

# ATTENTIONAL RESOURCES IN UNILATERAL SPATIAL NEGLECT



**Kjersti Mæhlum Walle**

*Sunnaas Rehabilitation Hospital*

*Department of Research*

*Department of Psychology*

*Faculty of Social Sciences*

*University of Oslo*

© **Kjersti Mæhlum Walle, 2018**

*Series of dissertations submitted to the  
Faculty of Social Sciences, University of Oslo  
No. XXX*

ISSN XXXX-XXXX

All rights reserved. No part of this publication may be reproduced or transmitted, in any form or by any means, without permission.

Cover:  
Print production: Reprosentralen, University of Oslo.

## ACKNOWLEDGEMENTS

*“In examining disease, we gain wisdom about anatomy and physiology and biology. In examining the person with disease, we gain wisdom about life.”*

*(Oliver W. Sacks)*

I would like to express my sincere gratitude to all the patients who have devoted so much of their time and energy to participate in this project. They allowed this study to be accomplished. Despite all the challenges they were faced with, they were willing to contribute in research so that it can assist others in the future. While spending their valuable time and effort, participating in this project, they taught me more than simply the clinical matters reported in this thesis, but also the important qualities in life: courage, persistence, patience, enthusiasm and kindness. Additionally, my sincere thanks to those who contributed as control participants as well as those who helped out in the pilot phase of our project.

I am deeply thankful to my supervisor, Prof. Bruno Laeng. You have been endlessly supportive throughout this project. Thanks to your initiative and perseverance to pursue new ideas we have arrived at the present findings. I am grateful for your valuable advice, our fruitful discussions, and your guidance throughout this journey. I would also like to express my gratitude to my co-supervisors, Dr. Jan Egil Nordvik and Dr. Frank Becker, who have also helped direct the aims and scopes of this project. I am grateful for all your insightful comments and observations as well as the challenging questions which have encouraged me to view our findings from different perspectives. Your optimism throughout this process has been very much appreciated.

Besides my supervisors I would like to extend my thanks to the rest of my project committee: Prof. Anne-Kristine Schanke, Dr. Thomas Espeseth, Dr. Markus Handal Sneve, Dr. Sveinung Tornås, Dr. Lars Tjelta Westlie, and Dr. Tor Endestad. I am grateful for your contributions in the planning of this project. Some of you have also co-authored in articles, and I appreciate all the meticulous comments and insightful suggestions you have made on earlier manuscripts.

I am grateful for all the inspiration and encouragement I have received from my colleagues at the Department of Research at Sunnaas Rehabilitation Hospital throughout this research project. A special thanks goes to Johan Stanghelle and Annette Juelsen who have been nothing but supportive, and to Solveig Lægreid Hauger for inspirational talks at the office. I am particularly grateful for the assistance given by Hillary Lynn Kyler: your help in testing patients, preparing data sets and co-authoring on one of the papers are so much appreciated. Thank you for all the fun days at the office. I would also like to express my appreciation to all Sunnaas colleagues down at the Aker Hospital Office for uplifting words and for welcoming me with an available desk at the office at any time.

Special thanks to my friends at the Department of Psychology at the University of Oslo for stimulating discussions, advice and support, and for all the fun we have had in the last few

years. In particular, I am grateful to Anine Riege, who has given me warm encouragement as well as constructive comments. Your brilliant idea of having a thesis bootcamp was priceless and clearly got me through some of the heavy lifting. I am also thankful for all the backing and enthusiasm I have received from Athanasia Monica Mowinkel, Unni Sulutvedt, Anee Karin Lee, Karine Porpino Viana, and Olga Chelnokova. Thank you also to Torgeir Moberget for lending me your office while you were at Berkeley.

I am appreciative to everyone who helped improve my work by providing useful advice and feedback. Thank you to Nikolai Olavi Czajkowski and Ragnhild Sørum Falk for your great statistical guidance, and Bjørn Tore Heyerdal who helped me with Excel formulas for preprocessing data. My cousin, Espen Rusten, who has been just as busy with his Ph.D. as I have been with mine, still showed up right away when I needed advice. Matthew Patten provided great advice and perspective during the last phase of the Ph.D. and also contributed by proofreading.

I would also like to thank Branka Spehar who allowed me an amazing research stay at UNSW Australia. You gave me and my family such a warm welcome and will always be appreciated.

A special thank you to the Norwegian ExtraFoundation for Health and Rehabilitation as well as Sunnaas Rehabilitation Hospital for funding my work. I am grateful to the Department of Psychology, University of Oslo, for granting me admission to the Ph.D. program.

I am privileged to have the most fantastic parents, Eva and Karl. You have always been there for me, and especially during these last few years you have helped in so many ways. I will be forever grateful for all the love and support that I receive from you. I would also like to thank my brother, Pål, and my sister, Heidi, for their continuous and unconditional support. I am so lucky to be your little sister. Heartfelt appreciations to my extended family who have contributed with so much love and care. Special thanks to all the friends that I have been blessed with. Thank you for still being there for me, although I have been buried in books and papers these last few years.

Last, but so definitely not the least, I owe my deepest gratitude to my wonderful husband Jan-Christian. With your encouragement, your invaluable pep-talks, your immense patience and all the healthy distractions you have provided me with during these years, you have made this adventure possible. While encouraging long hours at the office and rewarding me with the most tasteful gourmet dinners, you also made sure the PhD did not take over our lives. You believe in me like no-one else and you make me believe in myself. You, and our amazing, insightful and caring daughters, Alvilde Sofie and Emmeline Aurora, are what I value most in life. You have provided me with a sound perspective, taught me about the importance of a healthy work-life balance, and it is your endless love and support that have helped me complete this journey.

I love my family. This thesis is dedicated to them.

# TABLE OF CONTENTS

<b>ACKNOWLEDGEMENTS</b> .....	<b>III</b>
<b>LIST OF ARTICLES</b> .....	<b>VII</b>
<b>GENERAL SUMMARY</b> .....	<b>IX</b>
<b>INTRODUCTION</b> .....	<b>1</b>
VISUAL ATTENTION .....	2
CLINICAL ASPECTS OF NEGLECT .....	5
Spatial symptoms of neglect.....	7
Non-spatial deficits associated with neglect.....	9
THEORETICAL ACCOUNTS ON NEGLECT .....	11
The inter-hemispheric rivalry hypothesis .....	12
The attention-arousal hypothesis and hypokinesia.....	13
The impaired covert orienting of attention hypothesis .....	14
MEASURING THE PATHOLOGY OF ATTENTION .....	14
Eye-tracking .....	15
Pupillometry .....	18
Multiple object tracking (MOT).....	20
Binocular rivalry.....	22
<b>MAIN RESEARCH OBJECTIVES</b> .....	<b>24</b>
ARTICLE I:.....	24
Unilateral neglect post stroke: Saccade frequencies indicate directional hypokinesia while fixation distributions suggest compensational mechanism .....	24
ARTICLE II.....	25
Multiple object tracking and pupillometry reveal deficits in both selective and intensive attention in post stroke neglect.....	25
ARTICLE III.....	25
Binocular rivalry after right-hemisphere stroke: Effects of attention impairment on perceptual dominance patterns.....	25
<b>METHODOLOGICAL CONSIDERATIONS</b> .....	<b>26</b>
PARTICIPANTS.....	26
DESIGN.....	28
MATERIALS .....	28
Neuropsychological assessment .....	28
Recording eye movements and pupillary responses.....	31
Computerized experimental tasks.....	34
STATISTICAL ANALYSES.....	37

ETHICAL CONSIDERATIONS .....	38
<b>SUMMARY OF ARTICLES.....</b>	<b>41</b>
ARTICLE I.....	41
Unilateral neglect post stroke: Saccade frequencies indicate directional hypokinesia while fixation distributions suggest compensational mechanism .....	41
ARTICLE II.....	43
Multiple object tracking and pupillometry reveal deficits in both selective and intensive attention in post stroke neglect.....	43
ARTICLE III.....	45
Binocular rivalry after right-hemisphere stroke: Effects of attention impairment on perceptual dominance patterns.....	45
<b>DISCUSSION.....</b>	<b>47</b>
SPATIAL ORIENTING DYSFUNCTION AND FIXATIONAL COMPENSATION MECHANISMS .....	49
Fixational distribution reveals compensational mechanisms .....	49
Saccadic frequencies reveal a directional bias in orienting.....	51
RESOURCE ALLOCATION IN NEGLECT .....	52
Patient groups show reduced visual processing efficiency .....	53
Pupillary responses reveal markedly reduced attentional arousal regulation in neglect .....	55
Rivalry alternation rate suggests slowing of neural mechanisms.....	56
A LINK BETWEEN ATTENTIONAL RESOURCES AND SPATIAL ATTENTION.....	58
CLINICAL IMPLICATIONS .....	60
METHODOLOGICAL ISSUES AND LIMITATIONS.....	63
<b>CONCLUSION.....</b>	<b>66</b>
<b>REFERENCES .....</b>	<b>69</b>
<b>ARTICLES I-III.....</b>	<b>83</b>

# LIST OF ARTICLES

## ARTICLE I

Walle, K.M., Nordvik, J.E., Becker, F., Espeseth, T., Sneve, M.H., Laeng, B. (submitted). Unilateral neglect post stroke: Saccade frequencies indicate directional hypokinesia while fixation distributions suggest compensational mechanism.

## ARTICLE II

Walle, K.M., Nordvik, J.E., Espeseth, T., Becker, F., Laeng, B. (submitted). Multiple object tracking and pupillometry reveal deficits in both selective and intensive attention in post stroke neglect.

## ARTICLE III

Walle, K.M., Kyler, H.L., Nordvik, J.E., Becker, F., Laeng, B. (2017). Binocular rivalry after right-hemisphere stroke: Effects of attention impairment on perceptual dominance patterns. *Brain and Cognition*. ISSN 0278-2626. 117, 84-96. doi:10.1016/j.bandc.2017.06.007<sup>1</sup>

---

<sup>1</sup> Please note that an error was made in the scoring of the behavioral inattention test (BIT) in Article III. This error did not change the findings and conclusions drawn in the article and it has been corrected in a corrigendum published on the website of the journal. The corrigendum is placed after Article III in the present dissertation.



## GENERAL SUMMARY

Although the spatial deficit of unilateral neglect tends to receive much attention, it is evident that also non-spatial symptoms play central roles in this syndrome. The present dissertation is centered on the problem of resource allocation in neglect as well as considering the functioning of specific attention components in this syndrome. Three empirical studies were conducted and will be reported in three papers at the end of this thesis. Each study had a different approach in the investigation of attentional resource utilization in neglect patients. The thesis gives an outline of the main findings and discusses them in the context of each other.

Article I recorded eye movements while participants carried out a multiple object tracking (MOT) task. Eye fixation and saccade measures as well as accuracy scores were used to assess visual resource allocation and attention functioning in (i) right hemisphere stroke patients with a diagnosis of neglect, (ii) other right hemisphere stroke patients without neglect, and (iii) matched healthy controls.

Because increased frequencies of eye fixations have been associated with inefficiency in visual information processing in healthy participants (Goldberg & Kotval, 1999), we examined whether this measure would be a symptom of inefficient processing in the patient groups and for the neglect patients specifically. Fixation frequencies were accordingly considered as an index of efficiency and deployment of resources. Results revealed reduced efficiency in visual processing in both patient groups, with equally increased fixation frequencies. Several studies have also suggested that an increase in fixation rate may be used to enhance the performance in complex tasks (Kasarskis, Stehwien, Hickox, Aretz, and Wickens, 2001). Thus, Article I also sought to assess fixation rates in relation to task demands (in correct trials). Fixation rates increased across all groups when the target load was incremented from one to multiple targets. However, no further increase was detected when load went up from two to three targets. Intuitively, the increase in fixation rate may reflect the added component of divided attention in trials with multiple targets.

In addition to providing an index of the general utilization of visual resources, fixations were also assessed in relation to the spatial utilization of the visual field in Article I. The proportion of fixations in left and right fields were investigated in relation to the patients' scoring on neglect tests, to assess whether neglect severity would predict the spatial distribution of fixations and whether compensational mechanisms would be present in less

severe neglect. Results revealed that the spatial distribution of fixations was in fact predicted by the severity of neglect. Patients with severe neglect made more fixations in their right field, while patients with less severe neglect made more fixations in their left field. The leftward bias shown in patients with less severe neglect suggests the presence of possible compensational mechanisms for neglect, allocating additional attention resources into the left (problematic) field. Saccade rates were also investigated, taking into account whether they were directed leftwards or rightwards, in order to evaluate whether neglect patients would reveal a direction-specific bias and confirm a directional hypokinetic component in neglect (Heilman, Bowers, Coslett, Whelan, & Watson, 1985). Indeed, the frequencies of saccades in left and right directions revealed an expected direction-specific bias in neglect patients, in line with a directional hypokinesia account.

Article II presented the same groups of participants with the same MOT task and assessed their pupillary responses as well as their performance accuracy. It has recently been demonstrated that mental workload, as operationalized in the MOT task by the number of targets, is reflected in stepwise, proportional, increases in pupillary dilations (Alnaes et al., 2014; Wahn, Ferris, Hairston, & Koenig, 2016). Thus, by recording pupillary responses during task performance, we aimed to estimate possible limitations in patients' available attention resources. Both the patient groups revealed reduced pupillary dilations compared to the control participants, suggesting they had less available attention resources and could not elevate their attention arousal levels to the same degree as controls could. Notably, while pupillary dilations increased with enhanced load in the patients without neglect, no such increase could be detected in the neglect patients. The neglect patients' results could indicate that their mechanisms for regulating arousal in accordance with the varying task demands may have been deficient.

In addition to the MOT task, participants were presented with a static visual search (VS) task, where one target is embedded among a large number of distractors. This task was meant to represent an analogue of the classic bedside search tasks. The MOT task and the VS task were compared with regards to their ability to detect cognitive dysfunctions in different conditions of space (targets items being localized in the left or the right field). Performance accuracy scores in different conditions of mental workload were compared to assess divided attention abilities. Accuracy scores of the two tasks clearly showed that both the MOT and the VS tasks were able to detect spatial neglect symptoms through reduced performance in the left compared to the right field. In addition, the MOT task revealed reduced ipsilesional performance in neglect patients. This confirms that attention deficits in neglect are not limited

to the contralesional space (Weintraub & Mesulam, 1987). That neglect patients showed markedly reduced accuracy scores with higher load even in the right hemispace provides an indication that these patients have comprehensive problems with sustained and divided attention, and it fits well with the findings of bilaterally reduced arousal.

Differently from the previous two articles, which were based on a dynamic displacement of stimuli, Article III presented participants with a binocular rivalry task, where the stimuli dynamically replace one another, without any spatial change. Rates of perceptual alternations were taken to reflect the degree of available neural processing resources in that, reduced resources should result in slower conscious updating of the rival images. Article III assessed whether the degree of attention impairment (as indicated by BIT-scores) would influence the non-spatial mechanisms of rivalry dynamics.

Results revealed severely reduced rivalry alternation rates in neglect patients, suggesting a limitation in their available neural processing resources, whereas the patients without neglect were not as slowed in their perceptual alternations. Still, BIT-scores explained only a small part of the variance, suggesting that BIT-scores may not fully capture the attention pathologies that are involved in neglect.

In total, results suggest that not only spatial attention deficits are involved in the neglect syndrome, but that more general mechanisms of attention can be affected as well. Our findings show that both right hemisphere stroke patients with and without neglect may suffer from lowered arousal and reduced visual processing efficiency. Since only the neglect patient group failed to show signs of adjusting their arousal levels to meet with increasing task demands, this suggests that neglect may involve malfunctioning mechanisms for arousal regulation. Our group of neglect patients additionally showed more extreme slowing of rivalry alternations than the patients without neglect, providing another indication that their neural mechanisms were more negatively affected than those of the non-neglect patients. With the notion that attention is a limited resource that should be spent wisely (Kastner & Ungerleider, 2000), the ability to regulate the expenditure of attention resources in accordance with task demands should be of utmost importance. The amount of available resources and the ability to allocate them may also be imperative with regards to making use of compensational mechanisms for spatial deficits.



## INTRODUCTION

*Mrs. S., an intelligent woman in her sixties, has suffered a massive stroke, affecting the deeper and back portions of her right cerebral hemisphere. She has perfectly preserved intelligence—and humor. She sometimes complains to the nurses that they have not put dessert or coffee on her tray. When they say, ‘But, Mrs. S., it is right there, on the left’, she seems not to understand what they say, and does not look to the left. If her head is gently turned, so that the dessert comes into sight, in the preserved right half of her visual field, she says, ‘Oh, there is it—it wasn’t there before’.*

*(Sacks, 1985/2007, p. 81)*

Mrs. S. suffers from unilateral spatial neglect (USN), which is a neurological condition often associated with right hemisphere brain injury (e.g., Mesulam, 1981; Heilman & Valenstein, 1979; Stone, Halligan, & Greenwood, 1993; Parton, Malhotra, & Husain, 2004; Corbetta & Shulman, 2011). This syndrome reveals itself through reduced perception, exploration, and responsiveness to stimuli in the contralesional side of space (Heilman, Valenstein, & Watson, 2000; Behrmann, Watt, Black, & Barton, 1997; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). As described in the quote above, such patients will often have difficulties attending to objects positioned to their left, sometimes leading to complaints of not being given dessert or coffee. In some cases neglect patients may only shave or apply make-up to the ipsilesional half of their face, they may struggle with reading, getting dressed, and colliding into things located in their contralesional space. Even when explicitly told to direct their attention to the left, they are sometimes unable to do so.

