Lateralization of Spatial Attention in the Human Brain: a ‘Virtual Lesion’ Approach.

by

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Abstract

The ability to direct attention to different locations in space appears to require the involvement of cortical networks located in the parietal lobe in the human brain. The cognitive deficits of neglect and extinction resulting from lesions in or near the parietal cortex suggest that there is a functional lateralization of cortical networks mediating attention, with the right parietal cortex supporting to a greater degree the ability to attend to contralateral space than the left parietal cortex. The investigative technique of Transcranial Magnetic Stimulation (TMS) allows to model cognitive deficits resulting from lesions in brain areas near the head surface by temporary reversible deactivation of neural processing in a small region of the brain surface.

Using this technique I conducted a series of experiments aimed at establishing the effectiveness of different experimental paradigms for biasing the attentional function in a way similar to the attentional shifts observed in neglect and extinction. More specifically, I conducted a mapping study (Experiment II) in order to determine which locations in the parietal lobe are most directly involved in the performing of spatial attention tasks, which can serve as a basis for doing future experiments using these locations. In a related study (Experiment III) I examined the effect of focal deactivation in the occipital cortex in order to separate the purely visual effects on performance from the attentional effects and to establish whether occipital cortex plays a role in the distribution of spatial attention along the left-right dimension. I also studied in more detail the distribution of spatial attention along the viewing horizon in a topographic study of intact and TMS-modulated attention in a paradigm which involved not only unilateral but also bilateral deactivation (Experiment IV). Finally, I performed a study which compared the effects of the two techniques of online and
offline deactivation which have been employed in the other experiments (Experiment V).

In a separate series of experiments, using only behavioral methods without TMS, I studied the nature of the interhemispheric connections and the interactions between the two brain hemispheres by testing the effects of symmetry perception (symmetrical arrangement of the stimuli as well as symmetry of the perceived objects) on performance. Unlike the TMS studies which examined the involvement of bilaterally distributed cortical regions in spatial attention, these studies focused on the connections between those regions and their effect on the overall processing of information in the brain, part of which is the spatial attentional function. I conducted three different experiments with a similar behavioral paradigm of brief presentation of symmetrically arranged unilateral or bilateral stimuli, but with stimuli of different degree of complexity: abstract shape objects with mirror symmetry (Experiment VI), simple shape objects (lines) with mirror symmetry (Experiment VII) and non-shape objects (dots) for which symmetry is not relevant (Experiment VIII). The aim of these experiments was to reveal any facilitatory or inhibitory effect on the perception of an excentrically located stimulus from another stimulus located contralaterally at the same excentricity.

Based on the findings from the experiments I was able to delineate a contiguous region in right parietal cortex whose deactivation results in a significant bias of spatial attention towards the ipsilateral side of space, thus confirming the hypothesis that spatial attention is functionally lateralized. The findings also support the idea of the competitive nature of the interactions between the two hemisphere resulting in a
dynamic balance in the intact state. This balance can be perturbed by unilateral deactivation, with the right hemisphere being more susceptible to modulation than the left hemisphere, and it can be paradoxically restored by bilateral deactivation. Both online and offline stimulation can be used to achieve the deactivation effect, however the parameters of the experimental paradigm need to be fine tuned very carefully in order to produce a measurable effect. The interhemispheric connections mediate the competitive balance between the two hemispheres by exchanging predominantly excitatory signals, but the facilitation and inhibition effects on performance seem to involve higher-order representations of distributed neural activity, which do not necessarily result in a low-level point-to-point activation exchange between homologous regions in the two hemispheres. These findings are interesting both from a theoretical perspective as refining the methodology for producing reversible ‘virtual lesions’ and reinforcing some of the existing hypotheses about the neural basis of spatial attention, as well as from a practical viewpoint in helping to devise methods for the restoration of the attentional function in conditions like neglect and extinction.
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Chapter 1. Introduction

1.1 Overview of the project

The central goal of my research work was to investigate the phenomenon of lateralization of attentional mechanisms in the human brain. Spatial attention is a fundamental neural function underlying many aspects of perception, cognition and action. Its lateralization in the human brain is currently poorly understood, but may be related to the unique evolutionary specialization of the human cortical hemispheres. A better understanding of the mechanisms of attention in general and its lateralization in particular can help to explain behaviorally observed aspects of intact and impaired spatial attention. This is of great interest to basic neuroscience and is also important for clinical applications.

I intended to use the ‘virtual lesion’ technique of Transcranial Magnetic Stimulation (TMS) to create temporary deactivations in specified areas of the cerebral cortex in normal human subjects, and measure the deactivations’ impact on psychophysical variables related to the subjects’ visuo-spatial performance against a baseline condition.

A central part of my research represents the topological mapping study aimed at measuring the contributions of parietal and occipito-parietal cortex areas to spatial attention. Based on neurological and neuroimaging evidence, these areas have been found to be involved in implementing the function of spatial attention. However, current understanding is based on a very diverse compilation of studies using different
techniques and explanatory paradigms. To my knowledge, until now there has been no comprehensive study that compares the contribution of all hypothesized posterior cortical sites to spatial attention in a systematic way, and the aim of my work will be to fill that gap. The study aimed to assess comparatively the extent and magnitude of the TMS-induced effects in the left and right hemisphere, as well as detect possible ipsilateral enhancement of attentional function in the occipital regions of the cortex. As an additional outcome it determined the sites of most effective TMS-induced interference with spatial attention functions (‘hot spots’), which provides vital information for subsequent experiments.

Another comparative study was designed to measure the topography of intact and TMS-impaired attention over the entire width of the visual field (up to 90 degrees eccentricity in both visual fields), using the equipment available at Prof. Diederich’s lab at IUB. It serves as a baseline for modeling the mechanisms underlying the variability in the data obtained by the mapping study. The two studies address more basic research questions through the use of well-established experimental paradigms and familiar phenomena like the deactivation of cortical areas through TMS and the resulting bias in spatial attention.

In addition to the basic research questions, I also addressed experimentally other controversial issues concerning the functional mechanisms of spatial attention and the technical effectiveness of the investigative technique of TMS. These include the competitive nature of the interhemispheric interactions, which may play a significant role in phenomenon of lateralization of functions in the brain, such as spatial attention, language, tool use etc. Anatomically, the interactions between the two
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hemispheres are mediated directly via the fibers forming the corpus callosum (although they still pass through interneurons) and indirectly via subcortical interhemispheric fibers, and therefore it was worthwhile to study how the activity in one brain area may affect the performance in the contralateral brain areas connected to it in terms of competition or facilitation. Understanding the mechanisms of the interactions between connected brain areas in the two hemispheres proves very useful for understanding the reasons for the existence of the lateralization phenomena and their mechanisms of operation.

Overall, my dissertation research consists of a series of experiments focused on several specific issues within the broader framework of the topic of lateralization of spatial attention, which complement each other and contribute to the understanding of different aspects of the phenomenon, rather than delving deeper into one specific question and confirming one specific hypothesis while rejecting others. This is a feasible approach since the investigative technique of TMS is relatively new and the mechanisms and the efficiency of its modulatory effects on brain activity are not firmly specified, making it worthwhile to explore different possibilities and address specific controversies which are ripe to be settled experimentally.

1.2 Theoretical Background

1.2.1 The research problem context

The need to study spatial attention

The problems related to spatial attention are studied within the context of the broader issue of attention and its role in the cognitive architecture of the human brain and
mind, studied by numerous scholars in various disciplines, such as psychology, philosophy of mind, cognitive science, neuroscience, neurology, and artificial intelligence. Within neuroscience, it is investigated through anatomical studies of the brain, studies of neuropathological conditions, psychophysical experiments with healthy participants, functional imaging and other techniques for measuring brain activity, brain activity modulation techniques, such as TMS, animal studies, and other methods. The issue of lateralization presents a unique challenge to researchers, trying to explain it both from a developmental and ontological perspective.

Phenomenologically, attention appears as an undivided and homogeneous ability, which can be varied in intensity. Anatomically, however, it is implemented by the cooperative and/or competitive interactions of cortical areas in two similar, but possibly structurally differentiated, cerebral hemispheres. Selective impairment of these cortical regions, as resulting from strokes and other focal injuries, produce a plethora of unexpected and unusual phenomena, which do not have a simple and straightforward explanation. Most of the patients are able to recover most of their normal functioning within weeks or months after the injury, but about 25% suffer long-lasting attentional deficits (Kerkhoff, 2001), which can be treated efficiently only if we have adequate understanding of the mechanisms of spatial attention.

**Methodological issues**

We can study unfamiliar systems by contrasting their performance in different cases, between which the system is structurally changed. In the case of investigating brain phenomena evidence comes from two major sources: the behavior of healthy people, usually gathered in psychological and psychophysical experiments, and impaired behavior, which can be studied either in clinical or experimental settings. When we
know that a certain brain area is not functioning any longer, due to a permanent or temporary lesion, and we observe different behavior concerning spatial attention, we can conclude that the affected area plays a role in implementing attentional functions. However, it may not be the only area involved, and its contribution may not correspond directly to the observed deficit since the observed attentional effect may arise indirectly via modified activity of other areas or neural mechanisms (Young et al., 2000). Indeed, the brain is a very complex system and all these methodological issues arise frequently in the process of its investigation. As it will be shown below, there is a large body of evidence about the functioning of attention accumulated from cases where it is impaired, and there are many alternative ways of explaining these data.

**Definition of spatial attention**

**Spatial attention** refers to the ability of biological organisms to select a specific region of space as a dominant source of input to their sensory system, leading to enhanced processing of the stimuli that exist in this region of space. It is believed that this function is realized primarily in posterior parietal and occipito-parietal cortex, with the likely involvement of other cortical (e.g. prefrontal) and subcortical structures. In addition, there is a large body of evidence for functional and structural asymmetry of these brain areas, leading to a complex pattern of behavioral effects involving spatial attention and orientation. According to brain area connectivity and function one can distinguish between bottom-up, or evoked, and top-down, or guided, attention processes. These play different roles in creating awareness and volition, and are thus linked to the major issue of consciousness and the fundamental nature of the human mind.
How to measure spatial attention

Since attention is a property of the neural activity inside the brain, it is only possible to measure it indirectly with psychophysical behavioral methods. Common paradigms for measuring asymmetry in spatial attention are line bisection and line cancellation, unilateral and bilateral stimulus presentation (with or without cueing, which serves to direct attention to a particular location before the stimulus presentation), visual search, dichotic listening, etc. The large variety of attentional tests employed by different researchers complicate the comparison of results between experiments. Additional complications stem from the fact that attention is a complex function modulated by the activity in various brain regions and cannot be correlated with some measure of activity in one specific region. For example, line bisection (where the requirement is to put a mark exactly at the middle of lines drawn on a sheet of paper) and line cancellation (where the requirement is to just mark lines drawn on a sheet of paper) appear to be closely related tasks, but Ferber and Karnath (2001) were able to demonstrate a double dissociation between them. Some of their stroke patients showed impairments in the line bisection task but not in the line cancellation task and vice versa. This raises the more fundamental question of whether it makes sense to think of neglect (see section 1.2.2 below) as a single, distinct deficit. There has been an attempt to define a battery of tests that could dissociate the contribution of different attentional functions (Fan et al., 2002), but it is based on a specific theory of the anatomical and functional determinants of attention, which is not universally accepted. In general, increased attention is considered to be instantiated by relatively higher activity in some neuronal networks compared to functionally similar networks which process unattended information of the same type (Driver et al., 2001).
A more basic problem associated with measuring attention in TMS (see section 1.2.6 below) experiments is how to distinguish between induced attentional deficits and induced visual field deficits, such as scotomas and hemianopia, in the case of employment of visual tasks as a research method. The problem is not merely technical in nature, but also theoretical, since neural activity in strictly visual areas of the brain receives top-down modulation from activity in higher areas involved in attentional functions (Pascual-Leone and Walsch, 2001). In this way, spatial attention is part of the regular visual information processing and it is not always meaningful to distinguish between the two types of processing. Alternatively, one can distinguish between global attentional function and specific visual attentional functions, e.g., for motion, color, orientation, or some other property of the visual sensory data. In this way it would be possible to investigate visual deficits related to a conjunction of spatial location and sensory data modality, and to measure the influence of the modulation of general spatial attention on them. This theoretical paradigm would parallel more closely the anatomical and functional organization in human cortex, with primary visual cortex implementing specialized attention functions and parietal cortex being the primary locus for global attention, but this distinction is not clear cut and fixed.

1.2.2 Evidence from conditions of imbalanced functioning of spatial attention
Impairment of spatial attention: neglect

One of the most interesting and informative pathological conditions related to spatial attention is unilateral spatial neglect. It is defined as “a failure to report, respond, or orient to stimuli in the contralesional hemispace that cannot be attributed to sensory or motor impairments” (Bowen et al., 1999). This means that it is a deficit that is solely attentional in nature, occurring even if the purely visual sensory mechanisms are still intact. It is characterized by a right – left asymmetry, where right hemisphere damage is more likely to result in contralateral, left neglect. Spatial neglect can be classified into

- allocentric (pertaining to external space), egocentric (pertaining to one’s own body) and object-centered (pertaining to individual objects) deficits
- representational neglect (for imagined scenes)
- motor neglect (for execution of movements, rather than perception)

Spatial neglect is usually a consequence of right inferior parietal or temporoparietal lobe damage, but may also arise subsequent to lesions of the frontal or cingulate cortex, or to a variety of subcortical structures (Jewell et al., 2000). Subcortical structures involved in spatial neglect are (on the right side) the putamen in the basal ganglia, the pulvinar in the thalamus and, to a lesser degree, the caudate nucleus. They are connected to the superior temporal gyrus and form a coherent anatomical network (Karnath et al., 2002). Heilman et al. (2002) discussed the possibility of neglect symptoms induced by an intentional deficit due to unilateral lesions of limbic structures contributing to cholinergically based arousal.
Unawareness of the deficit (anosognosia) is frequent in neglect, but not limited to it\(^1\). This is a very peculiar condition, exemplifying some more fundamental principles of brain functioning. Although it is important for understanding the phenomenon of neglect, it is usually studied more extensively in the context of psychology rather than neuroscience and I will abstain from discussing it in my work.

**Impairment of spatial attention: extinction**

Extinction is a phenomenon often associated with neglect. When two stimuli are presented simultaneously in the two hemifields of space, one of them fails to be perceived, that is, it becomes extinguished, while it is perceived if it is presented alone. Different explanations of the phenomenon are put forth in terms of overall cost of attentional processes, spatial biases and impairment of spatial attention (as in neglect), object recognition and feature binding (Gestalt stimuli ameliorate extinction), and neuroanatomical determinants such as brain area connectivity and bilateral lesions (Mattingley, 2002). Extinction-like effects can be induced in normal subjects by producing ‘virtual lesions’ with TMS (Pascual-Leone, 1994) and can be used for studying the distribution of spatial attention. I intend to employ this kind of extinction paradigm for measuring the level of spatial attention at a given eccentricity. The paradigm consists of presentations of two perithreshold stimuli in the two lateral visual hemifields, symmetrically across the vertical midline. This resembles the real-world situation of having to attend to two objects located in the two halves of space. While healthy people can do it with ease, patients with the extinction deficit find it difficult or impossible to detect the contralesional object..

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\(^1\) It occurs also in Wernicke’s aphasia, severe amnesia, dysexecutive (problem-solving) deficits after frontal lobe lesions or psychiatric disease, and other conditions.
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Imbalance in intact spatial attention: pseudoneglect

Another related phenomenon, which is observed in neurologically normal subjects, is pseudoneglect. It refers to the bias in normal subjects to bisect lines to the left (i.e., in the opposite direction with respect to the dominant bias in spatial neglect). It shows that one can study lateralization also in healthy people, although one should combine the evidence from intact and impaired subjects with caution. Pseudoneglect is age-dependent – there is small leftward bias in young and middle-aged subjects, but significant rightward bias in old subjects (Fujii et al., 1995). Handedness is also found to play a role in pseudoneglect, with dextrals being slightly more biased to the left than sinistrals. There are also some indications that males might be slightly more lateralized than females (Jewell and McCourt, 2000). However, a major problem with generalization of the findings is the large inter-subject variability in direction and magnitude detected by some studies. Methodology may also affect our understanding of the problem, since forced-choice procedures produce significantly larger effect size estimates than do method-of-adjustment procedures. Many other factors can introduce bias. For example, a significant scanning effect has been found in the direction from which scanning is initiated when bisecting a line (Jewell and McCourt, 2000). Bias can be introduced also by seemingly unrelated conditions, like perceiving numbers for example. Fischer et al. (2003) have found that perceiving a digit shifts attention to the left for low digits and to the right for high digits for time periods longer than 300ms.

1.2.3 Conceptual models of intact attention

Disbalanced attention, as in conditions like neglect and extinction, is studied within the context of the functionality of intact attention. Many theoretical frameworks have
been proposed to explain the exact details of the functioning of intact attention, offering possibility of determining which part(s) of the attentional mechanism is affected in impaired or artificially perturbed conditions. Some of the earliest models proposed by Posner et al. (1987) subdivide the attentional process into several components: alerting, interrupting, localizing, disengaging, moving, engaging and inhibiting. This approach partitions the attentional mechanism into several modules with differentiated anatomical localization in the brain. Another subdivision of the attentional function is proposed again by Posner and Petersen (1990). They describe three different attentional functions, namely a) orienting to sensory events, b) detecting signals for focal (conscious) processing, and c) maintaining a vigilant or alert state, which are mediated by different anatomical regions partially lateralized in one of the hemispheres, depending on the task at hand.

Instead of focusing on functional components of the attentional process, other researchers have tried to develop models of attention based on the constrains inherent in the attentional functions. Duncan (1984) distinguishes between object-based, discrimination-based, and space-based theories of attentional limitation, suggesting that attention operates on features processed simultaneously or serially. Treisman and Gelade (1980) have developed an elaborate theory explaining how the features in the visual information are bound by attention into representation of objects and has provided details about which parts of this process occur in parallel and which parts can be processed only serially. Theories of feature-binding use the metaphor of the ‘spotlight’ of attention, illuminating items in the visual information stream and thus enhancing their processing and possibly binding together features detected at the early stages in the visual system. In contrast to this view, embraced by many researchers as
the classical explanation of attention, Desimone and Duncan (1995) developed a model conceiving of attention as an emergent property of many neural mechanisms working to resolve competition for visual processing and control of behavior. This biased competition model focuses on yet another aspect of the attentional phenomenology, namely the interaction between the different components of the attentional process.

1.2.4 Conceptual models of neglect and impaired attention

Similarly to the models of attention, the great variety of non-intuitive effects observed in neglect and pseudoneglect studies has led to formulation of multiple hypotheses trying to explain one or several of them.

Attentional theories

The most common explanation links neglect-like phenomena to attention mechanisms. In one of the first attempts to explain neglect, Kinsbourne (1970) suggested a model of mutual hemispheric inhibition mediated primarily via the corpus callosum. According to this model, damage to a hemisphere results in an attentional imbalance. While the damaged hemisphere is hypoactive and attention to space opposite to the lesion is reduced, the undamaged hemisphere becomes hyperactive and attention to the same side as the lesion (ipsilesional) is enhanced. Later he proposed also an orienting vector model which does not contain a mechanism that explains the bias.

Heilman et al. (1993) suggested that the left hemisphere attends to right space, whereas the right hemisphere attends to both sides. Bias in this case is induced by the hypoactivity of the damaged hemisphere (Heilman et al., 2003).
Mesulam (1998) restated Heilman’s hypothesis in anatomical terms: there is a right hemisphere neural representation for both sides of space, while in the left hemisphere it is only for the right side of space.

Treisman (1982), and later Posner and Driver (1992), introduced the popular metaphor of a “spotlight of attention.” Neglect in this case is cast in terms of a deficit in disengaging attention from an ipsilesional focus towards a new stimulus on the contralesional side. Anderson (1996) proposed that neglect is due to damage of a visual salience map located predominantly in the right hemisphere in the human.

**Representational theories**

The next group of explanations is formulated in terms of the representational character of neural processes in the brain. In this case neglect is seen in general as an impairment of one side of a particular spatial representation (Deco, Rolls 2002). Bisiach and Luzzatti (1979), Bisiach et al. (1981) postulated that perception of sensory events requires their mental representation. According to this explanatory paradigm, neglect results from an impairment in the representation of the contralesional space and body. There is only one topological spatial map, in contrast to Gaffan and Hornak’s idea (1997) that each hemisphere contains a topographically organized memory map of the contralateral visual world, which is disrupted in neglect.

Rizzolatti et al. (1997) suggested that different parts of extrapersonal and body space are motorically coded or represented by different neural structures. A lesion of these structures causes contralesional neglect.
Transformation theories

There have been also attempts to explain neglect as a failure in the transformational mechanisms that relay the signal originated in the sensory system from one brain area to another. Vallar, (1997) Karnath, (1997) and Colby (1998) claimed that acting in space requires a transformation of the various sensory input information from sensory (visual, auditory, tactile, olfactory) into motor coordinates which operate in body-part-centered coordinates (eye-, hand-, arm-, head-centered). This coordinate transformation is thought to be impaired in neglect. However, their theory applies only to egocentric neglect.

Cerebral balance theories

Finally, some researchers have tried to understand neglect as a phenomenon of disturbance of the cerebral balance. Lomber and Payne, (1996), Payne et al. (1996) performed neglect studies in cats and found that it is not the absolute level of neural activity within each cerebral hemisphere that determines neglect, but the relative (im)balance between cortical and subcortical structures in the lesioned and intact hemisphere. Complex excitatory and inhibitory interactions occur on a cortical and subcortical level between the lesioned and the nonlesioned hemisphere, probably via callosal fibres (Payne et al., 1991). Hilgetag (2000) and Hilgetag et al. (2001) describe a case of restored attentional behavior after a paradoxical bilateral lesioning of posterior parietal cortex or superior colliculus in cats and suggest a computational model that reproduces this behavior. The same effect can be induced in humans with transcranial magnetic stimulation of the parietal cortex in the healthy hemisphere, which would lead to a transient decrease of activity in this hemisphere, and might consequently reduce left sided neglect by
changing the cerebral (im)balance (Hilgetag et al., 2001; Brighina et al., 2003; Oliveri et al., 2001).

These theories are not mutually exclusive, rather, they focus on different issues and for that reason they create different explanatory paradigms. The explanations that they provide are often complementary and only in rare cases they lead to contradicting hypotheses which can be settled experimentally.

**Fronto-parietal disconnection theories**

Maintaining the proper balance between the activity in different cortical areas not only across the two hemispheres but also within a single hemisphere proves to be crucial for the adequate performance of the cognitive functions according to the findings of Corbetta et al. (2005). Using fMRI they detected abnormal levels of activation in structurally intact dorsal and ventral parietal regions in patients with right frontal damage, lasting for a limited period of time after the brain injury. The patient showed neglect like symptoms which correlated in time with the abnormal activation patterns. This finding suggests that imbalance not only in the conventional locus responsible for the neglect symptoms, but also in anatomically distant but functionally related areas, can have an effect on the distribution of spatial attention. Thiebaut de Schotten et al. (2005) found further support for the idea that frontal areas play crucial balancing role in the attentional network. Using intraoperative electrical stimulation they deactivated cortical and subcortical regions and observed neglect-like shifts of attention in a line bisection task, where patients were asked to judge and mark the exact middle of straight lines. When attention is shifted, the judgment is inaccurate and the marks indicating the middle of the line are shifted to one side. The
strongest effect was produced during the deactivation of the superior occipitofrontal fasciculus, a poorly studied parietal-frontal pathway, which suggests that fronto-parietal disconnection can lead to strong unilateral neglect, probably due to a disbalancing effect on cortical regions.

1.2.5 Computational and mathematical models of neglect and attention

In addition to the abundant theoretical explanations, many researchers have attempted building computational and mathematical models that can account for some of the observed phenomena.

Pouget and Sejnowski (1997) proposed a model based on a neural network with radial basis response functions, consisting of modules for V1, thalamus (eye position), parietal cortex (spatial map), superior colliculus (eye movements), and premotor cortex (reaching).

Levitan and Reggia (2000) investigated lateralization in self-organizing neural networks with different levels of excitation and inhibition mediated via a corpus callosum connection. They found that a mixture of large number of excitatory and a small number of inhibitory fibers in the corpus callosum leads to symmetrical topological maps in the two hemispheres. Above a certain threshold they observed a sharp transition to lateralization in the direction of the more active or the larger hemisphere.

Deco and Rolls (2002) proposed a complex mathematical and computational model of spatial and object-based visual neglect, with modules for V1, inferior temporal cortex (IT) (object representation), and posterior parietal cortex (PP) (spatial representation).

In the object-based neglect model, V1 and PP consist of spatial maps and are connected topologically according to a Gaussian function of distance to the
corresponding node. IT consists of nodes coding for objects. When PP is lesioned by introducing a gradient of activation bias, the network settles in a final state where activation in PP is slightly higher for locations on the right side of an object than for those corresponding to the left side.

