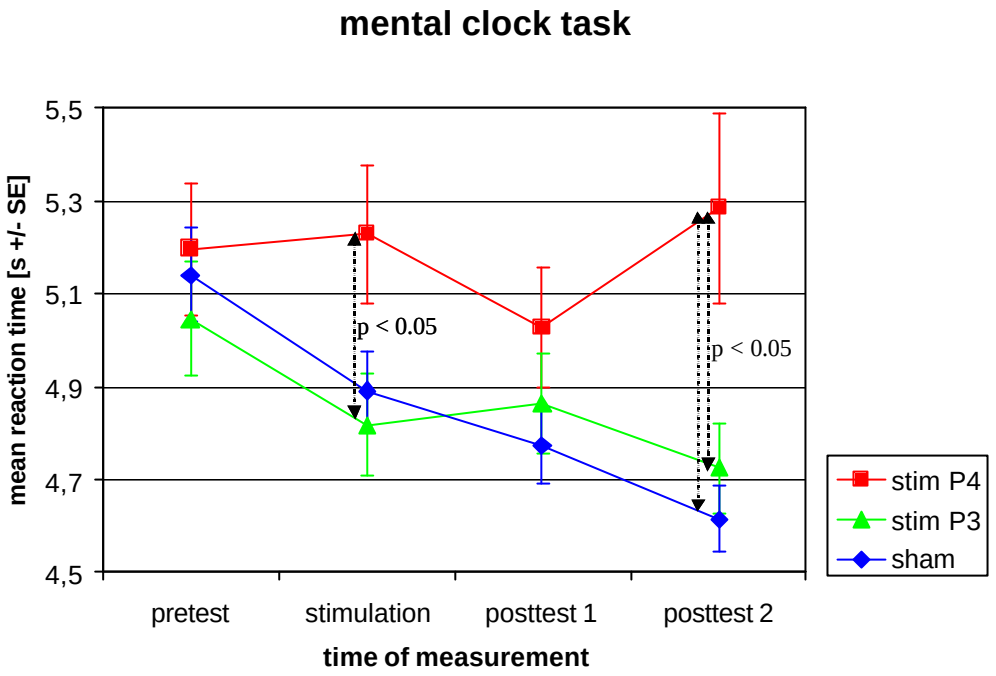

Figure 12a: Mean reaction times in the mental clock task at the four times of measurement (pretest, stimulation, posttest 1 and 2) for the three groups.

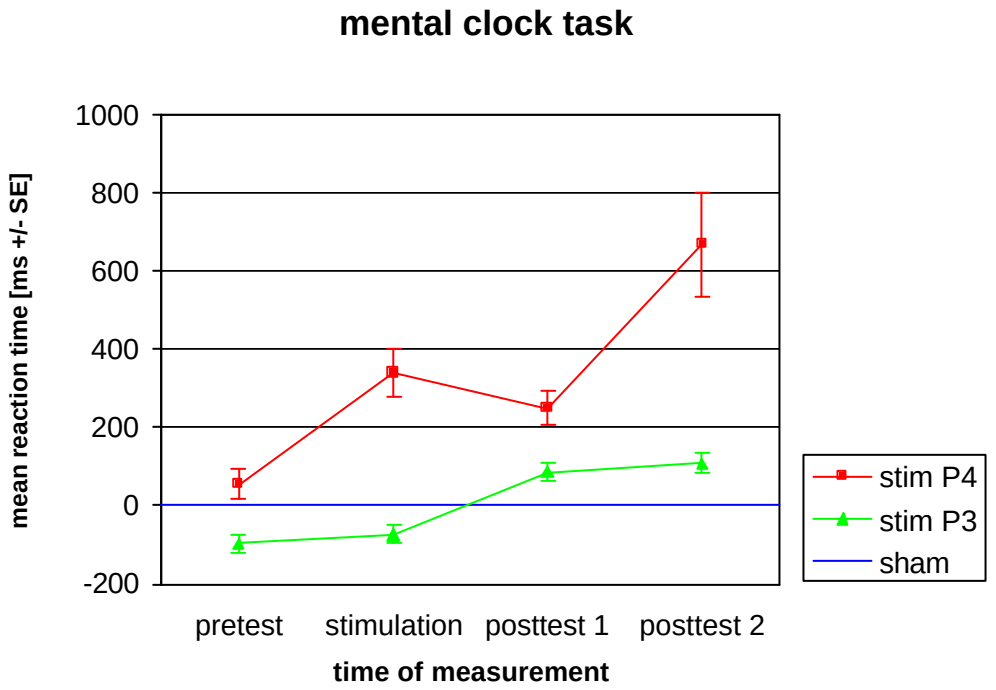

Figure 12b: Difference between the mean reaction time of the sham group (blue baseline) and both stimulation groups in the mental clock task at the four times of measurement.

The one-way ANOVA for the mental clock task showed a significant difference in mean reaction time between the groups during stimulation (F [2, 57] = 3.476; p = 0.038; $?^2$ = 0.109) and in posttest 2 (F [2, 57] = 6.940; p = 0.002; $?^2$ = 0.196). As the computed Scheffé procedure reveals, this significant group main effect was again due to a significant difference only between the stim P4 group and the sham group, while the stim P3 group showed no significant difference in comparison to the sham group at any of the times of measurements (Figure 12a, b).

After including the time of measurement as a separate factor in the statistical analysis a two-way ANOVA for repeated measurements was computed in order to test for possible interactions between the group factor and the time of measurement. The two-way ANOVA for the visual angle condition revealed a significant interaction between the group factor and the time of measurement only for the comparison between stim P4 and the sham group (F [3, 57] = 8.827; p = 0.00; $?^2$ = 0.188), while the stim P3 group showed no significant difference in its change between the time of measurement in comparison to the sham group (F [3, 57] = 0.231; p = 0.874; $?^2$ = 0.006).

For the visual color discrimination task no significant interactions between either of the groups and the times of measurement were found.

In the mental clock task a significant interaction between the group factor and the time of measurement again was only found in the comparison between the stim P4 and the sham group (F [3, 57] = 3.931; p = 0.01; $?^2$ = 0.094), while no significant interactions between the group and time of measurement factor was

found when comparing the sham group with the stim P3 group (F [3, 57] = 1.846; p = 0.143; $?^2$ = 0.046).

In order to control for possible effects of rTMS on motor response as a confounding effect on the performance in the visuospatial tasks, an additional finger tapping task for each hand was included in the experimental design of the rTMS experiment. Subjects were asked to repeatedly tap the left mouse button as quickly as possible, independently with their right and left index finger. This task was supposed to measure potential differences in mean motor response performance between the groups at the four different times of measurement. As the results of these two finger tapping tasks illustrated in figure 13 and 14 reveal, no significant group differences for the left or the right finger tapping task were found at any of the times of measurement.

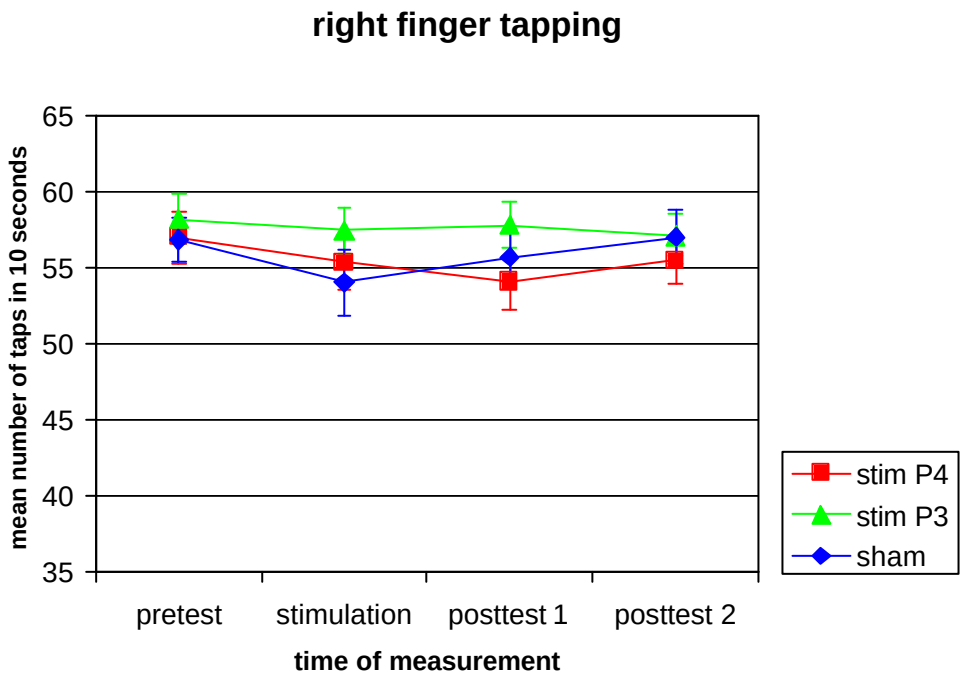

Figure 13: Mean number of taps within a time interval of ten seconds for the right finger at the four times of measurement (pretest, stimulation, posttest 1 and 2) for the three groups