Neglect deficits can take many forms, both in terms of the spatial frames of reference in which they occur (e.g., Laeng, Brennen, Johannessen, Holmen, & Elvestad, 2002) and in terms of the modalities that are affected. The present work focuses mainly on neglect in the visual domain, but the syndrome can extend into the auditory, the somatosensory, and the motor modalities (Clarke & Bindschaedler, 2014; Driver & Mattingley, 1998). The visuospatial symptoms of neglect cannot be accounted for by damage to the sensory or motoric systems alone (Heilman et al., 2000; Behrmann, Ghiselli-Crippa, & Dimatteo, 2001). Instead, several higher-level cognitive accounts have been proposed to explain the

mechanisms behind neglect. It has been suggested that key mechanisms of attention are compromised by damage to the right hemisphere and that this affects the patient's ability to distribute attention towards the contralesional field (Behrmann et al., 1997; Heilman et al., 2000; Posner & Petersen, 1990; Posner, Walker, Friedrich, & Rafal, 1984). However, neglect is a multifaceted syndrome and patients' symptoms as well as their anatomical injuries can vary widely (Karnath, Ferber, & Himmelbach, 2001). Even though there are shared denominators in what areas of the brain that, when injured, commonly result in neglect, there is not a particular region that is always affected (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta & Schulman 2011). Furthermore, brain injuries that lead to neglect often extend to areas of the brain that are not related to neglect and additional symptoms may thus make interpretations and generalizations difficult. Nevertheless, the study of people with lesions and attention impairments can shed light on the processes involved in visual attention.

The present work will focus on attention functioning and cognitive resource utilization in stroke patients with and without neglect, with reference to the three articles included in the thesis. The introduction presents the key concepts relevant in the discussion of the articles. First, some components of visual attention are presented and discussed in light of two influential attention models. Afterwards, clinical aspects of neglect are described, outlining variations of spatial as well as non-spatial symptoms associated with the syndrome. A relevant selection of theoretical accounts attempting to explain neglect then follows, before a description of the chosen tasks and techniques of the present study for investigating resource allocation as well as other aspects of attention in neglect. The next section of the dissertation presents the research objectives of the current work. Then a methodological section follows, presenting the reasons for choosing the present design, materials, and procedures. The summary of each paper reports the main results and conclusions. The discussion gives an outline of the findings and discusses them in terms of their theoretical, clinical, and methodological implications, also pointing out their limitations, before the conclusions of the present work finalize the thesis.

## **VISUAL ATTENTION**

In an ever-changing environment, a fundamental mechanism in visual attention is the ability to select and enhance the perception of relevant visual stimuli while ignoring irrelevant stimuli, an ability termed *selective visual attention* (Bundesen & Habekost, 2008; Kim &

Cave, 1999; Stevens & Bavelier, 2012). The selective attentional processing of information based on their spatial location is referred to as *spatial attention* (Vecera & Rizzo, 2003).

Several theoretical accounts have been put forward to explain attention and the mechanisms behind, though it is beyond the present dissertation to review them all. A particularly relevant theoretical contribution, though, derives from Kahneman (1973), as he integrated *intensive* as well as *selective* aspects of attention in his theory of *attention and effort*. While many early accounts place their emphasis solely on selective aspects of attention (Broadbent, 1958; Kim & Cave, 1999; Treisman, 1964), Kahneman (1973) highlighted that attention not only involves the selective aspect of what one attends to, but also the degree to which one applies oneself. According to Kahneman, attentional effort is an important theoretical construct related to mental work and task demands. When task complexity and demands are elevated, more processing resources are required in order to perform the task and accordingly there is an increased need of attentional effort investment. Furthermore, as task demands increase and effort investment rises towards the maximum processing capacity, the intensity level of the attention processing rises. The intensive aspect of attention is thus related to effort rather than to mere wakefulness, and is defined as the amount of processing resources invested relative to the maximum capacity of resource investment (Kahneman, 1973). It should be noted that while Kahneman assumes that attentional capacity is limited, these capacity limits are also thought to depend momentarily on the levels of arousal: as arousal rises, capacity increases. Arousal is further thought to be regulated on the basis of feedback from the activities being carried out, that is, enhanced task demands call for increased arousal levels. The concepts of attention intensity, amounts of resources, and attentional capacity are thus all connected terms in Kahneman's theory of attention and effort.

Kahneman did also refer to Berlyne (1960) who had originally suggested a link between attention intensity levels and physiological arousal as measured with electrophysiological methods. While Berlyne's focus was restricted to involuntary attention, the additional aspect of attentional effort was highlighted in Kahneman's account. He suggested that arousal is involved in exercising attentional effort and that attention processes should accordingly be reflected in several physiological indicators of arousal, like pupillary dilations and skin conductance (Kahneman, 1973).

Another account particularly relevant to the present work is the model of attention introduced by Posner and Petersen (1990). Three central ideas are emphasized in their model: First, different anatomical regions of the brain carry out specific cognitive operations and the attention system is an anatomically independent system that interacts with other processing

systems. Second, there exists neither a single center for attention processing in the brain, nor is attention a general function of the brain working as a whole, rather there is a system comprised of a number of interconnected neural networks that coordinate the mechanisms and processing of attention. Third, the attention system can be separated into subsystems of attention, with different anatomical networks representing the differential attention processes.

Their system model presents three distinct but interconnected neural networks that contribute to the cognitive concept of attention: 1) *the alerting network*, which includes mechanisms for alertness, vigilance, and arousal (this corresponds to the ‘intensive’ attention, in Kahneman’s terms); 2) *the orienting network*, which produces shifts of attention in space by disengaging the focus from the former location, moving the focus, and finally re-engaging attention at another location in space (this corresponds to ‘selective’ attention, in Kahneman’s terms); and 3) *the executive network*, which predominantly exercises cognitive control and maintains focal attention, by exerting influence over the orienting and alertness systems (this corresponds to both ‘selective’ and ‘intensive’ attention, in Kahneman’s terms, but more in terms of goals and decision making). This network is also involved in conflict resolution between disagreeing thoughts, feelings, and responses (Posner & Petersen 1990; Posner, 2008; Petersen & Posner, 2012).

According to Posner and Petersen (1990), the neural networks for mechanisms of alerting, orienting, and executive attention can be separated from one another not only in terms of their anatomy but also by their chemical modulators (Posner & Rothbart, 2007; Posner 2008). Norepinephrine regulates the alerting network, which consists of the locus coeruleus (LC), right frontal cortex, and areas of the parietal cortex. Acetylcholine (ACh) modulates the orienting network, which is composed of the superior parietal cortex, temporal parietal junction (TPJ), frontal eye fields (FEF), and the superior colliculus. Dopamine is the modulator of the executive attention network and this network consists of the anterior cingulate cortex (ACC) which has been suggested to play a role also in regulating LC activity (for a comprehensive review see Aston-Jones & Cohen, 2005), regions of the basal ganglia, and lateral ventral as well as prefrontal structures (Posner & Rothbart, 2007).

The present work attempts to isolate and measure the functioning of specific mechanisms of attention in patients with brain lesions as well as their attentional resource allocation and expenditure. Article I investigates selective and spatial aspects of attention as well as participants’ use of visual processing resources, as all this can be reflected in eye-tracking measures like spatial fixation distributions, overall fixation frequencies as well as direction-specific saccadic frequencies. Article II places the main focus on intensive aspects

of attention such as attentional load, attentional effort, and physiological arousal (indicated by task evoked pupillary responses), as it considers the participants' expenditure of attentional resources. Article III takes a different approach to assessing neural processing resources, as it investigates the efficiency of perceptual processing mechanisms in binocular rivalry and views this in relation to the participants' attention functioning. The thesis will discuss attentional aspects like intensive attention (arousal), spatial attention, and divided attention. We stress the analogy between the alertness component of the attention model of Posner and Peterson (1990) and Kahneman's (1973) intensive aspect of attention, which can be indexed with arousal measures like pupillometry. Spatial attention relies on orienting mechanisms that can be expressed through eye-tracking measures and task performance. *Divided attention* (the ability to split the attentional focus into multiple foci and attend to several elements simultaneously) can be reflected in task performance and is also thought to rely on the capacity of intensive attention as well as orienting of attention.

## **CLINICAL ASPECTS OF NEGLECT**

In 2010 it was estimated that about 15,000 people suffer a stroke in Norway each year and that these numbers will likely increase by 50% over the following 20 years due to an increasing elderly population (Indredavik, Salvesen, Næss, & Thorsvik, 2010). Stroke can be caused by ischemia (absence of blood to a region of the brain) or hemorrhage (ruptured blood vessels resulting in a bleeding within the brain). Severe cognitive and physical disabilities are unfortunately common consequences of stroke and one such type of cognitive mechanism is attention. While attention may be impaired in several possible ways, one attentional disorder often occurring after brain lesions is *unilateral spatial neglect*. The prevalence of neglect after stroke has varied in its reports, from numbers as high as 90% (Massironi, Antonucci, Pizzamiglio, Vitale, & Zoccolotti, 1988) down to a minimal 8% (Sunderland, Wade, & Langton-Hewer, 1987). Such statistics are likely influenced by patient selection criteria, operational definitions of neglect, and methods of assessment used (Bailey & Riddoch, 1999; Bowen, McKenna, & Tallis, 1999; Ferro, Mariano, & Madureira, 1999). A large study assessing 171 patients in the acute phase after stroke, reported that as many as 82% of right hemisphere stroke patients showed visual neglect in the acute phase, while also 65% of left hemisphere stroke patients had visual neglect during this phase (Stone et al., 1993). While neglect is commonly found in the acute phase of strokes, whether they occur in the left or the

right hemisphere, the hemisphere of injury has been found to be a good predictor of the severity and degree of neglect. Right hemisphere stroke more commonly results in severe and lasting neglect, which is the reason why neglect has been most investigated with right hemisphere injuries (Heilman & Valenstein, 1979; Stone et al., 1993; Corbetta & Shulman, 2011).

Neglect should be seen as a loss of perceptual awareness and not sensory loss, that is, visual neglect is not the same as blindness (Driver & Mattingley, 1998), which can co-occur as an independent problem called *homonymous anopia* (sensory loss of parts of the visual field). In fact, there is clear evidence that neglect is not attributable to some form of sensory deficit. For example, the neural underpinnings of neglect involve a widespread network of cortical areas, subcortical nuclei and white matter tracts, but essentially these do not include any primary sensory areas of the cortex (Serences & Kastner, 2014). Furthermore, lesion studies have shown that when macaques receive lesions causing neglect, this alters only late visually-evoked potentials, indicating that the more cognitive components of the neural network are affected (Watson, Miller, & Heilman, 1977). In addition, fMRI activation patterns in patients with extinction (a form of neglect) show that early visual areas of the right hemisphere can still be activated by neglected stimuli even though the patient is not aware of them (Rees et al., 2000). As Driver and Mattingley (1998) argue, the initial stages of visual processing can be fully intact in neglect (e.g., preserved image segmentation processes) and some degree of shape and color encoding may even occur with neglected stimuli. Unilateral visuospatial neglect should accordingly be sharply distinguished from the visual field deficit of hemianopia. However, multiple or large lesions can cause both deficits to co-occur in a same patient.

Another remarkable deficit of perceptual awareness—which is quite common in the neglect syndrome, especially in the early stages—is that the patients are unaware of their attentional impairment or underestimates how it affects perception and behavior. This type of unawareness is termed *anosognosia*, and like unilateral neglect, it is strongly associated with right hemisphere brain injuries (Jehkonen, Laihosalo, & Kettunen, 2006; Vocat, Staub, Stroppini, & Vuilleumier, 2010). The presence and degree of anosognosia is also positively correlated to the severity of neglect (Orfei et al., 2007; Clarke & Bindschaedler, 2014). As a patient's awareness of the deficit increases (becoming less anosognosic), the recovery from neglect is more likely to progress (Azouvi, Olivier, de Montety, Samuel, Louis-Dreyfus, & Tesio, 2003; Clarke & Bindschaedler, 2014).

Over time, neglect patients often show spontaneous recovery (Corbetta et al., 2005); however, a study by Nijboer, Kollen, and Kwakkel (2013) reported that 40% of neglect patients still showed signs of neglect a year after the stroke. Even with spontaneous recovery patients may show a deficit termed *extinction*, where symptoms of neglect only present themselves when there is strong competition among stimuli. The patients are typically able to attend to isolated stimuli in the contralesional visual field but fail to do so when competing distractor stimuli are present in the ipsilesional visual field (Posner et al., 1984; Weintraub & Mesulam, 1987; Robertson, 2001; Husain, 2008; Geeraerts, Lafosse, Vandenbussche, & Verfaillie, 2005). Commonly, by increasing the number of distractors in the ipsilesional space, visual attention towards the contralateral space will tend to be more impaired (Kaplan, et al., 1991).

### **Spatial symptoms of neglect**

Neglect involves peculiar *spatial* symptoms that have been subject to research in numerous studies. These spatial symptoms can be expressed within different frames of reference and in different spatial domains. Sometimes symptoms are well pronounced, other times they may only emerge in certain challenging situations (like in cases of extinction). Neglect may even occur in the representational space of memories and mental imagery (Bisiach & Luzzatti, 1978).

#### *Frames of reference in neglect*

The frame of reference in which neglect occurs could be of relevance when interpreting data from neglect research. A common classification distinguishes between *egocentric* and *allocentric* reference frames of neglect (Chatterjee, 1994; Behrmann, Ghiselli-Crippa, Sweeney, Di Matteo, & Kass, 2002; Tipper & Behrmann, 1996). Egocentric neglect refers to the neglect of spatial locations dependent on the viewer's orientation and midline (viewer-centered). Further, an egocentric frame of reference can be determined in relation to retinotopic, head-centered, or body-centered coordinates (i.e., with reference to the patient's eyes, head, or body; Behrmann et al., 2002). In order to assess whether the neglect can be referred to in terms of eye-, head-, or body-centered coordinates, one may systematically

change the position of these possible references, one at the time, and consider what regions are neglected in the different situations.

Neglect may also occur independent of viewpoint, thus with an allocentric reference frame, meaning that specific objects in space (object-centered or object-based neglect) or fixed environmental boundaries (environment-centered neglect) define the reference frame for what is likely to be neglected (Chatterjee, 1994; Umiltá, 2001). As such, the edges of a box or a screen, or the walls of a room may define what is left and what is right, and accordingly what will be neglected by the patient. Tilting an object may also lead to different parts of the object being neglected in different patients (Umiltá, 2001), as even the orientation of an object may in some cases define what is perceived as the left and right side of the object (object-centered neglect), and in other cases not (object-based neglect).

Interestingly, neglect can occur at the same time in several reference frames (e.g., egocentric and allocentric coordinate systems; Behrmann & Moscovitch, 1994; Laeng et al., 2002). Behrmann and Moscovitch (1994) proposed that stimulus properties influence what reference frames apply in neglect. This could at least in part explain the differential neglect symptoms found in different patients. Moreover, a dynamic view on the acting frames of reference for stimulus representations has been proposed (Karnath & Niemeier, 2002) where the brain organizes and reorganizes representations continuously in line with changing strategies and task requirements. Thus attention may operate on different frames of reference, depending on what area of space is considered relevant for the particular task. As the frames of reference for neglect can be dynamic and depend on stimulus properties or task demands, the present work made no attempts to assess the specific reference frames at work in the individual patient's neglect.

### *Spatial dimensions and spatial domains of neglect*

As spatial dimensions in the three-dimensional physical world are defined according to three orthogonal axes (horizontal, vertical and radial), it has been suggested that neglect may also arise along any of these dimensions. Although neglect is often associated with an attention bias in the horizontal dimension, it has also been reported comparable biases in the vertical and the radial dimensions (Chatterjee & Coslett, 2003; Shelton, Bowers, & Heilman, 1990; Adair, Williamson, Jacobs, Na, & Heilman, 1995). Vertical neglect would involve neglect of either the upper or lower vertical space, while radial neglect is related to distance. With regards to distance, neglect sometimes only occurs in specific spatial domains: some patients

may for example exhibit symptoms of neglect only in their personal (body space), peripersonal (close to the body, space within reach) or extrapersonal (the space that is far beyond reach) space (Cherney, 2002).