Corchs and Deco (2002) propose a similar model for visual attention. Ivry and Robertson (1998) base their modeling work on neurological evidence of segregation of processing of spatial information in the two hemispheres based on spatial frequency, with the left hemisphere working preferentially with higher frequency representations and the right hemisphere with lower frequency representations. They propose a two-stage model that can reproduce neglect phenomena, including object-based neglect. In the first stage there is attentional selection of the sensory input, that is, the non-relevant part of the sensory data is filtered out. In the second stage there is a differentiated processing of the selected data in the two hemispheres at different spatial frequencies.

1.2.6 The issue of lateralization from a broader perspective

There has been a broader discussion on the issue of lateralization, which spans many scientific disciplines and is best studied with interdisciplinary approaches. Some other functions besides attention, most notably language, have a very well expressed anatomical asymmetry, while others, like handedness, have strong behavioral but very weak, if any, anatomical lateralization. Corballis (2002) considers the co-occurrence of language and handedness dominance in the same hemisphere as evidence for their common origin from a precursor system for tool use and gesturing, as proposed by Calvin and Bickerton (2000). Another important piece of evidence is the location of mirror neurons in F5 of the macaque cortex, which is homologous to Broca’s area in
humans, which supports the idea that language is derived from gesture skills. More support is provided by Karnath et al. (2001), who question the widely held belief that parietal cortex is the primary brain area mediating spatial attention. Instead, they suggest that this role is played by the right posterior temporal cortex (within the superior temporal gyrus), which is complementary to language cortex on the left. There is some evidence that lateralization of handedness and language is a genetically determined phenomenon, (Geschwind et al., 2002) although its mechanism and the genes involved in it are still unknown (Geschwind et al., 2001).

Substantial knowledge about lateralization comes also from animal studies. Cats have been employed extensively as models for spatial attention, and the evidence suggests that this function is symmetrical in the cat brain (Hilgetag et al., 2001). Pigeons have been found to have lateralization in about 20% of the cases, with equal distribution on left and right, and the rest are non-lateralized (Keysers et al., 2000). Monkeys exhibit more complex patterns of lateralization resembling the findings in humans (Fernandez-Carriba et al. 2002, Hopkins 1997, Bradshaw and Rogers, 1993).

1.2.7 The investigative technique: TMS

Finally, I want to describe briefly the technique of TMS that I intend to use in the experimental approach. Transcranial magnetic stimulation (TMS) is a method for causally interfering with the processing of information in the brain, in contrast to the better known imaging techniques like functional Magnetic resonance Imaging (fMRI), Positron Emission Tomography (PET), Electroencephalography (EEG), etc., which provide a correlation measure of neural activity with behavior. The core idea of the technique is to produce very brief (lasting about 1ms) pulses of strong magnetic field (due to rapidly rising or falling electrical current) near the scull. The magnetic field
penetrates deeper into the cortex and in turn induces minute electric currents in the
cortical tissue. These currents interfere with the signaling between the neurons and in
this way affect normal mental processing. Depending on the stimulation parameters,
mainly frequency and duration of the pulses, TMS can produce either excitatory or
inhibitory effects (perturbations of neural processing are easier to induce than
facilitations). It should be pointed out that its effects are completely reversible and it
conforms to very strict standards of safety (Wassermann, 1998).

The duration of a single TMS pulse is on the order of 1ms and subsequently its
immediate effect is limited to a time window of 1-5ms. However, there is a
cumulative effect of delivering subsequent pulses over the same location. Delivering
2-5 pulses separated by 50 ms time intervals effectively inhibits cortical activity in the
affected area during the whole period of stimulation (50-200 ms) (Bestmann et al.,
2002). Repeated TMS (rTMS) over several minutes leads to a decrease of cortical
excitability if it is applied at a frequency of 1Hz or less, while frequencies of 5Hz or
more lead to increased excitability (Walsh et al., 2002 p.78). Thus, single-pulse TMS
or short pulse trains of rTMS are used in so called on-line paradigms, where
stimulation is delivered during the actual psychophysical experiment, while long-
duration rTMS is used in off-line paradigms, where the participants receive
stimulation for 10-20 min before the psychophysical experiment and the inhibitory or
excitatory effect of the stimulation lasts for a comparable time period after that
(Walsh and Pascual-Leone, 2003).

There are several parameters that can vary in the TMS procedure. These are the
number of pulses, intensity, interpulse interval, time of onset relative to the visual
stimulus, site of stimulation (on the skull), coil orientation, and coil angle (normal to the skull surface). Since there are many degrees of freedom, only one parameter should be varied at a time in order to ensure comparability of the results. It should be noted also that due to the penetrating efficiency of the magnetic field, which goes to about 35 mm in depth from the coil surface (Mills, 1999, p.10), and the folding of the cortex, anatomically proximal areas may receive different levels of stimulation compared to anatomically more distal areas.

1.3 Existing studies related to my project

My research work is placed within a larger context of collaborative investigation of spatial attention done at several research institutions. It draws on previous work done by Prof. Hilgetag and his collaborators at Beth Israel Deaconess Medical Center in Boston and the Department of Neurology at Rostock University. Hilgetag et al. (2003) describe an experiment involving event-related and rTMS deactivation on sites P4 and P3 from the international 10-20 system for positioning of EEG electrodes (see Fig. II-1), in right and left parietal cortex, respectively. It involves an experimental paradigm very similar to the one I will use in the mapping study. The results confirmed both the pseudoneglect phenomenon observed in the baseline condition and the effect of impairment of spatial attention for stimuli presented contralaterally to the site of stimulation. They also provided some evidence for ipsilateral enhancement of function, which supports the idea of competition between corresponding regions in the two hemispheres. Since this experimental paradigm proved to be efficient in detecting the functional lateralization of spatial attention, I plan to adopt it for the purposes of my study.
Chapter 1. Introduction

Unilateral impairment of spatial attention, expressed as induced visual extinction in healthy subjects through unilateral TMS, has been described initially by Pascual-Leone et al. (1994), and replicated later in multiple related experiments done by different researchers.

Asymmetrical impairment is reported in most studies, with the right hemisphere being the more vulnerable one. Müri et al. (2002) found an effect of double-pulse TMS over the right posterior parietal cortex (PPC), but not over the left PPC. Oyachi and Ohtsuka (1995) applied single-pulse TMS to PPC in a memory-guided saccade task and also observed an effect only on the right side. Leff et al. (2001) found right PPC to be involved in the preparation of the scan path for saccades at the initiation of reading, while left PPC was employed for the maintenance of saccades during the reading process.

There are multiple other publications of studies investigating the issue of timing of brain processes in PC related to spatial attention. The effect of TMS on visual areas in the occipital cortex is another major area of research. Fernandez et al. (2002) describe a mapping study of phosphene thresholds in occipital cortex using equipment and methodology similar to the one I plan to use.

1.4 Overall organization of the experimental studies

The experiments are divided in two groups: TMS studies of the parietal lobe plus a TMS study of the occipital lobe, and behavioral studies of symmetry and
interhemispheric connections. They differ not only in the investigative technique that is employed, but also in the scope and nature of the theoretical questions they address. However, they are designed to answer complementary questions on the nature of the hemispheric interactions. The TMS studies explore the competitive nature of the interhemispheric interactions, mediated via transcallosal connections projecting onto inhibitory interneurons, while the behavioral studies reveal the existence of facilitatory transcallosal communications, leading to priming effects from stimuli presented laterally in one of the visual hemifields on the ipsilateral hemisphere, but only at the level of higher-order perceptual representations. Thus, the two most important structural features leading to the lateralization of spatial attention are studied – the existence of two hemispheres and their connections.
Chapter 2. Experiment I - The Race model

2.1 Introduction

The independent race model proposed by Raab (1962) offers an explanation of the observed effect of somewhat unexpected (also called “paradoxical”) facilitation of the response when an increased number of targets is present, instead of the expected opposite effect which might be caused by the higher load on the cognitive system. Raab formulated it in terms of “statistical facilitation” resulting from the summation of the probabilities to respond to stimuli processed via independent channels. If two or more stimuli carrying redundant information about the same outcome are processed independently of each other in parallel, then the mean time required for the decision-making process will be fastest in the case of the highest number of stimuli present, because the process will finish when any one of the stimuli gets processed (hence the name “race model”). A single stimulus will get processed slower on average and the mean reaction time in this case will be slower.

There are other, more complex versions of the race model. The coactivation model proposed by Miller (1982) replaces the independent mechanisms at the final decision-making stage with a single mechanism which receives as input integrated information

* This experiment does not involve the use of TMS, but it illustrates the behavioral paradigm used in the subsequent TMS experiments and for that reason it is included in this section.
from the multiple independent sources. An even more complex model was proposed by Mordkoff and Yantis (1991), involving interaction between the independent channels at all stages of the signal processing (hence it is called the interactive race model). More formal treatment is provided in Bundesen (1990) and Bundesen (1998) as part of a more general computational model of visual attention. This computational model was used in a TMS study in order to evaluate quantitatively the finding of involvement of right PPC in top-down modulation of visual selection (Hung et al., 2005).

The aim of the present study was to detect eventual differences in the speeds of processing of single and bilateral stimuli using the same behavioral paradigm as in the later experiments. The paradigm consists of presentations of single stimuli in the left and the right visual hemifield, as well as bilateral stimuli in the same locations as the unilateral ones. The stimuli need to be perithreshold, i.e., difficult to detect, in order to increase the cognitive load on the visual system and to allow for improvements in detection performance to be registered. According to the race model, the multiple stimuli in the bilateral stimulus presentation should be processed faster than the single ones. Since the reaction times depend on the speed of the motor response in addition to the purely perceptual processing, the motor response component may affect the difference between the reaction times for single and multiple stimuli. For that reason, two versions of the behavioral test were performed – one with a single button response and one with three-button response. The definition of the task differed too. In the single button case the task was simply to detect anything presented on the screen, while in the three-button response it was to identify one of three different stimulus patterns – left, right or bilateral. This paradigm allowed to distinguish
between low-level, perceptual processing in the case of simple detection of stimuli and high-level, conceptual processing in the case of identification of stimuli. In the simple detection task the multiple stimuli should have an advantage in terms of reaction times according to the race model, but in the more complex identification task the top down modulation from the higher cognitive processing may lead to a different pattern of results.

2.2 Method

Participants

The participants were 6 IUB undergraduate students, 3 male and 3 female, receiving course credits as compensation for the participation in the experiment. All received detailed instructions and signed a written agreement form prior to the commencement of the experiment.

Equipment

The stimuli were presented on a Sony GDM-F520 Trinitron color display monitor with 100Hz frame rate and 1008x770 pixels resolution. The presentation was controlled by a Visual Stimulus Generator system from Cambridge Research Systems (Rochester, England) equipped with a four-button response box.

Stimuli

The stimuli were small black dots (2x2 pixels) presented against gray background. They were flashed briefly for a period of 40ms at 23 degrees eccentricity either to the left, to the right or on both sides (bilaterally) of the centrally presented fixation cross. One trial consisted of 1500ms fixation cross, a variable interval of 250 to 750 ms of blank screen, a brief flash of the stimuli for 40 ms and a response interval of 1000ms
during which a blank screen was presented (see Figure I-1 below). There were 20 trials with each type of stimulus (left, right, and bilateral) plus 20 catch trials with no stimulus, for a total of 80 trials. The order of presentation was randomized.

![Figure I-1. Time course of one trial.](image)

**Procedure**

The participant was seated in front of the monitor, with the head positioned on a chin rest, and received brief instructions. In condition A the participant had to respond by pressing a single button on a CT3 response box located on the table in front, after a detection of any stimulus, while in condition B the response was made with three buttons – the left one for a left stimulus, the right one for a right stimulus and the top one for a bilateral stimulus. After a brief practice the participants learned quickly to use the top button in the bilateral condition.
2.3 Results

As figures I-2 and I-3 indicate, in the one-button response condition the mean reaction time in response to a bilateral stimulus was faster than the mean reaction time in response to a single stimulus, while in the three-button response condition exactly the opposite was the case. The differences are statistically significant according to a two-sample t-test assuming equal variances ($t(175) = 3.25, p < 0.01$ for the one-button test; $t(172) = -6.72, p < 0.01$ for the three-button response test). The difference was larger in the three-button response condition, and the mean reaction times were slower on average compared to the one-button response condition.

![Graph showing reaction times for condition A](image)

Figure I-2. Reaction times for condition A (one-button response).
Chapter 2. Experiment I - The Race model

2.4 Discussion

As suggested by the independent race model, multiple stimuli produced faster reaction times when a single response was required to any number of stimuli. The special configuration of the stimuli placed mirror-symmetrically to the fixation cross did not change the nature of the facilitation effect. In the condition B, when the decision-making process had several alternatives instead of one, the facilitation effect was not observed. In this case the opposite seems to happen – multiple stimuli compete for the same processing resources which results in slower reaction times in the case of bilateral stimuli. Further evidence for the increased complexity in the final stages where decision making occurs offers the fact that the mean reaction times are overall slower in condition B. This suggests a further decision-making stage added on late in the process, where the incoming information from the independent channels might be processed serially and not in parallel.
Chapter 2. Experiment I - The Race model

The experiment confirmed the hypothesized effect of the higher order cognitive processes on the reaction times, resulting in slower identification and faster recognition for multiple stimuli compared to the single ones, but there is one caveat. The motor component of the response needs to be compared for the three fingers in condition B. There is no reason to suspect that it will vary significantly, but an additional control experiment testing the speed of reaction for each finger separately is needed to clarify this issue. Despite that, this experiment still managed to reveal that higher order cognitive processing is involved in the behavioral paradigm which will be used in subsequent experiments employing TMS perturbation of spatial attentional processing in the brain, and suggests that this processing can be disrupted selectively with the stimulation.
Chapter 3. Experiment II – Attentional Mapping study

3.1 Introduction

A number of experiments have demonstrated both inhibitory and excitatory effects of the stimulation over parietal cortex. The most popular stimulation sites are P3 and P4 of the international 10-20 EEG positioning system (Muri et al., 2002; Hong et al., 2000; Kessels et al., 2000; Pascual-Leone et al., 1994.) Other studies have used the P5 and/or P6 sites, which are more ventral and more occipital (Klimesch et al., 2003; Fierro et al., 2000; Fierro et al., 2001). All studies consistently found stronger effects of the stimulation over right parietal cortex and weaker or absent effects over left parietal cortex, although the stimulation and the task paradigms differed across studies. Thus, Muri et al. (2002) found deterioration in detection rates for P4 but not P3 in an online stimulation study with a visuospatial attention paradigm. Similarly, Pascual-Leone et al. (1994) also found deterioration of detection rates for both P4 and P3, but only in the case of bilateral stimuli presentation, similar to the effect of extinction in patients with brain lesions. Kessels et al. (2000) detected only deterioration of the speed of the reaction as a result of high-frequency online stimulation, but no change of the rate of correct responses. Fierro et al. (2000) found an effect of online rTMS delivered to P6 but no effect for P5 in a line bisection task.

The drawback of using head coordinates like the sites of the 10-20 EEG system is that the underlying anatomical landmarks in individual brains may have different locations with respect to the head coordinates which means that the anatomical structures that get stimulated using head coordinates will be slightly shifted across individual subjects. Using 3D positioning systems like Brainsight (Rogue Research Inc.,
Canada) in combination with structural brain scans allows for maximum
coregistration of the anatomical site of the stimulation across subjects, but it still
leaves open the possibility that performance may differ because of different functional
specialization of the anatomical regions in individual subjects. Furthermore, there is
added imprecision of the site of stimulation due to the difficulty of the task of keeping
the coil exactly tangential to the surface of the skull, i.e., small amounts of lateral
tilting may result in significant dislocations at the surface of the cortex, thus affecting
different cortical regions and effectively enlarging the site of stimulation. The
advantage of using the head coordinates is that this method is much simpler and faster
and easier to implement than the anatomical coregistration.

Although multiple studies have already shown that TMS over some parietal sites like
P4 and P6 can produce an attentional deficit similar to those of neglect and extinction,
the question still remains whether these are the only sites that are susceptible to
attentional modulatory effects, and which is the site (or sites) where stimulation is
most efficient. These questions can be answered by testing and comparing
systematically multiple locations over the parietal cortex with the same behavioral
paradigm. Such a design can also potentially discover effects of the stimulation over
left parietal cortex in locations other than the ones used in the earlier studies (P3 and
P5), although the effects in right parietal cortex should be more pronounced. This
experiment aims to produce that kind of systematic comparison of the effectiveness of
the stimulation over parietal cortex locations, as well as to examine the degree of the
lateralization of the attentional function in parietal cortex by comparing the
performance of the left hemisphere vs. the right hemisphere.
Chapter 3. Experiment II – Attentional Mapping study

3.2 Method

Participants
The participants were 8 undergraduate students from the International University Bremen, 3 male and 5 female, ages 20 to 23, median age 21. All were predominantly right handed according to the Edinburgh questionnaire for handedness (Oldfield, 1971). All had normal or corrected to normal vision (3 of them wore glasses during the experiment).

Equipment
The stimuli were generated by a Cambridge Research Systems Visual Stimulus Generator running on a desktop PC with Windows 2000. They were displayed on a backprojection screen with a Barco Cine 8 CRT projector with frame rate set to 100 Hz. The responses were collected with a 4-button response box, which is a standard part of the VSG system. The luminosity of the screen was measured with a Gossen Mavolux 5032 B light meter with attached focusing lens. The TMS pulses were generated by a Magstim Superrapid device, triggered by the VSG system, and delivered to the skull with a 70 mm figure-of-eight coil. Ambient light was provided by two standing lamps situated behind the participant.

Stimuli
The stimuli were tiny black horizontal lines ranging between 3x1 and 8x1 pixels, presented against dark grey background (0.2 on a scale from 0–black to 1–white) with luminosity of 0.6 to 0.7 lux. They were presented either on the left, on the right, or on both sides of a central fixation cross, at an eccentricity of 24 degrees. The eye to screen distance was 52cm. The presentation sequence in one trial was 1500 ms
fixation cross, a variable blank interval of 250-500 ms, stimulus presentation for 40
ms, a response interval of 1000ms, and 2000ms delay before the next trial.

**Procedure**

Performance was tested in 2 experimental sessions on different days consisting of 11
runs of the experimental procedure with breaks inbetween. In each session 9 different
locations situated in one hemisphere were tested, preceded and followed by a sham
run (a total of 11 runs). The locations were situated 2 cm apart on a 3x3 grid, where
the rightmost and the leftmost points in the middle row of the grid coincided
respectively with the P3 and P4 locations of the International EEG system,
respectively (see Fig. II-1 below).

![Figure II-1](image_url)

**Figure II-1. The international 10-20 EEG electrode placement system. The grid
locations on the left side are indicated with red dots.**

The positions were marked on a Lycra cap which the participants were wearing during
the TMS session. The grid was oriented parallel to the midline fissure, which made
one of its diagonals nearly vertical and the other one nearly horizontal with respect to
the ground. The order of testing the locations was different in each session, and was
arranged so that the distance between two consecutive locations would be maximized.
It always started or ended in the central location of the grid. Across all participants the
average order of appearance of any given location was near the middle of the
sequence which means that the different sequences were well counterbalanced. This
was done in order to avoid artificial effects from any eventual differences in the
performance between the beginning of the session and its end, when participants may
have gotten tired or some adaptation effects may have changed their perception
abilities. The order of stimulation of the two hemispheres was also counterbalanced;
in half of the cases the left hemisphere was stimulated first and in the other half it was
the right hemisphere.

At the start of the session the participant was seated comfortably on a chair with
adjustable height and positioned his or her head on a headrest mounted on the table in
front. In the first session the experiment began with a titration procedure used to
determine the optimal size of the stimuli, when they were hard to detect, but the
performance was still over 50% correct responses. In most cases the optimal size was
4 pixels, and in some cases it went as low as 3 pixels and as high as 8 pixels.
Performance for the optimal size ranged from 60% correct to 80% correct responses.
All participants reported that they can detect the stimuli but it is not easy to do so
because they are very faint. In the second session there was no titration procedure, but
the participants performed a brief practice run of the experiment with the size used in
the first session in order to get accustomed to the routine.
One experimental run consisted of 64 trials of about 5 sec. in duration, making a total of about 5 minutes. The 64 trials were made up of 4 blocks of 16 trials, containing 5 left stimuli, 5 bilateral stimuli, 5 right stimuli, and 1 catch trial without stimuli in a random order. After each run there was a 5 minute break before the next one in order to minimize carry over effects from the stimulation.

TMS Procedure

Three pulses of TMS were applied to a location on the skull at 50ms, 150ms, and 250ms after the onset of the stimulus respectively. The stimulation was delivered with a 70mm figure-of-eight coil (Magstim Inc., Dyfed, UK). The intensity was determined individually for each participant as the highest intensity that did not induce phosphenes overlapping with the stimuli for any of the chosen locations of the grid, or the highest intensity which was not felt uncomfortable by the participant. The used intensities varied from 65% to 80% of the stimulator output. For the sham TMS sessions the coil was held perpendicular to the skull, touching the central location of the grid with one of its sides. For the active TMS it was oriented at 45 degrees angle with respect to the horizontal plane.

3.3 Results

The performance of the participants in the different stimulation conditions (9 different locations plus 2 sham stimulation sessions) was evaluated in terms of reaction times and detection rates. Abnormal reaction times (outliers) did not have an effect on the means, because for each participant first the median reaction time was computed for each condition, and from this data the means across participants were obtained. This method avoids the problem with outliers arising when only averages are computed.
The reaction times results did not show any significant differences across the stimulation conditions. The responses to the bilateral stimuli were slower than the responses to the unilateral stimuli, as expected for a 3-button response paradigm which identifies the location of the stimulus (see Experiment 1 on the Race Model). The detection rates for unilateral stimuli and the proportions of unilateral detections for bilateral stimuli were affected more strongly and more systematically by the stimulation, leading to statistically significant differences for some stimulation locations.

Figure II-2. Percentage of left vs. right unilateral detections for bilateral stimuli when TMS was applied over the right hemisphere. The difference for locations 2-1 (P4) and 2-2 is statistically significant.

Figure II-2 above is a map showing the bias in detection of left vs. right stimuli in the cases when a bilateral stimulus was presented but the participant detected a single
stimulus either on the left or on the right. In the sham conditions there is no statistically significant preference either for the left or for the right stimuli. In the active stimulation conditions the detection rates for the right stimuli are usually higher than the rates for the left stimuli, but the difference is significant only for locations 2-1, corresponding to P4 of the international 10-20 EEG positioning system, (t(7) = -2.79, p < 0.05) and 2-2 (t(7) = -3.39, p = 0.01). The significance was tested with a pairwise T-test, uncorrected for multiple comparisons. After a Bonferroni correction with alpha level set at 0.005 the difference is no longer significant. It should be noted that in these two conditions we can observe both deterioration of performance on the left side compared to baseline (the sham conditions) and improvement of performance on the right side. However, these two comparisons are not statistically significant.

Figure II-3. Percentage of left vs. right unilateral detections for bilateral stimuli when TMS was applied over the left hemisphere. Location 2-1 corresponds to P3.
Figure II-3 above shows the same map as Figure II-2 but for the stimulation locations over the left hemisphere. Note that the ordering of the locations is left-to-right mirror-symmetric to that in Figure II-2, which reflects the actual physical arrangement of the locations on the surface of the head. Location 2-1 corresponds to P3 of the international 10-20 EEG positioning system in this case.

The performance in the sham conditions again shows no statistically significant bias to the left or to the right. This is the case also for the active stimulation locations, where the detection on both sides seems to be very well balanced and consistent in terms of the number of detected stimuli. The detection rates on the right side for locations 2-1 and 2-2 are slightly lower than the rates on the left side, which is exactly opposite to the situation with the right hemispheric locations, however, the difference is very small and it is statistically non-significant.
Figure II-4. Percentage of left vs. right unilateral detections for unilateral stimuli when TMS was applied over the right hemisphere. Locations 2-1 corresponds to P4.

Figure II-4 above shows a map of the performance for unilateral stimuli for locations over the right hemisphere. The bars show the percentage of correct detections of unilateral stimuli on the left and on the right. Again, location 2-1 corresponds to P4.

The performance in both sham conditions is very well balanced and there is no preference for one of the sides. The number of correct detections dropped substantially in the second sham condition compared to the first one, which might be due to fatigue accumulated during the course of the experimental session. Also, the second sham condition is slightly disbalanced, with the stimuli on the right being better detected than the stimuli on the left.
The performance in the active stimulation conditions does not show any big differences between left and right in most of the cases, and none of the differences is statistically significant. Locations 2-1 and 2-2 have the largest disbalance, as in the case with the bilateral stimuli (Figure II-2), and it is going in the same direction, with the right stimuli being more readily detected than the left stimuli. The number of detections in all of the cases falls between the values in the sham conditions, i.e., the detection of unilateral stimuli was best in the first sham session, somewhat lower in the active stimulation sessions, and worse in the last sham session.
Figure II-5. Percentage of left vs. right unilateral detections for unilateral stimuli when TMS was applied over the left hemisphere. Location 2-1 corresponds to P3. The difference for location 2-2 is significant.