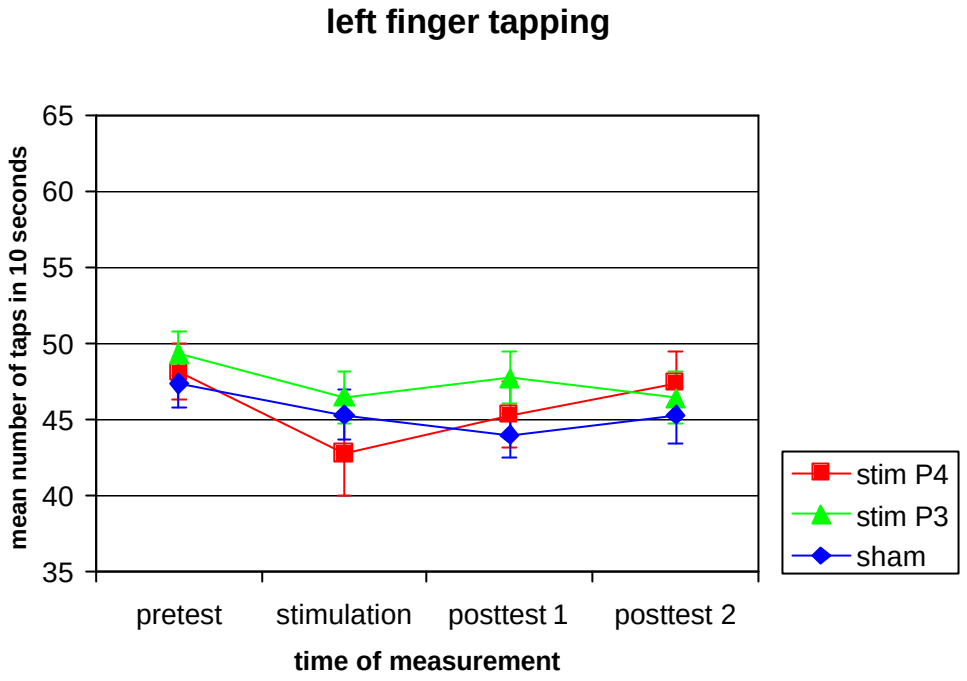

Figure 14: Mean number of taps within a time interval of ten seconds for the left finger at the four times of measurement (pretest, stimulation, posttest 1 and 2) for the three groups

Since the three groups were not statistically matched for gender or handedness, both variables were separately included as independent factors within a three-way ANOVA in order to test for possible interactions of second order between gender, group and time of measurement or handedness, group and time of measurement. No significant second order interactions for any of the tasks were found.

4 Discussion

4.1 Objective of this dissertation

The main objective of this dissertation was to combine evidence from functional magnetic resonance imaging (fMRI) and repetitive transcranial magnetic stimulation (rTMS) to investigate the functional relevance of unilateral parietal activation for the performance of perceptual visuospatial processing and visuospatial imagery tasks.

This multi-methodological approach was supposed to take functional imaging one step further by elucidating causal relationships between localized brain activity and cognitive functions and by revealing the specific functional contribution of a certain brain area during the execution of a multi-component task.

While fMRI passively measures the brain activity as a dependent variable during the execution of different cognitive tasks, rTMS has the capacity to actively manipulate brain activity as an independent variable and to investigate the influence of this experimentally induced alteration of brain activity on the performance of the respective tasks.

In comparison to studies that combine functional imaging with neuropsychological deficits occurring in structural brain damage (Price et al., 1999), the functional deficits induced by rTMS are far more temporary, caused by transient functional lesions controlled by the experimenter, and are hence not superposed by functional reorganization (Walsh and Rushworth, 1999) or the functional impairment of remote areas (diaschisis) (Seitz et al., 1999).

Furthermore, in case of a task-correlated distributed network, in which several brain areas are associated with the execution of a complex cognitive task, the methodological approach of combining evidence from fMRI and rTMS could be capable of distinguishing the specific contributions of each area during the execution of such a complex task.

This dissertation is thus based on two different techniques which were both used to investigate the functional relationship between brain activation patterns and the execution of visuospatial tasks. Whereas in the first part of this dissertation, the brain activation patterns during the execution of perceptual visuospatial processing and visuospatial imagery were measured as dependent variables, the second part turned these task-correlated activated brain areas into independent variables by systematically manipulating the excitability of these areas within an experimental design. The aim was to combine evidence from two different techniques of cognitive neuroscience for the mutual investigation of the neuronal substrates in visuospatial processing. While the first part used fMRI to exactly identify the brain areas activated during the performance of the visuospatial tasks, in the second part rTMS was used to induce transient functional lesions in these identified brain areas and to systematically investigate the influence of the experimental manipulation of brain activation levels on the behavioral performance of the visuospatial tasks.

4.2 Pilot study

Due to the innovative character of the intended methodological approach and especially the uncertainty whether rTMS as a research tool has the physical capacity to actually reach the targeted cortical areas within the parietal lobules,

a pilot study was conducted in order to test this principal capability of manipulating parietal structures and changing the respective performance in the visuospatial tasks by rTMS on a behavioral level.

This pilot study also consisted of an fMRI part that aimed to localize the areas of activation during the execution of perceptual visuospatial processing and an rTMS part that was intended to investigate the influence of rTMS-induced functional lesions to the activation sites on the performance of these visuospatial tasks. The visuospatial functions investigated were limited to perceptual visuospatial processing, based on visually presented tasks, which required the discrimination of different angles. To control for the specific effect of the manipulation on visuospatial tasks, a non-spatial task that only required the discrimination of colors was included in the experimental design.

As described in the discussion part of the pilot study, the execution of the perceptual visuospatial task during fMRI was associated with a significant BOLD signal increase in the superior parietal lobe (SPL) of both hemispheres. This significant activation of parietal areas during the performance of visuospatial tasks is in accordance with prior results using similar task protocols (Cohen et al., 1996; Goebel et al., 1998; Haxby et al., 1994; Poldrack et al., 1998). Since the execution of the included color discrimination task led to no significant parietal activation, these observed BOLD activation levels in SPL reflect a modulation of cortical activity that is related to the visuospatial component in the angle discrimination and conjunction tasks.

The conducted rTMS experiment of the pilot study revealed that rTMS applied to the parietal cortex led to a significantly impaired performance in the visuospatial tasks in comparison to a control group, whereas the performance in the color discrimination task was unaffected by parietal rTMS.

The results of this pilot study thus revealed the suitability of the used perceptual visuospatial paradigm to induce a visuospatial demand that results in a task-correlated increase of neuronal activity in parietal structures. Moreover the pilot study showed that the observed parietal activation not only accompanies the execution of perceptual visuospatial processing, but that the performance in these visuospatial tasks can be selectively impaired by disrupting the neural activity in these activated brain areas with rTMS.

With respect to the intended objective of this pilot study these results provide strong evidence for an actual causal relationship between parietal cortex activation and the performance of perceptual visuospatial tasks. Furthermore, these results revealed that the experimental combination of fMRI and rTMS has the potential to systematically investigate causal brain-behavior-relationships and in particular that rTMS as a research tool is physically capable of interfering with neuronal activation of structures within the parietal regions, resulting in respective alterations of task performances (for details see chapter on pilot study).

4.3 Main study

The main study of this dissertation was based on the results of the pilot study. This study aimed to systematically investigate the brain activation patterns

associated with perceptual visuospatial processing and visuospatial mental imagery. Hence, a visuospatial mental imagery task requiring the discrimination of angles of mentally imagined analoque clocks was included in the stimulation protocol. This enabled the comparative investigation of spatial operations on visually presented as well as mentally imagined stimuli. In order to control for possible effects of rTMS on motor responses, a finger tapping task for both hands was also included. Furthermore, unlike in the described pilot study, rTMS was applied to both parietal lobes separately in order to systematically investigate the specific contribution of parietal activation to the performance of visuospatial processing and visuospatial imagery independently for both hemispheres. The used rTMS stimulation protocol transiently suppresses the cortical excitability of the stimulated brain areas during as well as for several minutes beyond the rTMS stimulation period. In order to obtain systematic information on the time course of the potential behavioral effect, the influence of this rTMS-induced manipulation of brain activation on the performance of the perceptual visuospatial, and visuospatial imagery tasks was measured at four different times: as a pre-test, during TMS (stimulation), immediately after TMS (post-test 1) and 12 minutes after TMS (post-test 2).

The methodological approach of this main study provided the possibility to investigate the causal relationship between unilateral parietal activation and the execution of visuospatial tasks, based on physically presented as well as mentally imagined stimuli, and presents the first systematic experimental investigation of potential functional hemispheric asymmetry of parietal activation for visuospatial processing and visuospatial imagery.

4.3.1 fMRI results of the perceptual visuospatial tasks

The fMRI results of the two perceptual tasks revealed that the performance of the perceptual visuospatial task (angle discrimination) was accompanied by a significant BOLD signal increase in the primary visual cortex, the right middle frontal gyrus, the precuneus and the left and right SPL in comparison to baseline. In contrast to this occipito-parietal activation network associated with the angle discrimination task, the performance of the perceptual non-visuospatial task (color discrimination) was only accompanied by a significant activation in the right superior occipital gyrus, the lingual gyrus and the primary visual cortex.