Vertical and radial neglect are mostly associated with bilateral lesions (Chatterjee & Coslett, 2003) as damage to the temporoparietal regions may lead to neglect of the lower and near personal space, while damage to ventral temporal structures is associated with neglect of the upper and far extrapersonal space (Chatterjee & Coslett, 2003; Shelton et al., 1990; Adair et al., 1995). The current work involves patients with unilateral lesions and thus no vertical or radial neglect is expected. Accordingly, the focus is placed on horizontal neglect and attention functioning after stroke to the right hemisphere.

Remarkably, neglect not only involves the pathological exploration and responsiveness to stimuli in actual physical space but, as a well-known experiment by Bisiach and Luzzatti (1978) reported, it can also occur for invisible scenes, that is, in the purely representational space of memories. Bisiach and Luzzatti included patients from Milan, all with left sided visual neglect, who were asked to imagine that they were standing by the cathedral at the Piazza del Duomo in Milan and to describe what they could see from there. The patients well described the places and scenes on the right from their imaginary standpoint, but failed to report what should have been seen on their left. When asked to change their point of view by 180 degrees and instead look towards the cathedral, the same patients reported places and scenes that they had previously failed to mention, as these were now placed in their right representational space.

### **Non-spatial deficits associated with neglect**

Since the spatial pathologies of neglect are so specific and prominent and can have dramatic consequences in daily living, yet still they vary greatly between individuals, these characteristics have received much attention in neglect research. However, neglect has also been associated with non-spatial (intensive) deficits, like lowered alertness, vigilance and arousal (Hjaltason, Tegner, Tham, Levander, & Ericson, 1996; Robertson et al., 1997; Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998; Yokoyama, Jennings, Ackles, Hood, & Boller, 1987; Heilman, Schwartz, & Watson, 1978). In addition, neglect has been linked with a protracted attentional blink (Husain, Shapiro, Martin, & Kennard, 1997), reduced temporal resolution of attention to apparent (illusory) motion (Battelli et al., 2001),

and reduced visual short term memory capacity (Duncan et al., 1999). Husain and Rorden (2003) point out that non-spatial pathologies and non-lateralized components may also play significant roles in this syndrome as they may interact to exacerbate neglect. Such non-lateralized components may not be specific to neglect—as they may occur independently of neglect as well—and accordingly findings from other branches of cognitive neuroscience research may contribute to shed light on the mechanisms at work in neglect. Moreover, Husain and Rorden argue that some neural regions that are typically (although not necessarily) injured in neglect patients could carry out spatially lateralized as well as non-lateralized functions. They emphasize that mechanisms that are not spatially lateralized, but are reduced in combination with disrupted lateralized attention mechanisms, should be investigated further, as they may have a say in the likelihood of recovery from neglect and accordingly could also be crucial targets for treatment.

#### *Alertness, vigilance and arousal*

The ability to increase or uphold response readiness relies on *alertness* and *vigilance* or, in other words, the *intensive* aspect of attention. An alert state involves arousal, which enhances and facilitates stimulus processing and response output so that performance may be improved (Samuelsson et al., 1998; Corbetta & Shulman, 2011). Moreover, arousal is reflected in several measurable physiological processes, like pupillary dilations and skin conductance (Kahneman, 1973). Vigilance implies the ability to maintain an alert state over time (Corbetta & Shulman, 2011) and is also referred to as *sustained attention*. A distinction can be made between two forms of alertness: the intrinsically initiated (tonic) version which is associated with top-down control of attention, and the externally initiated (phasic) alertness which is related to bottom-up influence from our external environment (Aston-Jones & Cohen, 2005). Both intrinsic top-down preparation for a task and external bottom-up signals (leading to phasic alertness) may affect the speed and efficiency in resolving the task (Sturm et al., 1999; Sturm & Willmes, 2001).

Unilateral spatial neglect has been associated with non-spatial attention impairments (Hjaltason et al., 1996; Husain et al., 1997; Robertson et al., 1997). Robertson and Frasca (1992) emphasized the right hemisphere's special role in alertness and vigilance functioning. For example, right hemisphere stroke patients have not been found to exhibit the typical heart rate changes (a measure of arousal) during an attention demanding task (Yokoyama et al., 1987) and also not to produce the typically reduced galvanic skin response (GSR) to electrical

stimulation (Heilman et al., 1978) as seen in left hemisphere patients. Thus, Robertson and Frasca (1992) pointed out that a right hemisphere injury may lead to a non-spatial vigilance and alertness impairment (due to a right hemisphere vigilance circuit being disrupted) as well as a spatial attention impairment (caused by disruption of the attentional orientation mechanism). Based on Posner and Peterson's (1990) theoretical account, they further suggested that the presence of such non-spatial attention impairments combined with the spatial attention impairments may explain why neglect is commonly more persistent in right than left hemisphere injuries.

Alertness has been proposed as a foundational prerequisite for other types of attention (Raz & Buhle, 2006). Indeed, a study by Hjaltason and colleagues (1996) showed that the severity and presence of neglect can be predicted by sustained attention performance and this relation could not be explained by lesion extent, as patients with impaired sustained attention did not have larger lesions. Several subsequent studies have confirmed such a link between spatial inattention in neglect and measures of intensive attention (sustained attention and alertness; Robertson et al., 1997; Samuelsson et al., 1998).

## **THEORETICAL ACCOUNTS ON NEGLECT**

The clinical picture of neglect shows wide variation between individuals, which may perhaps be expected as the locations and extensiveness of brain injuries that may result in this disorder may also vary largely. Such variations complicate the matter of explaining the mechanisms behind neglect. Over the years several types of dysfunctions have been suggested to explain the syndrome, for example: impaired attention towards the contralateral hemisphere (Heilman & Valenstein, 1979); hyperattention (magnetism) towards the ipsilesional field due to asymmetrically opposed vectors of attention being released (Kinsbourne, 2006); reduced (intentional) motoric behavior (Heilman et al., 1985); impairments of one or more components in a four-component, integrated network for modulation of directing attention (Mesulam, 1981); a deficit in the attentional disengagement procedure from ipsilesional stimuli (Posner et al., 1984), or in the orienting of attention in the contralesional direction (Posner, Walker, Friedrich, & Rafal, 1987); damage to the mechanisms that perform the mappings of stimulus saliency and spatial locations (Anderson, 1996); and finally, it has also been advanced, based on the idea that each hemisphere represents the contralateral space predominantly though not exclusively, that partial damage or dysfunction of neural

populations in one hemisphere creates a pathological gradient in the number of cells representing contralateral spatial locations (Pouget & Driver, 2000).

Some theoretical accounts are based on the premise that neglect is a consequence from asymmetries in the internal mental representations of space (e.g. Bisiach & Luzzatti, 1978; Pouget & Driver, 2000). Most commonly, the syndrome, including the asymmetric imagery impairments, is thought to result from attention impairments (Heilman & Valenstein, 1979; Kinsbourne, 2006; Mesulam, 1981; Posner et al., 1984; Robertson, 2001). Other non-attentional impairments, like motoric impairments i.e. reduced initiation of movements towards the contralesional side (Heilman et al., 1985), and working memory impairments (Husain, Mannan, Hodgson, Wojciulik, Driver, & Kennard, 2001) may cause neglect per se or exacerbate the attentional deficit. The present work is mainly focused on perceptual neglect and attention functioning and three relevant theoretical accounts relating neglect to attention deficits are presented in the following text.

### **The inter-hemispheric rivalry hypothesis**

During the 1970s Marcel Kinsbourne proposed an *inter-hemispheric rivalry hypothesis*, which is one of the earlier attentional accounts on neglect (Kinsbourne, 1970, 1977). This account proposes that neglect is due to disrupted inter-hemispheric rivalry due to the right hemisphere injury. Kinsbourne (1970) assumes that the left hemisphere tends to orient attention towards the right while the right hemisphere tends to orient attention towards the left, and that attentional orienting is determined through inhibition of one hemisphere by activation of the other hemisphere. The account further suggests that there is normally an innate bias, where the left hemisphere more strongly forces attention towards the right, compared to how much the right hemisphere exerts leftwards attention (Kinsbourne, 1987). Due to this bias, an injury to the right hemisphere affects the inter-hemispheric rivalry differently than a left hemisphere injury. Specifically, right hemisphere injuries may leave the left hemisphere hyper-activated leading to a strong rightwards orienting bias. Left hemisphere injuries, on the other hand, do not as easily produce a leftwards orienting bias because the orienting response of the right hemisphere is initially weaker and more is required for it to oppress the left hemisphere influence (Kinsbourne, 2006). Kinsbourne's theory predicts a gradient in degree of attention functioning from the left to the right, and thus it can explain findings of a relative rightward attention vector in neglect that is present even within the right field (Kinsbourne, 1987, 2006).

Studies have for example shown reduced attention dynamics (indexed by reaction time) towards stimuli presented to the left of other stimuli, even though both stimuli were well within the right visual field (Ladavas, 1987).

### **The attention-arousal hypothesis and hypokinesia**

Heilman and Valenstein (1979) put forward an *attention-arousal hypothesis*, suggesting neglect results from an arousal deficit. According to this account, damage to the cortico-limbic-reticular loop leads to impairment in arousal that prevents necessary preparation of actions in the right hemisphere, thus inhibiting attention functioning in this hemisphere. The result is *hemispacial hypokinesia* (Heilman & Valenstein, 1979) or, as also proposed in one of their later studies, *directional hypokinesia* (Heilman et al., 1985; Heilman et al., 2000). Hypokinesia refers to a reduced or slowed motor control; i.e., a deficit in planning and initiating movements (Heilman et al., 1985; Behrmann et al., 2001), and accordingly hemispacial or directional hypokinesia affect the ability to attend to the contralateral side of space.

Heilman and Valenstein (1979) proposed that while both hemispheres are able to mediate their own arousal response, the right hemisphere additionally mediates the arousal of the left hemisphere better than the left hemisphere mediates the right hemisphere arousal. Furthermore, they suggest that this asymmetry is what explains the more severe cases of neglect being linked with right hemisphere injuries rather than left hemisphere injuries. As the right hemisphere is more capable of producing a left hemisphere arousal response when the left hemisphere is injured neglect occurs to a lesser extent with left hemisphere injuries. In contrast, a right hemisphere injury would produce a bilateral arousal defect, as the right hemisphere normally mediates more bilateral arousal than the left hemisphere. Accordingly, arousal is reduced asymmetrically between hemispheres, with the right hemisphere being more hypo-activated, and preparations for actions in this hemisphere are inhibited. Studies confirming bilateral arousal defects in patients with right hemisphere injuries would support this theoretical proposal (Heilman & Valenstein, 1979).

Finally, the attention-arousal theory offers an explanation for how damage to different areas of the brain may lead to similar symptoms of spatial neglect, as it suggests that damage to pathways of the cortico-limbic reticular formation loop may suffice to disrupt the mediation of arousal and thus alter attention functioning (Heilman & Valenstein, 1979).

### **The impaired covert orienting of attention hypothesis**

Posner and colleagues (1980, 1984, 1987) put forward an account that explains neglect by *impaired covert orienting of attention*. Based on the idea of three neural networks of attention, where one of these represents orienting of attention, Posner et al. (1984) proposed that any shift of visual attention involves three processes. First, attention is disengaged from the current locus of attention, then attention is moved to a new location, and lastly attention needs to be engaged at the new location. Posner et al. (1984) asked patients with parietal lesions to covertly orient their attention towards a target that was positioned on either the left or right side of space, after being presented with a central cue or a brightening of a peripheral box. They found that reaction times were shortened by valid cues for both left and right sided targets, which implied that these cues helped orient attention in both directions. However, when invalid cues were presented, the reaction times were differently affected for right and left targets. Invalid (left) cues for right sided targets would only slightly prolong reaction times, while invalid (right) cues for left sided targets, would increase reaction times much more. These findings were viewed as signs of visual extinction, and to explain this extinction effect the authors referred to the three processes proposed to be involved in the orienting of visual attention. The patients' ability to orient attention covertly both to the left and to the right after valid cues, suggest their ability to engage attention at the stimulus is intact. The extinction effect produced by invalid cues for contralesional stimuli, however, indicates that patients may have problems disengaging attention from an ipsilesional stimulus, which is needed in order to produce a movement of attention towards the contralesional field. Parietal brain injuries were thus linked with a disruption of orienting mechanisms, as they were suggested to produce a deficit in the ability to disengage attention from an ipsilesional stimulus when attention was already oriented to the ipsilesional stimulus.

### **MEASURING THE PATHOLOGY OF ATTENTION**

The current work investigates attention mechanisms in patients with brain lesions, and specifically in patients with neglect. A number of different tests, commonly paper-and-pencil tests, have been developed since the syndrome entered the neurological nosology (Hartman-Maeir & Katz, 1995). However, paper-and-pencil tests differ widely in their sensitivity

(Lindell et al., 2007), and since neglect is most likely a multifactorial, clinical syndrome (Lindell et al., 2007), different tests may detect or fail to detect neglect in different patients. A battery of neglect tests termed the Behavioral Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987) includes a variety of different assessments to detect neglect. Unlike many neglect tests, this battery has been standardized (Hartman-Maeir & Katz, 1995) and it is, by some, considered a gold standard for neglect assessment (Halligan, Marshall, & Wade, 1989). In the present work, the conventional subtests of this BIT battery were used to evaluate symptoms of spatial attention impairments. We further contributed with new assessments of attentional resource utilization based on eye-tracking and pupillometry measures during a dynamic multiple object tracking (MOT) task. Spatial attention was also investigated through eye tracking measures, and spatial as well as non-spatial mechanisms were also assessed through performance on the MOT task. Because MOT has not been researched as extensively as other tasks in relation to spatial attention functioning in neglect, another more traditional measure was included: a visual search task, where participants were required to locate a target letter amongst distractors. Finally, binocular rivalry was added as a paradigm for testing non-spatial aspects of neglect, by considering perceptual processing dynamics in relation to attention impairment.

## **Eye-tracking**

When we make a visual fixation, the eye's fovea lingers on a single location or over a specific object in space (Rayner, 1998). Between fixations the eyes move so as to align the fovea with another particular part of the scene for the next fixational input, and this rapid, ballistic eye movement is called a saccade (Hall, 2004; Rayner, 1998). Because the very high saccadic speed makes it difficult to acquire sharp visual images, visual input is suppressed during saccades and most visual information gets encoded during fixations (Vallines & Greenlee, 2006; Hall, 2004). This makes fixation distribution an appropriate measure in research on visuospatial attention.

The role of attention is to facilitate and enhance perceptual processing (Bashinski & Bacharach, 1980; Hawkins et al., 1990). Since visual input is typically being encoded during visual fixations (Hall, 2004; Rayner, 1998), a common assumption in eye-tracking research is that an individual's attentional processing is directed through the locus of the fixation, a notion often referred to as the eye-mind hypothesis (Just & Carpenter, 1980). By recording

fixation data, we may accordingly learn what visual information is encoded and what participants are attending to (Just & Carpenter, 1976). A problem with this notion though, is that the orienting of attention in space also can be obtained covertly, without any movement of the gaze (Posner, 1980). However, limitations in covert orienting of attention have been demonstrated. For example, in a study by Hoffman & Subramaniam (1995) it was shown that healthy participants were unable to orient attention towards one location and simultaneously initiate a saccade towards another location. The authors suggested that attention may actually guide saccades, by preparing the saccade before it is carried out, or possibly even by initiating the saccade. Moreover they argue that shifts of attention may happen much faster than changes in eye position (Hoffman, 1975; Hoffman & Subramaniam, 1995), and that it thus makes sense that spatial attention could, during one fixation, decide the location for the subsequent fixation. Indeed, based on neuroimaging research showing activation of overlapping neural networks during tasks of overt and covert attention, it has been suggested that oculomotor and visuospatial attention mechanisms may be tightly integrated (Corbetta et al., 1998). A theoretical account that specifically challenges the notion of attention systems being independent control mechanisms separated from those of sensorimotor integration is *the premotor theory of attention* proposed by Rizzolatti, Riggio, Dascola, and Umiltà (1987). According to this account spatial attention is generated from activation of the same neural circuits that are used to plan and execute motoric actions towards specific locations in space. It is the degree of activation in these circuits that differentiate spatial attention from movement execution (Rizzolatti, Riggio, & Sheliga, 1994; Craighero & Rizzolatti, 2005).

The non-invasive, infrared eye-tracking method offers continuous detailed registration of a participant's eye movements. Since visuospatial attention is suggested to be an important component in generating voluntary saccadic eye movements (Hoffman & Subramaniam, 1995) and gaze fixations provide information about what stimuli is the likely focus of attention (Just & Carpenter, 1976), it follows that research on eye movements may offer an effective method to study attention and attentional deficits.