Figure II-5 above shows the same information as Figure II-4 but for the stimulation locations over the left hemisphere. Again, location 2-1 corresponds to P3 and the ordering of the locations is inverted compared to Figure II-4.

The performance in the sham conditions in this case is similar to that in the sham conditions over the right hemisphere. The performance is well balanced but it deteriorates substantially in the second sham condition compared to the first one. Also, the second sham condition is more disbalanced, with the stimuli on the left being better detected than the stimuli on the right.
Chapter 3. Experiment II – Attentional Mapping study

Similar to the case with the bilateral stimuli (Figure II-3) in most of the active stimulation conditions the detection of stimuli on the right side was better than the detection of stimuli on the left side. For location 2-2 this difference is statistically significant (pairwise T-test, t(7) = 3.63, p < 0.01), also when corrected for multiple comparisons with a Bonferroni correction. As in the case of stimulation over the right side (Figure II-4), the performance in the active stimulation conditions is lower than the performance in the first sham condition but higher than the performance in the second sham condition.

3.4 Discussion

The results from the mapping study suggest that there is a region in the right parietal cortex which is more directly involved in the spatial attention function and whose deactivation by rTMS produces a detectable deficit for attending to the contralateral side of space, similar to the extinction phenomenon in patients with right parietal brain lesions. This region has an elongated shape and extends from location P4 of the 10-20 EEG positioning system about 2-3 cm in the frontal-ventral direction (approximately at 45 degrees downwards and to the front of the head). Anatomically, this corresponds roughly to a region extending from the intraparietal sulcus, over which P4 and P3 are usually found (Herwig et al., 2003), ventrally into the angular gyrus and possibly further down into the supramarginal gyrus. Although the effect was measured at two specific points – P4 and a point 2 cm away from it - it is safe to assume that the stimulation of any point inbetween or within a 2 cm radius from any of those two points would produce the same effect since there would be a significant overlap between the affected brain regions in the case of using the two specific points and the case of using any point in close proximity to them (Valero-Cabre et al., 2005).
Since the effect was statistically reliable only when using the most optimistic statistical comparison – an uncorrected t-test – but did not stand the Bonferroni correction for multiple comparisons, which is the most conservative way of verifying the significance of the effect, it is not possible to conclude that spatial attention can be reliably affected by the stimulation of the region around P4 with the stimulation parameters employed in this study, but only that it can be affected to a certain degree, which may or may not produce observable effects depending on the behavioral paradigm which is used to test the distribution of spatial attention. Further testing would be necessary in order to evaluate the magnitude of the effect for any specific behavioral paradigm by employing a simple comparison between two stimulation locations, one within the identified region as the site of interest and another one in the parietal cortex as the baseline condition.

It is interesting to note the fact that the disbalancing effect on the right side was produced only for bilateral stimuli but not for unilateral. This might suggest that the stimulation may have produced an extinction-like effect but not a neglect-like effect. Such a hypothesis seems plausible since there is a dissociation between neglect and extinction (Kerkhoff 2001), however extinction is more often found in cases of deeper, subcortical lesions (Vallar et al., 1994), while neglect is associated with cortical lesions in right parietal cortex (Vallar, 1993). Additionally, there was an ipsilateral enhancement of detection performance, which suggests that the attentional bias produced by the stimulation was more general in nature and not just a decreased ability to detect one of a pair of stimuli. The observed effect might still be neglect-like in nature, and the reason that only the bilateral stimuli were affected and not the
unilateral ones might be that the bilateral stimuli are more sensitive to disturbance compared to the unilateral ones.

On the other hand, only the unilateral stimuli but not the bilateral ones were affected by the stimulation of location 2-2 in the left hemisphere. Although the effect was statistically significant, the absolute values of the detection rates were comparable to those for the other stimulation locations and the difference was much smaller than the differences found in the right hemisphere effects. It is quite possible that a neglect-like effect was produced also in the left hemisphere for the contralateral side of space. Such an effect has been reported already for the P3 site using functional interference produced by rapid rate rTMS (Pascual-Leone et al., 1994), but it seems to be a much more rare occurrence than the effects on the right side. Although we did not observe any neglect-like effect in location 2-1 on the left side (the P3 site), given the fact that it has been observed in other studies and the fact that on the right side both location 2-1 (P4) and 2-2 produced an effect, we could hypothesize that the same region in the left hemisphere participates in attentional processing and is susceptible to neglect-like effects, however for some reason it is more difficult to disrupt its functioning with TMS.

In general, we can conclude that TMS can disbalance attention towards the ipsilateral side and away from the contralateral side of space when applied to most of the parietal cortex, however the effect differs in magnitude for the different locations. There is one contiguous region in posterior parietal cortex where stimulation can produce a more readily detectable shift of attention in a random sample of people, but without a guarantee that it would work for any given individual. The effect is more readily and
more reliably produced on the right side compared to the left side of the brain, which indicates that it probably models the neglect or extinction syndromes. The presence of the ipsilateral enhancement phenomenon provides support for the cerebral balance hypothesis, as described in the introduction, suggesting improved performance due to disinhibition of the left hemisphere following a deactivation of an area in the right hemisphere. This phenomenon, however, might be explained in the light of the representational theory of neglect, by assuming that the representation of space shifts from the areas deactivated by TMS to adjacent cortical areas. This claim, however, cannot be substantiated by anatomical or other evidence and remains highly speculative.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

4.1 Introduction

The interference effects of TMS on the detection of visual stimuli has been studied systematically with different paradigms for over a decade. Repetitive TMS over occipital cortex (sites O1 and O2 of the International 10-20 EEG positioning system) has been shown to interfere with the perception of stimuli presented in the contralateral hemifield (Pascual-Leone et al., 1994). In a pioneering study of the effects of TMS on visual perception, Pascual-Leone et al. stimulated with trains of five pulses at 25Hz at 115% of motor threshold at different locations, including O1 and O2. The rTMS interfered with the ability of the participants in the experiment to perceive clearly visible asterisk stimuli presented contralaterally to the site of stimulation. Since the stimulation was well above the motor threshold, it most likely produced visual artifacts, like noise, phosphenes or scotoma, which were the main cause of the interference. A drawback of this study is that it did not consider the phosphene threshold, which is the minimum intensity of stimulation over visual cortex needed to produce visual artifacts (phosphenes), but used the motor threshold instead. A later study (Boroojerdi et al., 2002) showed that phosphene thresholds are as a rule higher than motor thresholds within subjects and found no correlation between the two. The site of induced phosphenes has been shown to overlap with the induced virtual scotoma (Kammer, 1999). In Kammer’s study the induced scotomas were of magnitude 8dB or more and very focal. This shows the suitability of
phosphenes for determining a location of stimulation, which can interfere with the
detection of visual stimuli.

Epstein et al. (1996) performed a more systematic investigation of the effect of single-
pulse TMS delivered over occipital cortex on the perception of a briefly disappearing
asterisk among an array of other asterisks. Since the stimulus was difficult to detect,
stimulator output as low as 55% produced a robust interference effect. The
interference effect was strongest in the interval 50-90ms after the stimulus
presentation. Epstein et al. report also that by repositioning the coil at different
locations rostrally, i.e. in the up-down direction, they managed to produce suppression
in the lower and middle field of vision, but not in the upper one. These are interesting
results since they suggest that stimulation below the phosphene threshold can interfere
with detection of peri-threshold visual stimuli and that there may be a differential
effect on the perception in the upper and lower visual fields.

Gerschlager et al. (2001) have demonstrated that subthreshold 1Hz rTMS can have a
lasting inhibitory effect in lateral premotor cortex. The effect of 1500 pulses of
stimulation at 1 Hz (or 25 min) was strongest after 900 pulses (or 15 min) and
outlasted the stimulation for at least 15 min after its end. Similar effects of
subthreshold low frequency stimulation were found by Romero et al. (2002) in the
motor cortex. Multiple other studies have established the generally inhibitory effect of
low frequency stimulation (less than 1Hz) and excitatory effect of higher frequency
stimulation (over 5Hz, typically 20Hz) in motor cortex (Gangitano et al., 2002; Maeda
et al., 2000; Siebner and Rothwell, 2003). This finding can be generalized for the
entire cortex and the same pattern of results depending on the frequency of the
stimulation is expected to be found in the other cortical areas, as suggested by the finding of Valero-Cabre et al. (2006) of suppressed and facilitated metabolism evoked by low and high frequency TMS in the cat brain and the frequency specific changes in regional cerebral blood flow reported by Rounis et al. (2005).

This study aims at investigating the effect of rTMS delivered off-line to occipital cortex (site O2) with intensity below the phosphene threshold on the ability to detect stimuli in the contralateral and ipsilateral visual fields. It uses the same behavioral paradigm as the mapping study of the parietal cortex (see Chapter 3), and could potentially reveal whether the effects from the stimulation of the parietal cortex might be due to visual effects rather than attentional shift, in case of obtaining similar results, or it could reinforce the conclusion that parietal stimulation indeed affects attention, in case there are no disbalancing effects in this study. This is important because in order to claim that stimulation of parietal cortex produces neglect like effects, which concern the attentional but not the visual system, we need to exclude the possibility that the stimulation is producing visual artifacts like subthreshold scotoma or is in some other way affecting visual areas by spreading activation. This experiment is targeting the primary visual areas directly and seeks to establish the long-lasting effect of the stimulation of performance in a behavioral paradigm identical to the one used in the attentional mapping study. It consists of two experiments, which differ only in the frequency of the applied stimulation. The first experiment is with subthreshold stimulation at 1Hz, which is expected to inhibit the detection of stimuli in the contralateral visual hemifield, and the second one is with stimulation at 20Hz, which is expected to have the opposite effect, i.e., to facilitate the detection of stimuli in the contralateral visual hemifield. In order to detect potential
effects of the stimulation in retinal locations other than the ones affected by the experimental paradigm, a standard ophthalmologic perimetry test will be conducted before and after the stimulation. It measures the perceptual threshold over the entire visual perimeter of up to 30° excentricity and therefore can detect potential localized changes in the perceptual threshold produced by the repetitive stimulation.

4.2 Method

Participants

The participants were 11 healthy undergraduate students at IUB. All had normal or corrected to normal vision. Four of the participants were male and seven were female. They all were predominantly right-handed according to the Edinburgh handedness test (Oldfield, 1971). The participants were well trained on the behavioral experimental paradigm but were unaware of the purpose and the stimulation parameters of the experiment.

Equipment

The stimuli were presented on a back projection screen with a Barco Cine 8 (Barco N.V., Kortrijk, Belgium) projector positioned below eye level behind the screen. This setup produces a bright spot effect on the screen at the location where the line of sight from the eyes to the lenses crosses the plane of the screen. The effect is reduced via a contrast modulation kit installed inside the projector. The lightning in the room was dim and it was held constant at one fixed level, which made the contrast of the stimuli with the screen background low, thus allowing for a less steep detection curve with respect to stimuli of varying size.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

The presentation sequence was produced with a mobile VSG system (Cambridge Research Systems) running on a Dell notebook computer situated near the projector and occluded from the participant by the screen. The responses were collected with a 4-button response box of which only 3 buttons were used. The participants typically used their index, middle, and ring fingers to respond to the stimuli, although some preferred to use the pinkie instead of the ring finger for more convenience.

The transcranial magnetic stimulation was delivered with a Super Rapid magnetic stimulator from Magstim Inc (Dyfed, UK) using a 70-mm figure-of-eight coil. Occasionally cooling packs were placed on the coil during the stimulation in order to prevent overheating.

Procedure

Before and after the psychophysical experiment all participants performed a perimeter test on a Humphrey Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany). We used the Fastpac procedure with the Central 30-2 threshold test, which was with duration of about 8 min because of the time constraints of the duration of the TMS effect. The stimulus size was changed to II instead of III because it resembled better the stimuli in the experimental paradigm. The psychophysical experiment was performed twice – first as a baseline condition before the TMS and then as an experimental condition after the TMS. The procedure started with seating the participant at the field analyzer with an eye patch over the left eye to enable viewing only with the right eye. After some brief instructions the participant’s eye gaze was calibrated with the automatic routine of the field analyzer and the presentation of
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

stimuli in the entire visual field was started. The participant had to respond to the stimuli by pressing a button on a hand-held mouse-like device.

The psychophysical experimental procedure consisted of a titration routine followed by the actual experiment. The titration served to determine a size of the stimuli which was difficult enough for the participant to perceive, without resulting in complete failure of perception. Usually two adjacent sizes, e.g. 3 pixels and 4 pixels, resulted in markedly different performance rates, with the smaller size being detected in a small number of trials, typically 20-30%, and the larger size being detected in most of the trials, typically 80-90%. The actual experiment was run with the minimum size that participants were able to perceive at all. The detection rate typically increased slightly when a single size was used in all trials.

The participants were seated comfortably in front of the screen and instructed to position their head on a chin rest and stay in that position for the duration of the experiment. Then they were given instructions to fixate at the center marked with the cross all the time during the experiment and to respond quickly to the stimuli by pressing the corresponding button on the response box. They were told that if they are not sure they saw a stimulus they should not press any button. The titration routine also served as practice for using the response box and getting familiar with the paradigm. After titration all participants responded that they are already comfortable with performing the routine and that they respond more or less automatically.

One trial in both the titration routine and the experiment consisted of a fixation cross presented for 1500ms, followed by a variable blank interval between 250 and 500 ms.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

The 250 ms variability range is large enough to induce uncertainty in the expectation about the timing of the onset of the stimulus, and on the other hand small enough to avoid the loss of concentration in the attentive effort the participants make in anticipation of the stimulus. After the blank interval tiny black dots of the size determined with the titration routine were presented for 40 ms. The duration of 40 ms is sufficient for the stimulus to be perceived, but too short for interhemispheric cooperation in its processing. In other words, the signal produced in the contralateral hemisphere does not have sufficient time to get across to the other hemisphere while the stimulus is still on. In addition, the short presentation time avoids the problem of saccadic eye movements which can change the location of the projection of the stimulus on the retina. There is simply not enough time for an overt orienting reaction towards the stimulus, which may be caused by its presentation. After the stimulus there was a response period of 1000ms during which the participant had to press a button if he or she detected something on the screen.

The stimuli were presented in 4 different configurations. There was either one dot on the left side at 23 degrees eccentricity, or one on the right side at the same eccentricity, or two dots both on left and right, or no dots at all. The presentation order was random, with 20 trials of each left, right, and bilateral stimuli and 10 blanks, for a total of 70 trials. The response was made with the left button (index finger) for the left stimuli, the right button (ring finger) for the right stimuli, and the top button (middle finger) for the bilateral stimuli. The response for the bilateral stimuli was not as intuitive as the other two but after a small number of trials it was learned quickly by the participants. This paradigm is similar to the one employed by
Hilgetag et al. (2003) in their study of bilateral competitive processing of visual spatial attention.

**TMS**

TMS was delivered to a location on the head where after stimulation the participants reported seeing phosphenes, or some kind of visual disturbance, on the lower left side of the screen when seated in the same position as for the experiment. First, a cap was put on the head of the participant, which enabled us to mark locations with a pen or a marker. Then the locations of O1 (in the left brain hemisphere) and O2 (in the right brain hemisphere) were marked after measuring distances respective to the inion and the nasion along the meridians of the head surface. We used suprathreshold single pulse stimulation on locations near O2 initially in order to elicit visual artifacts in the visual field of the participant. The orientation of the coil was horizontal with respect to the midline passing through the center of the figure of eight and parallel to the handle (perpendicular to the line connecting the two coil circles from the figure of eight). The coil was held with the handle towards the left side of the head.

The stimulation was performed against a background of a checkerboard pattern, similar to the paradigm used by Kamitani et al. (1999). After some phosphenes or dark spots (scotomas) and streaks were detected by the participant, we used a hunting procedure (gradual shifting of the stimulation location) for finding a location that produced the artifacts in the desired location, i.e. to the left of the center, preferably covering the location where the dots were presented during the experiment. The hunting procedure usually produced a location almost exactly overlapping with O2.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

After the proper location was found, the intensity of the stimulation was gradually reduced until the stimulation produced no noticeable visual effects. The threshold was estimated to be at the last intensity which produced some effects. 90% of this threshold was chosen for the subsequent rTMS session. The rTMS session itself consisted of 900 pulses at 1Hz in experiment 1 with a total duration of 15 minutes. It has been demonstrated that this paradigm produces a virtual lesion effect which lasts at least about 15 min after the end of the stimulation (Gerschlager et al., 2001). In experiment 2 the same number of pulses was delivered in the same period of time but in trains with frequency of 20Hz. A single train had 20 pulses and lasted one second, after which there was a 19 second waiting interval and then the next train was applied. This stimulation paradigm conforms to the safety guidelines for TMS (Wassermann, 1998).

Summary

The entire procedure consisted of a perimetry test of about 7-9 minutes, titration for about 8 minutes, a baseline psychophysical experiment of 5 minutes, hunting for the appropriate location for stimulation for about 15 minutes, stimulation for 15 minutes, a retest with the psychophysical experiment and a retest with the perimetry machine. The total duration was approximately 2 hour, together with the time for instructions and small breaks.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

4.3 Results

Experiment 1 (1Hz stimulation)

**TMS: coil position and stimulation intensity**

The coil location varied between 3 and 5 cm to the right of the inion (along the x axis) and between 1.5 and 3 cm to the front of the inion (along the y axis). The intensity threshold varied between 35% and 60% of the output of the Magstim Super Rapid device, with most of the threshold being near the upper limit (50%-60%). The stimulation intensity varied respectively between 30% and 54%.

**Psychophysical experiments**

The size of the stimuli varied between 2 and 5 pixels with most participants being assigned a size of 3 pixels.

![Figure III-1. Reaction times before and after TMS.](image)
The reaction time averages of the median, computed only from the correct responses, for the single stimuli were not affected significantly by the stimulation, while the response to the bilateral stimuli became faster (fig III-1). A one-tailed t-test comparing the mean reaction times for the bilateral stimuli in the baseline versus the post-TMS condition showed that the speed-up was significant only at the 0.05 level (p = 0.047). Overall, the response to the bilateral stimuli was slower, which is consistent with our earlier findings investigating the race model of decision making (see Experiment I).

Figure III-2. Error rates before and after TMS. (Vertical axis – average number of incorrect responses)

The change in error rates was consistent with that of the reaction times. The number (and percentage) of errors in the single stimulus conditions increased only minimally,
while the number of error in the bilateral condition increased significantly (fig III-2),
indicating a trade-off between speed of reaction and accuracy of response.

Figure III-3. Breakdown of the erroneous responses for bilateral stimuli before
and after TMS. (Vertical axis – average number of incorrect responses)

If we look at how the participants responded to bilateral stimuli when they gave an
incorrect response, we will see that most often the bilateral stimulus was perceived as
a single stimulus on the left side. We can observe also that in the baseline condition
the participants were equally likely to perceive the bilateral stimulus as either a left
stimulus or a right stimulus or not to perceive it at all. In the post-TMS condition,
besides the increased likelihood of perceiving a left stimulus, they showed a slightly
increased tendency not to respond.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

Perimetry

The results from the Central 30-2 threshold test computed from all participants are shown below. The test provides values for the sensitivity threshold (in dB) for 19 locations in each quadrant of the visual field and the sum of those values gives the quadrant total. Figures III-5 and III-6 show the averaged values by participant of the differences between the quadrant totals in the pre-TMS test and the post-TMS test. It should be noted that the quadrant totals are a cumulative measure of the sensitivity. The variations at each individual location are smaller than the quadrant total differences, but they are not uniform and probably constitute a very noisy measurement of the real physiological sensitivity threshold.

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Figure III-4. An example of the data from an individual Central 30-2 threshold test. The diagram shows the intensity threshold values in the Post-TMS minus the pre-TMS test (i.e., the difference of the two tests) for one participant in experiment 1. The sums for the quadrants are indicated in the corners. Positive values indicate decreased threshold (the participant became more sensitive after
TMS than before), negative values indicate increased threshold. The unit of measurement is dB.

Figure III-5. Post-TMS minus pre-TMS intensity threshold values in % of dB, quadrant totals only. (Up = upper hemifield, Down = lower hemifield)
Figure III-6. Post-TMS minus pre-TMS intensity threshold values in % of dB, quadrant totals only, with standard errors. (Up = upper hemifield, Down = lower hemifield)

These results show notable facilitation of stimuli detection after TMS in the upper left, upper right and lower right quadrants, but only slight facilitation in the lower left quadrant. The facilitation in the lower hemifield was overall less than that in the upper hemifield.

Experiment 2 (20 Hz stimulation)

Psychophysical experiments

The size of the stimuli varied between 2 and 5 pixels with most participants being assigned size 3.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

Figure III-7. Reaction times before and after TMS in experiment 2.

Unlike experiment 1, where only the reaction times for bilateral stimuli became faster after TMS, in experiment 2 the reaction times for unilateral stimuli are also sped up, although not significantly. As before, the response to the left stimuli is the fastest one, then the response to the right stimuli and the response to the bilateral stimuli is the slowest one. This is in line with the race model and with the speed of motor activation of the different fingers.
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

Figure III-8. Error rates before and after TMS in experiment 2. (Vertical axis – average number of incorrect responses)

The error rates in experiment 2 seem to be unaffected by the stimulation. This is in contrast with experiment 1, where the performance for bilateral stimuli deteriorated. After 20 Hz stimulation we do not see significantly deteriorated performance for any of the stimuli.
Figure III-9. Breakdown of the erroneous responses for bilateral stimuli before and after TMS in experiment 2. (Vertical axis – average number of incorrect responses)

The participants were most likely not to respond to the bilateral stimulus in the cases when they made an error in the baseline condition, but after the stimulation they tended to perceive it more often as a left stimulus and less often as a right stimulus. The differences, however, are not statistically significant.

**Perimetry**

There was a strong facilitation of the visual sensitivity in the lower left quadrant and only minimal facilitation in the upper left and the lower right quadrants. There was a
slight sensitivity decrease in the upper right quadrant. Overall, the facilitation was
more pronounced in the lower visual field compared to the upper one.

Figure III-10. An example of the data from an individual Central 30-2 threshold
test. The diagram shows the intensity threshold values in the Post-TMS minus
the pre-TMS test (i.e., the difference of the two tests) for one participant in
experiment 2. The sums for the quadrants are indicated in the corners. Positive
values indicate decreased threshold (the participant became more sensitive after
TMS than before), negative values indicate increased threshold. The unit of
measurement is dB.
Figure III-11. Post-TMS minus pre-TMS intensity threshold values in % of dB, quadrant totals only, in experiment 2. (Up = upper hemifield, Down = lower hemifield)
Chapter 4. Experiment III - The Effect of TMS on the Occipital Lobe

Figure III-12. Post-TMS minus pre-TMS intensity threshold values in % of dB, quadrant totals only, with standard errors in experiment 2. (Up = upper hemifield, Down = lower hemifield)

4.4 Discussion

The increase in error rates is consistent with the speed-up in reaction times, resulting in a trade-off between the two. It seems that in the post-TMS condition the participants were quicker to make the decision regarding what they saw, which resulted in a higher number of erroneous responses.

The main observation from our study can be stated concisely as global facilitation with local inhibition of the perception in the hemisphere contralateral to the location...
of the stimulation superimposed on it. In experiment 1 the perimetry test showed the least increase in sensitivity in the lower left quadrant, which is consistent with the expected inhibitory effect of the 1 Hz stimulation of that part of the visual field. In experiment 2 we saw the opposite effect – increased sensitivity in the lower left quadrant, which is what we would expect from an excitatory effect of the stimulation.

The inhibition result is consistent with findings in similar experiments. Brighina et al. (2003) produced reduction in reaction times after stimulation of O2, but not after stimulation of O1, in a 1Hz, 10 min rTMS paradigm similar to the one deployed in our study. The task involved perception of illusory and real contours of Kanizsa squares before and after the TMS. Touge et al. (2001) suggest that rTMS operates via reduction of the excitability of cortical neurons in motor cortex, and the effect gradually wears off after voluntary contractions of the related muscles. We can speculate that analogously to this effect, only the excitability of groups of neurons in the stimulated cortex was reduced, leading to the observed local deterioration of performance.