Hence, although both perceptual tasks were performed on the basis of physically identical task stimuli and merely differed in the visuospatial demand of the required performance presented by the task instruction, a differential activation pattern for the perceptual visuospatial task in comparison to the perceptual non-visuospatial task was observed. The fMRI results of the two perceptual tasks thus revealed a specific involvement of the parietal cortex in perceptual visuospatial processing. This result was further supported by the computed statistical relative contribution (RC) map of activated brain areas contrasting both perceptual tasks directly. This angle versus color discrimination RC map revealed that the right middle frontal gyrus, the precuneus and the left and right SPL are only significantly activated during the performance of the visual angle discrimination, but not during the color discrimination task. The result thus suggests a specific role of bilateral parietal activation for perceptual visuospatial processing.

The described bilateral parietal areas that were significantly activated during the performance of the angle discrimination task were located directly below the vitamin E capsules that mark the positions P3 and P4 of the international 10-20 EEG system. In terms of this surface location reference, the fMRI results of the two perceptual tasks revealed a significant activation in bilateral parietal areas below the positions P3 and P4 only during the performance of the visual angle discrimination task, but not during the visual color discrimination task.

4.3.2 fMRI results of the visuospatial mental imagery tasks

The fMRI experiment for the visuospatial mental imagery task was based on an event-related design. This enabled the measurement of the temporal sequence of activated brain areas following each single trial of the visuospatial imagery task (for details see methods).

For subjects that were asked to respond with their right hand, a sequence of significantly activated brain areas was observed, starting with significant activation in left and right Heschl´s gyrus, gyrus frontalis medialis (supplementary motor areas (SMA)), left precentral gyrus (frontal eye fields (FEF)), left middle frontal gyrus, precuneus, left and right posterior parietal cortex (PPC), right middle frontal gyrus and finally left primary motor cortex (PMC).

A similar activation pattern was observed for the subjects responding with their left hand. The first significant BOLD signal increase after stimulus onset was again observed in the left and right Heschl´s gyrus, followed by the left precentral gyrus (FEF), the gyrus frontalis medialis (SMA), left precuneus, left

superior parietal lobule and left inferior parietal lobule, followed by the right precuneus, the left and right precentral gyrus and finally the right superior parietal lobule.

This sequence of significantly activated brain areas can be interpreted as the neuronal correlate of the temporal sequence of mental processes occurring during the execution of the visuospatial mental imagery task. The described temporal sequence of activated brain areas starts with bilateral activation in the primary auditory cortex, following the onset of the acoustic stimulation with the expected hemodynamic delay. This externally controlled and objectively measurable component thus marks the starting point of the investigated mental operations underlying the execution of the visuospatial imagery task. The endpoint of the mental processes is defined by the button press of the subject, which is associated with a significant activation in the contralateral motor cortex.

Similar to the execution of perceptual visuospatial tasks, the performance of the visuospatial imagery task was accompanied by a significant bilateral activation in the posterior parietal cortex. Hence, visuospatial operations upon visually presented and mentally imagined stimuli seem to share the same neuronal structures within the posterior parietal cortex that underly these operations.

However, the execution of the visuospatial imagery task was accompanied by several brain areas that were additionally activated between primary auditory cortex (acoustical stimulus onset) and contralateral motor cortex (button press). These additional areas included the SMA, FEF as well as further prefrontal areas and represent the neuronal correlates of an information processing

sequence. The specific contribution or role of these task-correlated brain areas can be interpreted as the neuronal substrate of specific components and requirements of the more complex visuospatial mental imagery task.

Following the bilateral activation in primary auditory cortex, both groups showed a significant activation in the gyrus frontalis medialis. This anatomical region represents the so-called supplementary motor area (SMA) which is generally associated with increased attention and the planning of motor processing (Posner et al., 1990). The also observed activation in the left precentral gyrus, the so-called frontal eye fields, has also been found in several other imaging studies on mental imagery and is most likely associated with the attentional demand required in mental imagery (Mellet et al., 1996; Goebel et al., 1998). The activation in the FEF has also been observed in working memory tasks (Ungerleider et al., 1998) and thus activity in this region may underlie the memory activity involved in the visuospatial imagery task.

The significant activations in the left and right middle frontal gyrus observed in subjects that had to respond with their right hand, represent frontal regions that have been reported to be activated in imagery tasks where the mental image had to be formed on the basis of verbal definitions (Mellet et al., 1998a). Moreover, similar to activation in the FEF, these frontal regions have been associated with different working memory tasks (Jonides et al., 1993; Courtney et al., 1996; 1997).

Combined activation of frontal and parietal regions has been reported for several visuospatial tasks (Haxby et al., 1994; Corbetta et al., 1993) and tasks requiring spatial working memory (Jonides et al., 1993; Courtney et al., 1996).

In accordance with these results on an involvement of a fronto-parietal network in visuospatial processing, the fMRI results in the visuospatial imagery task of this dissertation suggest that an information exchange between frontal and parietal areas also underlies visuospatial processing when the spatial operations have to be performed upon a mentally imagined stimulus.

However, although each of these different cortical areas activated during the execution of the visuospatial imagery task are primarily associated with one of these specific functions, there is probably not a mono-directional association between a particular cortical area and a respective function or subfunction (Mesulam, 1999).

Another noticeable result is the bilateral button press-related primary motor cortex activation for subjects with left button press in contrast to the mere left primary motor cortex activation for subjects responding with their right hand. It can be speculated that this different result between subjects with left and right button press is brought about by the handedness of the subjects. All subjects in the fMRI experiment were right handed. Due to the principle of contralateral innervation, the left motor cortex represents the dominant motor area in right handed subjects. In the group that had to respond with their right hand, the right button press thus resulted in an expected contralateral activation in the left primary motor cortex. The subjects that had to respond with their left hand were

right handed subjects that were forced to respond with their left hand by the given instruction. In this case, although the contralateral right motor cortex is activated as expected, the dominant left motor cortex is additionally activated in correspondence with the button-press-related activation in the right primary motor cortex.

The crucial parietal activation during the performance of the visuospatial imagery task was located directly below the capsules marking the positions P3 and P4 of the international 10-20 EEG system. Hence, visuospatial functions based on visually presented and mentally imagined stimuli are accompanied by significant activation increases in similar structures within the parietal lobules that correspond to the same surface location references.

4.3.3 Conclusion fMRI study

The fMRI part of the main study revealed that the parietal cortex is significantly activated during the performance of visuospatial tasks, both based on visually presented as well as mentally imagined stimuli.

The fMRI results on the visually presented tasks revealing a significant activation of parietal areas during the performance of perceptual visuospatial tasks largely confirmed the findings from the pilot study on the same paradigm. In both studies the most prominent differences in cortical activation during the detection of angles compared to that of variations of color were found in the superior intraparietal sulcus (IPS) bilaterally (see pilot study).

During the execution of the visuospatial mental imagery task the fMRI results revealed a more complex fronto-parietal activation network. In this context it can be discussed to what extent this fronto-parietal activation network is specific to visuospatial mental imagery tasks since there is convincing evidence for the activation of a fronto-parietal network during both spatial and non-spatial attention tasks (Wojciulik and Kanwisher, 1999).

However, although heterogeneous stimuli and tasks produce parietal activation (Culham and Kanwisher, 2001), a large body of neuropsychological literature points to a particular role for the posterior parietal cortex (PPC) in visuospatial functioning. Evidence from lesion studies seems to confirm the neurophysiological finding of multiple space representations in the PPC (Colby and Goldberg, 1999; Landis, 2000; Marshall and Fink, 2001).

The fMRI results of the visuospatial mental imagery task also revealed a bilateral parietal activation, suggesting that both hemispheres contribute to the execution of visuospatial imagery. This result is in contrast to most clinical evidence that revealed visuospatial deficits mainly in patients with lesions to the right parietal lobe (Vallar et al., 1998; Mesulam, 1999; Driver and Vuilleumier, 2001).

However, some clinical studies showed no right hemispheric dominance for visuospatial imagery tasks (Mehta et al., 1989; Newcombe and Ratcliff, 1989), and some imaging studies reported a hemispheric asymmetry during tasks involving visuospatial attention (Nobre et al., 1997).

Hence, the evidence regarding lateralization and hemispheric asymmetry during visuospatial imagery tasks is highly inconsistent between neuropsychological and functional imaging studies as well as within the functional imaging literature.

It has been speculated that the degree of lateralization of parietal activation depends on the visuospatial task demand. Carpenter et al. (1999) used fMRI to investigate the cortical activation patterns during mental rotation and were able to reveal a monotonic increase of activation in the left and right intraparietal sulcus with respective increase in angular disparity in the mental rotation task. The authors speculated that an increasing demand in the execution of visuospatial tasks could result in a recruitment of the left hemisphere by the right hemisphere. This recruitment would be prevented in cases with right hemispheric lesion.

Besides this quantitative explanation, it could additionally be speculated that left and right parietal regions could reflect different components that underlie the execution of the complex visuospatial imagery task.

Since the rTMS study of this dissertation was explicitly conducted to systematically investigate the potential functional hemispheric asymmetry of parietal activations for the execution of visuospatial functions, a more detailed discussion and interpretation of the observed bilateral parietal activation and potential association with specific distinguishable task components will be presented in the context of the results and conclusions from the rTMS study.