To date, there have been several studies assessing overt orienting abilities in neglect patients. One study demonstrated that neglect patients would fail to make saccades towards targets in the contralesional visual field in as many as 25% of trials, and suggested this reflected a strong inhibition of the arousal response (Girrotti, Casazza, Musicco, & Avanzini, 1983). When neglect patients did manage to make saccades towards left hemispace targets, these saccades had slower latencies than saccades directed rightwards, which was taken to reflect hypoarousal. Slowed leftward saccadic latencies have been confirmed in later studies

as well (Karnath, Schenkel, & Fisher, 1991; Behrmann et al., 2001). One of these further showed that neglect patients' saccadic latencies were slower for leftwards directed saccades within the left field specifically, but not within the right field (Behrmann et al., 2001). The authors proposed that neglect involves a spatially dependent and direction-specific hypokinesia component (Behrmann et al., 2001). Saccades in the left hemispace have also been found to be reduced in amplitudes while increased in frequencies, compared to saccades in the right hemispace (Girotti et al., 1983), specifically so in a stimulus-driven task while not in an exploratory task (Niemeier & Karnath, 2003). While the exploratory task did not reveal direction-dependent saccadic properties, the right field was clearly more explored than the left field in this task, suggesting rather a field-specific, exploratory deficit (Niemeier & Karnath, 2003). Notably, when prompted, patients have shown abilities to direct their gaze, head, and eye-in-head towards the left just as well as control participants (Karnath, Niemeier, & Dichgans, 1998). Taken together, the evidence suggests that neglect may involve space- and/or direction-specific deficits in orienting, and a number of different saccadic properties may thus provide useful information in the study of neglect. Also, the specific demands of a task, whether it requires mere visual exploration or the pursuit of stimulus movements, are also relevant for the outcome of testing, so these also need to be taken into consideration when interpreting results.

In addition, fixation patterns have been used to assess mechanisms of neglect. Behrmann et al. (1997) demonstrated completely opposite patterns in the fixation distributions of neglect and hemianopic patients during a visual search task. Neglect patients exhibited a steep gradual increase of fixations from left to right while hemianopic patients showed a steep gradual decrease in fixations from left to right. While neglect patients had difficulties searching the neglected field, hemianopic patients searched their hemianopic side more than their ipsilesional side, supposedly as an act of compensation for the visual field loss. Another study by Ishiai (2006) assessed fixational patterns in neglect patients during a line bisection task. They revealed a tendency to fixate at a point of the line to the right of the center, where they also tended to mark their perceived midpoint. The left side of the line was hardly fixated at all. Fixational distributions may thus serve as a measure reflecting a participant's utilization of the visual field as well as strategies and compensational mechanisms at use.

The rate of fixating has been found to reflect aspects of cognitive processing like efficiency (Goldberg & Kotval, 1999) and expertise (Krieger et al., 2016; Reingold, Charness, Pomplun, & Stampe, 2001; Reingold & Charness, 2005). Higher fixation rates may for example suggest inefficient processing, as more fixations are needed to take in the relevant

information (Goldberg & Kotval, 1999). Moreover, the research literature within sport psychology on the so-called “quiet eye” suggests that the precision of aiming movements (e.g. basketball, darts, rifle-shooting) may be influenced by the duration one locks the gaze onto the target stimulus before, during, and after the movement (Williams, Singer, & Frehlich, 2002; Behan & Wilson, 2008). Additionally, in complicated tasks, an increase in fixation rate has been found to predict improved performance (Kasarskis et al., 2001), signifying that a participant’s fixation rates may also reflect allocation of resources or effort investment. However, task demands obviously are relevant for the interpretation of fixation frequencies as one may benefit from making fewer or more fixations depending on the goal of the task. The present study investigates fixation rates as they may provide information about the participants’ available processing resources as well as the efficiency with which such resources are being used.

## **Pupillometry**

More than a century ago, the German neurologist Oswald Bumke postulated that: "Every active intellectual process, every psychical effort, every exertion of attention, every active mental image, regardless of content, particularly every affect just as truly produces pupil enlargement as does every sensory stimulus" (Bumke, 1911 p. 23-24, as cited in Beatty, 1982). Links between pupillary responses and different types of mental activity have later been confirmed in several studies (Hess & Polt, 1964; Kahneman & Beatty, 1966; Hyönä, Tammola, Alaja, 1995; Laeng, Sirois, & Gredeback, 2012). Of particular interest in the current work is the link with attentional arousal (Alnaes et al., 2014; Wahn et al., 2016).

The pupil diameter has been found to increase incrementally when cognitive load increases and there is a raise in the required effort investment (Hess and Polt, 1964; Kahneman & Beatty, 1966; Beatty & Lucero-Wagoner, 2000). When maximum cognitive capacity is reached, the pupil stabilizes at this enlarged size (Granholm, Asarnow, Sarkin, & Dykes, 1996). However, if the maximum processing capacity is exceeded the pupil diameter shortly levels down again, suggestively reflecting a suspension of the processing effort (Peavler, 1974). Similarly, a constriction of the pupil back to the baseline level has been shown after the report of rehearsed words or digits in a short-term memory task, which may reflect the withdrawal of invested resources as they are no longer needed (Kahneman & Beatty, 1966). Pupillometry as a method thus provides a sensitive measure reflecting the

extent and limits of processing capacity (Peavler, 1974; Granholm et al., 1996), which is important when investigating patients suffering from attentional deficits.

The mechanisms behind arousal are also highly associated with the right hemisphere (Robertson & Frasca, 1992), and one may therefore expect that right hemisphere damage will cause deficits of arousal. Although arousal is often seen as a general and non-spatial mechanism, it has also been suggested that this mechanism may be of relevance to the severity and persistence of spatial attention deficits in neglect (Hjaltason et al., 1996; Husain & Rorden, 2003; Robertson, 2001).

Evidence has suggested that cognitively driven pupillary changes may reflect activation of the locus coeruleus (LC), which triggers a release of norepinephrine (NE), a neurotransmitter associated with attention and arousal (Schwarz & Luo, 2015). Further, it is proposed that LC activity may work in two different modes, the tonic and the phasic activation modes (Aston-Jones & Cohen, 2005). The tonic mode of activation is used when one needs to explore the visual field, and LC neurons are then more responsive to new and intriguing stimuli (reflecting processes of bottom-up attention) afore task-relevant stimuli. The phasic mode of activation on the other hand, is used when task-relevant stimuli must be focused on (often reflecting processes of top-down attention). These modes are thus working to optimize performance by either broadening the scope of attention or by adjusting attention filters (Laeng et al., 2012).

With pupillary responses being taken as a sensitive, consistent, and reliable physiological marker for invested attentional effort or allocation of attentional resources to a task (Kahneman, 1973, 2011), they should provide a relevant measure in the research on attention pathologies. Still, few neglect studies have utilized this measure. Kim, Schwartz, and Heilman (1999) did record the pupillary changes of neglect patients and healthy controls as they read digits presented in their left or right hemispace (i.e., the space to the side of the patient's body midline). Control participants exhibited pupillary dilations in both hemispaces, but with larger dilations in the right hemispace than in the left hemispace. The authors suggested the asymmetry could be explained by the attention-arousal hypothesis. Accordingly, attending the right hemispace would produce bilateral hemispheric activation leading to more arousal than attending the left hemispace which would mainly produce right hemisphere activation (Heilman, & Valenstein, 1979; Kim et al., 1999). In neglect patients, pupillary dilations were only detected in the right hemispace, which they explained by an attention-arousal deficit. This would also be in line with the attention-arousal hypothesis, as disrupted processing in the damaged right hemisphere would lead to bilaterally reduced

arousal, with a bias in the activation between hemispheres because the left hemisphere would still mediate arousal in the left hemisphere. The study of Kim et al. (1999) only included two neglect patients and a group of six control participants. The authors suggest a larger sample of stroke patients, with and without neglect, would be beneficial to see if the neglect condition alone or the right hemispheric lesion in general leads to in the pupillary deviations from what would be considered normal responses in the control group. This was investigated further in Article II of the present work, using pupillary measures during a dynamic attention task. By varying the spatial presentation of the task as well as task requirements we aimed to learn more about how arousal mechanisms may be affected by stroke, and in neglect specifically.

### **Multiple object tracking (MOT)**

As our visual environment appears to us as being in continuous motion (e.g. when at a busy crossing, a playground, or a sports field), an essential role of attention is to selectively attend to and be able to keep track of relevant moving stimuli while ignoring irrelevant stimuli (Battelli et al., 2001; Makovski, Vazquez, & Jiang, 2008). The classic paper-and-pencil tasks traditionally used to assess spatial attention (neglect tests) are static and cannot simulate the dynamic features of our daily surroundings. Thus, a test that includes an assessment of sustained attention to real motion may represent these real life challenges more accurately. The present work used the Multiple Object Tracking (MOT) task to assess dynamic aspects of attention as well as the abilities to divide attention over several objects simultaneously and sustain this state of affairs over time (at least several seconds).

In a MOT experiment, participants are required to track a number of identical objects, moving independently and unpredictably around in a field of identical distractors for a predetermined set of time (e.g., 5 seconds). As the objects suddenly stop moving around, the participant is asked to give a *full report* of which objects are the tracked targets or, as it was the case in the present MOT studies, a *partial report* with one object being highlighted and the participant being asked whether this is one of the target items tracked (e.g., Alnaes et al., 2014).

One key feature of the MOT task is that it requires the ability to sustain attention, as participants need to keep track of targets over time. Moreover, with multiple target objects to track, the attentional focus needs to be divided into multiple foci (Holcombe & Chen, 2013). Sustaining these multiple attentional foci over time is quite demanding, especially for patients

with brain injuries, but this feature of the task resembles common demands of everyday tasks, like safely crossing a busy street, watching kids at the playground, etc. The MOT task thus holds a form of ecological validity that static tests cannot provide.

With unilateral right hemisphere stroke commonly resulting in spatial inattention, measures providing information about spatial attention mechanisms are clearly of interest. As MOT requires shifting of attention over the visual field in various directions, the task may in combination with eye-tracking measures provide information of neglect patients' attentional orienting mechanisms. Moreover, by alternating between presenting the task in left and right parts of space, more information on the functioning of spatial attention mechanisms may be provided.

Another essential quality of the MOT task is that the aspect of intensive attention can easily be drawn into the equation since attentional task load is clearly operationalized by the number of target items to track and the number of distractors to ignore (Alvarez & Franconeri, 2007). That is, a stepwise increase in the attentional task demands is achieved by increasing, in different trials, the number of target objects to be tracked simultaneously (Scholl, 2009). Furthermore, since the task is computerized and dependent on presentations on a screen, it can be straightforwardly combined with eye-tracking, which has the added value of making possible an examination of the intensive aspect of attention through the participants' pupillary responses during the task.

Only a few studies have so far utilized the MOT task in the assessment of stroke patients with neglect. One study by Battelli et al. (2001) used it to assess high-level motion processing mechanisms in patients with neglect, as compared to mechanisms of low-level motion and illusory motion. While neglect patients showed reduced high-level (attentive) motion performance on the MOT task when presented in the contralesional hemifield, they were found to perform at normal levels when the task was presented in their right side of space. However, this study only included 3 neglect patients, which raises questions about its generalizability or representativeness. The study nevertheless suggests that some neglect patients are able to perform the MOT task under specific conditions. Other studies have, however, by comparing neglect patients performance in the left and right side of space, also revealed ipsilesional deficits in these patients (Cusack, Carlyon, & Robertson, 2000; Duncan et al., 1999; Kristjansson & Vuilleumier, 2010). Thus, with the MOT paradigm offering a useful tool for investigating multiple aspects of attention simultaneously, we thought it reasonable to utilize this task to assess the functioning of different aspects of attention in the ipsilesional field of neglect patients.

## **Binocular rivalry**

When two different images are presented at the same time, one to each eye, and their contents overlap the same spatial location, a fascinating perceptual phenomenon occurs that is termed binocular rivalry (Logothetis, Leopold, & Scheinberg, 1996; Tong & Engel, 2001). Although the stimuli presented remain constant and visible at all times, the opposing images are perceived separately, one at the time in alternating fashion so that perceptual awareness can be dissociated from the global visual input (Clifford, 2009). Reciprocal suppression and awareness during rivalry are key processes in what is consciously perceived (Tong, Nakayama, Vaughan, & Kanwisher, 1998). Thus, binocular rivalry offers a unique prospect to study processes of visual awareness and perception (Crick and Coch, 1998). Leopold and Logothetis (1999) specifically suggest that higher, mainly non-sensory, fronto-parietal brain structures linked with the planning and motor programming of for example exploratory eye movements and shifts of attention, may directly intervene in the processing of the visual input and initiate a reorganization of activity throughout the visual cortex. While these fronto-parietal brain structures may influence rivalry dynamics through perceptual organization, they are also important in selective attention. Thus, by looking closer at the rivalry dynamics of clinical populations with dysfunctional attention mechanisms, we may learn more about the role of attention in binocular rivalry as well as the functioning of these patients' neural processing mechanisms. Since the conflicting stimuli of the binocular rivalry task are presented in exactly the same spatial location of the visual field, this opened for an assessment of how altered non-spatial attention mechanisms after stroke may affect neural competition during rivalry.

Surprisingly little research has assessed rivalry in patients with brain damage. Bonnef, Pavlovskaya, Ring, and Soroker (2004) assessed alternation rates in right hemisphere stroke patients and healthy controls and found that patients overall had slower alternations than healthy participants. Furthermore, a subgroup of patients suffering from unilateral spatial neglect showed slower alternations than non-neglect stroke patients, which in principle undermines the idea that neglect is just a spatial deficit, and suggests instead that more central mechanisms of attention play significant roles in neglect. Another stroke patient study conducted by Daini et al. (2010), however, did not detect differences between patient subgroups on a comparable task. The authors argued that those mechanisms that slow down

rivalry rates in patients should accordingly not be associated with neglect specifically. The two mentioned studies thus report conflicting evidence regarding the role of neglect in binocular rivalry. Increasing evidence from different types of studies suggests, however, that non-spatial attention mechanisms may be involved in neglect (e.g. Hjaltason et al, 1996; Robertson et al, 1997; Samuelsson et al, 1998). Thus, with a new and larger sample of patients, we aimed to re-examine how non-spatial attention in the neglect syndrome may influence binocular rivalry dynamics.

## MAIN RESEARCH OBJECTIVES

The field of attention research and even the literature on the neglect syndrome are too vast to be covered in full in this thesis. Rather, the present three articles have narrowed down the possible research perspectives into specific questions that may provide only fragments within a larger context, but that could still help improve the understanding of attention in general and of attention pathology specifically. After stroke, different types of attention impairments are commonly observed, and by examining and comparing the functioning of different attention components as well as utilization of resources in neglect patients, non-neglect stroke patients, and healthy controls, we may shed light on processes and organizational principles of the attention systems. Further knowledge of the mechanisms behind attention pathology may also benefit future development of rehabilitation techniques.

### ARTICLE I:

#### **Unilateral neglect post stroke: Saccade frequencies indicate directional hypokinesia while fixation distributions suggest compensational mechanism**

Article I aims to utilize eye-tracking measures in the examination of different aspects of attention functioning in patients with right hemisphere stroke and to specifically evaluate the symptoms of unilateral neglect with dynamic stimuli. We expect neglect patients to have a biased spatial distribution of fixations towards the right hemispace and that this bias will be more pronounced in patients with severe neglect.

The second aim is to assess whether a direction-specific bias in saccade frequencies is present in neglect patients, thus indicating a directional hypokinetic component in neglect. We expect the number of saccades directed rightwards will significantly exceed the number of leftwards directed saccades in neglect patients.

Finally, we investigate the role of fixation frequencies and visual processing efficiency. Patients are expected to show increased fixation frequencies compared to controls, reflecting reduced efficiency and increased use of visual processing resources. This increase in gaze activity is also expected to be larger in neglect patients than non-neglect patients in proportion with the degree of attention impairment. Fixation frequencies are also expected to increase for all groups as load increases and more spatial information is required.

## **ARTICLE II**

### **Multiple object tracking and pupillometry reveal deficits in both selective and intensive attention in post stroke neglect**

Article II has two main goals. The first is to assess potential deficits in attentional arousal using pupillometry measures. Pupillary responses can give an indication of available attentional resources or the ability to use them in the task at hand. We predict neglect patients and patients with right hemisphere stroke will show reduced pupillary responses compared to controls, due to having less attention resources to draw from.

The second aim is to investigate aspects of attention pathology through performance measures in different conditions of a dynamic multiple object tracking (MOT) task as well as a static visual search (VS) task. We predict neglect patients will have reduced accuracy scores in the left hemispace compared to the right hemispace and also that the dynamic stimuli will allow probing ipsilesional attentional deficits better than the conventional visual search task.

## **ARTICLE III**

### **Binocular rivalry after right-hemisphere stroke: Effects of attention impairment on perceptual dominance patterns**

Article III seeks to assess how a right hemisphere stroke, and neglect specifically, affects binocular rivalry alternation rates. Based on the hypothesis that right hemisphere's stroke reduces arousal and general attentional resources, we predict that both patient subgroups will show slower alternations than the control group and that neglect patients will have the lowest alternation rates. By taking into account the patients' scores on a battery of attention tests (BIT), it is further examined how the degree of attention impairment may be related to the dynamics of rivalry mechanisms. We predict that alternation rate will decrease with a decrease in BIT-scores.