Thut et al. (2003), on the other hand, found an affect of left occipital stimulation after 10 min of 1Hz rTMS on late visual evoked potentials and visual-induced alpha desynchronization, but not on early visual evoked potentials, from which they conclude that the stimulation interferes with higher-order visual processing and not simply with the visual input. It suggests a role for top-down influence from other areas on occipital cortex, which produces also distal modulation of the brain activity affecting the behavioral responses. This is in line with the finding of Oliveri et al. (2005) that stimulation of one area (in this case left cerebellum) can produce
facilitation in another area (the contralateral motor cortex) via reduced inhibition of the deep nuclei. Although it involves anatomical brain structures markedly different from the ones we are investigating, it exemplifies the general mechanism of cortico-cortical facilitation.

Repetitive magnetic stimulation can spread also via cortical mechanisms, by changing the excitability of the interneurons mediating intracortical inhibition (Lorenzano et al., 2002). In our case we can speculate that the produced inhibition of occipital cortex and possibly some surrounding areas led to disinhibition of other areas, which normally exert top-down influence on the occipital cortex and this resulted in the observed global facilitation of the response.
Chapter 5. Experiment IV – Attentional Perimeter Study

5.1 Introduction

Several studies of neglect and extinction in brain-damaged patients have implicated right parietal cortex in mediating visuospatial attention (Mesulam et al. 1981, Vallar et al. 1998). These investigations were complemented by ‘virtual lesion’ studies involving transcranial magnetic stimulation (TMS) over parietal cortex in an attempt to probe the functional impact of brain lesions in that area. An interesting question arising in these studies is the nature of interactions between the two hemispheres and the relative balance of mutual inhibition and facilitation which is mediated via interhemispheric fibers For example, Sack et al. (2002) have used rTMS over parietal P3 and P4 locations, as defined by the international EEG system, in order to study mental imagery and visuospatial attention. They found that only stimulation to the right parietal lobe impaired performance, which they interpreted as evidence that the right parietal lobe may be able to compensate for a temporary suppression of the left one. They propose functional asymmetry between left and right parietal cortex as plausible explanation of the observed phenomenon, compatible with the hypothesis proposed by Mesulam (1999), that the left hemisphere controls shifts of attention only contralaterally, while the right hemisphere directs attention bilaterally, thus participating in a bilateral attentional network for the right hemispace.

Apart from functional asymmetry, another possibility is to consider explanations involving the levels of inhibition and facilitation between the two hemispheres. Communication between the two hemispheres via the corpus callosum can be facilitatory if it is mediated by excitatory synapses, or it can be inhibitory if inhibitory
synapses are involved. The observed phenomenon of small facilitation of responses ipsilateral to the site of stimulation (Walsh et al., 1999; Hilgetag et al., 2001) suggests that there is disinhibition of the attentional function in the contralateral hemisphere as a consequence of the virtual lesion induced by TMS. Thus, one can hypothesize both excitatory and inhibitory interactions between the hemispheres with some asymmetry resulting in differential functionality in the two hemispheres. Evidence for the existence of such interactions offers the study of Gorsler et al. (2003), which found that high frequency magnetic stimulation of the right motor cortex increases the excitability of left motor cortex, while low frequency decreases it. While the exact mechanism of the inhibitory effect of low frequency stimulation is still unclear, the transfer of the inhibitory effect to the contralateral hemisphere can be explained by propagation of the signal via excitatory fibers over corpus callosum and the action of the same mechanism in the contralateral areas of the cortex.

Walsh et al. (1999) performed a conjunction visual search experiment and found that magnetic stimulation of the left parietal cortex also impaired performance in terms of reaction time. In another task involving feature detection they found ipsilateral enhancement of performance again after stimulation of left parietal cortex. Hilgetag et al. (2001) found that there was ipsilateral enhancement in the detection of perithreshold stimuli after stimulation of both left and right parietal cortex (the locations were stimulated separately, not in combination). This shows that disinhibition can work in both directions, while the classical neglect and extinction phenomena speak for asymmetry in the mechanism of disinhibition. Hilgetag et al. also noted that the enhancement after right parietal rTMS was more pronounced, which fits with the idea of right-hemispheric representational dominance, as proposed
by Mesulam (1999). These findings cannot be explained by a simple assumption of a
global facilitatory effect of TMS, but rather suggest a role for competition between
the various cortical and subcortical structures forming the network of spatial attention.
Further complicating the picture of competitive interactions is the finding of Walsh et
al. (1998) that there is intrahemispheric competition between different extrastriate
visual areas which leads to mutual inhibition. In their study they found that
stimulation to area V5 not only inhibits the perception of motion but also facilitates
performance in task involving other modalities like color and form processing.
Similarly to the interhemispheric disinhibition phenomenon they interpret these
results as disinhibition in a network of extrastriate cortical areas.

Animal studies have also contributed to the understanding of the lateralization of
spatial attention and the cortico-subcortical networks that mediate it. Studies in the cat
have shown that lesioning or deactivating cortical areas in visual or suprasylvian
cortex or the superior colliculus leads to unilateral spatial neglect (Sprague, 1966;
Lomber & Payne, 1996; Hardy & Stein, 1988). Cats’ visual attention was tested in a
semicircular arena allowing the presentation of stimuli at fixed eccentricities spaced at
10° intervals (see Fig. 1 below). The attentional function was impaired for all
eccentricities in the contralesional visual field and was intact for all eccentricities in
the ipsilesional field. Subsequent cooling deactivation of the contralateral
homologous region restored the capability of the cats to attend to the entire visual
perimeter (Payne et al., 1996; Lomber & Payne, 1996; Lomber et al., 2002; Payne et
al., 2003), which supports the idea that the attentional deficit is due to the imbalance
rather than the absolute level of activation of the respective cortical and subcortical
regions participating in the attentional network. The attentional network in the cat’s
brain, however, does not seem to be lateralized like in humans, since lesions on the left or on the right affect to a similar degree the attentional function for contralateral space. In spite that difference, one would still expect that the two systems are similar enough in their organization that the basic effects of rebalancing and paradoxical restoration of function after a secondary lesion would apply also for humans.

The present study aims at clarifying the issues of the lateralization of competitive and facilitatory interactions between the two hemispheres and the possible rebalancing of attention in a more systematic way. The goal is to measure the strength of the attentional function across the entire visual space and how it is affected by unilateral and bilateral magnetic stimulation. Our experimental paradigm resembles the one used in the cat studies, allowing us to establish whether the functional interaction between left and right parietal cortex and the paradoxical restoration of attention observed in cats can be replicated in humans.

The study consisted of two experiments performed separately and differing only in the stimulation paradigm. The first experiment consisted of two stimulation sessions – the first one active and the second one active or sham. It showed an effect only in the case of two consecutive active sessions. The second experiment was conceived in order to disambiguate the effect of the combination of two consecutive active stimulation sessions by performing only the first active session, without a following sham or performing an active second session preceded by sham.
5.2 Method

Participants

Participants were 8 students from IUB, 3 male and 5 female (age range: 19-22 years, mean age: 20). At the beginning of the experiment they read and signed informed consent forms. All were predominantly right-handed, according to the Edinburgh handedness test (Oldfield, 1971) (average score: 86%) and all had normal or corrected-to-normal vision.
In the second experiment the participants were 2 male and 2 female students at the IUB, ages 19 to 26, average 21.5. All were predominantly right-handed according to the Edinburgh handedness test and all had normal or corrected-to-normal vision.

**Equipment**

The experiment was performed on a custom built table with red-light LED’s arranged in a semi-circle around the subject at regularly spaced eccentricities: 10, 30, 50 and 70 degrees in the left and right visual fields (see fig. IV-1). Subjects used a head rest, such that the LED’s were placed at eye level and at a distance of 120 centimeters to the subject. A fixation LED was placed straight in front of the participant which had to be fixated by the participant throughout the experiment. Stable fixation was monitored with an Eyelink II eyetracking system (SR Research, Osgoode, Canada). Subject responses were recorded with a custom-built 10-finger keyboard of which the two keys situated at the tips of the thumbs were used. The table and the eye tracker were controlled by 3 PC’s running in a separate room. The presentation of the stimuli was executed by custom software running under real-time Linux operating system.
The transcranial magnetic stimulation was delivered with a Super Rapid magnetic stimulator from Magstim Inc (Dyfed, UK) using a 70-mm figure-of-eight coil.

**Procedure**

The participants were comfortably seated in a chair and instructed to rest their head on a chin rest, which was fixed on the table. The first procedure, done only once, at the beginning of the experiment, was a titration procedure for determining a suitable intensity level for each participant. The goal of this procedure was to set the intensity level for the outmost LED near the perceptual threshold of the participant, which would result in a detection rate as close as possible to 50%. This level of detection would allow us to observe both eventual improvements and eventual deteriorations in
performance, which may result from the stimulation effect. The procedure consisted of presentation of stimuli at 70 deg eccentricity at 4 different intensity levels of increasing brightness. There were 20 trials of each intensity level plus 10 trials without a stimulus (catch trials). The order of presentation was randomized. The participant had to respond to the stimuli in the left or right periphery by pressing a button on the left or on the right, respectively, with the index finger of the respective hand. The background illumination in the testing room was maintained constant across subjects and sessions by using a lightmeter to measure and adjust the illumination levels.

One or two experimenters were observing the titration standing behind the participant. After several minutes it became evident whether the participant was able to see any of the stimuli and at what intensity. If the range of intensities was too low or too high, a new range was entered in the program controlling the presentation of the stimuli on the LED table and the titration procedure was repeated. The titration procedure was performed with different intensities until we found an intensity value for which the performance of the participant was about 10% correct responses. At the next highest intensity the performance was usually around 90%, i.e., there was a sharp drop-off in performance between two subsequent intensity levels. (For very few of the participants the drop-off was more gradual.)

The experimental procedure consisted of presentation of stimuli at 4 different angles of eccentricity on both sides (a total of 8 spatial locations) – 10, 30, 50, and 70 degrees on left and right, respectively. There was a fixation light presented centrally, right in front of the participant, lasting for about 2 seconds. After a variable interval
between 750 to 1000 ms, one of the 8 LED’s at the aforementioned locations flashed briefly for 40 ms and the participants had 1000 ms time to respond to the stimulus by pressing a button corresponding to the side on which the stimulus was flashed. Subjects were instructed to respond as quickly and as accurately as possible. For stimuli on the left, the left button was pressed with the index finger of the left hand, and for stimuli on the right the same was done with the right index finger. After the button response the participants had to verbally indicate the eccentricity at which they judged they spotted the stimulus, by saying “ten”, “thirty”, “fifty”, or “seventy” respectively. This check was included in order to evaluate the accuracy of detection performance in the visual periphery. Two evaluators sat in the room and documented the responses of the tested subjects during each run. Their records were compared at the end of the experiment for potential disagreements. There was a 2 second break between two consecutive trials, with the central fixation light off, which was sufficient for the verbal response and for preparing for the next trial. Special emphasis was put in asking the subject to first respond and only after a finger response was completed to report verbally the perceived eccentricity of the LED flash.
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Figure IV-3. Time course of one trial.

There were 20 stimuli repeats at each eccentricity plus 20 blanks (catch trials) for a total number of 180 trials in one experimental session. The order of the presentations was randomized and counterbalanced within 4 blocks of 45 trials each, that is, each block had 5 repeats at each eccentricity plus 5 blanks.

Each time before running the actual experimental procedure, participants completed a practice session with the intensity of the stimuli set at the same level as in their last experiment. This served also to confirm that they responded equally well to stimuli of the selected intensity. In case their performance strongly deviated from their past performance, the intensity level was adjusted one level down or up. This occurred in about 30% of the experimental sessions.
One experimental session consisted of practice, baseline experiment, TMS delivered to P3 and/or P4, post-TMS experiment and retest experiment. The same presentation sequence was used in all 3 runs of the experimental procedure. This was noticed by some of the participants, as informal conversations after the experiments indicated.

**TMS procedure**

The stimulation was done at positions P3 and P4 of the international EEG 10-20 coordinate system. We determined the positions by measuring distances along the meridians on the head of the participant and marking the locations on a Lycra cap which the participants were wearing during the TMS session. First we determined the locations of Pz and P7 or P8, and P3 and P4 were taken to be the midpoints between these two pairs respectively (see diagram below).

![Figure IV-4. The international 10-10 EEG electrode placement system.](image)
Figure IV-5. Saggital (left) and transversal (right) view of the stimulation locations P3 (top) and P4 (bottom) for participant CB.

During active stimulation the center of the figure of eight coil was placed over the stimulation site and the two rings were extending in the frontal and occipital directions. Sham stimulation was performed with the coil positioned perpendicular to the surface of the head with one of the rings touching the stimulation site.

The first round of stimulation consisted of 30 min 1 Hz rTMS, a total of 1800 pulses, at 40% intensity of the stimulator output. In each session we had to exchange the coil near the middle of the time period because of overheating. This produced an
interuption of about 10-20 sec. The second round was a 10 min 1 Hz rTMS or sham
delivered contralaterally, a total of 600 pulses. The interval between the first round
and the second round was also 10-20sec. This stimulation procedure was designed to
produce a functional overlap between the effects of the two consecutive stimulation
sessions, allowing us to study the effect of the simultaneous bilateral deactivation of
parietal sites. Earlier studies have shown that the effect of 1Hz repetitive stimulation
persists after the end of the session at least for about the same time as the duration of
the stimulation session itself. Thus, the initial 30 min session would be expected to
produce an effect lasting for 30 min. after its end, and the 10 min. session would
produce at least a 10 min. effect. This would produce effectively a 10 min. time
window after the end of the last stimulation where both effects would be present. In
the case of sham stimulation in the second session only the effect from the first
session would be present, and it would be tested during the same phase (i.e., the last
10 minutes) as in the case of active second session stimulation.

The stimulation was performed right next to the door giving access the sound-
insulated testing room to prevent any damage to the eye-tracking equipment. After the
stimulation the participants were instructed to move as little as possible and were
brought to the table by rolling the chair from the location of the stimulator to the table.
After that the head-mounted eye tracking system repositioned and calibrated. All
those operations (from the end of the stimulation to the onset of testing) did not take
longer than 1 minute in any session.

In the first experiment there were 4 different stimulation conditions:
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1) P3 TMS, P4 TMS
2) P3 TMS, P4 Sham
3) P4 TMS, P3 TMS
4) P4 TMS, P3 Sham

The order of P3 and P4 sites, as well as the order of active and sham conditions, were counterbalanced across participants according to the following schedule:

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P4T-P3S</td>
<td>P4T-P3T</td>
<td>P3T-P4S</td>
<td>P4T-P3S</td>
<td>P3T-P4T</td>
<td>P4T-P3T</td>
<td>P3T-P4S</td>
</tr>
<tr>
<td>2</td>
<td>P3T-P4T</td>
<td>P3T-P4T</td>
<td>P4T-P3S</td>
<td>P4T-P3S</td>
<td>P3T-P4T</td>
<td>P4T-P3S</td>
<td>P4T-P3T</td>
</tr>
<tr>
<td>3</td>
<td>P4T-P3T</td>
<td>P4T-P3S</td>
<td>P3T-P4T</td>
<td>P4T-P3S</td>
<td>P3T-P4S</td>
<td>P4T-P3S</td>
<td>P3T-P4T</td>
</tr>
<tr>
<td>4</td>
<td>P3T-P4S</td>
<td>P3T-P4S</td>
<td>P4T-P3T</td>
<td>P4T-P3S</td>
<td>P3T-P4S</td>
<td>P3T-P4S</td>
<td>P4T-P3S</td>
</tr>
</tbody>
</table>

Table IV-1. Stimulation conditions by participant and session in experiment 1.

In the second experiment there were one or two consecutive stimulation sessions. The first lasted always 30 minutes, while the second was with duration 10 minutes. There were 4 different stimulation conditions:

5) P3 TMS
6) P3 Sham, P4 TMS
7) P4 TMS
8) P4 Sham, P3 TMS
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The way it is different from the previous experiment is that there is no second session in cases 1 and 3, and the effect of the stimulation is tested immediately thereafter with the behavioral test. In cases 2 and 4 a sham stimulation is performed in the 30-minute session, which should produce no TMS effect, but the rest of the effects will be still present (noise, twitching, etc.).

The order was counterbalanced across participants according to the following schedule:

<table>
<thead>
<tr>
<th>Session</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P4T</td>
<td>P4S-P3T</td>
<td>P3S-P4T</td>
<td>P3T</td>
</tr>
<tr>
<td>2</td>
<td>P4S-P3T</td>
<td>P4T</td>
<td>P3T</td>
<td>P3S-P4T</td>
</tr>
<tr>
<td>3</td>
<td>P3S-P4T</td>
<td>P3T</td>
<td>P4T</td>
<td>P4S-P3T</td>
</tr>
<tr>
<td>4</td>
<td>P3T</td>
<td>P3S-P4T</td>
<td>P4S-P3T</td>
<td>P4T</td>
</tr>
</tbody>
</table>

Table IV-2. Stimulation conditions by participant and session in experiment 2.

Summary

In summary, each session consisted of some practice for about 5 min, which was also used for determining the right intensity level, baseline experiment for about 12 min, finding P3 and P4 for about 5-10 min, rTMS on one side for 30 min, rTMS contralaterally for 10 min (not done in some cases in experiment 2), post-TMS experiment for about 12 min, break for about 10 min and retest experiment again for about 12 min.
We hypothesized that TMS over P4 or P3 followed by Sham TMS on the contralateral side would produce a long lasting effect modeling the neglect syndrome (slower reaction times and lower performance levels) for stimuli in the visual hemifield contralateral to the stimulated site, accompanied by improvements (faster reaction times and higher performance levels) for stimuli in the ipsilateral visual hemifield. The effects were expected to be more evident and longer lasting after P4 than after P3 stimulation. In both cases the effects were expected to wear off quickly and performance to return to near-to-normal levels during the retest run.

In the case of P3 or P4 stimulation followed by active contralateral stimulation, we expected a total or partial relative cancellation of the previous effects, since they would diminish the contralateral hyperexcitability generated by unilateral TMS and thus balance the effects of transcallosal inhibition between P3 and P4.

The inhibition and disinhibition effects were expected to be stronger and statistically significant for peripheral excentricities in the monocular visual field (the visual perimeter accessible only to one eye), whereas mild or no effects were expected for pericentral eccentricities in the binocular visual field.

5.3 Results

Reaction Times

General characteristics

First, we can observe that for all TMS conditions we obtain the characteristic downwards convex curves for the reaction times in response to stimuli presented at
different eccentricities (see Figures IV-6 and IV-7 below). In general, it takes more time to react to stimuli presented more peripherally than to more central stimuli. This is true both before and after TMS, but the effect seems to be more pronounced in the before TMS condition.

In all charts the reaction times for the left hemifield are slightly faster than the corresponding ones for the right hemifield, especially at the 10 degrees eccentricity locations. This may be an equipment artifact. After several sessions we noticed that the left and the right buttons had different tension, which made the pressing of the right button more difficult. The experiment was carried out until the end in the same fashion.

There are three distinct cases with respect to the eccentricity variable. The first case is eccentricity of 10 degrees, which is very easy to see, being closest to the fovea. The reaction times for this eccentricity are fastest and there is virtually no possibility of making a judgment error regarding the location of the flash when it comes from 10 degrees eccentricity. The second case are the locations at 30 and 50 degrees eccentricity. They are somewhat slower, although the stimulus is still clearly visible, well above threshold and probably at ceiling. The third case are the locations at 70 degrees eccentricity. The stimuli are at threshold at these locations and can be missed easily. The reaction times are even slower, due to the added uncertainty regarding the detection of the stimuli, and they show larger variance due to the fact that the average might include a lower number of positive detections.
Figure IV-6. Reaction times for right TMS followed by left sham.

Figure IV-7. Reaction times for left TMS followed by right TMS.

In the right TMS followed by left sham condition (fig. IV-6) we can observe that the reaction times after TMS, in both the post TMS and the retest sessions, are faster than the reaction times in the baseline condition for all eccentricities. In the left TMS followed by right TMS condition (fig. IV-7) the post-TMS reaction times are faster than the baseline, but the retest ones are generally close to the baseline, indicating a rebound effect. In general, the baseline, post-TMS and retesting reaction time curves
Chapter 5. Experiment IV – Attentional Perimeter Study

have different relative shapes, which supports the conclusion that the observed general facilitation effects are not just due to practice-related learning or fatigue.

The reaction times for individual excentricities in the stimulation conditions in the second experiment, namely, unilateral stimulation only or sham stimulation followed by contralateral active stimulation, did not differ significantly across conditions and there were no statistically significant effects. There was a small facilitation effect in some cases, most notably in the left sham followed by right TMS condition, but the magnitude of the differences was relatively smaller compared to the first experiment.

In summary, TMS had an overall facilitatory effect on the reaction times, with local inhibitory effects related to the site of stimulation. An initial 30 min session of TMS over right PPC produced larger speed-up in the reaction times on average than the same session over the left side. Paradoxically, right TMS followed by left sham produced a more balanced effect than right TMS followed by left TMS. Left TMS seems to have produced little speed-up effect, if any, in all cases it was applied, both in the long 30 min session and in the short 10 min session. In both cases of a single TMS session, i.e. when followed by a sham session, we observe larger speed-up at the 70 degrees excentricity locations compared to the case of two real TMS sessions. This happens regardless of the side of stimulation.

The reaction times from the retest session usually follow the pattern of the post-TMS session, sometimes being somewhat faster and sometimes somewhat slower. We can conclude that there was no significant rebound effect expressed in reaction times, although there were non-systematic effects which are difficult to characterize.
If we disregard the eccentricity of the stimulus and collapse the reaction times by visual field, we can observe that there are statistically significant improvements in the reaction times after TMS, but only in the bilateral condition. The effects were stronger for right followed by left TMS, and stronger for the left compared to the right visual field. The improvement for the right TMS (location P4) followed by left TMS (P3) condition for the left visual field was significant at the level of $p<0.01$, and for the right visual field it was significant at the level of $p<0.1$. The improvement in the left TMS (location P3) followed by right TMS (P4) condition for the left visual field was significant at the level of $p<0.1$, and for the right visual field it was significant at the
level of p<0.5. The unilateral stimulation conditions show the same trend of improvement in the reaction times, but these trends were not statistically significant.

The unilateral stimulation paradigms in experiment 2 produced some statistically significant unilateral facilitation effects valid for the entire visual hemifields (fig. IV-9). The 30 min stimulation of left PPC (site P3) produced facilitation of the responses to stimuli on the right side (paired t-test, p=0.01) and the 30 min left sham followed by 10 min right active stimulation produced again facilitation on the right (paired t-test, p < 0.01). The other stimulation conditions did not produce significant differences in the reaction times pooled together for the entire hemifields.

Figure IV-9. Reaction times in experiment 2 collapsed for visual field. (LVF = Left Visual Field, RVF = Right Vis. Field, gray=baseline, orange=post-TMS; *: p<0.05)
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**Error Rates**

The error rates deviate significantly from 0% only for the 70 degrees excentricities on left and right. At all other excentricities they are nearly 0%. This can be seen on fig. IV-10. (Please, note, that for better visual representation of the data the figure shows number of correct responses, rather than number of errors.)

![Error Rate Chart](image)

**Figure IV-10. Example of an error rate chart for all excentricities.**

There is also a small number of errors at 50 degrees excentricity, but the amount is negligible. Basically, there is a sharp drop-off in the number of errors which occurs somewhere between 70 degrees and 50 degrees excentricity, most likely near 70 degrees because the titration was done for this location. Therefore, it is meaningful to consider only the error rates for the 70 degrees excentricity locations and to exclude the other locations from the following discussion.

In the right TMS followed by left TMS condition the average error rate after the TMS for both 70 degrees locations was higher than the average error rate in the baseline condition by 11%. Similarly, in the left TMS followed by right TMS condition the
error rate increases, although by a smaller amount (5%). In general, one can say that bilateral TMS had a balanced effect of reducing detection performance, with the longer TMS session on the right side being more effective than the opposite arrangement. The differences, however, are not statistically significant.

The right TMS followed by left sham condition produced a more imbalanced effect, with the number of errors increasing on the right side after TMS by 21% but remaining almost unchanged on the left side (3% increase). The left TMS followed by right sham condition also produced a high increase of errors on the right (18%) and a relatively smaller one on the left (8%). The differences, again, are not statistically significant.

The stimulation conditions in experiment 2 did not produce any statistically significant differences in the error rates for the 70 degrees locations and in almost all of them the post-TMS error rates remained virtually unchanged compared to the baseline. Only in the 30 min left PPC condition (site P3) the error rate on the right side dropped at about half the baseline error rate. In all conditions the error rate on the left was much higher than the error rate on the right.
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Motor Thresholds

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<tr>
<th></th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>Avg</th>
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<tbody>
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<td></td>
<td>56</td>
<td>45</td>
<td>50</td>
<td>66</td>
<td>57</td>
<td>50</td>
<td>55</td>
<td>67</td>
<td>56±8</td>
</tr>
</tbody>
</table>

Table IV-3. Motor threshold for the right hemisphere for all participants individually (P1 to P8) and an average with standard deviation. The values represent % of the stimulator output.