4.3.4 rTMS results

With regard to the identified areas of significant activation during the performance of the perceptual visuospatial and visuospatial imagery tasks, unilateral rTMS was applied to left and right parietal cortex independently in order to investigate the functional relevance of the identified bilateral parietal activation for the actual performance of the respective visuospatial tasks.

For the visual angle discrimination task, the group that was stimulated over the right parietal cortex (P4) showed a significant increase in reaction times during and immediately after the stimulation (post-test 1) in comparison to the control group. In post-test 2 this difference decreased and ceased to be significant. The group that was stimulated over the left parietal cortex (P3) showed a monotonic decrease in reaction times from pre-test to post-test 2, comparable and thus not significantly different at any of the times of measurement from the performance of the control group.

The performance in the visual color discrimination task was not affected by right or left parietal rTMS at any of the times of measurement. As revealed by the fMRI study, the execution of this non-visuospatial task was not accompanied by parietal activation. Hence, a systematic significant manipulation of the performance in this task by parietal rTMS was not expected. This result can be interpreted as further support for the specificity of the parietal rTMS effect on visuospatial functions.

Unilateral parietal rTMS also had no effect on the subject's performance in the left or right finger tapping task. At no time of measurement was a significant

difference between the groups in the performance of these two motor response tasks observed. Similar to the visual color discrimination task, this result supports the specificity of the rTMS effect on visuospatial functions and moreover excludes the possibility that the observed significant differences in visuospatial task performances are causally determined by an effect of parietal rTMS on the motor responses.

In the visuospatial mental imagery task only the group that was stimulated over the right parietal cortex (P4) showed a significant impairment of performance in comparison to the control group during the rTMS stimulation as well as in post-test 2. The group that was stimulated over the left parietal cortex (P3) again showed no significant difference in the visuospatial imagery task in comparison to the control group at any of the times of measurement.

The results of the visuospatial imagery task are thus similar to the results of the perceptual visuospatial task. Both tasks revealed that only rTMS over the right parietal cortex significantly impairs performance of these tasks during as well as following the rTMS stimulation period.

However, it has to be noted that unlike in the visual angle discrimination task, the difference between the group that was stimulated over right parietal cortex and the control group was not significant in post-test 1, but again significant in post-test 2. Hence, even twelve minutes after the end of the actual stimulation period, the performance of the subjects stimulated over P4 was still significantly impaired in comparison to the control group.

Originally post-test 2 was included in the experimental design in order to provide the possibility to obtain information on the time course of the rTMS-induced behavioral effect. It was assumed that any rTMS-induced effect on task performance would have disappeared at this time of measurement and thus document the reversibility of the transient functional lesion. In the visual angle discrimination task, post-test 2 proved to fulfill this purpose since the significant difference between right parietal stimulation and control group occurred during and immediately after the stimulation period in post-test 1, but disappeared again in post-test 2. The rTMS results in the perceptual visuospatial task at the four times of measurement thus revealed the temporal character of the rTMS-induced visuospatial performance impairment as intended by the experimental design.

However, the results of the visuospatial imagery task at the four times of measurement did not fully reveal the temporal character of the rTMS-induced behavioral effect, since the performance impairment of the right parietal stimulation group was still significant in post-test 2, between twelve and twenty-two minutes after the end of the actual stimulation period, representing the last time of performance measurement in the experimental design.

Besides the general implications that arise from such a result and which will be discussed in the general conclusion part below, this significant difference between right parietal stimulated subjects and controls in post-test 2 puts the focus on the question of the persistency of rTMS induced behavioral effects.

In order to exclude the possibility of rTMS induced long-term effects, subjects that showed a significant impairment in post-test 2 were identified and retested several weeks after the end of the experiment. This post-hoc identification of subjects within the stim P4 group that still showed a significant impairment in post-test 2 revealed that the significant group effect was brought about by five subjects, or twenty-five percent, of the twenty subjects in the stim P4 group. These subjects were contacted and retested under equal conditions without rTMS. The analysis of the reaction times during this retest revealed that the performance of all of these subjects in the visuospatial imagery task had returned to the pretest level. Hence, although the precise time course of the rTMS-induced effect remains speculative, a long-term or even permanent rTMS-induced effect on visuospatial imagery task performance could be excluded.

4.3.5 Conclusion rTMS study

In sum, the rTMS experiment revealed that only right parietal rTMS leads to an impaired performance in the perceptual visuospatial as well as the visuospatial imagery tasks, while left parietal rTMS has no significant effect on the task performance in comparison to a control group. The specificity of this rTMS-induced effect on visuospatial functioning is supported by the observation that neither left nor right parietal rTMS led to a significant impairment in the included non-visuospatial tasks at any of the times of measurement.

These rTMS results thus show that, although the execution of visuospatial functions based on visually presented as well as mentally imagined stimuli is associated with a significant increase of bilateral parietal activation, only an

rTMS-induced transient disruption of the right parietal activation actually results in an impaired performance of the visuospatial tasks correlated with this activation.

Moreover, the finding that only suppression of the right IPS region by rTMS led to behavioral effects on spatial tasks in visual perception during rTMS and immediately after TMS (post-test 1) is in accordance with most of the neuropsychological literature, which points to a prominent role for the right parietal lobe in visuospatial functioning (Vallar et al., 1998; Mesulam, 1999; Driver and Vuilleumier, 2001) and suggests that the finding of impaired performance of the angle discrimination task after rTMS over the parietal midline revealed in the pilot study could be attributed to the part of the induced magnetic field that affected the right hemisphere. While the effect found in the pilot study had consisted of a mere disruption of the normal learning effect, the main study even showed a significant impairment of task performance during and after rTMS. This stronger effect is probably brought about by the increased specificity of the unilateral stimulation. Additionally this stronger effect can be interpreted as a consequence of the higher TMS intensity used in this study (130 % MT) in comparison to the pilot study (80% MT), confirming the evidence of combined fMRI/rTMS studies revealing an intensity-dependent effect of rTMS on local brain activity (Bohning et al., 1999).

In the field of visual imagery, the neuropsychological evidence parallels that from functional imaging studies in that similar mechanisms seem to govern the spatial analysis of imagined and perceived objects (Farah et al., 1989; Trojano and Grossi, 1994). Several neuropsychological and imaging studies proposed a

dominant role of the left hemisphere in imagery (Farah et al., 1985; D 'Esposito et al., 1997). However, the fMRI experiments reported in this study demonstrate a bilateral parietal activation during the execution of visuospatial imagery and suggest that visuospatial imagery is associated with a more distributed activation than thought previously.

In accordance with this bilateral parietal activation during visuospatial mental imagery, Formisano et al. (submitted) distinguished a cluster in PPC that was activated early during visuospatial imagery and showed a bilateral distribution (but left predominance) from a late cluster that was confined to the right PPC. The *duration* of activation of the early cluster and the *onset* of the (late) right cluster correlated with reaction time. It was suggested that the early and late clusters support different components of the cognitive process, for example the generation and subsequent analysis of the visual image. These findings are in accordance with several studies proposing a model of bilateral activation in visuospatial imagery. These modular models suggest that the generation of mental imagery from memory relies primarily on structures in the posterior left hemisphere, while visuospatial operations on these images rely primarily on structures in the posterior right hemisphere (Farah et al., 1989).

The fMRI results of bilateral parietal activation during visuospatial imagery in the main study of this dissertation could therefore be interpreted as supporting such a modular model of visuospatial imagery. Nonetheless, while fMRI alone can provide the temporal sequence of activation during the mental clock test (see Formisano et al., submitted), it reveals little about the functional relevance of this activation and about compensatory mechanisms. This dissertation was able

to address this issue using unilateral rTMS to disrupt transiently the activation of either hemisphere and study the respective effect of this unilateral functional lesion on task performance.

The labeling of the TMS stimulation sites (P3 and P4) with vitamin E capsules revealed that TMS was applied over the parietal areas most strongly involved in the mental clock task (Tables 4; 6; 7).

The effect of rTMS on task performance revealed a hemisphere-specific effect of parietal stimulation. While there was consistently no significant difference between the sham and the left stimulation (P3) group, subjects who were stimulated over the right parietal lobe (P4) performed significantly worse (measured by reaction time) than the other groups during and after rTMS.

The results of this dissertation thus contribute significant new constraints to the modular model of bilateral activation in visuospatial imagery by revealing a bilateral parietal activation during the execution of visuospatial tasks, both based on physically presented as well as mentally imagined stimuli, but a hemispheric asymmetry in the functional relevance for the performance of these tasks with the right PPC being able to compensate for suppression of the left PPC, but not vice versa. One of these constraints affects the claimed lateralization of different aspects of the visuospatial imagery process. If left hemispheric activation underlies image generation and right hemispheric activation reflected the visuospatial operations on these images, a suppression of either of these clusters would lead to impaired task performance. If some components of the cognitive task are supported by a spatially more distributed

network than others, they will suffer less disruption from focal functional lesions. In the case of the present study the later (exclusively right parietal) cluster is fully affected by rTMS over right PPC while the earlier (and more distributed) cluster is not wholly disrupted by the corresponding treatment of the left PPC. The functional lesion of the right PPC might thus have affected a highly localized functional cluster while the functional lesion of the left PPC could be compensated for by other parts of the network.