## METHODOLOGICAL CONSIDERATIONS

The sample, design and procedures of our studies as well as group and patient demographics are described in detail in each of the three articles at the end of this thesis. This section will discuss the sample recruited as well as the reasoning behind the experimental design with regards to questions of validity. As defined in Stangor (2014): *Internal validity* is referred to as “the extent to which we can trust the conclusions that have been drawn about the causal relationship between the independent and dependent variables” (p. 234). *External validity* regards “the extent to which the results of a research design can be generalized beyond the specific way the original experiment was conducted” (p. 261). *Generalization* is “the extent to which relationships among conceptual variables can be demonstrated in a wide variety of people and a wide variety of manipulated or measured variables” (p. 261). The materials and analyses that were used are also considered in this section, as well as some relevant ethical issues in patient research.

### PARTICIPANTS

In order to include as many participants as possible in the study, all data for the three papers were collected in parallel. Thus, all three papers are based on the same sample of 26 right hemisphere stroke patients and, mostly, the same healthy control participants. Due to technical errors, two of the control participants in Article III had missing data in the MOT studies (Article I and II) and hence two additional control participants were included in Article I and II taking their place. Groups were matched to the best of our abilities on the criteria of age, sex, handedness, and ocular dominance so that no demographic comparisons between groups or subgroups presented significant differences. Matching of groups was done as this protects internal validity; ensuring that the between-group comparisons of the computerized experimental tests are not influenced by specific potential confounding variables. Participants did not receive any payment for participation. The criteria for inclusion of patients were: 1) age of 18 years or older, 2) magnetic resonance imaging (MRI) or computed tomography (CT) revealing a unilateral right hemisphere brain injury resulting from an ischemic or hemorrhagic stroke that occurred less than 12 months before study inclusion

(previous strokes to the same hemisphere were allowed), and 3) no history of neurological injury previous to the right hemisphere stroke(s) and no presence of hemianopia.

Healthy control participants inclusion criteria were: 1) age of 18 years or older, 2) no present or previous history of illness or damage to the central nervous system.

Exclusion criteria for all participants were: 1) severe cognitive deficits, such as dementia, 2) presence or history of severe psychiatric disorders (psychosis, severe depression), defined as being hospitalized for psychiatric disorders, or medicated for more than 6 months 3) presence or history of substance or alcohol abuse.

Based on these inclusion and exclusion criteria, potential participants for the patient group were consecutively identified through inspection of the medical journals of patients admitted to the stroke section of Sunnaas Rehabilitation Hospital. There was no random selection of participants, which could lead to potential biases in the selection process. Sunnaas patients differ from the stroke population in general, due to specific criteria for patient enrollment (age, severity of stroke, the hospital's rehabilitation services, etc.). Moreover, with all participation being voluntary, it is also likely that certain subgroups of patients were more likely to participate than others. For example, patients who suffer from serious fatigue may more likely decline an invitation to participate, compared to less fatigued patients. These potential selection biases may have produced a stroke patient sample that is not representative for the general stroke population. Even so, other studies in the literature are likely to suffer from similar biases and, in this respect the present study may not be exceptional.

In fact, a number of choices must be made when planning an experiment, which may involve an exchange of costs and benefits. The relationship between internal and external validity is for example often considered a trade-off relationship. Jimenes-Buedo & Miller (2010) argue that the more experimental control that we exercise in order to isolate our experimental factors from potential confounds (to ensure the effects found are attributable to the investigated factors), the more questionable is it that the findings are representative of occurrences in the external world, since typically several factors may interact in a real world setting. The same authors argue that internal validity is also considered a prerequisite to external validity, as we are dependent on some experimental control in order to be able to say anything about the outside world. Essentially, the balance between internal and external validity must be carefully considered, as it undeniably impacts how broadly one may generalize from the findings. Our choices in criteria for inclusion and exclusion were made with emphasis on protecting internal validity. However, we also needed to make sure the

project was feasible, thus for practical reasons, no randomized selection was applied and patients were selected from the available pool.

## **DESIGN**

All three papers used mixed, between/within-subject, experimental designs. In neglect studies, between-groups comparisons are necessary. By comparing neglect patients to both healthy controls and stroke patients without neglect, the design aims to isolate characteristics of all three groups. The within-group studies are used so that each participant is his/her own control, which eliminates the possibility that individual differences influence the results. This is important as patients with brain injuries may differ, despite having injuries in similar structures in the brain. Further, with limited access to patients appropriate for inclusion (this being dependent on the number of patients with relevant injuries being admitted to the hospital), a within-subjects design provides a means to increase power, as it reduces error variance. However, a disadvantage with a within-design is the need to control for order effects and carry-over effects. The present design was counter balanced in combination with Latin-square ordering of specific conditions (Wallis & George, 2011) for both within and between factors. To avoid expectancy effects, the order of trials (with regards to whether yes or no responses would be correct) was also pseudo-randomized. With a number of variations in stimulus presentations and variables, the experiment was complicated and long. To ensure that participants, and particularly the patients, did not experience too much fatigue, data was collected over at least three days, with the possibility to take multiple breaks between trials.

## **MATERIALS**

### **Neuropsychological assessment**

#### *General Cognitive Functioning*

To test the patient's general cognitive functioning, we used the subtests Vocabulary and Matrix reasoning from the Wechsler Adult Intelligence Scale version III (WAIS-III; Wechsler, 1997). One patient had been administered the subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) during the clinical assessment at

the hospital and, accordingly, these subtests were used instead. Control participants were not administered these tasks.

The Vocabulary subtest of WAIS-III gives an estimate of the individual's semantic knowledge, verbal comprehension, and expression. Participants are in this test asked to name objects in pictures or to define words that are presented to them. The Matrix Reasoning of WAIS-III is a nonverbal abstract problem-solving task that evaluates the individual's perceptual organization and reasoning abilities. In this task the participant is presented with a series of designs with a part missing. Five alternative choices are given, out of which one will complete the design, and the participant is asked to choose the correct one.

The Vocabulary subtest of the WASI battery is somewhat comparable to the Vocabulary subtest of the WAIS III as it is designed to measure an individual's word knowledge and verbal concept formation. Also, the Matrix Reasoning subtest of the WASI is quite comparable to that of WAIS III as this subtest taps fluid intelligence, classification and spatial ability, broad visual intelligence, knowledge of part-whole relationships, simultaneous processing, and perceptual organization.

The subtests used are not sufficient to provide a full-scale intelligence measurement, but offer an indication of the general cognitive functioning of the patient. There were a few patients who scored relatively low on one or both of these tasks. The patient group had an average S-score of 7.66 ( $SD = 3.54$ , min = 3, max = 16) on the Vocabulary subtest, placing their performance below the norm mean of 10; however, the scores were well within one standard deviation. On the Matrix Reasoning subtest, the patient group average S-score was 6.53 ( $SD = 3.20$ , min = 3, max = 14), a score close to, but not within, a standard deviation of the norm mean of 10. Most patients had scores within a standard deviation of the norm mean of their age group, however as indicated from the minimum and maximum values the variability within the group was large.

### *Neglect tests*

The six conventional subtests of the Behavioral Inattention Test (BIT; Wilson et al., 1987) were used to provide a measure of neglect symptoms or milder forms of inattention in the patients. The conventional subtests of the BIT battery are all basic paper-and-pencil tasks, presented on a separate sheet of paper placed straight in front of the patient. The conventional subtests include star cancellation, letter cancellation, line crossing, line bisection, representational drawing, and figure and shape copying. The BIT-scores for all the subtests

for all participants are presented in the articles. The highest possible total score is 146 on the BIT-test. A patient does not necessarily display neglect symptoms in every subtest. Although some of the subtests may potentially be more sensitive in revealing neglect, different subtests may reveal the presence of neglect in different patients. Thus, the present study used each patient's total score in order to determine whether neglect was present (using a cut-off at 129, in accordance with the BIT manual).

### *Visual Field Deficits*

Importantly, both visuospatial neglect and hemianopia may occur simultaneously in a patient, or they may occur in isolation. Accordingly hemianopia provides a possible confound in neglect studies, as it may be difficult to disentangle the two disorders from each other (Walker, Findlay, Young, & Welch, 1991). Detailed information of lesion locations may help determine which of the two disorders, is cause to the observed problems with the contralesional field. Injuries to the visual system (occipital cortex, visual pathways, optic chiasm, the retina of the eye) are likely to cause visual field loss (Fitzpatrick, 2004), while damage to other areas of the brain, like parietal or frontal injuries, may result in neglect or extinction (Vallar, 1998).

Some indications to whether visual unawareness is due to neglect or hemianopia may also be provided through neuropsychological tests, like perimetry assessments and neglect tests. The Friedman Visual Field Analyser 2 (Clement Clarke International Ltd) was administered to the patients in order to assess whether they suffered any vision loss. During such a perimetry test, an individual's light sensitivity in different locations of the visual field is tested while the eye(s) of the participant is fixated on a point at the center of the screen, and stimuli presentations are alternated between unilateral and bilateral presentations. Some patients did show reduced detection of stimuli in their left visual field, which could be due to either neglect or vision loss, but no one met the requirements of a hemianopia diagnosis as they all displayed an ability to detect at least some stimuli in the left visual field.

### *Questionnaires*

All participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), which is a well-known measurement scale used to determine a person's handedness (which refers to the dominance of the left or right hand) in everyday activities. EHI requires for the individual to report which hand is his or her preferred hand, as well as the strength of this preference, in

carrying out a number of activities, such as writing and drawing, throwing, and using utensils such as a toothbrush, knife, and spoon.

In addition, detailed health related information and demographics on each participant were registered through a few questionnaires in order to make sure that each participant met the inclusion criteria and that the groups and subgroups were matched on basic characteristics (e.g., age, sex, etc.), controlling for possible confounds.

### **Recording eye movements and pupillary responses**

The recent technological advances in infrared eye-tracking have made available a number of different measures through non-invasive, easy-to-use equipment. As such, our goal was to engage the patients' attention at various levels of operation during multiple object tracking and record their performance accuracy, their physiological pupillary responses to the task, as well as their eye movements.

#### *Eye-tracking*

Eye-tracking offers extremely precise quantitative evaluations of a person's oculomotor behavior. However, while eye movement recordings may provide a number of different measures, in the present work only three eye-tracking measures (fixation distribution, fixation frequencies, and saccade frequencies) were chosen for further examination, based on our theoretical predictions, in order to uphold statistical validity (Orquin & Holmqvist, 2017).

While the mean fixation rate per trial may reflect a visual processing efficiency and expenditure of visual processing resources, an assessment of fixation distribution between the left and right hemispace may give indications of how attention is spatially distributed and how the participant utilizes the visual field. As the spatial positions of fixations were determined with reference to the position of the head (which was directed straight forward), any potential bias found in fixation distribution would be referred to as a hemispatial bias. Saccadic properties are associated with mechanisms of orienting attention, and saccade frequencies were analyzed with regards to their directions (left or right) regardless of which hemispace they occurred in. Directions of saccades were based on eye-centered coordinates, as they were determined with reference to the initial position of the eye before the saccade started.

It should be mentioned that during fixations microscopic movements occur in order to uphold the stream of visual input. The image that falls on the retina cannot be too stable in order to keep neurons firing in the early visual regions of the brain (Pritchard, Heron, & Hebb, 1960; Rucci & Poletti, 2015). Fixational eye movements include microsaccades, ocular drifts, and ocular tremors (Rucci & Poletti, 2015). Eye-trackers with temporal resolution of 50Hz are rarely used for saccade research, as the temporal resolution lowers the precision of measurements (Beintema, van Loon, & van den Berg, 2005; Holmqvist, Nyström, Andersson, Dewhurst, Jarodzka, & Van de Weijer, 2011, p. 33). However, since our investigations depended only on the mere detection of saccades as well as their direction, a 50 Hz sampling rate should suffice. However, with such a low temporal resolution on our recordings, we decided to include only a subset of the saccades in the analyses. Only saccades which had amplitudes exceeding 1 degree visual angle were included, attempting to avoid the inclusion of micro-saccades (Hafed & Clark, 2002; Martinez-Conde, Macknik & Hubel, 2000) or glissades (Holmqvist, et al., 2011, p.317). With the neural limit to ocular motility in humans being at 45 degrees (Worringham, 1991, p. 548), saccades were also excluded if they exceeded 45 degrees visual angle. The measure of saccadic frequencies thus included saccades from 1 to 45 degrees amplitude.

It should also be noted that in addition to the saccadic eye movements, there are three additional types of eye movements: vergence movements, vestibulo-ocular movements, and smooth pursuit movements (Hall, 2004). The first two types of movements are not likely to occur in the data set of the present experiment. However, smooth pursuit movements, which are slower eye movements than saccades that follow a moving stimulus so that the stimulus is kept on the fovea, should commonly occur during tracking of stimuli. The present work does not separate saccades from smooth pursuit movements, due to the low temporal resolution of the eye-tracker used. Thus, the eye movements recorded in our study, which we refer to as *saccades*, may include both these two types of movements.

### *Pupillometry*

Most people associate pupillary dilations and constrictions with the well-known light reflexes, as these are large responses that can even be spotted with the bare eye (Beatty & Lucero-Wagoner, 2000). Pupillary dilations that are driven by cognitive and affective processing are much smaller than light reflexes, as they typically do not lead to more than 0.5 mm change in pupil size (Beatty & Lucero-Wagoner, 2000). Still, with the right equipment and an

appropriate experimental paradigm that allows for measures of a stable baseline, includes multiple presentations of stimuli, and provides good control over potential confounding variables (typically in a laboratory setting with strict control over stimulus properties and surroundings), systematic changes in pupil size related to task demands and effort investment may easily be detected.

Since the pupil is so sensitive to changes in light conditions, stimulus luminance provides a strong potential confound. Therefore, we kept luminance constant throughout the experiment: the luminous intensity that is emitted or reflected from the stimuli as well as the light in the experimental room (Holmqvist et al., 2011).

Another possible confound is fatigue, as pupillary dilations can also reflect fatigue (Beatty & Lucero-Wagoner, 2000). Testing patients with brain injuries, it is likely that they fatigue more easily than healthy controls (Cantor et al., 2008; Ponsford et al., 2012), and that droopy eye-lids may get in the way of good eye recordings (Holmqvist, et al., 2011). Moreover, in pupillometry as well as eye-tracking, accurate and precise measures are dependent on good calibration and visibility of the pupil (Holmqvist, et al., 2011). Calibration and validation of the eye-tracking were performed manually in every test session, making an effort to get as accurate and precise recordings as possible. Care was also taken to monitor patients during testing, making sure their eyes were sufficiently opened and suggesting frequent breaks to avoid fatigue.

The pupillary measures were recorded using an iView head mounted eye-tracking device (HED) (SensoMotoric Instruments, Berlin, Germany), which only tracks one eye. Every participant was therefore tested for ocular dominance by use of the Miles test (Miles, 1930), to ensure the dominant eye was being tracked, in order to achieve the best possible quality of the data (Holmqvist, et al. 2011).

The momentary change in pupillary diameter provides a useful psychophysiological marker as it provides a prompt, objective and precise measure of processing effort, capacity, and allocation or availability of attentional resources (Kahneman, 1973; Beatty, 1982; Beatty & Lucero-Wagoner, 2000; Laeng et al., 2012). In combination with the MOT paradigm, in which all conditions require sustained attention over time, and different conditions (e.g. load) necessitate different levels of effort investments, pupillary measures should thus provide a good index of the attention resources invested in the task.

## **Computerized experimental tasks**

### *Multiple Object Tracking (Article I & II)*

Article I and II utilized MOT to investigate different aspects of attention in stroke patients with and without neglect. Each participant viewed 120 different films, each presenting a trial of the MOT task, and they had simultaneously their pupillary responses and their eye movements recorded. The MOT films were shown during the course of at least two test sessions (or more, if a participant became fatigued). We used 24 of these films in Article I while the remaining 96 films, were used in Article II. We chose to keep the task demands quite low in the MOT task, with only 5 seconds of tracking, and with a set of eight objects presented within a tracking field varying the target load between 1, 2, and 3 targets. We varied the spatial presentation between the experiments of Article I and Article II.

The MOT trials of Article I had a square tracking field presented centrally. Object tracking would thus encourage eye movements in left and right directions, extending into both the left and right fields over the course of the trial. Furthermore, eye movements were recorded during task performance, which allowed for an assessment of oculomotor performance and patterns of fixation distribution in the different groups. Moreover, eye movement recordings allowed for an assessment of fixation frequencies which may reflect the efficiency in visual processing and the expenditure of visual processing resources in the different groups and during the different conditions of load.

Article II had the tracking area divided into two similarly sized, vertically-oriented, rectangular areas, and the target stimuli would only be presented in either the left or right tracking field in each trial. This allowed for an isolation of left versus right task conditions. Pupillary measures were recorded (as they provided an index of attention resource allocation) during performance of the MOT task. As the task requires sustained selective attention, elevated arousal levels were predicted during tracking, especially in conditions of increased attentional load. Moreover, as the task alternated between trials of tracking within the left or the right hemispace, it allowed for a comparison of arousal responses in the left and right hemispace. Thus, the combination of the MOT task and recordings of pupillary responses provides information about the several aspects of attention, including the intensive aspect, in stroke patients with and without neglect.