Table IV-3 above shows the motor thresholds taken over right motor cortex for all participants individually and their average. They can be subdivided into 3 categories: low, medium, and high, with low being ≤50, medium being >50 and <60, and high being ≥60. Thus we have 3 participants with low threshold, 3 with medium, and 2 with high threshold.

5.4 Discussion

The main finding from this experiment is the facilitation in terms of reaction times after sequential bilateral but not after unilateral deactivation of parietal cortical regions using the 1Hz TMS paradigm. This finding suggests that there are functional interactions between homotopic regions of the left and right PPC of a fairly complex nature, whose behavioral correlates cannot easily be hypothesized on the basis of simple add-on effects mediated by sign-constant transcallosal projections. They are produced by an offline 1Hz rTMS which has been found consistently to produce a functionally inhibitory effect on human cortex. The facilitatory effect may be called
“paradoxical” since an apparent lesion-like modulation of neural activity results in improved performance. It is similar to the effect of paradoxical attention restoration observed in the cat after a secondary lesion contralateral to the original one, which produces unilateral neglect (Lomber & Payne, 1996). If we focus on the effect for the entire visual fields, we can observe that it is not symmetrical. The perception of stimuli in the left visual field was more strongly affected by the bilateral stimulation, indicating that the right hemisphere, which processes the information from the left side of space, is more susceptible to the modulation produced by the TMS. This finding is in line with earlier research and the asymmetry of the unilateral neglect with respect to the side of space (Kerkhoff, 2001; Vallar, 1993). It confirms that downmodulating the activity in the right hemisphere produces stronger bias in attention, in this case towards the right side of space, than its counterpart in the left hemisphere (Hilgetag et al., 2001).

Unilateral stimulation over left PPC was able to produce an effect in the contralateral visual field immediately after the 30 min session but not after a 30 min session followed by 10 min of sham. The effect was facilitatory rather than inhibitory. This suggests that the duration of the stimulation may be a determining factor for the type of effect the stimulation has on performance. On the other hand, only 10 min stimulation of right PPC produced a disinhibition effect for stimuli in the right visual field, which seems to reinforce the earlier suggestion of higher susceptibility of the right PPC to modulation. It remains unclear, however, why the 30 min unilateral stimulation did not produce a significant effect on the right, suggesting that some other, unknown factors also play an important role.
An interesting question is what could be the reason that the sequential bilateral stimulation produced a stronger effect than the unilateral stimulation followed by sham? One possibility is that it is simply a learning effect, i.e., participants became faster because they learned the task and they performed better in the post-TMS trials.

There are several reasons why this is not a good explanation. Although some speed-up of the reaction times is present in all four stimulation conditions, which is consistent with a learning hypothesis, the same pattern of speed-up is not present in the data from the retest condition. In the retest which was done after the post-TMS session and a short break the reaction times either stayed the same or rebounded to higher values. If the learning effect was driving the reaction times lower, one would expect them to become even lower in the third session or to stay the same in case they reached a ceiling in the performance, but not to rebound. The rebound, however, could be due to another factor, such as fatigue, which was reported by some of the participants particularly after the third testing session. Another reason weakening the learning effect hypothesis is the fact that the order of the four stimulation conditions was randomized within participants. Thus, the order of the running of the stimulation condition sessions was counterbalanced and none of the conditions was appearing earlier than another with a higher frequency. If there was a learning effect, we would expect it to last also longitudinally across sessions, with the performance improving in the later sessions compared to the earlier ones. No such effect was observed, and the speed-up in the reaction times occurred in early as well as late sessions.

A more interesting hypothesis to discuss is to assume that the speed-up of the reaction times is a consequence of the stimulation applied to parietal cortex. There are two important observations that we can make in that respect. First, the 1 Hz stimulation,
which is known to be inhibitory with respect to the neural activity, produced
improved performance in terms of speed of reaction. Second, the effect was
significant after 30 min of stimulation on one side followed by 10 min of stimulation
on the opposite side, but not after 30 min of stimulation on one side followed by 10
min of sham stimulation on the opposite side. These facts speak for a complex pattern
of interacting effects as a result of the stimulation paradigm and against a simple
hypothesis of locally confined inhibition at the site of the stimulation. One plausible
explanation for the observed effects is to assume that in addition to the standard
inhibition effect of the stimulation, there was also a global facilitation effect which
was not confined to one hemisphere or one side of space but increased subjects’
alertness in general and lowered their perceptual threshold. This would explain why
the longer stimulation conditions produced a stronger facilitatory effect and why it
was distributed across the entire visual perimeter, enclosing both sides of space.

It would be worthwhile to try to estimate the magnitude of the hypothesized
interacting inhibitory and facilitatory effects from the reaction times in the four
different stimulation conditions. The first observation that we can make is that the
inhibitory effect must have been generally weaker than the facilitatory effect, judging
from the consistent improvement in the speed of reaction. The graphs for the reaction
times by eccentricity however suggest that the global facilitation effect is
differentially pronounced following stimulation on the right side versus stimulation on
the left side; it is stronger in both cases of 30 min stimulation of P4 on the right side
and weaker in both cases of 30 min stimulation of P3 on the left side. In addition, at
the 70 degrees eccentricity it is stronger in the active TMS followed by sham
conditions compared to the double active TMS conditions individually for each side.
This pattern of results suggests that the global facilitatory effect is induced more easily by stimulating the right hemisphere than the left one, and also that subsequent stimulation of the contralateral hemisphere counteracts slightly the facilitatory effect of the earlier stimulation, affecting only the most sensitive perceptual thresholds at the highest eccentricities. However, this hypothesis cannot be stated with confidence, due to the small size of the effects.

The inhibitory effect of the stimulation seems to be concealed in the reaction times by the superimposed stronger facilitatory effect, but the performance at the 70 degrees eccentricity consistently drops down after the stimulation, which may offer some clues to the nature and magnitude of the inhibitory effect. We can observe that the deterioration in the performance is more balanced after the balanced stimulation conditions (30 min of left TMS followed by 10 min of right TMS and vice versa) and stronger on the right side after the unbalanced stimulation conditions (30 min of left TMS followed by 10 min of right sham and vice versa). This pattern of results suggests that like with the facilitation, the inhibitory effect may not be confined locally to one hemifield of space but global in nature, affecting the entire visual perimeter. In addition, it could be hypothesized that inhibition eventually reaches a ceiling, first in the left hemisphere, which would explain the subsequent rebalancing after prolonged stimulation. In other words, the inhibitory effect does not progress at the end of the 40 minute combined stimulation period in the left hemisphere, which allows it to catch up in the right hemisphere and thus produce equal deterioration of performance on both sides as a result.
The described effects are not as clear cut and definitive as in earlier studies, but there is some common ground. Hilgetag et al. (2001) also stimulated P3 and P4 and found an increase in the detection of visual stimuli specifically on the ipsilateral side of the stimulation. This improvement was also accompanied by a bilateral lowering of reaction times after TMS, more strongly for ipsilateral stimuli (Hilgetag et al., 2003). These experiments also showed a significantly reduced detection of contralateral stimuli, but only if they formed part of a bilateral stimulus pair. Unilateral stimuli contralateral to the stimulation site did have a trend to diminished detection, but this was not significant. In the current paradigm we only used unilateral stimuli, and thus the observations in the two experiments appear broadly comparable.

In conclusion it should be noted that the hypothesized effects and their explanations described above are highly speculative and need to be verified by other studies in order to claim that they are of any scientific value. In any case, it is clear that the stimulation paradigm that we employed in the present study produced very complex pattern of results which arguably reflects the underlying complexity of the attentional networks in the brain. It argues strongly against a purely additive or subtractive reaction of brain systems to sequential stimulation of interconnected nodes within a network, in which the inhibitory or excitatory impact of a paradigm on a given location can be enhanced or decreased by the stimulation of other regions. It may be the case that the low stimulation intensity chosen for this experiment (40% of the stimulator output), which was well below the average motor threshold (56% of the stimulator output) and phosphene threshold, has a very different effect than the higher stimulation intensities typically employed by other researchers, which have been found to produce unilateral ‘virtual lesions’ simulating the attentional disbalance.
found in neglect patients. In other words, the lower stimulation intensity may not simply produce a less pronounced effect of the same kind as the high intensity stimulation, but something qualitatively different and more complex. The facilitation effects that we observed were anyway not strong enough to be considered statistically significant in the individual cases, which shows that low stimulation intensity is less efficient in modulating brain activity, as one might expect.
Chapter 6. Experiment V – Online vs. Offline Stimulation Study

6.1 Introduction

The attention topology experiment showed that 1Hz offline stimulation of both hemispheres of the brain can produce complex patterns of interaction between them, mainly facilitatory in nature. Unilateral stimulation did not produce significant effects, contrary to the expectations. In a new experiment we want to test whether online stimulation of parietal cortex can modulate attention, as suggested by earlier studies (e.g. Müri et al. 2002). The use of a similar paradigm as in the attention topology experiment would allow us to look for effects of bilateral deactivation produced with TMS, while avoiding some of the shortcomings of the combination of two offline stimulation sessions. In the case of a long offline stimulation session followed by a short one, as it was the case in the attention topology experiment, one could hope that the effects of each of the stimulations continue to exist independently in the brain for a certain time period and do not interact. The obtained results, however, suggest that an interaction may occur, i.e., the effect of the first stimulation session may be modulated and modified by the second stimulation session. If we were to employ offline stimulation followed immediately by a behavioral test with online stimulation of the contralateral hemisphere, this design would prevent the suspected modulation effect, at least at the beginning of the session.

Online stimulation has been found to interfere with attention processing only for a brief period of time after the application of the magnetic pulse. Reid et al. (2002) estimate the silent period of neurons in the motor cortex at about 300ms after
magnetic or electrical stimulation. The exact time of the application of the stimulation is also a factor in the effectiveness of producing attentional modulation. Müri et al. (2002) found that only a time window around 270 ms after stimulus presentation, not earlier than 120 ms and not later than 520 ms, allows for effective modulation of attention. Chambers et al. (2004) estimate this period at 100 ms to 370 ms after the onset of a visual target, based on the work of other researchers. It is not clear, however, whether there are any carryover effects, i.e., an effect due to the cumulative action of the pulses, which accumulates during the course of the online TMS session. One might suspect that such carryover effects take place since the online paradigm we used in this experiment resembles the offline stimulation, with 4 pulses delivered to parietal cortex on average every 7 seconds (the duration of two trials, one for active and one for sham stimulation), which makes a rate of about 0.5Hz.

Since it is unclear what is the exact time period after stimulus onset when stimulation is most effective, and in addition we know that the effect of the pulse is of limited duration, one has to develop a strategy which will ensure that the cognitive processing is disrupted during the entire time window when attention can possibly be modulated by TMS. The technique usually employed to this end is the use of multiple pulses separated by regular time intervals which cover the entire time window of attentional processing. An additional factor to be considered is the availability of stimulator equipment – single and double pulses can be generated by a Magstim and a BiStim configurations respectively, while a higher number of pulses require a device for generating repetitive TMS, like the Magstim Superrapid, which is not available to all research labs. Since we possess the necessary equipment for repetitive TMS, we are able to cover a longer period with a higher number of pulses and thus increase the
likelihood of producing an effect. It should be noted that with an increasing number of pulses used, the difficulties associated with carryover effects, coil overheating, and risk of producing seizures also increase, and one should always be careful to stay within a safety zone in terms of number of pulses and stimulation intensity. For this experiment a good combination of parameters seems to be 4 pulses at 45% starting at 70ms after stimulus onset and separated by 50ms intervals. An interval of 50ms is short enough to ensure that the effect of the pulse will be still present at the end of the interval, and the 70ms delay is the shortest interval when an effect from the stimulation was observed (Chambers et al., 2004).

6.2 Method

Participants

The participants in this study were eight undergraduate student at the International University Bremen, 3 male and 5 female, ages 20 to 23, median age 21. All had normal or corrected to normal vision and were right-handed according to the Edinburgh handedness test (Oldfield, 1971).

Equipment

The stimuli were presented on a backprojection screen with a Barco Cine 8 CRT projector equipped with a contrast modulation kit. The contrast was modulated in the left-right direction to reduce the brightness in the middle of the screen and thus to diminish the effect of a “hot spot” due to the positioning of the projector lenses along the line of sight of the participants when seated in front of the screen. The stimuli were produced via a Cambridge Research Systems VSG 2/5 system, which also included a 4-button response box used for collecting responses in terms of reaction
times and button choice, and which produced trigger pulses synchronized with the stimuli presentation for generating the TMS magnetic field pulses. The TMS pulses were generated with a Magstim Superrapid system with 4 boosters turned on, which was connected to the VSG computer board via a BNC cable and a break-out box with 25-wire cable (part of the standard equipment of the VSG system). The stimulation was delivered using a 70 mm figure-of-eight coil precooled to a temperature of 4-8 degrees Celsius with cool packs. The participants were seated in front of a table with a headrest mounted in the center, aligned symmetrically at the center of the screen.

**Stimuli**

The stimuli were tiny black dots appearing against a gray background at 23.5 degrees excentricity either on the left, on the right, or on both sides of the midline. The central location on the screen was marked by a fixation cross in black color, which disappeared before the onset of the stimuli. Two different sizes of the stimuli were used in order to detect eventual ceiling or floor effects in the detection performance. The smaller size served to detect improvements in detection performance due to the stimulation and the larger size served to detect deteriorated performance. The sizes differed always by only 1 pixel and varied between 1 and 4 pixels according to the titration procedure described below. At the lower left and right corners of the screen were projected markers signaling to the experimenter the orientation of the coil for the current trial. These were occluded from the visual field of the participant by two flaps attached to the sidebars of the headrest and did not affect the response.
Chapter 6. Experiment V – Online vs. Offline Stimulation Study

Procedure

The participants came for a practice and instruction session before the actual experimental sessions. They read and signed the necessary documents (information form, consent form for TMS, consent form for behavioral experiments, Edinburgh handedness test, and questionnaire I), got instructions on how to respond to the stimuli, and had a chance to perform a titration and one or more baseline sessions, until their responses became intuitive and they did not need to think about which button to press when the stimulus appeared.

The actual experimental session consisted of the following steps:

1) a titration procedure (only on the very first session),
2) taking the motor threshold (also on the first session only),
3) a baseline test without TMS (Baseline),
4) fitting the cap and marking P3 and P4,
5) experimental session with online TMS (Test 1),
6) 10-15 min break
7) 15 min 1Hz offline TMS
8) experimental session with online TMS (Test 2),
9) 15 min break
10) experimental session without TMS (Retest).

In the titration procedure stimuli of 4 different adjacent sizes were presented in a paradigm similar to the baseline (see below), and the sizes which showed performance nearest to 50% below and above this mark were chosen for the actual experiment. These were usually sizes 2 & 3 pixels, but also sizes 1 & 2 and 3 & 4 were used.
sometimes. As pointed out earlier, the sizes have to be such that the stimuli are detected sometimes, but not all the times. The difficulty in finding a good size lies in the fact that one of them sometimes were at ceiling or floor of the detection performance, and usually it happened that the performance for both was far from the midrange of 50% and was close to 0% (floor) or 100% (ceiling). However, the average performance of the two sizes combined was usually close to 50%. It should be noted that for some participants there was a difference in the performance rates for stimuli on the left and on the right side, but again the average was close to 50%.

The motor threshold was needed in order to estimate the strength of the used intensity with respect to the excitability of the cortex. Since the excitability of the cortical tissue can be different in different areas of the brain, it is not necessarily the case that the determined excitability level in the motor cortex can be used to make judgments about the excitability level of parietal cortex, which was the one of interest to us, but it is useful information nevertheless, which may suggest alternative explanations for the observed results in case it correlates with the magnitude of the observed effect of the TMS in the experimental conditions.

For the baseline test the participant was seated comfortably in front of the screen with the head positioned on the head rest and the right index, middle, and ring fingers on top of the 3 corresponding buttons of the response box. The presentation sequence during one trial was a fixation cross for 1500ms, a variable blank interval of 250 to 500 ms, a stimulus of 40 ms, and a response interval of 1000 ms. During the fixation cross interval were presented also the markers for the orientation of the coil, as mentioned above, which however were not visible to the participant. The test
Chapter 6. Experiment V – Online vs. Offline Stimulation Study

consisted of 210 trials in total that can be broken down according to the following scheme:

3 blocks x (5 repeats x 2 stimulus sizes x 3 stimulus locations (Left, Right, Bilateral) x 2 stimulation conditions (Active, Sham) + 10 catch trials) = 210 trials.

The order of presentation was randomized within each block. The catch trials contained no stimulus and required a non-response from the participant. The duration of one trial was about 3.5 seconds and the total duration of the test was approximately 12 minutes.

The marking of the locations of P3 and P4 on the cap required the partial drawing of the 10-20 coordinate system on the surface of the cap. For this purpose first the location of the inion was detected with manual palpation on the back of the skull. Then the locations of Cz, Oz, Pz, P7, and P8 were measured and marked using a flexible measuring tape. The locations of P3 and P4 were placed half-way between P7 and Pz, and P8 and Pz correspondingly. The participant was instructed not to take off or shift the cap until the end of the experiment.

The experimental session was the same as the baseline session, with the exception that stimulation was applied to the participant’s head during the course of the trial. Four TMS pulses were applied at 45% of the output of the Magstim Superrapid at intervals of 70ms, 120ms, 170ms, and 220ms after stimulus onset. The marker projected in the lower left and right corners of the screen signaled to the experimenter whether the current trial is with active or sham TMS. In case of active TMS the coil was placed
with the middle section of the figure-of-8 coil touching the skull at the marked
location (P3 or P4), and in case of sham TMS the plane of the coil was oriented
perpendicular to the surface of the head and the coil was touching the skull with the
external edge of the figure-of-8. This was necessary in order to preserve the effect of
the simultaneous burst of clicking noises and tapping effects present in the active
condition, which allows ruling out these effects as a potential cause or contributors to
the TMS induced effects. In this case, the sham condition is not run as an additional
session, but intermingled with real TMS trials. After each trial, no matter which
condition was indicated, the coil was lifted and placed again on its location on the
head. This ensured consistency of the participant’s sensation in every trial. Additional
tests with one of the experimenters in the place of the participant confirmed that the
touching sensation in the two cases was almost indistinguishable, and in the case of
high cognitive load during the course of the experiment one can claim with certainty
that the participants did not notice consciously which stimulation technique – active
or sham – was currently employed.

The short break after the online TMS session was necessary in order to diminish the
possible carryover effects from the accumulated action of the stimulation. Since, as a
rule of the thumb, the effects should not last longer than the duration of the preceding
stimulation, 15 minutes were deemed sufficient for avoiding those effects.

The 1Hz offline TMS was applied to the contralateral site with respect to the site of
online stimulation, i.e., at P3 or P4. The intensity of the stimulation was the same as in
the online condition – 45%. The stimulation was performed in the same location as
the behavioral test, with the participant seated in front of the screen and having his/her
head usually positioned on the head rest for convenience. Immediately after the end of
the offline stimulation the coil was exchanged and the next online session was started.
The stimulation in both sessions was done with precooled coils, which ensured that
they will not overheat during the entire period of the stimulation.

The subsequent online session and the retest were identical to the earlier online
session and the baseline respectively. After the end of the retest the participant was
asked to fill out the post-experiment questionnaire and to sign the time sheets.

**Summary**
The entire experiment lasted about two hours and consisted of a pre-stimulation
baseline, a test condition with online TMS only, a test condition with online TMS
counterbalanced by a preceding contralateral offline TMS, and a repeat of the baseline
without stimulation.

According to previous studies we hypothesized that active pulses delivered during the
time period between 120 to 220 ms after the stimulus onset at P4 and P3 should
impair the detection of contralateral targets in terms of both reaction times and
detection rates. Simultaneously, improved detection for ipsilateral targets at both
locations might occur. The effects would be higher for right parietal (P4) locations
than left parietal locations (P3). Sham TMS on P3 or P4 should yield no significant
effects. The effect of the off-line 1 Hz TMS of the contralateral hemisphere should be
to reduce the magnitude of both the neglect-like inhibition effects and the paradoxical
ipsilateral facilitation, since it is expected to generate a lasting decrease in the
activation in parietal regions and associated systems, that might partially or totally
match the interference caused by the 4-pulse bursts of on-line TMS on the contralateral side.

6.3 Results

Reaction Times

![Reaction time graph](figure-V-1)

Figure V-1. Reaction times by stimulus location and session for participants with Right Online stimulation.

As it is evident from the graph, there is no significant difference in reaction times between the different conditions. The only prominent feature of the reaction time graphs are the results from the baseline test, which are much slower than the rest in all 3 locations (left, bilateral, and right). One can also observe a small (about 20 ms)
facilitation of the results on the right side, i.e., ipsilateral to the stimulation, in the Test 2 Active stimulation condition. It is interesting to observe that this effect appears only in the presence of a counterbalancing offline stimulation, but it is not present in Test 1, when there was only online stimulation. As one might expect, overall the reaction on the left is faster than on the right and the response to the bilateral stimuli is the slowest. The differences are probably due to the combined effect of two phenomena: the speed of action of the fingers used for pressing the buttons and the slower cognitive processing of the double stimuli compared to the single ones. Thus, the index finger is faster than the ring and the middle fingers, which gives advantage to the button on the left and consequently to the left side. Note, that the results are shown for the two stimulus sizes combined together.

Figure V-2. Reaction times by stimulus location and session for participants with Left Online stimulation.
In this graph again we do not see significant differences between the different conditions. The baseline here is much slower only for the bilateral stimuli, and indistinguishable from the rest for the left and right stimuli. It is interesting to observe that the Test 2 Active stimulation result shows facilitation on the left side, although not that markedly different from the other conditions as in the right online case. This is the mirror image of the effect observed in the right online case. It also shows inhibition on the rights side, but again it is on the order of a few milliseconds difference and does not reach statistical significance. Here again the left response is the fastest and the bilateral is the slowest.

**Error Rates**

![Error Rates Graph](image)

**Figure V-3.** Error rates by stimulus location and session for participants with Right Online stimulation.
The error rates, just like the reaction times, do not show significant differences. In the right online stimulation condition it is evident that the retest performance was overall worse than the other conditions, which may be due to fatigue. The performance in the Test 2 Active stimulation condition shows again an interesting trend. The performance is facilitated on the left side by about 6% compared to the sham condition, while it is the worst on the right side except for the retest.

It is interesting to note that the performance on the left side is slightly better than on the right side, and both are better than for the bilateral stimuli. The difference between the single and bilateral stimuli may be explained by the fact that the bilateral stimuli are more difficult to perceive and the chances of making an error are intrinsically higher. The advantage of the left side may be due to lighting conditions or slight variations of the geometry of the setup of the experimental equipment.
Figure V-4. Error rates by stimulus location and session for participants with Left Online stimulation.

The graphs for the left online stimulation condition exhibit a similar pattern as those for the right online stimulation condition, and again we do not observe significant differences between the experimental conditions. The Test 2 Active stimulation results show a strong trend for impaired performance for the right (4% difference compared to the sham condition) and the bilateral (7% difference) stimuli. The overall performance for the right and bilateral stimuli in all conditions is also worse compared to the left online stimulation case, with 19% and 15% respectively, while the overall performance for the left stimuli is worse only with 9%. In general, the performance in the left online stimulation case seems to be notably worse than the performance in the right online stimulation case.
Table V-1. Breakdown of error rates for bilateral stimuli according to the actual response.

L = the Left button was pressed, R = the Right button was pressed

As we can see from the data in the table, there was no pronounced difference between the responses in the active TMS and the sham conditions in both tests. There is an overall bias to the left side, which has a higher response rate, but this effect is consistent for all conditions. In the right online TMS condition we can observe that the bias is slightly lower due to decreased rates for the response with the left button. The baseline and the retest also tend to have overall reduced rates of left and right button responses.
6.4 Discussion

In most general terms, the most significant observation from this study is that it did not reveal any statistically significant differences in the performance of the participants after the manipulation with TMS, although there were some interesting trends. This may be due to the fact that the stimulation intensity of 45% of the stimulator output was too low to produce measurable effects using the behavioral paradigm that was employed in this study. This possibility will be addressed in a follow-up study using a double-pulse paradigm with a higher stimulator intensity.