Such an explanation would be compatible with the current experimental evidence and theories on spatial hemineglect. Contralesional hemineglect in humans is almost always associated with right hemispheric lesions. This neuropsychological finding has been explained with an asymmetrical distribution of spatial attention (Mesulam, 1999), according to which the left hemisphere shifts attention in a contraversive direction while the right hemisphere directs attention in both directions (thus participating in a bilateral attentional network for the right hemispace). In this model, a lesion of the right hemispheric attention network would lead to hemineglect for the left hemispace (which is not within the attentional focus of the left hemisphere), whereas a corresponding left hemispheric lesion could be compensated for by the preserved (right) hemisphere which also covers the contralesional (right) hemispace.

The consideration of spatial hemineglect reveals important parallels to the present study. In both cases, the right hemisphere is capable of compensating for a disruption of the left hemispheric network for visuospatial processing. This suggests that while the cortical representation of some visuospatial functions

might be highly lateralized to the right hemisphere, other important functions have a bilateral distribution, which allows the right hemisphere to compensate for lesions of visuospatial regions in the left hemisphere, but not vice versa. The combination of evidence from event-related fMRI and unilateral functional lesions induced by rTMS in the presented series of studies thus contributed new constraints to modular models of bilateral activation in visuospatial processing and imagery.

5 General conclusion and suggestions for future studies

This dissertation revealed that the experimental combination of TMS and functional imaging represents an efficient and suitable methodological approach for the investigation of causal relationships between localized brain activations and the execution of particular cognitive functions.

Yet, besides the mere investigation of mono-directional causal brain-behavior-relationships, this dissertation demonstrated that the multi-methodological approach of combining event-related fMRI and multi-site rTMS within a carefully designed experimental setting enables the systematic and independent disruption of neuronal activity in different components of a task-correlated activation network with the respective possibility to reveal differential behavioral consequences of rTMS-induced functional lesions in different neuronal components on the actual task performances.

Despite the promising technical approaches in functional imaging and the respective postulated brain-behavior-relationships it has to be considered that few if any behavioral components and brain areas are connected via a simple monocausal one-to-one relationship. As a consequence of phylogenetic development, the brain probably consists of several redundant brain-behavior circuits. Most behaviors, especially the more complex ones like higher cognitive functions, might be modulated by multiple regions in multiple circuits. Hence a stimulation of one area within this network will lead to complex interdependent modulations of activity in connected areas and similar complex effects on behavior. A controlled and well considered experimental design, combining behavioral and physiological measures, is the basis for the distinction of the

different cognitive components of a complex mental process and their representation in a particular spatio-temporal pattern of brain activation.

This dissertation attempted to realize such a multi-methodological approach by combining evidence from functional imaging, TMS and behavioral measures. These three sources of information each contributed different insights to the neuronal substrates of visuospatial processing. Only through the mutual integration of these contributions, this methodological approach revealed new constraints on models of perceptual visuospatial processing and visuospatial imagery. The event-related fMRI experiment enabled the on-line tracking of the coordinated changes of neuronal activation in different brain areas within a spatially and temporarily distributed activation network. On the basis of these results, rTMS allowed the transient and independent modulation of the different components of this task-correlated activation network. Finally, the actual task performances of the stimulated subjects were measured within an experimental design, enabling the systematic investigation of the differential behavioral consequences of these rTMS-induced modulations.

Although the experimental design was carefully planned, the empirical results indicated that some factors could potentially be improved in future studies. One of these factors concerns the rTMS results of the main study. The analysis of the behavioral data revealed that the purpose of post-test 2 in the experimental design, originally included to reflect the temporal aspect of the TMS-induced effect by a within-group comparison, was chosen within a time-window not capable of representing such a temporal sequence, at least for the imagery task. Subjects showed a normal learning pattern during and after sham and left

stimulation, but performed significantly worse during and after rTMS to the right PPC. Unlike the effect on the visual angle task, which returned to baseline in the second post-test (12-22 minutes after the end of the TMS train), the effect on the mental clock task became even stronger in the second post-test. The duration of reduced excitability of cortical areas stimulated with the rTMS protocol applied in this study has been estimated between 5 and more than 15 minutes (Hilgetag et al., 2001). The finding of behavioral effects that lasted beyond 15 minutes and became even stronger with time underline the importance of longer observation windows in future rTMS studies. Evidence from physiological studies suggests that rTMS might affect the efficiency of synaptic transmission and thus lead to a cortical suppression of the stimulated area that lasts for hours (Wang et al., 1996). Future studies should thus be designed to measure task performance over a broader time-window, providing a quantitative estimate of the durations of the TMS effects on different perceptual and cognitive tasks.

Furthermore, based on the presented temporal sequence of activation related to visuospatial imagery from left to right parietal cortex and the revealed hemispheric asymmetry for the execution of visuospatial tasks, a measurement of the temporal aspects of the processing of visuospatial information in the parietal cortex by time-triggered single-pulse TMS can in the future lead to further and temporally more precise insights into the mechanisms of serial visuospatial information processing in the parietal lobes.

Hence, this dissertation made clear that no single research tool alone is suitable to completely unravel the functional complexity of brain-behavior-relationships.

Future studies need to be conducted with ever more specific experimental designs and sophisticated stimulation paradigms in order to address the questions which arose from the results of this dissertation. Moreover the technique of TMS still needs to be highly improved in terms of spatial resolution and in-depth penetration. Yet, this dissertation revealed that TMS, used in combination with functional imaging, is capable of revealing new insights into the location, timing, functional role and specific contribution of different brain areas for the execution of specific cognitive processes and can thus be considered a valuable research tool in cognitive neuroscience.

6 Summary

This dissertation combined evidence from functional Magnetic Resonance Imaging (fMRI) and repetitive Transcranial Magnetic Stimulation (rTMS) for the mutual investigation of the functional relevance of parietal activation in visuospatial information processing and visuospatial mental imagery.

Functional imaging studies provide information about local transient changes in neuronal activation during behavioral or cognitive tasks but reveal little about the nature of this activity. Information on the specific functional contribution of task-correlated neuronal activation for the actual task performance can be obtained by using rTMS to induce temporary regional deactivations. TMS enables to turn the physiological parameter of brain activity into an independent variable, controlled and manipulated by the experimenter, and to systematically investigate the effect of this neuronal manipulation on the actual performance of the cognitive tasks within a controlled experimental design.

The multi-methodological approach of combining event-related fMRI and multi-site rTMS used in this dissertation furthermore provided the possibility to systematically investigate the specific functional contribution of different neuronal components activated during the execution of visuospatial tasks, based on physically presented as well as mentally imaged stimuli. This approach enabled the explicit investigation of a potential functional hemispheric asymmetry of parietal activation for visuospatial processing and visuospatial imagery.

Prior to the main study of the dissertation, a pilot study was conducted in order to investigate whether rTMS as a technique is physically capable of reaching the targeted brain structures within the parietal lobe as well as to test the suitability of the created stimulation paradigms to actually result in a task-correlated increase of neuronal activity in these parietal areas. Due to this preparatory character of the conducted pilot study, the cognitive functions investigated were limited to visuospatial processing based on visually presented tasks. Moreover, the rTMS stimulation was restricted to one stimulation site of the parietal cortex since the main objective of this pilot study was to reveal the principal capability of parietal rTMS to manipulate the respective task performance.

In this pilot study, subjects saw sequences of colored clocks and performed a task that required them to discriminate angles, colors, or conjunctions of both. The study consists of two experiments. In the first experiment subjects had to perform the tasks during fMRI in order to localize the areas of activation during the execution of the different tasks. In the second experiment, a different set of subjects performed the same tasks before (pre-test) and after (post-test) having received real or sham rTMS at 1 Hz to the activated sites. The color discrimination task served as a control task for the specificity of the TMS effect on visuospatial tasks. The results revealed a differential effect of real rTMS on reaction times of the angle and color discrimination tasks. Only for the visuospatial tasks a selective enhancement of fMRI signal in the superior parietal lobule (SPL) and a selective impairment of performance after rTMS to this region in comparison to a control group was revealed. This pilot study thus showed that the parietal cortex is functionally important for the execution of

spatial judgements on visually presented material, and that TMS as an experimental tool has the potential to interfere with higher cognitive functions such as visuospatial information processing.

In the main study of this dissertation, spatial operations on visually presented as well as mentally imaged stimuli were investigated. The visually presented tasks were equal to the ones used in the pilot study and thus required the discrimination of angles or colors. In the mental clock task subjects were asked to imagine two analogue clock faces based on acoustically presented times, and to judge at which of the two times the clock hands form the greater angle. Subjects were asked to press the left mouse button if the hands of the first clock formed the greater angle, or the right mouse button for the second. Subjects' responses were registered by an optic fiber answer box and analyzed for reaction time and accuracy.