The MOT task was chosen for several reasons. The simplicity and flexibility of the MOT task design makes the task a potent experimental tool. MOT has the advantage that it is able to engage several components of attention, and one can easily vary the task demands of

the different components. By further combining task performance with measures of pupillary responses and eye movements, the experiments can provide information of attentional effort investment and shed light on mechanisms of shifting and splitting attention. The fact that the MOT task does not demand speeded motor responses is a valuable feature in studies on stroke patients, as individuals of this group have increased probability of suffering from motor impairments, which may contaminate behavioral data.

### *Visual Search (Article II)*

Each trial in our computerized visual search task started with the presentation of a diamond shaped fixation marker at the middle of the screen. Participants were to keep their gaze at this fixation point until a circle of letters appeared, one at each of the twelve locations corresponding to the hours on a clock face. Participants would then quickly search for the target letter X among these letters and as fast and accurately as possible respond ‘yes’ if the X was present and ‘no’ if not. The experimenter logged the response by using predefined keys on the keyboard.

One of the reasons for including the VS task, was that different versions of the classic visual search task (e.g., Treisman & Gelade, 1980) have been used extensively in neglect research (Behrmann et al., 1997; Weintraub & Mesulam, 1987). With little experience of using the MOT task with neglect patients, the VS task was included to provide a well-known baseline for spatial performance. The visual search task measured the ability to detect targets in left versus right side of space, thus assessing for the classic symptoms of neglect. We included two different conditions of visual search, often referred to as *Feature Search* (FS) and *Conjunction Search* (CS; Treisman & Gelade, 1980; Laeng, Brennen, & Espeseth, 2002). FS is a “pop-out” task where all distractors are the same letter (in this case O), which is accordingly presented at all locations or all locations except the target location. This task is associated with bottom-up attention processes (Koch & Ullman, 1985), as the target (in this case X) so clearly stands out, that bottom-up attention mainly facilitates the search. In contrast, all distractor letters in the CS task are different from each other and the target features (still the letter X) do not “pop out”. This search is more challenging and requires more top-down attention (Egeth, Virzi, & Garbart, 1984).

Our visual search task included 4 blocks of 24 trials, in total 96 trials. Two of the blocks would require feature search, while the two others would require conjunction search. Half of the trials in each block had no target present, while the other half of the trials had the

target presented at different locations. The order of trials was pseudorandomized, and the order of blocks was counterbalanced between participants with a Latin square design (*FS-CS-CS-FS* or *CS-FS-FS-CS*).

### *Binocular Rivalry (Article III)*

The binocular rivalry task was implemented using colored *anaglyphs* viewed through anaglyph glasses as this is a fairly simple and manageable technique for bringing about binocular rivalry. All anaglyphs were created using Anaglyph Maker version 1.08 (Sekitani, 2001); each anaglyph consisted of two differently colored (red and cyan) images superimposed on each other. These combined images were viewed through anaglyph glasses with different color filters for each eye (from [www.3Dstereo.com](http://www.3Dstereo.com), Las Vegas, NV), so the left and right eyes viewed a different image each (e.g. a house or a face). The task was divided into two parts administered at separate test sessions. In one session, four different anaglyphs were presented, and in the next session the same four anaglyphs but with opposite colors (thus presented for the opposite eyes) were used. One anaglyph consisted of an image of a face and one of a house, while the three others were Gabor grid anaglyphs.

All stimuli were presented centrally within the visual field so that both hemispheres of the brain would be receiving signals from both eyes. Stimuli were presented at a 42-degree viewing angle, thus within a large portion of the binocular visual field when looking at the center of the image. We instructed the participants to report whenever one stimulus could be considered more dominant than the other (i.e., we did not require full dominance). We made sure during practice trials that the participants understood the task requirements before they got started with testing.

We chose to include binocular rivalry to our assessment of neglect as this provides a non-invasive measure reflecting aspects of neural processing. Non-spatial, or global, attention deficits have been commonly observed in neglect (Hjaltason et al., 1996; Husain et al., 1997) and such deficits may influence the dynamics of the perceptual alternations.

Task demands of the binocular rivalry task are quite low, since the perceptual alternations happen spontaneously without need of effortful concentration. Thus, this task does not trigger in patients or other participants that they have to perform according to some standard.

## STATISTICAL ANALYSES

All data analyses were run on IBM SPSS® Statistics 21. The analyses included mixed between-within subjects repeated measures ANOVAs as well as simpler within subjects repeated measures ANOVAs, linear regressions, multiple linear regressions, and independent samples t-tests.

Different statistical tests are grounded on different sets of background assumptions. The validity of conclusions drawn from a statistical inference is dependent on the validity of the assumptions that are relevant for the test. If assumptions are violated, caution is needed, as the interpretation of the results changes. In some cases there are steps to take to rectify these matters, like transformation of data or using tests that correct for specific biases. In our studies we did encounter a few cases of violated assumptions, and our strategies to rectify these matters are explained below.

In Article I and II, we encountered cases of violated assumptions in a few mixed between-within subjects repeated-measures ANOVAs. One assumption that did not always hold was that of homogeneity of variances, i.e., whether they are equal between the groups compared in the analysis (Field, 2009). This assumption is specifically relevant for the comparisons made between groups (Allen, 2017). Potential consequences of breaking this assumption are dependent on whether or not the sample sizes of the compared groups are equal (Field, 2009). If there are no differences in sample size, the test is known to be quite robust (Field, 2009), although it may increase the chance of false positives (reporting significant differences that are not truly there; Harwell, Rubinstein, Hayes, & Olds, 1992). However, if group sizes are very different and homogeneity of variance is violated, then the F statistic may be biased. The significance level of the test can be either overestimated (and as such reduce the power of the test which makes the test more conservative) or the significance level may be underestimated (causing the test to be more liberal by increasing the chance of falsely reporting a significant difference that is not truly there). The direction of the bias in the F-statistic depends on whether the larger sample variances are associated with the large group or the small group (Field, 2009). Since two of our three groups (the patient subgroups) were quite similar in sample size while the third group (healthy controls) was larger than the patient groups, we decided to use a post hoc test that does not assume equal variances or equal sample sizes when the assumption of homogeneity of variances was broken. This way we reanalyzed the problem in question with different tests, making sure results were reliable. The

Games-Howell test, which is based on the q-statistic distribution, was used for this purpose (De Muth, 2014).

The other assumption that was violated, in specific analyses of Article I and II, was the assumption of sphericity, which refers to the equality of the variances of the differences between levels of the repeated measures factor (Singh, Rana, & Singhal, 2013). For the comparison of any two levels of a within-subjects factor, difference scores should have the same variance. There needs to be more than 2 levels of the independent variable for this assumption to apply. Repeated measures designs are vulnerable to the violation of sphericity, as the F-statistic is positively biased and this increases the risk of type 1 error (false detection of an effect that is not present; Lix, Keselman, & Keselman, 1996; Singh et al., 2013). In order to overcome this problem, we used the Greenhouse-Geisser estimates of sphericity, applying a correction factor to the degrees of freedom (*df*) to produce a valid critical F-value and reduce the chance for a type 1 error (Field, 2009).

In Article III, the rivalry alternation dynamics were investigated by use of t-tests and regression analyses. In one t-test, the group variances were significantly unequal as tested by Levene's Test for Equality of Variances. This was corrected for by instead using a t-test with a Welch-Satterthwaite approximation for the degrees of freedom that does not assume equal variances.

## **ETHICAL CONSIDERATIONS**

The research project was approved by the Regional Committees for Medical and Health Research Ethics, region South-East (2011/1589, REK sør-øst) and conducted in agreement with the declaration of Helsinki (World Medical Association [WMA], 2013).

As this is a clinical psychological research project involving both well-functioning individuals as well as individuals struggling with psychological and physiological disorders, we need to rely heavily on ethical considerations. Three imperative ethical issues are highlighted in this section. One important ethical issue concerns the participant's ability to give a truly informed consent. Another critical issue is the principle that the participant's health and integrity is not put at risk. A third relevant issue is the principle of confidentiality, which is essential at all levels of the research process, and highlighted here is the safe storage of personal and sensitive data.

It is of utmost importance that participants are well informed of their rights, and that they understand what accepting to participate entails. The experiments and procedure as well as the participant's rights when included in a study were therefore properly explained in person by the experimenter. In addition, the participants would all receive a written document including the same information, to read through and discuss with their closest family, before agreeing to take part in the experiments. Participants and relatives were encouraged to ask questions if they were uncertain about their rights or the procedures of the study. An important issue is that patients in a rehabilitation hospital may feel obliged to participate in a project that is carried out in their ward. Their dependency towards the hospital staff and the importance of the treatment they are receiving could also lead them to hold back negative responses when invited to volunteer as participants. All individuals invited were therefore clearly informed that participation was voluntary and that they could withdraw from the study at any time and without any explanation without suffering any consequences in their clinical care at the hospital. It was further stated that they had the right to get their data deleted at any time if that was their wish.

All participants gave their written informed consent, and there were no cases of doubt about any participant's ability to deliver informed consent. In a study of stroke patients, the disabilities resulting from the stroke may complicate the matter of communicating these rights to the patients. Patients may have problems focusing their attention over the course of this communication, and they may respond positively even though they have not fully understood what they are responding to. With all the variations in symptoms and disabilities after stroke, one must be cautiously clear in the communication, to ensure an informed consent.

To ensure that all patients included had an appropriate health condition, each patient's clinical journal was carefully assessed and their psychological and physiological condition was considered before inviting them to participate. Patients with serious cognitive deficits or psychiatric illnesses were not invited to participate, to ensure not risking a worsening of their condition. The clinical teams following up the patients were also asked to communicate to the research team if patients were in a cognitive and emotional state considered inappropriate for taking part in the study. All tests conducted and all methods used in this study involved minimal risk for the participants. If a participant at any point in time did not feel fit to continue testing for example due to fatigue, they were offered to complete the task at a later time and new test sessions were scheduled. Also, to avoid unnecessary overlapping of assessments during their stay at the hospital, parts of the neuropsychological assessment were

transferred to the project from the patient's neuropsychologist (mainly WAIS III subtest scores, and in one case WASI subtest scores).

The principle of confidentiality is grounded in a concern of privacy, which is important in any case. When studying patients who suffer from injuries that cause them pain and loss of abilities, this principle is of particular importance. In addition to being a vulnerable group, the patient group studied in this project includes only 26 patients, which makes it likely that information of some individuals (if they suffer a recognizable set of symptoms) could be traced back if all information is stored in the same place. To protect the privacy of participating individuals, the data collected in this project was de-identified, which implies that the participant's name, date of birth, or other data that could be traced were removed from the experimental data files and stored in a separate place, so that sensitive information would not be accessible to unauthorized people.

# SUMMARY OF ARTICLES

## ARTICLE I

### **Unilateral neglect post stroke: Saccade frequencies indicate directional hypokinesia while fixation distributions suggest compensational mechanism**

*Background/Objectives:* Advances in eye-tracking techniques have led to confidence regarding their clinical utilities, as these procedures are now ever more available and easily applicable, and they provide a non-invasive means to investigate neural processing in the brain. Neglect research has embraced the investigation of eye movements as these procedures may provide information of oculomotor functioning as well as utilization of the visual field. Article I sought to utilize fixation frequencies as a measure of visual processing efficiency and the allocation of processing resources. It was investigated whether this measure would detect lower efficiency in visual processing in stroke patients and specifically in neglect patients, and whether increased task demands would boost the usage of visual processing resources. In addition we aimed to evaluate the spatial distribution of fixations in neglect patients, in order to assess whether there was a rightward bias present in this group that would increase with more severe neglect. Lastly, we sought to investigate saccadic frequencies and assess whether orienting towards the right would occur more frequently than towards the left in neglect patients. If such a direction-specific bias in saccade rates would occur in neglect patients, this would be suggestive of a direction-specific hypokinetic component in neglect.

*Methods:* Participants performed a MOT task while eye movements were recorded. Accuracy measures were used to compare performance between groups and conditions of load (1, 2, or 3 targets). Fixation frequencies during correctly responded trials were compared between groups and between conditions of load. The proportions of fixations that were distributed between the left and right hemispace were assessed in relation to patients' scores on the Behavioral Inattention Test (BIT), checking if the degree of leftward inattention would be reflected in the spatial distribution of fixations. This was done separately for each of the patient subgroups, as BIT-scores were expected to predict fixation distribution across the field in neglect patients but not in non-neglect patients. Saccadic frequencies per left and right directions during correctly performed trials were compared in each of the three groups.

*Results:* The neglect patient group achieved the lowest accuracy scores, the patients without neglect performed markedly better, and the healthy controls clearly had the highest scores on the MOT task. Accuracy tended to decrease with increased load across all groups, however, this effect was only borderline significant. Comparing fixation frequencies between groups, both patient groups had increased frequencies compared to controls. Fixation frequencies were also clearly affected by load, as the fixation counts increased when more than one target was tracked. A bias in proportion of fixations distributed between left and right fields was demonstrated in neglect patients, and the direction of this bias was dependent on the neglect patient's BIT-scores (degree of neglect). Severe neglect led to the expected reduced proportion of fixations in the left compared to the right field; however, this bias shifted gradually from a rightward bias to a leftward bias as the BIT-score increased. As expected, BIT-scores did not predict the spatial distribution of fixations in patients without neglect. Saccade frequencies depended on direction in neglect patients, as this group made more saccades towards the right than towards the left. Controls demonstrated an opposite bias, having more saccades directed towards the left than towards the right. Patients without neglect had no direction-specific bias in saccade frequencies.

*Conclusion:* In line with our predictions, performance accuracy indicated a stepwise pattern of impairment between groups, with stroke patients, and especially neglect patients, showing reduced performance compared to controls. Patients made more fixations than controls, the patient subgroups did not differ significantly from one another, suggesting that the right hemisphere stroke in general affected the efficiency of visual processing similarly in both patient groups. The increase in fixation rate found across all groups when target load increased from one to multiple targets could reflect the added requirement of divided attention as the focus of attention may need to be switched more often to keep sufficiently updated on the locations of multiple targets. BIT-scores were predictive of the spatial distribution of fixations in neglect patients only, indicating that with severe neglect, patients had severe difficulties with directing their attention towards the left field, whereas less severe neglect symptoms opened for a change in this spatial fixation bias. In fact, patients with less severe neglect appeared to compensate for their left field inattention by making more fixations in this field than in the right one. The direction-specific bias in saccade frequencies found in neglect patients, suggests that neglect can involve a component of directional hypokinesia.

## ARTICLE II

### **Multiple object tracking and pupillometry reveal deficits in both selective and intensive attention in post stroke neglect**

*Background/Objectives:* While much research on neglect has emphasized the spatial deficit of this syndrome, it is evident that also non-spatial symptoms may play a central role. Several studies have highlighted such non-spatial deficits found in association with neglect, and it has been demonstrated correlations between neglect severity and the functioning of specific non-spatial attention mechanisms (e.g., sustained attention; Hjaltason et al., 1996). Moreover, spatial neglect symptoms have been shown to ameliorate when neglect patients' alertness levels are increased (Robertson, Mattingley, Rorden, & Driver, 1998). Including measures of non-spatial mechanisms as well as the spatial mechanisms may thus provide a fuller assessment of the mechanisms of neglect. The aim of Article II was to assess different aspects of attention pathology, both in the spatial and non-spatial domains. We administered a multiple object tracking (MOT) task combined with pupillary recordings and a visual search (VS) task. While the MOT and VS tasks would both provide information of spatial attention abilities, the MOT task would additionally reveal information about abilities to sustain and divide attention. Pupillary responses would reflect aspects of intensive attention; arousal levels and potential limitations in patients' available attention resources compared to controls.

*Methods:* Groups of right hemisphere stroke patients, 13 with and 13 without neglect, and a group of 26 healthy controls were presented with a MOT task and a visual search (VS) task. Pupillary responses were recorded during the MOT task. Each task had two spatial conditions (targets being presented in left or right space), and performance in the left and right space would give indications of spatial attention functioning. Performance was compared between tasks and groups to compare the tasks' ability to detect ipsilesional attention dysfunction. The MOT task also included three variations of difficulty, or cognitive load (1, 2, or 3 targets to track), and performance in single and multiple target conditions would reflect ability to sustain and divide attention. Additionally, pupillary responses were compared between load conditions and groups, in order to see how increases in cognitive task demands (target load) and corresponding effort requirements would be reflected in the pupil dilations in each group.

*Results:* In neglect patients, performance was especially reduced in the left hemispace compared to the right hemispace in both the MOT and the VS task. Neglect patients also revealed reduced accuracy scores in the right hemispace condition of the MOT task, as compared to the other groups. The effect of hemispace only applied for the load conditions of one or two targets, as performance in the three target condition was equally impaired in left and right hemispace (at chance). All groups showed decreased performance with increased load, but in neglect patients this effect could only be demonstrated in the right hemispace condition.