The trends which are evident mainly in the Test 2 Active stimulation results in both error rates and reaction times suggest that there was some effect from the offline stimulation when it was supplemented with online stimulation, and virtually no effect in all other cases. The reaction times exhibit a speed-up in the hemifield contralateral to the site of the offline stimulation and ipsilateral to the site of the online stimulation. This may be due to a disinhibitory effect of the offline stimulation to the hemisphere that was stimulated, or an inhibitory effect of the online stimulation for the stimulated hemisphere, which translates into a disinhibitory effect for the contralateral hemisphere. The two effects are complementary and both result in the disinhibition of the hemisphere subjected to offline stimulation. Since only the results in the Test 2 Active stimulation condition were affected, this suggests that there is a combined action of both inhibition-disinhibition mechanisms described above, and each of them on its own is incapable of producing an effect. The disinhibition effect of the 1Hz offline stimulation is paradoxical given the studies described in the literature, which have consistently found an inhibitory effect for this rate of stimulation (Walsh, Pascual-Leone 2003).
The error rates in the Test 2 Active stimulation condition are more contradictory. The effect from the left online stimulation corroborates the hypothesis of an inhibitory effect from this stimulation, since it increases the number of errors for stimuli in the contralateral hemifield. Thus, the effect of the left online stimulation is both more errors and increased reaction times on the right side. The effect of the right online stimulation, however, is reduced number of errors for stimuli in the contralateral hemifield. The reaction times, on the other hand, remain unchanged on the left side as a result of the stimulation, instead of being slowed down. Both effects speak for disinhibition of the hemisphere receiving the online stimulation, which is exactly the opposite trend to what is observed in all other cases.

If we consider the odd trend observed in the right online stimulation case as a random fluctuation in the results, we can claim that there is a fairly consistent picture of hemispheric interaction, consistent with the one observed in the attention topology experiment and the paradoxical restoration of attention in normal subjects (Hilgetag et al. 2001) and in the cat (Sprague, 1966). For that, however, we need to assume that offline stimulation produces disinhibitory, instead of inhibitory, effect, while the online stimulation produces an inhibitory effect as expected.

Special merit deserves the innovative design of the study of combining and contrasting the online and offline stimulation paradigms and the interleaving of the sham trials and the active stimulation trials. Although the interleaving technique requires some manual skills and concentration on the side of the experimenter, it has the added benefits of avoiding intersession effects like carry-over, learning or fatigue,
and has the potential of producing more credible results. It is recommendable that the
same method is used in a future experiment with higher intensities of stimulation,
which may produce stronger effects and thus lead to statistically significant results.
Chapter 7. Experiment VI - Mirror Image Identification

Synopsis of Part II

The experiments involving the TMS technique revealed that perturbation of specific brain areas in the two hemispheres leads to differential effects on cognitive performance and thus reaffirmed the idea of lateralization of brain function, more specifically of spatial attention. The conclusion from the mapping study and the attentional perimeter study is that the right hemisphere is more directly involved in mediating spatial attention, with a critical involvement of a region located over the intraparietal sulcus and the angular gyrus. The occipital lobe study confirms these findings indirectly by showing that modulating the activity of the occipital lobe does not lead to disbalancing of the spatial attention, but it has only an effect on the visual perception.

In addition to the findings about brain function, the experiments tackled a number of methodological issues. Different stimulation paradigms were tested and compared in terms of effectiveness and practical suitability, and the potential for restoring the balance of the attentional function by bilateral deactivation was explored with view on potential clinical application for treatment of attentional imbalance deficits. The ability to produce both contralateral deterioration and ipsilateral facilitation of performance after magnetic stimulation and the ability to restore the function after a secondary contralateral deactivation with magnetic stimulation casts the understanding of spatial attention in the light of the cerebral balance theory, which assumes that normally functioning attention is the result of a competitive balance between the activity in the two hemispheres. If this balance is disturbed and one of the hemispheres comes to dominate over the other one, part of the attentional perimeter
becomes neglected which leads to a cognitive deficit. The TMS technique is able to reproduce this phenomenon on a much smaller scale than the cognitive deficit resulting from brain lesions, which, however, is sufficient to model some aspects of the deficit and to study it in vivo. Usually, the brain is able to reorganize and recover from the impaired balance, both in the case of a lesion and after TMS, which makes the TMS technique safe for practical use.
Part 3: BEHAVIORAL STUDIES OF SYMMETRY AND INTERHEMISPHERIC CONNECTIONS

Chapter 7. Experiment VI - Mirror Image Identification

7.1 Introduction

The two hemispheres of the brain are connected via a bundle of fibers forming a body called the corpus callosum. Anatomical studies have tried to establish whether the connections are topological, i.e., there are specialized fibers connecting homologous areas on the left and the right side to each other. According to Berlucchi (1972) there is some evidence for compartmentalization of the corpus callosum in animals, while the evidence for humans is severely limited. The corpus callosum and the commissure of the superior colliculus have been found to be arranged topographically, linking corresponding mirror-symmetric eccentricities in the representations of the left and right hemifields (Behan & Kime 1996; Abel et al. 2000). A more recent review by Innocenti and Bressoud (2003) posits the existence of predominantly homotopic connections between homologous brain areas via the corpus callosum, but also some heterotopic connections between areas which are functionally similar. The vast majority of these connections are excitatory, though some of them may terminate on inhibitory neurons and thus mediate an inhibitory interhemispheric signal. This arrangement may account for the phenomenon of disinhibition observed in neglect patients and in the virtual lesion studies where enhancement of the performance is observed on the side ipsilateral to the stimulated hemisphere (Hilgetag et al., 2001). Similar disinhibition effects have been found between primary motor regions (Kobayashi et al., 2003; Kobayashi, 2003) or used to mediate recovery from
neurological conditions such as motor paralysis (Mansur et al., 2005), Broca’s aphasia (Naesser et al., 2005) and visuo-spatial neglect (Shindo et al., 2006) by transcallosally induced disinhibition. This body of observations suggests that as a general rule transcallosal projections might mediate net inhibitory interactions between homologue locations on both hemispheres.

The organization of the connections via the corpus callosum is suspected to play a role in the perception of vertical symmetry. According to the ‘callosal’ hypothesis originated by Mach nearly 100 years ago and extended by other researchers, vertical symmetry is more easily detected than symmetry in other orientations due to the bilateral anatomical symmetry of the brain (Herbert & Humphrey, 1996). The lower-level visual representation of a vertically symmetric object would also be anatomically symmetric in the two hemispheres of the brain, due to the topographic nature of the representation. This may influence the higher-level object representation in the later areas of the visual stream by creating an alignment, or matching patterns, in the two hemispheres independently. When these aligned higher-level representations interact via the homotopic connections of the corpus callosum, this would lead to mutual excitation, or boosting of the signal, and thus lead to facilitated perception.

Bar and Biederman (1998) performed an experiment where they primed subliminally their participants with pictures of different objects and found increased rate of detection when the same pictures were presented later. The detection rate decreased when the location of the object was shifted at about 5°, but the priming effect was still present. These results allowed them to conclude that the subliminal priming process
Chapter 7. Experiment VI - Mirror Image Identification

engages visual representations at an intermediate stage of the ventral pathway for shape recognition. Biederman and Cooper (1991) performed a similar experiment, but found a complete translational and reflectional invariance for the priming effect. They presented line drawings of familiar objects for 150ms followed by a mask, at 2.4° on the left or on the right of a fixation cross, and in the same or in an inverted orientation. The magnitude of the priming from the first to the second presentation was the same for all combinations of location and orientation. This is quite a remarkable finding, indicating that the mental representations of these objects activated in the experiment are at a highly abstract, purely conceptual level. Since the objects were presented very close to the midline and the inversion of the orientation was across the vertical axis, one may question whether the observed invariance may be due to the specific design of the early visual system leading to facilitated processing of exactly this kind of stimuli. More specifically, this could be the enlarged representation of the foveal and near-foveal areas, the mirror-symmetric interhemispheric connections, and the overlapping representation of the visual input near the midline.

The processing of stimuli along the horizontal axis versus the processing along the vertical axis may be fundamentally different, as suggested by a study examining the correlation between the EEG signal at homologue locations in the two brain hemispheres in response to horizontal vs. vertical apparent motion (Rose and Büchel 2005). The authors found that there is an increased oscillatory coupling in the gamma band between hemispheres when perceiving horizontal compared with vertical apparent motion. This finding suggests that the underlying physical activity in the brain may be more symmetrical for stimuli arranged along the horizontal axis versus those along the vertical axis, leading to some unique interactions between the
hemispheres producing the unusual effects associated with horizontal mirror
symmetry.

Against this controversial background, we devised a simple mirror image
identification experiment (Experiment 1) to explore the functionality of the
topographic, mirror-image connections mediating interhemispheric communication.
The hypothesis was that a brief presentation of an unfamiliar object in one hemifield
might prime the subsequent recognition of its mirror image in the opposite hemifield.
A control experiment (Experiment 2), in which the stimuli were presented along the
vertical axis rather than the horizontal one, was performed to verify that the observed
effects were not due to an unspecific mental operation of image flipping. Another
control experiment (Experiment 3) was performed when the participants were not told
that some of the stimuli were mirror images of others, but were instructed to respond
only when they see a different stimulus. This was done in order to assess the effect of
the top-down modulation on mirror symmetry perception due to the explicit
knowledge of the expectation of mirror images. A third control experiment
(Experiment 4), where the images were presented on the left and on the right along
the horizontal axis, but were flipped in the vertical direction to create the mirror
image, verified whether the high-level symmetry processing works equally well for
vertical as well as horizontal mirror symmetry.

7.2 Method

Participants
There were 10 participants in experiment 1 (Horizontal mirror object identification)
and 10 participants in experiment 2 (Vertical mirror object identification), all students
and staff from International University Bremen. 6 participants performed both experiments. In both experiments the sex ratio was 3 male to 7 female participants, and all except one were right handed according to the Edinburgh handedness test (Oldfield, 1971). All had normal or corrected-to-normal vision, and the ages ranged from 19 to 52 years, median age 32.

**Equipment**

The stimuli were presented on a Sony Trinitron GDM – F520 monitor with a flat screen with 49 cm diagonal (height 30 cm, width 39 cm), frame rate of 100 Hz, and resolution of 1008 x 770 pixels. The stimuli were generated by a Cambridge Research Systems Visual Stimulus Generator 2/5 system, using program code written in Delphi Pascal. The head was kept in a fixed position through a head rest for the entire duration of the experiment. The response was acquired with a 4-button response box, part of the standard VSG equipment, of which only two buttons were pressed with the left and right index fingers.

**Stimuli**

The stimuli were custom designed abstract shapes with flat upper and lower side and elongated along the vertical dimension, simulating a standing object (see Figure 1). They were rotated at 90 degrees for experiment 2 (Figure 2).
Figure VI-1. Examples of Stimuli used in Experiments 1, 3, and 4. The mirror-symmetric images in Experiment 1 and 3 were formed by flipping the original images along the horizontal axis, and in Experiment 4 along the vertical axis.

Figure VI-2. Examples of Stimuli used in Experiment 2. These are the same images as in the other experiments, but rotated at 90°. The mirror-symmetric images were formed by flipping the original ones along the vertical axis.

The stimuli were presented at 20 mm (2.6 degrees) or 40mm (5.2 degrees) distance from the central fixation cross to the inner edge of the image. They were situated to the left and right of the fixation cross in experiments 1, 3, and 4, and at the same eccentricity but vertically (up and down from the fixation cross) in experiment 2.
Chapter 7. Experiment VI - Mirror Image Identification

**Procedure**

A fixation cross appeared in the middle of the screen for 1000 ms, followed by a blank screen of a variable duration between 500 and 750 ms. After that a target stimulus was presented at 20mm distance either to the left or to the right of the fixation cross in the case of experiment 1 and experiment 3 or above or below the fixation cross in the case of experiment 2. The presentation lasted for 100 ms and it was followed by a blank screen of 500 ms and a probe stimulus for 1000 ms. The probe was presented either on the same side of the fixation cross or contralaterally, at one of two possible excentricities - 20 mm and 40 mm (approximately 2.6° and 5.3° respectively).

![Diagram of the time course of one trial in Experiment 1](image)

**Figure VI-3. Time course of one trial in Experiment 1**

The shape of the probe was either identical to the target or its mirror image, i.e., flipped horizontally in experiments 1, 3, and 4 or vertically in experiment 2. Thus, for each target there were 8 possible versions of the probe (2 sides x 2 excentricities x 2 orientations).
shapes). 8 different target shapes were used and each of them could be presented on each side, making for a total of 128 trials in one run of the experiment (8 target shapes x 2 sides x 8 probe shapes).

In experiments 1, 2, and 4 two runs were performed with a different task. In the first case the participants had to identify and respond only to the mirror image shapes of the probe, and in the second run they had to identify and respond to the same image shapes. In experiment 3 the same stimuli as in experiment 1 were presented, but the participants were asked to identify same or different images, instead of same or mirror ones. The response was given by pressing two of the 4 buttons on the response box. In experiment 1 these were the left and the right button, indicating the side on which the probe was presented. In experiment 2 the top and the bottom buttons were used, again with the two index fingers in whichever way was convenient for the participant. The order of the tasks was always the same – first the mirror/different images and then the same images. The participant had a chance to practice for a while before starting the actual runs until they became familiar with the experimental paradigm.

We hypothesized that performance levels for the correctly identified mirror images should be better in terms of reaction times when presented horizontally (left and right) rather than vertically (above and below). If the effects is preserved in the control experiments, this would indicate that the transcallosal facilitation effect occurs at the level of higher-order processing of the stimuli, while the opposite would indicate dissociation of the higher-order processes and lower-level interactions between the hemispheric representations.
7.3 Results

Figure VI-4. Reaction times for horizontally flipped images in experiment 1.

The main finding of this experiment can be seen on Figure VI-4 – identification of mirror symmetric images is facilitated with respect to the same images when the probe is presented contralaterally to the target, regardless of excentricity. Note that the figure shows both the data for the target presented on the left and on the right side in a single graph. I_2 shows the location of the probe, no matter on which side, and the other locations are ordered in increasing distance from the location of the probe.
Figure VI-5. Reaction times for vertically flipped images in experiment 2.

Unlike the horizontally flipped stimuli, the vertically flipped ones do not produce any significant differences in reaction times in the different conditions (see Figure VI-5). The reaction times, however, can be approximated with a linear function increasing with the distance from the target. Regression analysis was performed on the Horizontal case \((r^2 = 0.999)\) and Vertical case \((r^2 = 0.783)\).
Figure VI-6. Comparison between the reaction times for Mirror images in experiments 1 and 2.

The difference in reaction times for the horizontal stimuli between the same and the opposite side conditions, i.e., collapsed for eccentricity, is significant (see Figure VI-6), as confirmed by a paired t-test by participant (p<0.01). The difference in the vertical condition is not significant. There are also no significant differences due to the hand response (left or right index finger) or the direction of target – probe presentation (left to right or right to left).
Figure VI-7. Error rates (misses) for experiment 1 and experiment 2.

The error rates for mirror stimuli are higher as one might expect, with no significant difference between the same and the opposite side in both the horizontal and the vertical experimental condition. Possibly there is some advantage for horizontal mirror stimuli on the opposite side compared to the same side. The identification of a mirror stimulus presented at eccentricity 1, i.e., slightly offset from the target location, seems to be particularly difficult.
Figure VI-8. Reaction times for horizontally flipped images in experiment 3 when the task was “Same or Different”.

Figure VI-8 shows the reaction times from experiment 3 when participants were asked to identify different stimuli instead of mirrored ones. The curves made up from the values for the different presentation locations in both the different images and same images identification task are more or less flat, with no significant difference between the conditions in each location. The effect of translation observed in experiment 1 and 2 for same stimuli is absent here.
The reaction times in experiment 4, shown in Figure VI-9, are very similar to those in experiment 1, except for the fact that the identification of mirror images shown ipsilaterally to the target is somewhat faster. Nonetheless, the difference between the reaction times for the ipsilateral versus the contralateral side is statistically significant (paired T-test, p=0.01). For the same images there is again an effect from the translation of the images along the horizontal axis, as in experiments 1 and 2.

7.4 Discussion

The observed facilitation of the identification of mirror image stimuli presented in the contralateral hemifield is in line with the well established phenomenon of an apparent difficulty in the discrimination of images with mirror symmetry about the vertical
axis, evident not only in humans but in many other species as well (Bradshaw et al., 1976). The fact that facilitation was obtained independently of the excentricity of the presented stimuli suggests that the cognitive mechanisms mediating the mirror object identification in this task operate at a higher, more abstract level than simple pattern matching performed by the early visual system, such as the ones involved in the callosal information transfer mechanism described by Herbert & Humphrey (1996). This conclusion is reinforced by the finding that mirror symmetry both across the vertical axis (as in Experiment 1) and across the horizontal axis (as in Experiment 4) produce the facilitation effect, which suggest the involvement of higher-level cognitive representations of abstract shapes. Although our results do not contradict the callosal hypothesis of Herbert & Humphrey, they render it insufficient as an explanation for the observed effect, and necessitate its extension to mechanisms of higher-level cognition.

The identification of stimuli in the same orientation as the probe follows a different pattern of regularity – it becomes more difficult with increasing distance between the target and the probe, as seen in experiment 1, 2, and 4. This result to some extent conforms with the finding of Bar and Biederman (1999) of facilitated object recognition through subliminal priming in the same quadrant of visual space and only slight facilitation between quadrants. On the other hand, it runs against Biederman and Cooper’s finding (1991) of complete translational and reflectional invariance in supraliminal priming, from which they conclude that a higher-level representation of objects is engaged in the recognition process, which is independent of the representations of the location and left-right orientation of objects in space. Our experimental setup, however, differed from theirs in that the shapes were artificial and
difficult to distinguish, and that the target was presented without a mask and was immediately followed by the probe. There is also an important design difference between the two experiments, namely that in their experiment the shapes were meaningful objects, which probably engaged high-level conceptual networks, while the artificial shapes in our experiment may have failed to do so. Based on the observed effect one may argue that the artificial shapes engaged areas in the brain which are inbetween the initial, low-level visual processing (V1, V2) and the high-level, abstract object representation (IT). As Bar and Biederman (1998) point out in respect to their observation of a similar effect of translation on performance, the human homologue of area V4 in the macaque may contain the appropriate shape representation, since its neurons have receptive fields of sizes between 0.7° and 10° (Tanaka, Weber, & Creutzfeldt, 1996), which are about right to explain the observed translation dependence.

Translational invariance, however, was observed in experiment 3 when the task was modified from identification of mirror images to identification of different images. When the participants were unaware of the fact that the probes are mirror images of the targets, but they knew only that they are different images, the facilitation effect observed in experiment 1 disappeared. It may seem surprising that the task context should have such strong influence on performance, and it emphasizes the fact that higher-level cognitive mechanisms play an essential role in this task. Mental rotation, for example, may have been employed by the participants, judging from the absolute speed of the reaction times in experiments 1 and 3. The slowest reaction times in the mirror image condition are observed for ipsilateral probes in experiment 1 (around 700 ms), while the contralateral ones in experiment 1, as well as all locations in
Chapter 7. Experiment VI - Mirror Image Identification

experiment 3, are faster, with statistically indistinguishable values in the range of 600 to 650 ms. The result in experiment 1 may be due to the fact that mental rotation, or actually flipping in 3D, which would be the proper geometrical operation in this case, is more difficult to perform in place, rather than at a small distance, even if it is across the hemifields. In experiment 3, when the participants did not judge mirror symmetry, they may have not employed mental rotation which would result in faster processing times and the location invariance that was observed. This speculation, however, needs to be verified with additional experiments which would establish whether mental rotation is indeed taking place, or whether symmetry judgments employ other mechanisms.
8.1 Introduction

This experiment, like experiment VI, investigates the effects of mirror symmetry and homotopic interhemispheric connections using simpler stimuli which presumably activate only lower-level cognitive representations. The experimental paradigm consists of bilateral presentations of slightly tilted lines at some excentricity from the central fixation point which would make it difficult to perceive the tilt but correct performance would still be above chance. This will allow the detection of an eventual interference between the two symmetrically situated percepts and thus allow some inferences about the mechanism of homotopic interhemispheric connections. More specifically, an enhanced performance in the case of two matching stimuli would reinforce the idea of excitatory homotopic connections between the two hemispheres which would allow the activation patterns from one hemisphere to prime the activity in the other. The strength of the effect with respect to the results in experiment VI on mirror image identification will allow us to infer at which level of abstractness do the cognitive representations in the two hemispheres interact through the signal exchanged via the interhemispheric fibers. A relatively stronger interference effect in experiment VI, which involves higher-level mental representations, would indicate a higher level of abstractness, where the signal is carried by the group activity of populations of neurons and not the activity of single neurons. On the contrary, a stronger interference effect in the current experiment would indicate a relatively lower level of abstractness which may be encoded by the activity of individual neurons which are selectively tuned to lines with certain orientation.
8.2 Method

Participants
The participants were 10 undergraduate students at the International University Bremen, 5 male and 5 female. All received instructions before the experiment and confirmed verbally their agreement to participate. For their efforts they were rewarded with chocolate bars.

Equipment
The stimuli were presented on a Sony Trinitron GDM – F520 monitor with a flat screen with 49 cm diagonal (height 30 cm, width 39 cm), frame rate of 100 Hz, and resolution of 1168 x 875 pixels. The stimuli were generated by a Cambridge Research Systems Visual Stimulus Generator 2/5 system, using program code written in Delphi Pascal. The fixation on the screen was monitored with a 50 Hz Cambridge Research Systems infrared Video Eyetracker mounted on a rigid EyeLock™ headrest, compatible with the VSG system and operated from the same desktop computer. The response was acquired with a 4-button response box, part of the standard VSG equipment, of which only the left, the top, and the right buttons were used.

Stimuli
The stimuli were vertical lines of length 0.9 degrees (0.7 cm at 45 cm eye-to-screen distance) or a horizontal line of the same length. The vertical lines were either exactly vertical or the top half of the line was displaced with one pixel to the left or to the right. Thus, there were 4 types of stimuli – a horizontal line, a vertical line, a line slightly tilted to the left, and a line slightly tilted to the right. The fixation cross consisted of a crosshair with the same height as the stimuli, i.e., 0.9 degrees, and
width approximately one third of the height, or 0.3 degrees. To the left or to the right of the crosshair was displayed an arrow pointing to the right when it was on the right side and pointing to the left when it was on the left side. The smaller length of the horizontal bar of the cross was needed in order to bring the cue arrow closer to the center and to avoid any potential interference with the stimuli.

![Figure VII-1. Example of a screen with a tilted to the right vertical line on the right side and an exactly vertical line on the left side.](image)

**Procedure**

The experiment consisted of a practice session and an experimental session immediately after that. The experimental session consisted of 5 blocks of 30 trials each. The blocks were run independently of one another, i.e., the program for presentation of the stimuli and the eye-tracker had to be restarted for each block. The practice session consisted of several runs of one block, until the participant felt comfortable performing the task. One block contained all combinations of the 4 types of stimuli plus a no-stimulus condition (5 conditions in total) presented on one side.
with only the vertical lines (3 conditions in total) presented contralaterally. So, we have 5 types of lines x 3 types of lines x 2 sides = 30 trials. The order of presentation was randomized within the block. The total number of trials was 30 x 5 blocks = 150 trials for each participant, with 5 repeats for each stimulus condition.

One trial consisted of the presentation of the fixation cross plus the prime – a left or a right arrow – for 1000 ms, a blank screen of variable duration between 500 and 750 ms, a brief flash of the stimuli (vertical lines on the left, on the right, or on both sides of the cross) for 200 ms, and a response period of 1500 ms. The participants had to press the button corresponding to the tilt of the line on the side indicated by the arrow, so they had to concentrate on the orientation of that bar, while the bar presented contralaterally acted as a distracter. For example, in the figure shown above, the arrow points to the right side, where a vertical line tilted to the right is presented, therefore the correct response is to press the right button. The line shown on the contralateral side serves as a distracter.

8.3 Results

Error rates
Figure VII-2 Correct rate of responses broken down by stimulus type and distracter type.

The graph above shows the percent correct responses for each of the 3 types of stimulus in the presence of each of the 5 types of distracter on the opposite side. (Note that the side information is ignored in this graph, e.g. the cases of a right tilted line presented on the left plus a vertical line presented on the right and a right tilted line presented on the right plus a vertical line presented on the left are merged in one data point.) It is clearly evident that on average the vertical stimuli were the easiest to detect (the top-most line in the graph), followed by the right tilted lines (middle line) and then by the left tilted lines (the lowest line). The average rate of correct responses for distracters same as the stimulus is 63%, which is higher than the average rate of correct responses for distracters different from the stimulus (58%), but the difference is not statistically significant (p=0.4, two-tailed t-test). A two-way ANOVA with factors stimulus type and distracter type revealed a significant effect from stimulus
Chapter 8. Experiment VII - Line Tilt Detection

type (F=18.262, p<0.01) but not from distracter type. The post-hoc Tukey HSD test for stimulus type (left, right, and vertical) showed significant differences for all pairs of means of stimulus type (p<0.05).

Table VII-1 above shows that the left tilted line was mostly confused with a vertical line (in 44.4% of the cases, see the values in red and italics) as one might expect (the response in the case of a left tilted line stimulus was to press the button for the vertical line). The vertical line was confused slightly more often with a right tilted line than with a left tilted one (13.8% vs 11.2% respectively), which is coherent with the overall slight preference of detecting the right tilted line over the left tilted line. The
right tilted line was also mostly confused with a vertical line, although to a lesser degree than the left tilted line (only in 36.6% of the cases compared to 44.4%).