During the fMRI study the two visually presented tasks (angle + color discrimination) were performed in one session following the classical block design. The mental clock task was performed in one session on the basis of an event related design. Vitamin E capsules were used to mark the positions P3 and P4 of the international 10-20 EEG system on the scalp of each subject for coregistration with TMS. MRI data were acquired with a 1.5 T MAGNETOM Vision MRI scanner (Siemens Medical Systems, Erlangen, Germany) using the standard head coil. FMRI data analysis and visualization was performed using the BrainVoyager 4.5 software package. The statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time series of task-related functional activation (Friston et al., 1995). For

significantly activated voxels, the relative contribution *RC* between two selected sets of conditions in explaining the variance of a voxel time course were computed. An *RC* value of 1 (red) indicates that a voxel time course is solely explained with predictor 1, whereas an RC value of –1 (green) indicates that a voxel time course is explained solely with predictor *2* (Trojano et al., 2000).

In the rTMS-experiment, 60 subjects were randomly assigned into 3 groups (stimulation for 12 minutes at 1 Hz and 130% of motor threshold over P3 and P4, and sham). A custom TMS stimulator (MagPro, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. Magnetic pulses were delivered with a figure-eight-coil (Magnetic Coil Transducer MC-B70, Medtronic). Performance was measured at four different times: as a pretest, during TMS (stimulation), immediately after TMS (posttest 1) and 12 minutes after TMS (posttest 2). In order to control for possible effects of rTMS on motor response a finger tapping task for both hands was included at all four times of measurement. The used rTMS protocol has been shown to suppress transiently cortical excitability during as well as for several minutes beyond the rTMS stimulation period (Chen et al., 1997; Kosslyn et al., 1999; Pascual-Leone et al., 1994a).

The results of this main study revealed a selective enhancement of fMRI signal in the superior parietal lobule (SPL) bilaterally for angle discrimination and visuospatial imagery, but not for color discrimination. Yet, only the group which received rTMS to the right SPL (P4) showed a significant selective impairment of performance in the two visuospatial tasks during and immediately after rTMS.

The methodological combination of fMRI and rTMS hence revealed that although the parietal cortex is activated bilaterally during the execution of spatial judgements, only a disruption of the activity of the right parietal cortex leads to impaired visuospatial performance during and immediately after rTMS.

Based on these results, it was speculated that the bilateral parietal activations during visuospatial imagery represent the neuronal correlates of different mental components associated with the execution of the visuospatial imagery task. This interpretation was supported by the temporal sequence underlying the task-related activation network since the analysis of the event-related fMRI data revealed a temporal activation sequence which processes the information from left to right parietal cortex. The separate experimental manipulation of the neuronal excitability of these two spatially and temporarily distinguishable parietal activation clusters by multi-site rTMS revealed a functional asymmetry of parietal activation for the execution of visuospatial tasks. These results suggest a capacity of the right parietal lobe to compensate for a temporary suppression of the left hemisphere. This interpretation is also compatible with current theories of spatial hemineglect and constitutes new constraints for models of distributed information processing in the parietal lobes.

The experimental combination of fMRI and rTMS realized in this dissertation represents a methodological approach suitable to reveal new insights into the functional role and specific contribution of different brain areas for the execution of specific cognitive processes and thus valuable as a new and promising research approach in cognitive neuroscience.

7 Zusammenfassung in deutscher Sprache

7.1 Einleitung

Aus Untersuchungen mit unterschiedlichen Methoden der funktionellen Bildgebung geht hervor, dass mit der Bearbeitung kognitiver Aufgaben zur Messung visuell-räumlicher Fähigkeiten eine erhöhte Aktivierung im Parietalkortex einhergeht. Dies betrifft sowohl die Bearbeitung von Aufgaben mit visueller Reizvorlage (Goebel et al., 1998; Dierks et al., 1999; Poldrack et al., 1998) als auch solche mit mental vorgestellten Aufgaben (Alivisatos and Petrides, 1997; Cohen et al., 1996; Trojano et al., 2000).

Dieser vielfältig untersuchte und gut dokumentierte korrelative Zusammenhang von erhöhter neuronaler Aktivität im Parietalkortex, insbesondere im Lobulus parietalis superior (LPS), und verschiedenen Aufgaben zu visuell-räumlichen Fähigkeiten, kann als Hinweis auf eine kausale Beziehung zwischen dieser Kortexregion und der kognitiven Fähigkeit der visuell-räumlichen Informationsverarbeitung interpretiert werden. Jedoch stellt der korrelative Zusammenhang alleine methodentheoretisch keine Überprüfung eines tatsächlichen kausalen Zusammenhangs zwischen Hirnaktivität und kognitiver Leistungsfähigkeit dar und ermöglicht deshalb auch keine Aussagen über die funktionelle Bedeutung des Parietallappens für visuospatiale Leistungen.

In Untersuchungen mit funktioneller Bildgebung werden verschiedene indirekte Operationalisierungen neuronaler Aktivität als abhängige Variablen gemessen, deren Varianz in bezug auf das simultan zu bearbeitende Aufgabenparadigma zu erklären versucht wird. Analysiert wird demnach der Einfluss, den die Ausführung der als unabhängige Variablen vorgegebenen kognitiven Aufgaben

auf die Veränderung lokaler neuronaler Aktivierungsmuster ausübt. Eine experimentelle Unterscheidung funktionell relevanter von rein epiphenomenaler, oder exzitatorischer von inhibitorischer Aktivierung kann durch solch einen Untersuchungsansatz nicht geleistet werden. Die funktionelle Bildgebung kann in diesem Sinne lediglich Assoziationen, jedoch keine funktionellen Beziehungen zwischen kognitiver Leistung und Mustern kortikaler Aktivierung herstellen.

Um die Frage nach der funktionellen Relevanz kortikaler Aktivierungsmuster beantworten zu können, wurden Studien mit funktioneller Bildgebung mit Untersuchungen neuropsychologischer Defizite aufgrund struktureller Hirnschädigungen kombiniert (Price et al., 1999; Ng et al., 2000). In diesen Studien lässt sich allerdings das durch die strukturelle Läsion verursachte funktionelle Defizit nicht von möglichen Effekten aufgrund kortikaler funktioneller Reorganisation unterscheiden. Abgesehen davon handelt es sich bei den funktionellen Defiziten aufgrund struktureller Hirnschädigungen methodentheoretisch um sogenannte Organismusvariablen und somit nicht um gezielt induzierte und damit replizierbare Veränderungen neuronaler Aktivierungen im Sinne einer experimentellen unabhängigen Variable.

Demgegenüber ermöglicht die Methode der Transkraniellen Magnetischen Stimulation (TMS) unter Verwendung des physikalischen Prinzips der elektromagnetischen Induktion eine experimentell induzierte Manipulation lokaler neuronaler Aktivität. Transkraniell bedeutet hier, dass ein magnetisches Feld von außen durch die Strukturen des Schädels hindurch zu einer intrakraniellen Stimulation des Hirngewebes führt. Eine nahe der

Hautoberfläche gehaltene Spule liefert einen magnetischen Puls, der im Gewebe einen proportionalen Strom induziert. Es handelt sich also um einen magnetisch induzierten Reizstrom, der eine Stimulation der Nervenzellen bewirken kann, ohne dass hierzu eine direkte elektrische Stimulation notwendig ist, und der somit eine schmerzlose kortikale Stimulation ermöglicht. Die Methode der TMS ermöglicht aufgrund dieser kontrollierten, temporären und reversiblen Stimulation von kortikaler Aktivität die Überprüfung funktioneller Zusammenhänge zwischen umschriebener Hirnaktivität und kognitiver Leistungsfähigkeit.

TMS, appliziert in niedrigfrequenten repetitiven Impulsen (rTMS), führt zu einer Hemmung kortikal vermittelter Funktionen sowie Störungen oder Verlangsamungen von visueller Informationsverarbeitung (Amassian et al., 1989), visuellem Suchen (Walsh and Rushworth, 1999) und der Ausführung von Hand- (Desmurget et al., 1999) und Augenbewegungen (Ro et al., 1999), welche auch für Minuten nach Abschluss der Stimulation anhalten (Chen et al., 1997a).

Durch die gezielte niedrigfrequente Stimulation der mit visuospatialen Fähigkeiten assoziierten Hirnareale läßt sich über die Untersuchung der aufgrund dieser Stimulation möglicherweise meßbaren Veränderungen der visuospatialen Leistungsfähigkeiten und ihrer Aktivierungsmuster im fMRT die funktionelle Bedeutung dieser Hirnareale für diese Fähigkeiten experimentell untersuchen.

7.2 Empirischer Teil

Der empirische Teil dieser Dissertation besteht aus einer fMRT-Studie zur genauen räumlichen Lokalisation aufgabenkorrelierter parietaler Aktivierungen während der Durchführung visuospatialer Aufgaben sowie einem rTMS Experiment zur systematischen Untersuchung der funktionellen Relevanz dieser Aktivierungen für die tatsächliche Leistungsfähigkeit in visuospatialer Informationsverarbeitung und visuospatialer Imagination.