Control participants were found to have the most pronounced pupillary dilations and these were significantly larger than those of both the patient groups. Pupillary dilations were shown to increase with added load in both healthy controls and patients without neglect. Neglect patients, however, had no such significant increase in pupillary dilations with increased load, even though the analysis only included data from conditions where performance significantly exceeded the chance level.

*Conclusion:* The neglect patients demonstrated drastically reduced performance in the left hemispace on both the MOT and the VS task, which reflected their inattention towards the left. Moreover, MOT accuracy scores suggested that neglect patients' attention dysfunction was not limited to the left Hemispace, as this task also revealed reduced performance in neglect patients' right hemispace. While all groups showed decreased performance with increased load, this effect was only revealed in neglect patients' right hemispace, as this group exceeded the chance level performance only in the "one target" load condition in the left hemispace. Nevertheless, this does not rule out that such an effect could have been shown if task demands were lowered. In the right hemispace, the neglect patients were only able to track one and sometimes two targets, indicating severely reduced divided attention abilities.

The control participants showed the largest task evoked pupillary dilations, suggesting that this group has more attention resources to draw from. Both patient groups had reduced pupillary responses, indicating reduced attention resources. However, while increased load led to increased pupillary responses in patients without neglect, neglect patients revealed no such effect. The fact that neglect patients showed markedly reduced performance on the MOT task, severely reduced pupillary responses, and no effect of load on pupillary responses, can be interpreted two ways: It could indicate that our neglect patients had severely reduced attention resources to draw from, or alternatively, that their ability to regulate arousal in accordance with the task demands may have been impaired.

## ARTICLE III

### **Binocular rivalry after right-hemisphere stroke: Effects of attention impairment on perceptual dominance patterns**

*Background/Objectives:* Alternation rates in binocular rivalry may reflect efficiency of perceptual processing mechanisms and could give indications of the neural processing resources at use. A binocular rivalry task presents each of the eyes with conflicting stimuli in the same spatial location of the visual field. This allows for an investigation of how reduced non-spatial attention mechanisms due to stroke may influence perceptual alternations in binocular rivalry. By taking into account also the severity of attention impairments (as indicated by scores on the BIT battery), we may also get insights into the role of attention in binocular rivalry. Two previous studies have investigated rivalry in neglect and stroke, however, with somewhat diverging results regarding the role of attention in rivalry. Article III thus aimed to increase the sample sizes and compare rivalry dynamics in right hemisphere stroke patients with and without neglect, hoping to present a more reliable measure on rivalry dynamics in stroke and neglect.

*Methods:* A group of 26 right hemisphere stroke patients and a group of 26 healthy controls were administered a binocular rivalry test and rivalry alternation rates were compared between the groups. The patient group was further separated into groups of patients with or without neglect, and alternation rates of these subgroups were compared. A regression analysis was run including BIT-scores as a predictor variable to investigate what role attention dysfunction may play in altered dynamics of perceptual processing.

*Results:* The right hemisphere stroke patient group revealed slower alternation rates compared to the healthy control group. Dividing the right hemisphere group into subgroups of patients with and without neglect, it was evident that neglect patients had severely slowed alternation rates, as non-neglect patients had four times as many alternations per minute. The degree of attention impairment was also a predictor of alternation rates. BIT-scores could however only explain a small portion of the variance in such rates.

*Conclusion:* Article III confirms that binocular rivalry dynamics can be severely altered by a stroke, and that neglect may lead to a more extreme slowing of alternation rates. The severely reduced alternation rates may indicate a reduction in neural processing resources. Particular components of the alternation process may be disrupted, for example neural adaptation mechanisms (Bonneh et al., 2004) or mechanisms disengaging attention from a perceived image (Morrow & Ratcliff, 1988; Posner, Walker, Friedrich, & Rafal, 1984), however, more research is needed to clarify the specific mechanisms affected. With our neglect patients showing an extreme slowing in their alternation rates compared to the other stroke patients, this provides an indication that neglect involves more than just a spatial deficit; that more central mechanisms of attention can be affected in this syndrome as well.

## DISCUSSION

The main aims of the present study were to assess the deployment of attentional resources as well as the functioning of specific attention components in patients with right hemisphere stroke and neglect patients specifically. Visual processing efficiency and the availability and allocation of attentional resources were assessed through fixation frequencies and pupillary responses. In addition, perceptual processing resources were examined with binocular rivalry. Divided attention was assessed through performance in different conditions of load in the multiple object tracking (MOT) tasks. And finally, spatial attention mechanisms were investigated through spatial distributions of fixations in different groups, saccadic frequencies in relation to saccadic directions, and accuracy scores in conditions of left and right hemispace.

The efficiency of visual processing, measured through fixation rates, was found to be reduced in both groups of stroke patients compared to controls. However, no stepwise pattern of reduced efficiency with reduced attention functioning could be confirmed, as both patient groups had equally increased fixation rates.

As expected, the MOT paradigm revealed symptoms of spatial attention dysfunction in the neglect group, as their performance was more reduced when the task was presented in the left hemispace compared to the right hemispace. Fixation patterns also revealed a spatial bias in the neglect patients, but interestingly this bias varied in accordance with the patient's scores on the Behavioral Inattention Test (BIT). While the patients with more severe neglect symptoms typically had more fixations in their right hemispace, those neglect patients who exhibited symptoms to a lesser degree had an opposite bias with more fixations in their left hemispace. The gradual shift in spatial bias that occurred with increased BIT-scores was thought to reflect compensational mechanisms being at play in the patients with less severe neglect. Saccadic frequencies were found to be directionally dependent in the neglect patients, as more saccades were made towards the right than towards the left. We took this as an indication that oculomotor orienting mechanisms may play an important role in the neglect syndrome. Interestingly, our group of healthy control participants displayed an opposite directional bias in saccadic rates as compared to the neglect patients, which is in line with a previous study suggesting that normal participants distribute more attention towards moving objects in the left than in the right visual field (Bosworth, Petrich & Dobkins, 2012).

While both MOT and VS accuracy scores of the neglect patients revealed considerably reduced performance in the left field compared to the right field, the MOT task additionally revealed reduced performance in the right visual field. Our group of neglect patients was predominantly able to track only one target in the left field and at times two targets in the right field, suggesting that multifocal attention abilities were considerably reduced. Moreover, as task performance was not only reduced in the left visual field, but also in the right visual field, this suggests that in addition to the spatially dependent symptoms, these patients also suffered from general, non-spatial, cognitive dysfunction or, alternatively, an imbalance in shifting attention along a directional gradient. Furthermore, this marked impairment in multifocal attention may also be connected with disrupted arousal mechanisms.

There were clear indications of reduced arousal functioning in both patient groups compared to controls, suggesting right hemisphere stroke patients—at least the present sample—may have difficulties allocating the required resources to be able to solve the task. No stepwise decrease in arousal was found in relation to the groups' level of attention impairment in the overall measure of pupillary changes. However, there were indications that the neglect patients' arousal mechanisms were more severely disrupted than those of the other right hemisphere stroke patients tested. Taking the condition of load into account in the assessment of pupillary responses, it became clear that our group of right hemisphere stroke patients without neglect managed to regulate their arousal in line with the task demands, allocating more resources in the face of increased challenges. The neglect patient group, on the other hand, showed no such increase in pupil size with added load. This could be due to impaired mechanisms for regulating arousal, or it could be that they have fewer attention resources to draw from. There were no indications that arousal is spatially dependent as the neglect patients' pupillary responses in the left and right hemispace conditions were equally reduced.

Article III provided us with a different and additional measure that also reflected the patients' processing resources. Alternation rates during a binocular rivalry task clearly revealed a slowing of perceptual dynamics in stroke patients, with the mean alternation rate of controls being twice as high as the mean rate in the overall group of right hemisphere stroke patients. Furthermore, when dividing the group of patients into subgroups of neglect and non-neglect patients, it was evident that the slowing of rivalry dynamics experienced by our neglect patients was taken to an extreme since non-neglect patients reported four times as many alternations per minute. Markedly slow rivalry alternation mechanisms could be an indication of considerably reduced neural processing resources in this group or more

specifically a slowing of specific components of the alternation process, like neural adaptation mechanisms (Bonneh et al., 2004) or a disengagement procedure from attended percepts (Posner et al., 1984). As the neglect patients displayed such extreme slowing compared to the other right hemisphere stroke patients, it was investigated whether BIT-scores could predict alternation rates. Only a small portion of variance could be explained by BIT-scores, suggesting other factors may be more relevant in the slowing of alternation rates.

## **SPATIAL ORIENTING DYSFUNCTION AND FIXATIONAL COMPENSATION MECHANISMS**

It is not surprising that neglect patients exhibit symptoms of spatial inattention in the MOT task, as the syndrome is after all diagnosed on the basis of spatial symptoms. However, the present findings additionally reveal that performance is reduced in the right hemispace in the neglect patients, though not to the same degree as in the left hemispace. Similar findings have been reported in previous studies, demonstrating for example reduced reaction times towards both right- and left-sided stimuli in neglect patients compared to controls (Bartolomeo & Chokron, 1999; Weintraub & Mesulam, 1987).

The present work reports two findings that are of particular relevance for spatial aspects of neglect: 1) The spatial bias in fixation distribution shown by neglect patients was dependent on their BIT-scores, and 2) the saccade frequencies of neglect patients revealed an opposite directional bias compared to that of controls.

### **Fixational distribution reveals compensational mechanisms**

As it would normally be expected from patients with severe neglect (Behrmann et al., 1997), the gaze of these patients was mostly directed towards locations in their right hemispace. However, as scores on the behavioral inattention test (BIT) increased (indicating less severe neglect), the bias in the spatial distribution of fixations became weaker and ultimately shifted into a leftward bias instead. The neglect patients with the highest BIT-scores (i.e., they were still within the range of scores indicating neglect) actually made more fixations in their left hemispace than in their right hemispace. The direction of the spatial bias in fixation distribution was accordingly dependent on the severity of neglect. Moreover, the leftward bias found in some patients may reflect a strategy to overcome the leftward inattention problem by use of fixational compensation mechanisms. These patients seemed able to allocate more

visual resources towards their left hemispace than their right hemispace, so as to increase the information uptake from this part of the field.

While such compensational mechanisms have previously been reported in hemianopic patients, it has been assumed that compensating for spatial inattention is much more difficult for neglect patients (Girotti et al., 1983; Ishiai, Furukawa & Tsukagoshi, 1987; Behrmann et al., 1997). Patients with hemianopia have for example been shown to utilize predictive information of target locations to compensate for their visual field defect, while neglect patients in the same study failed to make use of the same information (Girotti et al., 1983). Moreover, Ishiai et al. (1987) showed that hemianopic patients without neglect were able to use compensational strategies trying to overcome their visual field loss by spending more time directing their gaze towards the hemianopic side of stimuli and making more step saccades (indicating search movements) on the hemianopic side than on the other side. This was further contrasted to patients who suffered from both hemianopia and neglect, as these patients demonstrated no such signs of compensation mechanisms. The authors suggested that with the additional neglect condition, a relative hypokinesia towards left hemispace occurred, leading to an inability to compensate for the visual field loss of hemianopia.

A study by Behrmann et al. (1997) elegantly plotted proportions of fixations across the field separately for a group of neglect patients and a group of hemianopic patients. The two groups showed completely opposite fixation biases. A steep negative linear relation between proportion of fixations and horizontal position was found in hemianopic patients, suggesting they are able to compensate for their visual field loss by directing their gaze more frequently towards the hemianopic side. Conversely, neglect patients showed a steep positive linear relationship with more fixations in the right field, and thus revealed no signs of compensational mechanisms at play. While Article I reports that patients with severe neglect show similar fixation patterns as seen in the results of Behrmann and colleagues (1997), it is additionally revealed that compensational fixation mechanisms may be present in some neglect patients who have less pronounced neglect symptoms. This suggests also that the presence of neglect may not necessarily be indicated by the spatial distribution of fixations, rather this distribution may reflect the degree of neglect or specific stages of the recovery process.

In the acute phase of a right hemisphere stroke, neglect patients are often *anosognosic*, meaning they are unaware of their deficit, or they tend not to recognize the severity of it (Clarke & Bindschaedler, 2014). Moreover, with anosognosia for neglect it would undeniably be difficult to implement compensational strategies to overcome leftward inattention.

However, we did not assess for anosognosia, as patients were no longer in the acute phase of the stroke. Nevertheless, the present findings suggest that compensational fixation mechanisms may be present in some neglect patients, at least at some point during their course of recovery. Further research may provide more knowledge of such compensational mechanisms and fixational distributions may be able to provide valuable information relevant to the patient's prognosis and choice of rehabilitation techniques.

### **Saccadic frequencies reveal a directional bias in orienting**

The present findings suggested saccadic rates to be dependent on direction in both the neglect group and the control group. Importantly, there were opposite biases displayed in the two groups with regards to direction.

The neglect group showed an expected rightward bias, making more saccades towards the right than towards the left, which is in line with theoretical accounts suggesting that directional hypokinesia constitutes a significant component in the neglect syndrome (Heilman et al., 2000; Ishiai et al., 1987). The fact that a direction-specific bias could be detected in saccade rates on correctly responded trials, suggests saccade properties offer a sensitive measure of neglect symptoms even in situations where patients apparently overcome their left-neglect sufficiently to manage the task successfully.

The direction-specific bias is also consistent with findings of Posner et al. (1987), who revealed a bias in the orienting response in patients with unilateral parietal lesions during Posner's cueing task. Their bias was related to the direction of the spatial shifts of attention, regardless of whether the target was presented in the left or right side of space. Thus, the authors suggested there was a direction-specific, rather than spatially dependent deficit in the disengagement procedure specifically. The present work shows similar findings and can thus also be interpreted in light of Posner and Petersen's (1990) theoretical account on attention, suggesting the orienting component can be affected in neglect.

However, signs of direction-specific deficits in neglect do not rule out the possibility that some patients may also suffer from hemispace-specific deficits. Evidence has been reported suggesting orienting deficits specifically within the left visual field in neglect patients with parietal injuries. One study investigated disengagement deficits with a different cueing paradigm, where the covert shifts of attention from invalid cues were made along a vertical axis within the same (either left or right) hemifield (Baynes, Holtzman, & Volpe, 1986). While that study reported generally slowed reaction times in groups of patients with

left or right parietal lesions compared to controls, it was also reported an additional slowing of orienting mechanisms within the contralesional hemifield in right parietal-lesion patients. As Article I did not separately assess saccades made within the left or right hemispace, it cannot be inferred whether hemispacial deficits in orienting were present in addition to the directional orienting deficit revealed.

While our group of neglect patients made more saccades towards the right than towards the left, the opposite pattern was revealed in the control participants as they made more saccades directed towards the left than towards the right. The pattern found in controls is consistent with previous reports of Bosworth et al. (2012) suggesting that normal healthy participants can have a tendency to show increased attention for objects in motion when they are presented within the left visual field compared to the right visual field. Bosworth and colleagues referred to split-brain research suggesting a specific role of the right hemisphere in spatial vigilance (e.g., Dimond, 1979), interpreting their findings as yet another indication of this relationship. The present findings may thus also be suggestive of right-hemisphere dominance in the mechanisms of spatial vigilance, as our controls show a comparable leftward bias, and our neglect patients show an opposite rightward bias that could be explained by disrupted spatial vigilance mechanisms of the right hemisphere.

## **RESOURCE ALLOCATION IN NEGLECT**

As highlighted throughout this thesis there is more to neglect than just spatial inattention. The neglect patients' visual processing, as reflected by fixation rates in Article I, seemed generally less efficient as they required more fixations to take in relevant visual information than controls did. Furthermore, it is apparent that they did manage to increase their expenditure of visual resources, though the severity of neglect appeared to be of relevance for how such compensational mechanisms were utilized across space. The current findings suggest that, in comparison with a group of normal healthy control participants, arousal mechanisms in the participating neglect patients were markedly weakened, reflecting less attentional resources being mobilized. Indeed, we found that the temporal dynamics of perceptual alternations during binocular rivalry were greatly reduced in our group of right hemisphere stroke patients and especially so in the neglect patients. Arousal, visual processing efficiency, and perceptual dynamics may all reflect allocation or availability of cognitive resources that are affected differently in each of the subgroups of patients tested, and even individually within these groups. Fixation frequencies were equally increased in the two patient groups as compared to

controls, suggesting inefficient processing and a general need for allocating more visual resources to the task. These increases in fixation rates could also indicate that both patient groups had an ability to initiate compensational mechanisms. However, only a proportion of the neglect patients (those with less severe neglect) seemed able to distribute these visual resources towards the contralesional field to compensate for their contralesional deficits. Arousal mechanisms and rivalry dynamics were shown to be particularly impaired in the group of neglect patients compared to the other groups of participants (right hemisphere stroke patients without neglect symptoms and healthy control participants).