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Response</th>
<th>Side of stimulus</th>
<th>Left</th>
<th>Right</th>
<th>Grand Total</th>
</tr>
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<tr>
<td>Left tilt</td>
<td>Right tilt</td>
<td></td>
<td>1.4%</td>
<td>3.8%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td>Vertical</td>
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<td>24.4%</td>
<td>44.4%</td>
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<td></td>
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<td>0.6%</td>
<td>1.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Left Total</td>
<td></td>
<td></td>
<td>22.0%</td>
<td>29.8%</td>
<td>51.8%</td>
</tr>
<tr>
<td>Vertical</td>
<td>Left tilt</td>
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<td>7.6%</td>
<td>3.6%</td>
<td>11.2%</td>
</tr>
<tr>
<td></td>
<td>Right tilt</td>
<td></td>
<td>3.6%</td>
<td>10.2%</td>
<td>13.8%</td>
</tr>
<tr>
<td></td>
<td>(blank)</td>
<td></td>
<td>1.4%</td>
<td>0.6%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Vertical Total</td>
<td></td>
<td></td>
<td>12.6%</td>
<td>14.4%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Right tilt</td>
<td>Left tilt</td>
<td></td>
<td>1.6%</td>
<td>0.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td></td>
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<td>2.2%</td>
</tr>
<tr>
<td>Right Total</td>
<td></td>
<td></td>
<td>23.8%</td>
<td>16.8%</td>
<td>40.6%</td>
</tr>
</tbody>
</table>

Table VII-2. Breakdown of the erroneous responses by button pressed and side of presentation of the stimulus

It is interesting to inquire whether the side of the presentation of the stimulus plays a role in the observed confusion effects. Table VII-2 above shows the breakdown of the erroneous responses according to the side of the presentation of the stimulus, which was ignored in the earlier charts. One can observe an interesting trend in the data related to the confusion rates discussed earlier. When a left tilted stimulus is confused...
with a vertical line (the response is with the button for vertical), this is more likely to occur when the stimulus is presented on the right side than on the left side (see the values in green and italics). Conversely, when a right tilted stimulus is confused with a vertical line, this is more likely to occur when the stimulus is presented on the left side than on the right side. In addition, the vertical line is more likely to be confused for a left tilted line than for a right tilted one when it is presented on the left side and vice versa, it is more likely to be confused for a right tilted line than for a left tilted one when it is presented on the right side.

Figure VII-2 depicts one more interesting fact: for vertical line stimuli when the distracter was an almost vertical line, both when it was tilted to the left and to the right, the rate of correct detections was slightly higher than the cases of no distracter or a horizontal line as a distracter. In the case of a right tilted stimulus, interestingly, the rate of correct detections was higher in the presence of a right tilted line as a distracter, than in the presence of a left tilted and vertical line. The rate was slightly lower, though, than the case of no distracter. In the case of a left tilted stimulus, contrary to the established pattern, again the right tilted distracter produces the highest facilitation of the correct response from all 3 vertical or nearly vertical line type of distracters. The horizontal line in this case has the highest facilitatory potential of all distracters, while the absence of a distracter is about as good as the presence of a vertical line.

**Reaction times**
The most prominent effect that can be seen in the reaction times graph above is that the response to the left tilted stimuli is on average slower than for the right tilted and the vertical stimuli no matter of the distracter type. Note that the magnitude of the effect is rather small, on the order of 3 ms, however the difference with both the vertical and the right tilted line results is significant (paired T-test, p<0.01).

Interestingly, the reaction time for the left tilted stimulus does not depend on the distracter type and is fastest in the absence of a distracter. The reaction to the vertical and the right tilted stimuli are slowest in the presence of a vertical distracter and are also fastest in the absence of a distracter. Another interesting observation is that the reaction times for vertical and right tilted stimuli are almost identical in all cases of a distracter except when it is absent, which slows down the response to a vertical stimulus more than that to a right tilted stimulus. Finally, the reaction times to a
horizontal line distracter for all stimuli are very similar to the reaction times for the absence of a distracter.

### 8.4 Discussion

The results both in terms of error rates and reaction times consistently show that the type of a distracter presented contralaterally affects the perception of a stimulus in a systematic way. They offer some support of the hypothesis of facilitation of the detection of mirror-symmetric stimuli due possibly to the topographic isomorphism of interhemispheric connections. There is also evidence for lateralization of the mirror symmetry detection mechanisms, although alternative explanations may be put forth.

The strongest evidence for the existence of mirror symmetry in the perceptual mechanism for processing of visual information along the horizontal plane comes from the symmetric arrangement of the response biases contained in the confusion rates (the percentages of incorrect responses) shown in Table 1 and Table 2 together with the impairment in terms of speed of processing evident in the reaction times results. Regarding the first effect (see Table 2), there is a tendency on both sides (left and right) to confuse a given stimulus for another one rotated outwards, i.e., a left tilted stimulus is more likely to be perceived as a vertical one when it is presented on the right side rather than on the left side, and vice versa. In addition, a vertical stimulus is more likely to be perceived as a left tilted one when it is presented on the left side, and correspondingly it is more likely to be perceived as a right tilted one when it is presented on the right side. This effect, however, might be due to a bias to press the button for the side on which the stimulus is presented, since attention is cued in the beginning of the trial in one direction. Thus, for example, if one hesitates
between pressing the button for a tilted or vertical stimulus when the stimulus is 
presented on the right side, and one chooses the tilted option, one would be more 
prone to press the right button than the left one because of the priming. This is exactly 
what we see in the results shown in Table 2 for a vertical stimulus and a right tilted 
response. Although this alternative explanation may seem more plausible than the 
mirror facilitation effect, nevertheless the data is consistent with mirror facilitation 
and this hypothesis cannot be ruled out.

As already mentioned, the speed of processing is affected by the type of distracter, 
which is also consistent with a mirror facilitation hypothesis. We can observe in 
Figure 2 that performance in terms of reaction speed is most obstructed in the case of 
an identical distracter on the opposite side for left tilted and vertical stimuli. We can 
hypothesize that when two different stimuli are presented, there is a higher probability 
that one of them may be identified with certainty and this will facilitate the 
identification of the other one by providing contrasting evidence. Thus, for example, 
if there is a left tilted stimulus on the left and a vertical stimulus on the right, one may 
identify quickly the left tilted one, and this would provide a contrast for the stimulus 
on the other side, which would appear somewhat different. If one hesitates regarding 
the right stimulus whether it is left tilted or vertical, the identification of the stimulus 
on the left will help exclude the first possibility, since it looks differently, and the 
choice for a vertical stimulus will be made faster. The same mechanism would operate 
in the other direction, if the vertical stimulus is identified with more certainty. In the 
case when the same type of stimulus is presented on both sides, one may get into a 
situation where both stimuli are not identified with certainty, which would lead to a 
longer hesitation before making the choice, and this would produce the pattern of
results as they are observed in the case of a left tilted and vertical stimuli. For the right tilted stimulus we have the opposite pattern – faster reaction time in the presence of a right tilted distracter. This may indicate the fact that the right tilted stimulus is easier to identify, which is to some extent confirmed by the error rate results, where the right tilted stimulus is identified correctly more often than the left tilted one, but less often than the vertical one. If it is indeed easy to identify, then the presence of a distracter of the same type would affect performance less than the presence of distracters which are more difficult to identify.

The fact that all 3 near-vertical types of distracters slow down performance compared to the absence of a distracter or a horizontal line can be explained with a mirror organization of the connections between the neural representations of the stimuli in the two hemispheres of the brain. Unlike the experiment on mirror object detection (see Chapter 7), where the target was presented before the probe and this produced a contralateral facilitation for mirror stimuli, in this experiment we present the stimuli on both sides simultaneously. This would lead to an interaction between the two representations which in the case of nearly vertical stimuli would be reinforcing in nature, since one would hardly expect that the connections are so precise that they would be able to make a distinction between the minimal tilt and the strictly vertical lines. Thus, the magnitude of any effects such as the ones described above will be boosted, and one would expect to find less pronounced effects in the case of absent mirror facilitatory connections. This proposition may be tested in an experiment with a slightly different arrangement than the current one, by presenting the stimuli along the vertical dimension, i.e., rotated at 90 degrees. In this case one would expect to find
less pronounced effects or no effects at all, as was the case in the mirror object
detection experiment.

The results also revealed a preference for the right tilt compared to the left tilt, which
may be due to some property of the experimental setup and less likely a feature of the
human visual perception system. It is expressed both in term of error rates and
reaction time. Interestingly, there is no trade off between speed and accuracy in the
results from this experiment. Faster speed of response goes hand in hand with higher
rate of correct detections. This speaks for strong biases in the mechanism for
identification of the stimuli, which need further exploration.
Chapter 9. Experiment VIII - Variable Excentricities

9.1 Introduction

It is well known that multiple stimuli are processed differently than single stimuli and possibly engage very different cognitive mechanisms. For example, the race effect discussed in experiment I shows that depending on the task, two stimuli may be processed slower or faster than a single one, leading to the proposition that different cognitive mechanisms operate at each instance. Thus, one can assume that in some circumstances the presence of additional stimuli is undesirable and they act as distracters with respect to the stimulus which requires reaction from the subject. The stimulus + distracter paradigm is used in many experiments of different nature in order to study different aspects of perception and cognition.

This study will examine the effect of a distracter presented at different locations contralaterally to a single stimulus in order to find out how symmetrical or asymmetrical arrangements of stimulus and distracter affect performance. This experimental paradigm may be able to confirm the hypothesis of the existence of homotopic interhemispheric connections and eventually to provide an estimate for their spatial extent by measuring how strongly performance is affected with increasing asymmetry of the stimulus arrangement (increasing offset from an anchor excentricity). It complements the other experiments on the interhemispheric connections and it differs from them primarily in that it uses point-like stimuli thus avoiding the activation of higher level cognitive representations of objects and shapes.
9.2 Method

Participants
In all studies the participants were undergraduate students from the International University Bremen. Study 1 had 9 participants, 6 female and 3 male. Study 2 had 10 participants, 6 male and 4 female. Study 3 had also 10 participants, 5 male and 5 female.

Equipment
The stimuli were presented on a backprojection screen with a Barco Cine 8 CRT projector equipped with a contrast modulation kit. The problem of a ‘hot spot’ due to the illumination of the screen directly from the lenses along the line of sight was avoided by setting the background color to black (no light). The stimuli were produced via a Cambridge Research Systems VSG 2/5 system, which also included a 4-button response box used for collecting responses in terms of reaction times and button choice. The participants were seated in front of a table with a headrest mounted in the center, aligned symmetrically at the center of the screen. The distance from the headrest to the screen was 50 cm.

Stimuli
The stimuli were tiny white dots appearing against a black background at different eccentricities either on the left, on the right of the midline. On the opposite side was presented a distracter of a larger size, whose purpose was to interfere with the perception of the perithreshold stimuli. The central location on the screen was marked by a fixation cross in black color, which disappeared before the onset of the stimuli. In study 3 one of the arms of the cross was drawn in the form of an arrowhead, serving
as a cue for the side of the presentation of the stimulus. The size of the stimuli was varied between 1 and 4 pixels according to the titration procedure described below.

**Procedure**

The participant was seated comfortably in front of the screen with the head positioned on the head rest and the right index, middle, and ring fingers on top of the 3 corresponding buttons of the response box in the case of a 3-button response, or just the index finger positioned on the top button in the case of a 1-button response. The presentation sequence during one trial was a fixation cross for 1000ms, a variable blank interval of 500 to 750 ms, a stimulus of 40 ms, and a response interval of 1000 ms.

**Study 1**

Before the actual experiment a titration procedure was run in order to determine the size of the stimuli which would produce the best trade-off between detection and non-detection. This type of stimuli is used in the other experiments employing the TMS technique and allow to detect both improvement and deterioration in performance. The goal of adjusting the size is to make the stimuli difficult to perceive, near the perceptual threshold of each individual participant. For this purpose an experimental session consisting of 160 trials was run, according to the following scheme:

10 repeats x 4 stimulus conditions x 4 sizes = 160 trials,
where the stimulus conditions were unilateral stimuli at 55 degrees excentricity either on the left or on the right (2 conditions), a bilateral stimulus at 40 degrees excentricity (1 condition), and no stimulus (1 condition). The sizes usually ranged from 1 pixel to 4 pixels, since 1 pixel can hardly be detected, while 4 pixels is well above threshold for people with normal vision. The size of the stimulus which produced a detection rate closest to 50% was chosen for the actual experiment.

One run of the actual experiment consisted of 80 trials in total that can be broken down according to the following scheme:

6 runs x ((17 excentricities x 2 sides (Left and Right) for unilateral stimuli = 34 trials) + (7 excentricities x 3 anchor excentricities x 2 sides for bilateral stimuli = 42 trials) + 4 catch trials) = 6 x 80 trials = 480 trials per participant.

The order of presentation was randomized within each block. The catch trials contained no stimulus and required a non-response from the participant. The duration of one trial was about 3.5 seconds and the total duration of the test was approximately 35 minutes. After each run the participant took a short break of less than a minute, or a longer one if needed, and then the experimenter started the next run.
Chapter 9. Experiment VIII - Variable Excentricities

The excentricities of the stimuli were as follows:

<table>
<thead>
<tr>
<th>Excentricity °</th>
<th>5</th>
<th>12.5</th>
<th>15</th>
<th>17.5</th>
<th>20</th>
<th>22.5</th>
<th>25</th>
<th>27.5</th>
<th>30</th>
<th>32.5</th>
<th>35</th>
<th>37.5</th>
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<th>42.5</th>
<th>45</th>
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<th>55</th>
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</thead>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Bilateral</td>
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<td></td>
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<tr>
<td>Anchor at 20°</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Anchor at 30°</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anchor at 40°</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

**Table VIII-1.** Excentricities of the presented stimuli. X indicates that this excentricity was used in the given condition.

The table above has 17 columns showing the different excentricities at which stimuli were presented. For unilateral stimuli there was one presentation at each of the excentricities. For bilateral stimuli for each anchor, i.e., a stimulus presented at a fixed excentricity on one side of the fixation cross, the marked excentricities show where on the opposite side was presented the second stimulus. Thus, the second stimulus could be at offsets of 2.5°, 7.5°, and 15° both inwards and outwards from the excentricity of the anchor. Again, there was one presentation at each excentricity during one run of the experiment.

The response was given by pressing one of 3 buttons on the response box: the left button for a left unilateral stimulus, the top button for a bilateral stimulus, and the right button for a right unilateral stimulus. The buttons were pressed using the index,
middle, and ring fingers, which were kept positioned on the surface of the buttons throughout the experiment.

**Study 2**

Study 2 was the same as study 1 except for the eccentricities used. In the titration procedure the unilateral stimuli were positioned at 30 degrees eccentricity and the bilateral stimulus was at 20 degrees. The eccentricities of the stimuli in the actual experiment are shown in the table below:

<table>
<thead>
<tr>
<th>Excentricity °</th>
<th>7.5</th>
<th>10</th>
<th>15</th>
<th>17.5</th>
<th>20</th>
<th>25</th>
<th>27.5</th>
<th>30</th>
<th>32.5</th>
<th>35</th>
<th>40</th>
<th>42.5</th>
<th>45</th>
<th>50</th>
<th>52.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bilateral</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anchor at 20°</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anchor at 30°</td>
<td>X</td>
<td>+</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>+</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anchor at 40°</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Table VIII-2. Excentricities of the presented stimuli. X and + indicate that this eccentricity was used in the given condition. (+ indicates a repeated eccentricity)

There are 15 eccentricities in total. The second stimulus in the bilateral case was at offsets of 5°, 10°, and 12.5° both inwards and outwards from the eccentricity of the anchor. Note that the pairs of 20° & 30° and 30° & 40° appear in two cases of an anchor. However, they are presented only once (because this is sufficient) and this is
marked by an X in the cases of anchors at 20° and 40°. The same pairs in the 30° case are marked with +.

**Study 3**

Study 3 was performed only with bilateral stimuli and with anchors positioned only at 30°, but with time offsets between the two stimuli. Of the two stimuli, one was larger, with size clearly above the perceptual threshold, serving as a distracter, and the other one was smaller, with size near the perceptual threshold, serving as target. The two sizes were determined in two separate titration procedures run one after another before the actual experiment.

In the first titration procedure, Titration (a), was done to determine the size of the distracter. For that purpose stimuli of 4 different sizes were presented at excentricity of 30 degrees. There were unilateral stimuli on the left and on the right, bilateral stimuli, and a no stimulus condition. Each condition was repeated 5 times, making the total number of trials 80 (4 sizes x 4 stimulus conditions x 5 repeats). The smallest size that achieved 100% detection rate was the one that was picked to be the size of the distracter.

The second titration procedure, Titration (b), was done to determine the size of the target stimulus. It consisted of presentations of the target on the left or on the right at 30 degrees excentricity together with a distracter of the size determined in Titration (a) exactly opposite to it. There were two additional catch conditions only with a distracter on left or right, but no target. Thus, the total number of trials was again 80
Chapter 9. Experiment VIII - Variable Excentricities

(4 target sizes x (2 target present conditions + 2 target absent conditions) x 5 repeats).

The side of the target was indicated before the presentation by an arrowhead present on one of the arms of the fixation cross. The participant had to indicate the appearance of the target by pressing a single button on the response box. The smallest size which was detected in over 50% of the cases was picked as the size of the target.

The actual experiment resembled Titration (b), but the location of the target and the temporal difference between the onset of the target and the distracter were varied according to the following scheme:

<table>
<thead>
<tr>
<th>Excentricity °</th>
<th>20</th>
<th>22.5</th>
<th>25</th>
<th>27.5</th>
<th>30</th>
<th>32.5</th>
<th>35</th>
<th>37.5</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal offset</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0 ms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>+5 ms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+10 ms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+15 ms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+20 ms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table VIII-3. Target conditions in Study 3.

In summary, stimuli were displayed at 9 different excentricities around 30 degrees in the case of no time offset, and at 5 excentricities in the case of a temporal offset. The anchor was always at 30 degrees on one of the sides, and the contralateral stimulus was at offsets of 0°, 2.5°, 5°, 7.5°, or 10°, i.e., the distance changed in steps of 2.5°. The presentation of the target at offsets of 0°, 2.5°, and 5° could be delayed by 5, 10,
15, or 20 ms. The presentation at the other excentricities was not delayed. An example of the sequence of presentation in the course of one trial is shown below.

Figure VIII-1. Example of a trial in study 3. The stimulus is on the right side, as indicated by the cue, and it is presented at a smaller excentricity than the distracter. The stimulus appears 5 ms earlier than the distracter and it is of a smaller size.

The more peripheral stimuli were further away from the viewer and more difficult to perceive, however, in order to have comparable results the same size had to be used for all excentricities and the titration was done for the excentricity of 30° which was in the middle of the investigated range.

**9.3 Results**
Figure VIII-2. Reaction times for the bilateral stimuli in Study 1. On the X axis are plotted the excentricities of the stimuli on the side opposite to the anchor in degrees of offset from the anchor’s excentricity. (The anchors were presented at excentricities of 20°, 30°, and 40°).

Figure VIII-2 above shows the averages of the reaction times for stimuli at different offsets with respect to the excentricity of the anchors, and the reaction times for anchors at 20°, 30°, and 40° excentricity. The stimuli were bilateral, with the anchor on one side and another stimulus on the opposite side at a given offset from the excentricity of the anchor. There is no large difference between the reaction times of the curves for the 20 and 30 degrees excentricity of the anchor, but the curve for the 40 degrees excentricity seems to be notably above the other two curves, i.e., the reaction times are slower at higher excentricities as one might expect. Also, the shape of the curves is concave, with higher excentricities having larger reaction times. It would be interesting to observe what happens at the anchor excentricities, since this case represents exactly symmetrical bilateral stimuli. On the left side one can observe
that at 30 and 40 degrees excentricity the reaction times for exactly symmetrical bilateral stimuli were smaller than those for slightly asymmetrical stimuli, namely locations L-2.5 and L+2.5 which were at an offset of 2.5 degrees from the anchor excentricity. This effect, however, is absent in the 20 degrees curve and also in the curves on the right side.

Figure VIII-3. Reaction times for the bilateral stimuli in Study 2. On the X axis are plotted the excentricities of the stimuli on the side opposite to the anchor in degrees of offset from the anchor’s excentricity. (The anchors were presented at excentricities of 20°, 30°, and 40°).

The results in study 2 are similar to those in study 1, except for the fact that the difference between the cases of different anchors and the curves associated with them are more pronounced. As expected, stimuli at smaller excentricities produced faster reaction times, as can be inferred from the positions of the curves relative to each other; the 20° anchor curve is below the 30° one, which is below the 40° curve. The difference in average reaction times between corresponding locations in the different anchor curves is on the order of 50ms. With respect to the anchor excentricities we
can note that in almost all of the cases the values at these locations are between the values for the next smaller excentricity and the next larger excentricity. Thus, there is no special effect in terms of reaction times related to the exactly symmetrical stimuli.

Figure VIII-4. Reaction times for the bilateral stimuli without time offset to the anchor in Study 3. On the X axis are plotted the excentricities of the stimuli on the side opposite to the anchor which was positioned at 30° excentricity.

Figure 4 above shows the distribution of reaction times at different excentricities in study 3 in the case when there was not time delay between the distracter (anchor) and the stimulus. This case is comparable to the ones in study 1 and 2, with the difference that more excentricities were probed and the distracter was larger than the stimulus. We can observe that the presence of a distracter at 30 degrees eccentricity contralaterally to the stimulus seems to interfere with the perception of the stimulus in a systematic way, as indicated by the increase of the reaction times centered around the 30 degrees eccentricity. More specifically, the reaction times have their peak
value at or near the 30 degrees excentricity and, roughly speaking, the values decrease gradually with increasing distance from this excentricity.

Figure VIII-5. Reaction times for the bilateral stimuli with time offset to the anchor in Study 3. On the X axis are plotted the excentricities of the stimuli on the side opposite to the anchor which was positioned at 30° excentricity.

The reaction times for stimuli presented after a delay respective to the distracter (Figure VIII-5) do not seem to show any consistent trend. The magnitude of the delay does not seem to play a role, except maybe for the difference between the 5 ms delay and the 20 ms delay. The response to a stimulus delayed 5 ms with respect to the distracter is consistently faster than the response to the 20 ms delay for all excentricities on the right side and only for the inward excentricities on the left side. The outward excentricities on the left side seem to show a small advantage for the 20 ms delay.
9.4 Discussion

Presentation of bilateral stimuli at variable excentricities seems to have no effect on performance in general. Symmetrical bilateral stimuli, which are hypothesized to evoke activation in homologous locations in the two brain hemispheres, are no different from asymmetrical ones in terms of performance, except maybe for the case of a more salient distracter presented contralaterally to the stimulus. In this case the evidence suggests that the distracter inhibits the processing of the contralateral stimulus when it is positioned exactly symmetrically to the stimulus, resulting in increased reaction times. The interference effect decreases in magnitude with increasing distance from the location homologous to the location of the stimulus. This effect may be produced by different mechanisms involving either inhibitory or excitatory interaction between the neuronal activity in the two hemispheres.