Die Stimuli des visuellen Paradigmas bestanden aus Sequenzen von Analoguhren mit einem gelben Ziffernblatt auf schwarzem Grund und zwei weißen oder gelben Zeigern. Der Winkel zwischen den Zeigern variierte in Schritten von 30 Grad. Die Probanden sollten immer dann eine Taste drücken, wenn eine zuvor definierte Zieluhr (Zielreiz) eingeblendet wurde. Zieluhren wurden je nach Aufgabenart definiert als Uhren mit Zeigern, die einen Winkel von 30 oder 60 Grad aufspannen (Winkel-Aufgabe) oder Uhren mit weißen Zeigern (Farb-Aufgabe). Die Instruktion zur Definition der Zieluhr wurde jeweils zu Beginn eines Aufgabenblocks visuell über den Bildschirm präsentiert. Als Operationalisierung der visuospatialen Informationsverarbeitung mental repräsentierter Stimuli wurde der „mental clock test“ von Paivio (1978) verwendet. Bei diesem Testverfahren werden den Probanden zwei Uhrzeiten akustisch dargeboten. Die Aufgabe besteht darin, sich die entsprechenden Zeigerkonstellationen dieser gehörten Uhrzeiten auf einer mental repräsentierten Analoguhr vorzustellen, miteinander zu vergleichen, zu entscheiden, welche der mental vorgestellten Uhrzeiten den größeren Winkel zwischen den Zeigern aufspannt und eine entsprechende Taste zu drücken.

Mit diesem Versuchsplan konnte zum einen untersucht werden, ob und inwieweit während der mentalen Diskriminierung von vorgestellten Winkeln im fMRT gleiche oder ähnliche Aktivierungsmuster auftreten wie während der Winkeldiskriminierung visuell dargebotener Stimuli, und ob sich diese Aktivierungsmuster imaginierter Stimuli unter dem Einfluss von rTMS in gleicher Weise als funktionell relevant erweisen wie die der visuellen Stimuli.

7.2.1 fMRT-Studie

In der fMRT-Studie wurden die zwei visuell dargebotenen Aufgaben auf der Grundlage eines klassischen Blockversuchsplans durchgeführt. Der mentalen visuospatialen Aufgabe wurde ein ereigniskorrelierter fMRT Versuchsplan zugrundegelegt.

Die Stimuli der beiden visuellen Aufgabenbedingungen wurden über einen LCD Projektor (EIKI LC-6000) auf eine Leinwand projiziert, die am unteren Ende des MRT-Scanners angebracht war. Über einen an der Kopfspule befestigten Spiegel konnten die Probanden, im Scanner liegend, auf die Rückseite dieser Leinwand schauen und die dort sowohl vertikal als auch horizontal gespiegelten Instruktionen und Stimuli während der Messungen sehen. Die mentale visuospatiale Aufgabe wurde mit Hilfe eines speziell konstruierten nicht-magnetischen akustischen Stimulationssystems dargeboten.

Vor den eigentlichen fMRT Messungen wurden bei allen Probanden die Punkte des internationalen 10-20 EEG Systems mit Hilfe handelsüblicher Vitamin E Kapseln markiert. Diese Kapseln produzieren ein durch den Scanner messbares Signal und sind dadurch bei der Auswertung der fMRT Daten als an

der Schädeloberfläche angebrachte Marker erkennbar. Diese Methode lieferte ein Oberflächenreferenzsystem zur Zuordnung der im fMRT gemessenen kortikalen Aktivierung zu standardisierten Referenzpunkten an der individuellen Schädeloberfläche jedes Probanden, welche zur zielgenauen Positionierung der TMS Spule im zweiten Teil der Studie verwendet werden konnten.

Die Analyse und Visualisierung der fMRT Daten erfolgte mit Hilfe der BrainVoyager 4.5 Software (www.brainvoyager.com). Die statistische Analyse der Varianz der physiologischen BOLD Signalveränderungen basierte auf der Applikation einer multiplen Regressionsanalyse für Zeitreihen aufgabenkorrelierter funktioneller neuronaler Aktivierungen (Friston et al., 1995), wobei dem Allgemeinen Linearen Modell (ALM) die z-standardisierten Volumen-Zeitverläufe jedes einzelnen Probanden zugrundegelegt wurden. Die Signalveränderungen während der visuellen Winkeldiskriminierung, visuellen Farbdiskriminierung sowie der mentalen visuospatialen Aufgabe waren die dabei interessierenden Effekte. Die Prädiktoren des ALM stellen die Aufgabenbedingungen selbst dar, wobei jeder Prädiktor durch eine zuvor erstellte Signalverlaufkurve mit den Werten 1 (für die Zeitpunkte der Stimuluspräsentation) und 0 (für die Zeitpunkte, in der diese Aufgabenbedingungen nicht präsentiert wird) definiert ist. Diese idealen Signalverlaufskurven werden dann auf der Basis eines linearen Modells zur Berechnung der hämodynamischen Antwort entsprechend dem Einsetzen des erwarteten BOLD-Signals verschoben (Boynton et al., 1996) und als Prädiktoren im multiplen Regressionsmodell zur Erklärung der tatsächlich gemessenen Varianz des physiologischen BOLD-Signals in das Modell aufgenommen. Für signifikant aktivierte Voxel wurde der relative Beitrag der

Erklärung der Varianz des physiologischen Signalzeitverlaufes zwischen verschiedenen Prädiktoren als Operrationalisierungen hypothesengenerierter und auf der Grundlage des Stimulationsprotokolls *a priori* angelegter Signalzeitverläufe berechnet. Hierbei wird die Differenz in den ß-Gewichten zweier Prädiktorsätze an der Summe dieser ß-Gewichte im Kontext des multiplen Modells relativiert. Dieser Quotient spiegelt somit als statistischer Index den relativen Anteil eines bestimmten Prädiktors oder Prädiktorsatzes an der Varianzaufklärung des BOLD Signals in einem bestimmten Aktivierungscluster wider.

Die fMRT Ergebnisse der beiden visuell dargebotenen visuospatialen Aufgaben ergaben, dass die Durchführung der visuellen Winkeldiskriminierung im Vergleich zur neuronalen Grundaktivierung in Ruhe von einem signifikanten BOLD Signalanstieg im primären visuellen Kortex, dem rechten Gyrus frontalis medius, dem Präcuneus sowie dem linken und rechten Lobulus parietalis superior begleitet ist. Im Unterschied dazu führte die Durchführung der visuellen Farbdiskriminierung lediglich zu einer signifikanten Aktivierung im rechten Gyrus occipitalis superior, dem Gyrus lingualis sowie dem primären visuellen Kortex.

Die fMRT Ergebnisse für die mentale visuospatiale Aufgabe zeigten ein komplexeres Aktivierungsnetzwerk, welches bezüglich seiner zeitlichen Struktur mit dem zeitlichen Ablauf unterschiedlicher mentaler Prozesse während der Durchführung dieser mentalen visuospatialen Aufgabe korrespondierte.

Die akustische Darbietung der mentalen visuospatialen Aufgabe war zeitlich von einem signifikanten Anstieg im primären auditorischen Kortex beider Hemisphären begleitet. Anschließend kam es zeitlich versetzt zu signifikanten Anstiegen der neuronalen Aktivität im Gyrus frontalis medialis, dem linken präzentralen Gyrus sowie dem linken und rechten posterioren Parietalkortex. Die Aktivierungssequenz wurde durch eine zeitlich mit dem Tastendruck des Probanden korrespondierende und kontralateral zur respondierenden Hand des Probanden lokalisierbare Aktivierung im primären Motorkortex abgeschlossen.
Diese Sequenz signifikant aktivierter Hirnareale während der Bearbeitung der Aufgaben mentaler visuospatialer Leistungen kann als neuronales Korrelat der korrespondierenden zeitlichen Abfolge unterschiedlicher mentaler Prozesse, die der Durchführung dieser Leistungen zugrundeliegen, interpretiert werden.

Zusammenfassend zeigten die Ergebnisse dieser fMRT-Studie, dass sowohl die perzeptuelle visuospatiale Informationsverarbeitung als auch die mentale visuospatiale Imagination mit bilateraler Aktivierung im parietalen Kortex korrelieren, die als gemeinsames neuronales Korrelat der modalitätsübergreifenden visuospatialen Verarbeitung zugrundezuliegen scheint. In bezug auf das durch die Vitamin E Kapseln umgesetzte Oberflächenreferenzsystem läßt sich diese bilaterale parietale Aktivierung direkt unterhalb jener Kapseln, welche die Punkte P3 und P4 des internationalen 10-20 EEG Systems markierten, lokalisieren.

7.2.2 rTMS-Experiment

Im rTMS Experiment zur experimentellen Untersuchung der funktionellen Relevanz der im fMRT identifizierten lokalen Aktivierungen für die tatsächliche

Leistungsfähigkeit in den untersuchten visuospatialen Aufgaben wurden sechzig Probanden per Randomisierung in drei Gruppen aufgeteilt.

Eine Gruppe wurde über dem linken Parietalkortex (P3) und eine zweite Gruppe über dem rechten Parietalkortex (P4) mit rTMS stimuliert. Eine dritte Gruppe erhielt eine Placebo-Stimulation und diente somit als Kontrollgruppe. Die gezielte und unabhängige unilaterale Stimulation der aufgabenkorrelierten Aktivierungsareale beider Hemisphären sollte die systematische Untersuchung einer möglichen funktionellen hemisphärischen Asymmetrie parietaler Aktivierungen für die Durchführung perzeptueller und imaginativer visuospatialer Leistungen ermöglichen.

Stimuliert wurde repetitiv bei 1 Hz mit 130% der individuellen Motorschwelle für zwölf Minuten, mit insgesamt 720 Impulsen. In früheren Studien konnte gezeigt werden, dass ein solches rTMS-Stimulationsprotokoll zu einer temporären, reversiblen Unterdrückung lokaler kortikaler Exzitabilität sowohl während als auch für einige Minuten nach Beendigung der eigentlichen Stimulation führt (Pascual-Leone et al., 1994; Chen et al., 1997; Kosslyn et al., 1999).

Die Leistungsfähigkeit in den visuospatialen Aufgaben wurde zu vier Testzeitpunkten erhoben: als Vortest, während der Stimulation selbst, im direkten Anschluss an die Stimulation (Nachtest 1) sowie zwölf Minuten nach Abschluss der Stimulation (Nachtest 2).

Die Ergebnisse des rTMS Experimentes in der visuellen Winkeldiskriminationsaufgabe zeigten, dass nur die Gruppe, die über dem rechten Parietalkortex (P4) stimuliert wurde, eine signifikant schlechtere Leistungsfähigkeit im Vergleich zur Kontrollgruppe sowohl während als auch direkt im Anschluss an die Stimulation (Nachtest 1) aufwies. Dieser signifikante Unterschied zwischen der rechtsparietal stimulierten Gruppe und der Kontrollgruppe war im Nachtest 2 wieder aufgehoben. Die Gruppe, die über dem linken Parietalkortex (P3) stimuliert wurde, zeigte dagegen zu keinem Zeitpunkt eine signifikante Verschlechterung der visuellen Winkeldiskriminationsaufgabe im Vergleich zur Kontrollgruppe.

Die Leistungsfähigkeit in der visuellen Farbdiskriminationsaufgabe unterschied sich zu keinem Zeitpunkt signifikant zwischen den Gruppen und zeigte sich demnach unabhängig von der applizierten unilateralen parietalen Stimulation. Wie aus den entsprechenden Ergebnissen der fMRT Analysen hervorging, zeigte die Durchführung dieser Aufgabe auch keinerlei Korrelation mit parietaler Aktivierung, womit eine Manipulation der Leistungsfähigkeit in dieser Aufgabe durch gezielte parietale Stimulation auch nicht zu erwarten war. Darüber hinaus kann die Unbeeinflussbarkeit dieser Aufgabe durch parietale rTMS als Hinweis auf die Spezifizität des durch TMS induzierten behavioralen Effekts für visuospatiale Leistungskomponenten interpretiert werden.

Im Falle der mentalen visuospatialen Aufgabe zeigte erneut nur die Gruppe, die über dem rechten Parietalkortex (P4) stimuliert wurde, sowohl während als auch im Anschluss an die Stimulation (Nachtest 2) eine signifikante Verschlechterung im Vergleich zur Kontrollgruppe. Die Gruppe, die über dem

linken Parietalkortex (P3) stimuliert wurde, zeigte dagegen wiederum zu keinem Zeitpunkt eine signifikante Verschlechterung der Leistungsfähigkeit in der mentalen visuospatialen Aufgabe im Vergleich zur Kontrollgruppe.

7.3 Diskussion

Mit Hilfe der zugrundegelegten experimentellen Kombination von Studien mit funktioneller Magnetresonanztomographie (fMRT) und Transkranieller Magnetstimulation (rTMS) konnte in dieser Dissertation gezeigt werden, dass, obwohl die Ausführung visuospatialer Aufgaben mit einer bilateralen Aktivierung im Parietalkortex korreliert, lediglich die TMS-induzierte temporäre Unterbrechung der neuronalen Aktivierung im rechten Parietalkortex zu einer signifikanten Verschlechterung in der Leistungsfähigkeit der damit assoziierten visuospatialen Aufgaben führt. Dies gilt sowohl für Aufgaben zur visuospatialen Informationsverarbeitung als auch für Aufgaben zur mentalen visuospatialen Imagination.

Dieser experimentelle Nachweis einer rechtshemisphärischen Dominanz in der funktionellen Relevanz parietaler Aktivierung für visuospatiale Funktionen wird durch entsprechende neuropsychologische Befunde unterstützt, die übereinstimmend eine stärkere visuospatiale Leistungsverminderung in Folge einer rechtsparietalen Läsion dokumentierten (Vallar et al., 1998; Mesulam, 1999; Driver and Vuilleumier, 2001).

Im Bereich der mentalen Imagination sind die Befunde bezüglich der Lateralisierung dieser kognitiven Leistung dagegen sehr uneinheitlich. Viele neuropsychologische Befunde und Studien auf der Grundlage funktioneller

Bildgebung postulieren eine dominante Rolle der linken Hemisphäre für mentale Imagination (Farah et al., 1985; D ‘Esposito et al., 1997).

Die Ergebnisse dieser Dissertation weisen dagegen auf eine stärker distribuierte bilaterale parietale Aktivierung für die Bearbeitung mentaler visuospatialer Aufgaben hin.

In Übereinstimmung mit der hier vorgefundenen bilateralen parietalen Aktivierung während der Bearbeitung mentaler visuospatialer Aufgaben, konnten Formisano et al. (eingereicht) mit Hilfe einer datengetriebenen statistischen Auswertung zwei separierbare parietale Aktivierungskomponenten unterscheiden.
Die beiden Aktivierungskomponenten dokumentieren eine zeitliche und räumliche Separierbarkeit, welche den beschriebenen fMRT Ergebnissen dieser Dissertation vergleichbar ist. Dabei konnte aufgrund der von Formisano et al. gewählten statistischen Auswertung weitergehend gezeigt werden, dass die zeitlich frühere parietale Komponente zwar linksdominant, aber dennoch tendenziell bilateral distribuiert ist, während die zeitlich spätere rechtsparietale Komponente eindeutig spezifisch rechtshemisphärisch lokalisiert ist.

Vor allem mit Bezug auf die zeitliche Sequenz von links- nach rechtsparietaler Aktivierung wurde in dieser Dissertation spekuliert, dass diese beiden parietalen Aktivierungskomponenten die neuronalen Korrelate qualitativ unterschiedlicher mentaler Prozesse darstellen. Aufbauend auf diesen Befunden und sich beziehend auf ähnliche Interpretationen gefundener bilateraler Aktivierungen bei mentaler Imagination (Farah et al., 1989), wurde ein modulares Modell

visuospatialer Imagination vorgeschlagen, welches aus einer zeitlich früheren linksparietalen Aktivierung, die mit der Generation des mentalen Abbildes in Verbindung gebracht wurde, sowie einer zeitlich späteren rechtsparietalen Aktivierung, die mit der eigentlichen visuospatialen Leistungskomponente assoziiert wurde, besteht.

Die reinen fMRT Ergebnisse alleine erlauben jedoch keine Aussage über die funktionelle Relevanz dieser zeitlich und räumlich separierbaren bilateralen Aktiverungskomponenten oder über eventuelle kompensatorische Mechanismen innerhalb dieses bilateral distribuierten Aktivierungsnetzwerkes.

Über die Identifizierung dieser raum-zeitlichen Aktivierungssequenz während visuospatialer Imagination hinaus, ermöglichte der multi-methodologische Ansatz dieser Dissertation aufgrund der separaten unilateralen rTMS-induzierten funktionellen Läsion die explizite und systematische Untersuchung der unterschiedlichen behavioralen Auswirkungen kontrollierter, temporärer Aktivierungsunterdrückung beider parietaler Komponenten.

Dieses rTMS Experiment ließ eine funktionelle hemisphärische Asymmetrie der parietalen Aktivierung für die Durchführung visuospatialer Fähigkeiten dergestalt erkennen, dass nur eine rechtsparietale Aktivierungsunterdrückung zu einer spezifischen Leistungsverschlechterung in den assoziierten visuospatialen Aufgaben führte.

Eine Erklärung für diese hemisphärische Asymmetrie wurde mit Bezug auf die beschriebene raum-zeitliche Separierbarkeit der beiden parietalen Aktivierungen in unterschiedlichen Kompensationsmöglichkeiten gesehen.

Während die Unterdrückung der mit der Abbildgenerierung assoziierten linksparietalen Aktivierung aufgrund der stärkeren bilateralen Distribuierung dieser Funktion durch den rechten Parietalkortex kompensierbar ist, führt eine Unterdrückung der die eigentliche visuospatiale Leistungskomponente widerspiegelnden rechtsparietalen Aktivierung aufgrund der höheren Spezifizität und Lokalität dieser Funktion zu einer behavioral messbaren Leistungsverschlechterung in der Ausführung der visuospatialen Aufgaben.

Der multi-methodologische Ansatz dieser Dissertation ermöglichte demnach die explizite experimentelle Untersuchung der funktionellen Beziehung zwischen unilateraler parietaler Aktivierung und der Ausführung visuospatialer Aufgaben, sowohl auf der Grundlage physikalisch präsentierter als auch mental vorgestellter Stimuli, und stellt die erste systematische experimentelle Untersuchung einer funktionellen hemisphärischen Asymmetrie parietaler Aktivierung für perzeptuelle visuospatiale Informationsverarbeitung und visuospatiale Imagination dar.

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