The first hypothesis is that the activity evoked by the distracter in the hemisphere where it is represented has an inhibitory effect on the homologous activity in the contralateral hemisphere. This would explain directly the observed increase in reaction time, since the inhibitory signal would interfere with the excitatory signal produced by the stimulus and it would take longer for the excitatory stimulus to reach the perceptual threshold and to initiate the response. Such an arrangement, however, is not supported by the anatomical and physiological evidence about the organization of the signaling across the corpus callosum. The nature of the interhemispheric connections is deemed to be predominantly excitatory, rather than inhibitory (Innocenti and Bressoud 2003). Although it is possible that the excitatory fibers linking the two hemispheres terminate on inhibitory interneurons and thus produce
eventually an inhibitory signal, it is highly unlikely that this happens only for the
neural activity related to stimuli at 30 degrees excentricity. If it is not that specific, but
a general feature of the visual system, than it would apply to all excentricities, which
would mean that there is a very strong mutual inhibition between the hemispheres,
and this contradicts the current evidence.
Thus, we have to explore another hypothesis, namely that the excitatory signal
somehow produces the delay in the processing of visual information in the
contralateral hemisphere. This could occur if the signal does not create a mental
representation which exactly matches the one corresponding to the actual stimulus,
but something different. In this case, the contralateral excitation evoked by the signal
corresponding to the distracter would act as noise with respect to the signal
corresponding to the stimulus, which would lead to competition between the two
signals and the need to disambiguate them, and this in turn would require processing
time and lead to the observed delay. This scenario is plausible since it is known that
more salient stimuli reach conscious perception faster than less salient stimuli. This
means that the signal generated by the distracter and acting as noise with respect to
the signal from the stimulus will be present before the latter and will be able to
interact with it. Although this scenario is plausible, it needs to be investigated further
in order to rule out alternative explanations.
Chapter 10. Conclusion

Synopsis of Part III

Part III investigated the role the interhemispheric connections play in the anatomical and functional organization of the brain. Since spatial attention is functionally lateralized but phenomenologically symmetric (i.e., events in the left and the right visual hemifield are perceived equally well), the question remains at which levels does the activity in one hemisphere differ from the activity in the other hemisphere and at which levels they are equally balanced. The three experiments in Part III studied the interhemispheric interactions at three different levels of cognitive representation: complex abstract shapes, simple features (lines), and shapeless objects (dots). The highest-order cognitive representations of the abstract shapes were found to interfere with each other in the two hemispheres as suggested by the observed priming effect on contralaterally presented images. Less interference was observed by the simpler stimuli, suggesting that the activity in the two hemispheres is more balanced at the level of more basic, simpler cognitive representations, possibly encoded with more local and spatially limited neural firing patterns, while the more complex and broader patterns of neural activity which possibly mediate the higher-order cognitive representations differ more substantially and potentially result in functional asymmetry and lateralization at the global level of brain activity.
Chapter 10. Conclusion

10.1 Methodological issues

10.1.1 Stimulation: when, where, and how strong

There can be a number of reasons why the stimulation that we applied in some of the experiments failed to produce significant unilateral disbalancing effect. First, in the case of online stimulation, there is the question of whether the timing of the application of the pulses with respect to the stimulus onset is the right one. One could address the timing issue by applying multiple pulses regularly spaced over the entire time window when attentional processing may reasonably occur – this would be the range of 50ms to 500ms after stimulus onset. This approach, however, is limited by practical concerns regarding safety and coil overheating. There is a trade-off between the number of pulses in a sequence one can use and the intensity of the magnetic field that can be employed before facing the practical problems of safety and overheating. With a higher number of pulses spaced at about 50ms one can cover the entire time window of possible attentional processing and thus ensure that the disruptive effect of TMS will interfere with the neural correlate of attentional processing in the brain; however, in this case one has to employ a relatively low intensity of stimulation, which may not have enough power to interfere with the attentional component of the neural signal and thus fail to produce an observable effect. We can also choose to employ stronger intensity, at or above the motor threshold, effectively increasing the volume of space where the magnetic field has enough strength to scramble the
signaling between individual neurons, and thus we can increase the likelihood that the magnetic pulse will interfere with the large-scale phenomenon of directing one’s attention to one side of space, produced by the coherent signaling of large-scale attentional networks of neurons. In this case the number of pulses has to be limited to 1 or 2, effectively covering a range of not more than 100ms, according to the generally accepted guidelines for TMS safety (Wassermann, 1998). The maximum duration for a train of pulses at a rate of 20Hz (i.e., spaced 50ms apart) and with intensity of over 200% of the motor threshold should not exceed 100ms. In some cases when the motor threshold is higher it would be safe to use trains with duration of up to 500ms at the desired intensity, but in cases of low motor threshold (down to 35% or 40% of the stimulator output) the safety limit would be 100ms. Since we want to have a fixed number of pulses throughout the experiment we have to use the lowest common denominator, i.e. the 100ms limit. However, the use of a low number of pulses leads to the problem of determining the exact moment in time when the magnetic pulse has a maximum effect on the processing of attentional information. This can be done with a chronometry study where pulses are applied at different delays after the onset of the stimulus and performance in a behavioral task is compared across the different time delay conditions.

Another factor which may affect the efficiency of the stimulation is the location on the skull where the stimulation is applied. The figure of eight coils that we employ produce maximum effect in a region of about 2-3 cm in diameter underneath the center of the coil. This is insufficient to cover the entire region of the parietal lobe supposed to participate in attentional processing. It is expected that the effectiveness of stimulation over different locations of the parietal lobe will affect to a different
degree the ability to attend to lateral spatial locations which will be measurable in the performance in a behavioral task of the kind that we used in the online-offline experiment. Thus, by comparing the performance at different locations of stimulation, one should be able to find the ‘hot spot’ of attentional processing, which would be the location where the introduced bias in stimuli perception is maximal. This was done in the mapping study, which localized attentional processing in the right hemisphere to a location extending laterally from P4, but did not find a corresponding location in the left hemisphere. It should be noted that the anatomical lateralization of the spatial attention function does not always occur in the right hemisphere, but is only more frequent there. It is strongly correlated with handedness, with right-handed individuals having right parietal regions more involved in spatial attention, while left-handed individuals exhibit the opposite pattern of lateralization (Mevorach et al., 2005). In our studies we had almost exclusively right-handed participants, which resulted in the standard observation of lateralization to the right hemisphere.

The third and as it seems decisive factor for the efficiency of the stimulation is the stimulation intensity. The experiments with 40% or 60% intensity of the stimulator output produced some modulation of the responses going in the expected direction, but no statistically significant differences. Only the mapping experiment where the intensity varied from 65% to 80% of the stimulator output produced statistically significant modulation of the performance. Therefore, in order to produce a measurable behavioral change the stimulation has to be applied at the right location, at the right time after stimulus onset, and with sufficiently high intensity. There are drawbacks, however, to the use of higher intensities of stimulation. These are expressed in the enlarged cortical area affected by the stimulation and the possibility
of spreading the inhibitory effect to functionally connected areas. Although it may achieve the desired effect, it would be more difficult to pinpoint the precise area involved in the studied function in the case when more areas are affected by the stimulation, which would render the results less meaningful. Another problem are the side effects accompanying the magnetic pulses. These are the tapping sensations and the clicking noises, which grow stronger with increasing intensities and may even reach discomforting levels. In a spatial attention paradigm they may alert the participants to the location and side of space where they are sensed and in this way they may become a confounding factor affecting the final results. Despite all those potential problems, higher intensities within the safety guidelines might be the better choice, because of the inherent resilience of the visual system to interference and its plasticity. The challenge for future experiments is to find the optimum balance of parameters of the stimulation.

10.1.2 The choice of online vs. offline stimulation

We used both online and offline stimulation in our experiments with mixed results. The offline stimulation seems to have produced an effect in the attention topology experiment, while online stimulation was effective in the mapping study. They both failed to produce significant effects in the other studies probably because of insufficient intensity. Increasing the intensity, however, leads to additional complications. One has to worry about staying within the safety limits, interruptions due to coil overheating, causing discomfort to the participants, producing phosphenes and scotomas, and the effect of the loud noise. Some of these issues are avoided in the offline paradigm, however in this case there is the additional question of how long the effect of the stimulation lasts after the end of the stimulation and whether it
diminishes with time. The attention topology study suggested that the effect persists for quite a long time, longer than the duration of the stimulation, however there may be individual differences. Ultimately, the choice of the offline vs. the online paradigm is a complex one and depends on the aims of the study in question.

10.1.3 The effect of phosphenes and scotomas on performance

Phosphenes and scotomas may act like distracters and affect performance in the online paradigm even though stimulation is usually applied after the presentation of the stimulus. Phosphenes were reported by the participants in the mapping study in some cases, most often when the stimulation location was closer to the occipital lobe. Most of the time they said that the phosphenes had some distracting effect but did not affect correct detection, even when they were close to or overlapping with the location of the stimulus (which was a very rare case). The results from the experiment also did not show any abnormalities for the cases when phosphenes were reported by the participants. In any case, if there is an effect it would have affected only the reaction times by delaying the response for stimuli on the contralateral side for more occipital stimulation locations. The results do not show such a delay, which leads to the conclusion that even in cases when stimulation over parietal sites leads to occasional phosphenes this does not interfere with performance in general. However, this is not the case with stimulation of occipital cortex, as earlier studies show (Pascual-Leone et al., 1994).

Scotomas also do not seem to be a concern for the experimental and stimulation paradigms that we used. They have been reported in studies involving stimulation of occipital cortex (Kamitani et al., 1999) with relatively high stimulation intensities, but
even in this case they have been quite focal, which makes the likelihood of
overlapping with the stimulus location relatively small. As we observed in our study
of the effect of offline rTMS on the occipital cortex, the performance in the behavioral
task did not change significantly, indicating that no scotomas which obstructed the
perception of the stimuli were produced, although we saw a change in the perceptual
threshold for point-like visual stimuli as determined by the perimetry test.

10.1.4 The effect of sham

In several of the experiments we performed multiple sham stimulation sessions in
order to check for any bias that may be introduced by the side effects of applying
magnetic pulses to the skull, like noise and mechanical sensations. The performance
in different sham sessions within subject was not consistent, which means that other
factors affect performance like fatigue, light adaptation, carry-over effects from the
stimulation, or simply individual variations in concentration and attention. In the case
of online stimulation there have been some indications (from the online vs. offline
experiment and the mapping study) that sham stimulation on one side draws attention
to stimuli presented ipsilaterally to the stimulation. The detection of single stimuli on
the side of the stimulation in cases of bilateral presentation consistently goes up, and
the detection of single stimuli contralateral to the stimulation consistently goes down,
although by very small percentages. It represents a minor effect which does not
produce significant differences in performance.
10.1.5 Other factors: trunk orientation, setup geometry, near vs. far space, glasses, practice, instructions, fatigue

Other factors like trunk orientation, the geometry and the alignment of the experimental setup, individual differences between the left and the right eye vision, fatigue, etc. may affect the bias in the responses to left vs. right stimuli. Grubb and Reed (2002) report that rotating the trunk of the participants at 15 degrees to the left introduced neglect-like bias in their reaction times for stimuli presented on the left and on the right. Bjoertomt et al. (2002) found that TMS over parietal cortex was effective in producing neglect-like deficits for stimuli presented in near space (50cm away) but not in far space (150cm away). The alignment of the screen with respect to the eyes and the position of the projector behind the screen may make the stimuli on one side a little easier to detect which will appear as a bias in the performance. Also, some of the participants in our experiments had asymmetrical vision deficits which lead to different biases in the detection of the left vs. the right stimuli. For all these reasons the absolute levels of detection of left vs. right stimuli may not actually reflect a bias in the attentional function, and would more likely be due to other factors. However, if these factors are kept constant across sessions they would have equal impact on the absolute levels of detection in the baseline and in the experimental conditions and therefore will not obscure any real effects of the stimulation, which would be evident in the comparison between the baseline and the experimental conditions. Therefore the experimental conditions have to be kept the same during the entire period of experimental testing and the participants need to be positioned in the same way and given the same instructions in all experimental sessions. They need to be given enough practice before each session in order to get used to the experimental routine and to adjust to the lab environment.
10.1.6 Choosing the right stimuli

In order to assess the ability to attend to lateral spatial locations we need to present stimuli which are difficult to perceive, but still can be detected correctly by the participant in the majority of the cases. Usually we aim for detection rate of around 60% which allows both for registering deterioration and improvement in performance. Different detection rates can be obtained by varying the size of the stimuli; the smaller ones are more difficult to perceive than the larger ones. It is possible also to vary the contrast between the stimulus and the background, however this option has the drawback that it may engage different populations of light-perceiving cells in the retina (rods and cones) and as a consequence different perceptual mechanisms, which could make the results incomparable between subjects. The problem with varying the size is that we use very small size, on the order of 2-5 pixels, which makes the detection rate curve for the varying size very steep. In other words, the detection of stimuli with two adjacent sizes may go from very low (around 20%) to very high (around 80%) with no level in between. The steepness of the curve can be reduced by lowering the contrast between the background and the stimulus. Since it is good to keep the stimulus color exactly black (contrast level 0), this means that we need to lower the contrast of the background. This technique has the added benefit that it reduces the ‘hot spot’ effect caused by the projector, which is the bright spot appearing on the screen where the line of sight between the eyes and the lenses of the projector intersect the plane of the screen. With lower contrast of the background the overall brightness of the light emitted by the lenses is lower and thus their visibility through the semitransparent screen is reduced.
10.2 Hemispheric dominance

The two hemispheres of the brain have more or less mirror-symmetric structure with complementary functional specialization of the homotopic regions of the cortex. This means that if a region is specialized for certain function in one hemisphere, its counterpart in the other hemisphere would perform the same function. However, there are some notable exceptions, like language and spatial attention, which are found to be lateralized to one of the hemispheres, which is considered to be dominant for the respective function. Language is more often lateralized to the left hemisphere and spatial attention to the right one, but all combinations are possible and have been demonstrated by imaging experiments (Floel et al., 2005; Floel et al., 2005a). This leads to the question of what is the role of the non-dominant hemisphere in the information processing related to the lateralized function and whether the activity in the homotopic areas of the cortex in the non-dominant hemisphere can have an effect on the processing in the specialized areas in the dominant hemisphere. From the mirror images experiment we saw that viewing images on one side of space facilitates the processing of mirror symmetric images presented contralaterally, which suggests that activity in one hemisphere may prime the other hemisphere for correlated activity. This can be achieved by simple transfer of activation via homotopic interhemispheric connections. Also, from the attention topography and the mapping studies we saw that inhibiting activity in one hemisphere can lead to improvement processing of stimuli in the other hemisphere, suggesting again some correlation between the activity in corresponding regions on both sides of the brain. However, the fact that higher level cognitive representations, like abstract shapes and attention to one side of space, suggest also that the activity pattern in one hemisphere as a whole
interferes with the activity pattern in the other hemisphere. So, what can we say about the interactions between the hemispheres as a whole?

According to the mainstream theoretical model the nature of the interaction between the two hemispheres is competitive (see the section on cerebral balance theories of neglect in the introduction). Each hemisphere on its own is capable of processing only part of the sensory information, with the left hemisphere being more prone to detail, abstract reasoning, etc. and the right hemisphere being more holistic, emotional, non-linguistic, etc. (Hellige, 2001). When both hemispheres work together by exchanging information via the corpus callosum the final product is a combination of the specialized processings of each hemisphere. When one hemisphere is lesioned, or they cannot exchange information via the corpus callosum like in the split brain patients, the inherent biases in the processing of information from the dominant hemisphere become prominent.

Slow repetitive TMS can model these biases through its deactivation effect. When applied to one hemisphere it would disbalance the performance in a left-right symmetrical paradigm. However, in the attention topography experiment it did not produce unilateral effect, only a bilateral one. This suggests that bilateral stimulation is more than a simple sum of the two unilateral stimulations. The online-offline experiment confirms the fact that unilateral stimulation may not have enough power to produce a significant disbalance, although it seems to be able to tip the scales.

The mapping study on the other hand produced evidence for the lateralization of spatial attention. It found stronger effect of the stimulation of the right hemisphere
compared with the left hemisphere. This is in line with the phenomenology of neglect in patients affected from stroke, where damage to the right hemisphere is more likely to produce a deficit. We observed both a contralateral inhibition and ipsilateral disinhibition, which supports the hypothesis of the competitive nature of the interaction between the two hemispheres, in line with the cerebral balance hypothesis of the cause of the neglect phenomenon. This pattern of results, however, did not appear in all participants. There were some rare exceptions where the effect looked more undifferentiated or even reversed. This may be attributed to the fact that spatial attention is not always lateralized to the right hemisphere, as other studies have shown (Mevorach et al., 2005). In addition, Mevorach et al. (2006) have shown that the right and the left hemispheres have a differential role in the mechanism of guidance of attention to a salient stimulus. Using rTMS deactivation, they found that right PPC is involved in the guidance of attention toward salient stimuli, whereas left PPC mediates the ability to bias selection away from salient stimuli. In our experiments we used paradigms which required guidance towards salient stimuli and hence the modulatory effects were related to the right parietal cortex. These findings underscore once more the complexity of the interactions between the two hemispheres and the lateralization of different functions to one or the other hemisphere.

10.3 The nature of the interhemispheric connections

The results from the mirror images experiment, which supports the hypothesis of excitatory homotopic connections between the two hemispheres, and the phenomenon of contralateral disinhibition as a consequence of the inhibitory effect of the magnetic stimulation on one of the hemispheres allow us to draw some conclusions regarding
the nature of the interhemispheric connections in the brain not only at the more
abstract level of interhemispheric interactions and dominance, but also at the level of
anatomical structures. Anatomical studies have established that the callosal
interhemispheric connections are largely excitatory (Bloom and Hynd, 2005).
However, the presence of only excitatory connections cannot explain the disinhibition
phenomena like the facilitation of the responses for stimuli ipsilateral to the
stimulation site that we observed in the mapping study and also reported in earlier
studies (Hilgetag et al., 2001). There are various proposals on how to explain
disinhibition. One hypothesis is that the excitatory connections activate inhibitory
interneurons in the contralateral hemisphere which effectively turns the excitatory
signal into an inhibitory one. In addition, Reggia et al. (2001) suggest that subcortical
inhibitory connection can explain the competitive interactions between the two
hemispheres, even in the absence of inhibitory signals through the corpus callosum.
Studies of the cat brain, where lesions to the superior colliculus contralateral to a
cortical lesion lead to rebalancing of the attentional network, are compatible with this
subcortical inhibition model and provide further support for it (Hilgetag et al., 1999;
Payne and Rushmore, 2004). It is not clear yet, however, whether the cat model is
applicable to the human brain as well, since such studies cannot be carried out in
humans and the ‘virtual lesion’ technique of TMS does not reach to the deeper
subcortical structures. Still, it remains a plausible explanation.

Can we explain competition alternatively as a product of solely excitatory signals? It
would be possible if we make the assumption that the excitatory signals form patterns
of activation, which we may also call neural representations of information, and these
patterns of activation can reinforce each other if they have matching shapes, but also
can suppress each other in case they are incoherent. From patients with large unilateral brain lesions and split brain patients we know that the left and the right hemispheres process information differently on their own. For example, the left hemisphere on its own is biased towards rational thinking and small details in the perceived visual images, while the right hemisphere is biased towards emotional states and large features of the visual images. The normal processing of information is a result of the interference of the patterns of activation in the two hemispheres which in a sense suppresses the individual biases and leads to a combined and more complex neural state of activation. In the case of a TMS deactivation of a region in one of the hemispheres, the patterns of activation which would interfere with the processing in the corresponding region in the other hemisphere is scrambled and thus fails to modulate it. Although the level of activity in the stimulated region is not reduced, the signal that it produces is more random and thus has a smaller potential to modify the patterns of activity in the other regions to which it is connected; it can only make them more noisy. In this way the inherent biases in the distal regions will become more pronounced, which can be interpreted as disinhibition.

In terms of attention this mechanism could explain the deterioration of performance on the side contralateral to the stimulation and the enhancement of performance on the ipsilateral side, but it still does not explain the asymmetry between the left and the right side, namely, the fact that stimulation over right parietal cortex produces a stronger bias of attention. One could speculate that this phenomenon has something to do with the specialization of the right hemisphere for larger holistic features of the representation of the external environment. At the neural level this would mean that the neurons in the right parietal cortex have larger receptive fields than their
counterparts in the left parietal cortex, although to my knowledge there is no physiological evidence for this. Whatever the neural mechanism may be, the representation of larger features would consist of fewer, more coherent parts and in this way it would be more vulnerable to a focal lesion, like the one produced by a magnetic pulse. The vulnerability stems from the fact that a powerful pulse, even if it does not affect the whole population of neurons forming a coherent part of the representation of space, would still affect the entire representation and alter its content, while in the case of a representation consisting of large number of smaller parts it would affect a relatively smaller proportion of the constituent parts. The degree of connectedness of the parietal regions to other regions in the same hemisphere may not be the same on the left and on the right, especially if the receptive fields of the neurons are of different size, and this would also affect the vulnerability of the neural representations to focal lesions.

There are many open questions like the ones mentioned above, which would be better answered provided there is a richer anatomical knowledge regarding the transcallosal interhemispheric connections. However, there are some promising technological developments, like the combination of TMS and fMRI, including connectivity mapping with Diffusion Tensor Imaging (DTI), which have the potential to elucidate the layout of the connections, their type (inhibitory or excitatory), and their effectiveness. Some pioneering studies have already revealed the potential of this technique in normal and pathological brains (Bohning et al., 1998; Bestmann et al., 2003). It is the only way to study the connectivity of the human brain in vivo, and therefore it is of great importance for the future theories of interhemispheric interactions.
10.4 The nature of the neural representation in the parietal cortex

Parietal cortex belongs to the so called association cortex, which processes information at an intermediary stage between the low-level perceptual representations and the high-level abstract cognitive representations. Since the paradigm used in the mirror image experiment suggests that the interhemispheric excitatory connections facilitate high-level representations, it would be interesting to explore whether TMS to any region in the parietal or prefrontal cortex would eliminate the facilitation effect. Such a study would help clarify the nature of the representations in the parietal cortex.

It would be interesting to check also whether the most effective ‘hot spot’ of TMS interference coincides with the functionally most active region, as measured with fMRI. This would support the idea that there is a build up of excitatory signal which gets transferred to the homotopic location in the other hemisphere.

10.5 Applicability to neglect and extinction: potential for recovery

The TMS experiments showed both the potential of unilateral stimulation to disbalance attention, as well as the potential for rebalancing after subsequent contralateral stimulation. The rebalancing effect and subsequent restoration of function have been well documented in animal models. Complete restitution from neglect in cats has been achieved through permanent or reversible lesions of the contralesional superior colliculus or the intercollicular commissure (the so called
‘Sprague effect’) (Sprague, 1966) and also of the contralesional intact regions in the posterior parietal cortex (posterior middle suprasylvian region) (Lomber and Payne, 1996; Payne et al., 2003), which has been referred to as ‘Payne-Lomber effect’. This evidence suggests that TMS can be used for treatment of unilateral neglect following a lesion to the right parietal cortex. Indeed, such an ameliorating effect in humans has been already reported (Brighina et al., 2003). In addition, Vuilleumier et al. (1996) reported a case in which recovery from neglect induced by a right parietal stroke occurred following a second parietal stroke in the homotopic region in the left hemisphere. Another example that has been referred to as a human version of the original ‘Sprague effect’ reported the reversal of a unilateral deficit in the left visual field after a right frontal stroke by a growing tumor affecting the left superior colliculus (Weddell, 2004). We can conclude from all this that the TMS treatment may be able to speed up recovery in cases of reversible neglect or even treat chronic neglect. The mapping study established the most effective region for stimulation in the right parietal cortex and this information could be very useful for eventual future therapy applications.
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<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Bilateral</td>
<td>Pertaining to both sides (left and right).</td>
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<tr>
<td>Contralateral</td>
<td>Pertaining to the other side (left or right).</td>
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<tr>
<td>Cortex</td>
<td>The outer layer of the brain, also called ‘gray matter’, associated with conscious functions.</td>
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<tr>
<td>Dextral</td>
<td>A person with a dominant right hand. (see also Sinistral)</td>
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<tr>
<td>Excitation</td>
<td>Neural activity leading to facilitation of neural activity at another location. (see also Inhibition)</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>A defect in the optic pathways in the brain resulting in vision loss in half of the field.</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>Paralysis of one side of the body.</td>
</tr>
<tr>
<td>Hemisphere (brain)</td>
<td>One of the two anatomical halves of the brain.</td>
</tr>
<tr>
<td>Inhibition</td>
<td>Neural activity leading to suppression of neural activity at another location. (see also Excitation)</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>Pertaining to the same side (left or right).</td>
</tr>
<tr>
<td>Ipsilesional</td>
<td>Pertaining to the same side where the lesion is.</td>
</tr>
<tr>
<td>Lateral</td>
<td>Pertaining to the notion of side (left or right).</td>
</tr>
<tr>
<td>Lateralization (brain)</td>
<td>Functional or anatomical asymmetry between homologous brain areas on left and right.</td>
</tr>
<tr>
<td>Lesion</td>
<td>Injury leading to a deficiency.</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>The area of cortex on the back side of the head associated primarily with vision.</td>
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<tr>
<td>Paradoxical lesion</td>
<td>A lesion, contralateral to an existing lesion, reducing the magnitude of the existing unilateral spatial attention deficit.</td>
</tr>
<tr>
<td>Visual field deficit</td>
<td>Inability to perceive stimuli due to deficits that can be attributed solely to the visual system.</td>
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<tr>
<td>Parietal cortex</td>
<td>The area of cortex near the top of the head associated primarily but not exclusively with spatial knowledge.</td>
</tr>
<tr>
<td>Pseudoneglect</td>
<td>Refers to the bias in normal subjects to bisect lines to the left (i.e. in the opposite direction with respect to the dominant bias in spatial neglect).</td>
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<tr>
<td>Sinistral</td>
<td>A person with a dominant left hand. (see also Dextral)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>Pertaining to a number of anatomical structures below the cortex (limbic system, brain stem, cerebellum).</td>
</tr>
<tr>
<td>Transcranial</td>
<td>Going ‘through the skull’.</td>
</tr>
<tr>
<td>Volition</td>
<td>The faculty of voluntary action.</td>
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