### **Patient groups show reduced visual processing efficiency**

Eye movement measures, such as the fixation rate during task performance, have been associated with aspects of cognitive processing (Goldberg & Kotval, 1999; Krieger et al., 2016; Reingold et al., 2001; Reingold & Charness, 2005; Kasarskis et al., 2001). For example, fewer fixations have been associated with higher efficiency (Goldberg & Kotval, 1999) and also with higher expertise (Krieger et al., 2016; Reingold et al., 2001; Reingold & Charness, 2005). Article I revealed increased fixation frequencies in patients with brain injuries compared to healthy controls, which we suggested indicated a generally reduced efficiency in the utilization of information from each fixation in the patient groups. It may be that with inefficient visual processing of each fixation, more fixations are required to allow the same amount of information to be processed. However, it has also been demonstrated in healthy participants that during performance in challenging tasks, an increase in number of fixations can also predict better performance, regardless of whether the individual is an expert or a novice in the given field (Kasarskis et al., 2001). Thus, fixation rates may also reflect some form of effort or resource investment to the task.

The cognitive effort required to manage the MOT task is thought to increase with each added target in the different workload conditions. Since the current results also revealed an increase in fixation rates across all groups when multiple (as opposed to single) targets were tracked, we surmise that the effort or resource investment was boosted when the fixation rate was increased. However, it should be noted that the observed increase in fixation rate did not continue stepwise for each level of added load but rather it appeared to reflect the transition from tracking one single target to tracking multiple targets in general. The increase in fixation rate for multiple targets may therefore be accounted for by the added component divided attention. Keeping track of multiple targets likely requires more frequent shifts of attention, as

attention is shared between multiple foci and accordingly there may be a need for more frequent attentional updates on each of the different targets' spatial positions in order to avoid losing track of them. Frequent shifts and thus increased fixation rates are likely to facilitate the tracking in multiple target conditions, while a more steady pursuit of the single target will suffice in the single target condition.

The fixation rate during task performance may thus serve as an indication of the efficiency in visual processing, as the number of fixations needed to manage the task could reflect the amount of information acquired from each fixation: With high efficiency in the information uptake the need for additional fixations would accordingly decrease. At the same time, the increased fixation rates may also reflect an ability to allow an increase in the input volume for processing in order to meet with higher task demands. Such increases in fixation rates were observed in all groups as conditions of load were adjusted to include divided attention.

Consistent with the above points, the fixation frequencies reported in the present study can be seen as suggestive of reduced visual processing efficiency in both patients groups suffering from right hemisphere stroke. Additionally, it appears that all groups were able to allocate more visual processing resources when divided attention was added to the task requirements, as they had increased fixation frequencies in multiple target conditions. Fixation rates carried no indications that the general reduction in visual processing efficiency was worse in the neglect patients than the right hemisphere stroke patients without neglect symptoms. As such, we may infer that the reduced efficiency was not related to the neglect per se; however, as Husain and Rorden (2003) highlight, lateralized and non-lateralized mechanisms may interact in neglect and affect the outcome of the spatial disorder.

Although the fixation rates of the two patient groups were comparable, the performance measures suggested that the neglect patients struggled more with the MOT task. The fixation mechanisms may only have provided slight improvements in neglect patients' task performance. Looking at the distribution of fixations across the field, it is evident that our group of neglect patients distributed their visual resources unevenly: It appeared that a proportion of the patients were able to target mechanisms that increase fixation rates in attempts to compensate for their spatial inattention.

## **Pupillary responses reveal markedly reduced attentional arousal regulation in neglect**

Selective attention is grounded on the idea that our resources are limited, and accordingly it is important to employ them wisely (Kastner & Ungerleider, 2000), placing our focus on the most relevant information and ignoring unnecessary distractions (Kim & Cave, 1999). Kahneman (1973) emphasized the aspect of available resources and the concept of attention intensity. With elevated task demands the amount of processing resources required to solve a task is increased and there is an increased need of attentional effort investment. Pupillary responses have been associated with the cognitive effort invested in a task, since task-evoked pupillary dilations have been found to increase stepwise with added cognitive load (Kahneman & Beatty, 1966; Kahneman, Tursky, Shapiro, & Crider, 1969; Kahneman, 1973). Furthermore, it has been shown that this relationship between invested effort and pupillary dilations may be demonstrated through the MOT task (Alnaes et al., 2014; Wahn et al., 2016). In addition, a previous study by Kim et al. (1999) has reported deviations in the pupillary responses of two right hemisphere stroke patients with neglect as compared to the pupillary responses of a healthy control group, in line with the idea that neglect involves an arousal deficit. However, the study mentioned could not infer whether it was neglect per se or the right hemispheric lesion in general that led to these deviations.

In Article II we showed that pupillary responses were reduced in both our patient groups, which signifies that a right hemisphere stroke can lower arousal levels and reduce the available attention resources. Interestingly, while patients without neglect increased their pupillary dilations when the task load was elevated, neglect patients showed no signs of adjustments in these arousal levels when the task demands were altered. Thus, in light of Kahneman's (1973) model of attention and effort it appears that although the patients without neglect showed signs of reduced available resources, they still managed to regulate their expenditure of resources in accordance with task demands. In contrast, the neglect patients appeared to have problems allocating resources and showed no changes in the use of resources when task demands were increased further. This could either be due to severely limited resources, a deficit in the mechanisms that allocate them when task demands increase, or possibly a combination of the two. Moreover, the present findings show that problems with arousal caused by stroke to the right hemisphere can be more extreme when neglect symptoms are also present. However, no causal inferences can be made from this study regarding the relation between neglect and reduced arousal.

Since arousal appears to be so low in our neglect patients, it is not surprising that their task performance was reduced. The neglect patients did show considerably lower scores than the other groups. Note that the analyses on pupillary responses only included correctly responded trials in conditions where response accuracy significantly exceeded chance levels. This was done in order to ensure that results reflected states when participants attended to and were committed to the task at hand.

The present findings of impaired arousal in the neglect patients support the range of previous studies suggesting that non-spatial deficits are relevant for the neglect syndrome (Karnath, 1988; Hjaltason et al., 1996; Husain et al., 1997; Robertson et al., 1997; Samuelsson et al, 1998).

### **Rivalry alternation rate suggests slowing of neural mechanisms**

The dynamics of binocular rivalry alternations may also give indications of an individual's ability to access neural processing resources. Article III assessed such dynamics in right hemisphere stroke patients and control participants, and also compared alternation rates in subgroups of the patients with and without neglect symptoms. While the right hemisphere stroke patients in general had slower alternation rates than the controls, it was strikingly clear that rivalry mechanisms were much slower in the neglect patients than in the patients without neglect. This suggests neglect patients may experience a more extensive loss of, or inaccessibility to, neural processing resources.

It should be noted that that perceptual adaptation mechanisms are thought to be involved in producing rivalry alternations (Kang & Blake, 2010; Paffen & Alais, 2011; Zaretskaya, Thielscher, Logothetis, & Bartels, 2010) and that these mechanisms may be disrupted in neglect (Bonneh et al., 2004). According to this perspective, rivalry occurs in the early cortical areas where monocular inputs are initially combined and a conflict between inputs first emerges. It has been suggested that when rivaling images are presented to the two eyes there is reciprocal inhibition between the two monocular neural populations. One percept will first achieve perceptual dominance while the other is suppressed, however adaptation mechanisms are assumed to gradually weaken the signals of the dominant input. As these signals weaken, the balance between the competing inputs is altered and a perceptual switch occurs (Paffen & Alais, 2011). With this in mind, slower rivalry dynamics found in stroke patients may likely result from impaired adaptation mechanisms (Bonneh et al., 2004). The extreme slowing of perceptual alternations in the present sample of neglect patients may also

be explained by problems with disengaging from an attended stimulus in order to reorient the attention to another stimulus (Morrow & Ratcliff, 1988; Posner et al., 1984).

Previous research has shown a correlation between scores from the Behavioral Inattention Test (BIT; Wilson et al., 1987) and binocular rivalry alternation rates (Bonneh et al., 2004) and Article III re-examined this. Although faster rivalry dynamics were typically found with higher BIT-scores also in the present study, a regression analysis revealed that these scores were only able to explain a small part (15.7%) of the variance across the whole right hemisphere patient group. While neglect patients' rivalry mechanisms were clearly more affected than those of other right hemisphere stroke patients, the BIT, which mainly assesses the spatial symptoms of neglect, does accordingly not cover in full the pathologies of neglect. Previous research has suggested that the degree of neglect may be linked with the degree of non-spatial attention impairments (Bartolomeo & Chokron, 2002; Husain & Rorden, 2003). We should consider that such non-spatial factors may offer appropriate explanations to the slowing of rivalry mechanisms. We learned from Article II that the same groups of patients had reduced pupillary responses, especially the neglect group which did not show any sign of enhanced arousal when load was increased. Given the severe deficits in the mechanisms for regulating arousal, such deficits are consistent with a slowing of rivalry dynamics.

Fixation frequencies reported in Article I suggested that both subgroups of patients were equally impaired in visual processing efficiency. However, in Article III it was evident that the neglect patients showed an extreme slowing in rivalry alternation rates, even compared to the non-neglect patient group. Thus, while fixation processing mechanisms may have been impaired in both of our patient groups, attention arousal and rivalry rates were more severely reduced in the neglect patients. We note that eye-movements have also been suggested to influence fluctuation rates during binocular rivalry (Sabrin & Kertesz, 1983). However, van Dam & van Ee (2006) found that eye-movements are not primarily the cause of fluctuations, but instead they increase at the time of perceptual change as an added effect. The authors further concluded that the bottom-up influence of retinal image changes may be stronger. Although eye-movements have not been found to cause a change in perceptual fluctuation, it is a factor that could have an influence when the functionality of the attention system is reduced (e.g., in stroke patients). By utilizing eye-tracking during binocular rivalry with anaglyphs (for an example, see Chelnokova & Laeng, 2011), it may be possible to investigate the role of eye-movements during alternations.

## **A LINK BETWEEN ATTENTIONAL RESOURCES AND SPATIAL ATTENTION**

The distributed processing hypothesis proposes that damage to one neural network may weaken the functioning in another neural network. Specifically, different individuals with neglect often suffer from injuries to different regions of the brain, even so (at least in part) the same mechanisms of attention are affected (Corbetta et al., 2005). Interestingly, unilateral stroke patients have demonstrated weakened performance in contralesional space (as opposed to ipsilesional space) on visual awareness tasks when task demands increase (Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010). Thus, it has been suggested that the mechanisms of contralesional spatial awareness may depend on the available amount of attentional resources (Bonato, 2012). Several studies suggest a link relating the severity of neglect with the degree of sustained, non-spatial attention functioning (Robertson et al., 1997; Hjaltason et al., 1996). The present work adds to a range of studies showing the presence of non-spatial deficits in addition to the better known spatial deficits in neglect patients. The impaired arousal regulation that was revealed in Article II and the slow dynamics in resolving perceptual conflicts that were shown in Article III seem particularly pronounced in the neglect group tested, while the fixation frequencies reported in Article I suggest that a right hemisphere stroke in general may lead to less efficient visual processing. It remains unclear whether a similar conclusion could be drawn regarding the effect of left hemisphere strokes. Coexistence of, and correlations between, spatial attention deficits and reduced non-spatial resources do not alone imply a causal relationship between non-spatial deficits and the neglect syndrome. However, a previous study by Robertson et al. (1998) showed that the spatial symptoms of neglect could actually be modulated by changing the participant's alertness levels. Accordingly, it has been proposed that non-spatial attention functioning may be crucial for the manifestation and recovery outcomes of neglect. Further, it has been stressed that the restoration of non-spatially lateralized attention functioning should be targeted in rehabilitation research since this may be a crucial factor for the retrieval of normal spatial attention functioning (Robertson, 2001).

Another line of evidence that suggests a link between arousal and spatial attention is provided by functional neuroimaging studies. Several neuroimaging studies have found overlapping areas of activation in the brain when healthy participants have been engaged in alertness tasks and spatial attention tasks, specifically in the right parietal lobe which is often injured in patients with neglect (Sturm et al., 1999; Sturm & Willmes, 2001). The idea that attention is the product of interacting processes supported by different neural networks

(Corbetta, Patel, & Schulman, 2008; Corbetta & Schulman, 2011; Posner & Petersen, 1990) also implies that one attentional process could influence the activity of another and that overlapping neural activity could suggest a location where this occurs. The overlapping neural activity from two different processes could also explain how both processes can be affected by an injury to the given region.

One proposed mechanism for non-spatial attention modulation involves the Locus Coeruleus – Norepinephrine (LC-NE) system. The discharge of Norepinephrine (NE) throughout the brain is thought to be essential for mechanisms of attention, arousal and cognition (Schwarz & Luo, 2015). Animal studies suggest that a small nucleus called Locus Coeruleus (LC), located in the dorsal pons of the brainstem, sends extensive projections to the brainstem, cerebellum and cortex to release NE (Jones, Halaris, McIlhany, & Moore, 1977; Aston-Jones & Cohen 2005). It has accordingly been proposed that the LC-NE system may be an important component in neglect, as disruptions in the activation of the LC (due to injuries to the actual LC or to neurons projecting signals between LC and parietal regions) may result in reduced attention arousal, potentially affecting the processing of target stimuli in the left side of space (Robertson, 2001). Corbetta and Shulman (2011) argue that while disrupted interhemispheric interactions are a key factor in producing the spatial gradient in neglect, arousal is a modulator to this gradient. Thus, neglect may be further exacerbated by reduced arousal functioning. This fits well with the proposed role of the right hemisphere in arousal mechanisms. The present findings show particularly reduced mechanisms for regulating arousal in the patients with neglect and are thus consistent with this idea.

Findings from studies of healthy participants are also suggestive of a link between alertness and spatial attention. A number of studies, including the present one (Article I), have shown indications of a slight but consistent, initial, leftward, spatial attention bias in healthy participants, and this bias is respectively of the opposite direction than that shown in left spatial neglect patients (Bowers & Heilman, 1980; Bosworth et al., 2012). For example, Bosworth and colleagues (2012), who specifically used moving stimuli as did two of the articles in the present work, revealed increased attention in the left visual field compared to the right visual field. In Article I, the healthy control sample revealed a leftward bias as saccade frequencies were direction-specific. The controls made a higher number of leftwards than rightwards directed saccades, a pattern opposite to that found in the neglect patients. Interestingly, initial leftward biases found in healthy participants have been shown to be reduced with lowered alertness (Dufour, Touzalin, & Candas, 2007) and, in some cases, even to shift towards a rightward bias when alertness is lowered further (Manly, Dobler, Dodds, &

George, 2005). Thus, it appears there may be a link between spatial attention biases and non-spatial attention functioning, so that one may change with changes in the other, and this is evident in healthy controls (Dufour et al., 2007; Manly et al., 2005) as well as neglect patients (Robertson et al., 1998).

Interestingly, research on attention deficit hyperactivity disorder (ADHD) supports the idea of a connection between alertness and spatial attention. It is known that individuals with ADHD often have problems with vigilance, struggling to sustain appropriate alertness levels (Tucha et al., 2006a; Tucha et al., 2006b) and it has been shown that some individuals with ADHD tend to favour the right side over the left side, though to a lesser degree than neglect patients (Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995; Dobler et al., 2005; Sheppard, Bradshaw, Mattingley, & Lee, 1999). Moreover, when these individuals are successfully medicated with stimulants increasing their levels of arousal, their rightward bias ceases to exist (Sheppard et al., 1999). The spatial bias may not be universal in ADHD as some studies have also failed to detect such biases (Aliabadi et al., 2011). The idea that several mechanisms may work together in attention, however, may explain such variations in symptoms, as differential types of malfunctions to this system open for differential symptoms. Taken together, higher alertness has been associated with increased leftward attention, while lower alertness has been associated with increased rightward attention and such patterns has been demonstrated in neglect, ADHD, and in healthy subjects.

The binocular rivalry measures in Article III revealed an extreme slowing of perceptual alternations in the present sample of neglect patients, which only in part was related to the degree of spatial symptoms reflected in the patients' BIT scores. Impaired arousal mechanisms that have in previous studies been found to correlate with the severity of spatial neglect, may better predict the slowing of rivalry dynamics. Neglect patients in the present study did also reveal reduced attention arousal during MOT. However, without having directly investigated the relation between the degree of arousal deficits and the severity of spatial neglect, we can only maintain that the present findings suggest resource allocation can be severely reduced in several aspects of cognitive functioning in neglect.

## **CLINICAL IMPLICATIONS**

The present findings contribute to the understanding of the mechanisms behind neglect. We have clearly shown that neglect patients may struggle with weakened resources, as the present sample showed severely reduced attention arousal measures, their perceptual switches during

binocular rivalry were extremely slow, and they showed increased fixation rates during multiple object tracking compared to the healthy control participants. Knowing that such resources may be scarce in these patients, it is essential that we achieve further insights into the workings of such mechanisms, as well as their potential mediating and modulating effects on each other and on other aspects of cognitive functioning, like spatial attention. As we become more familiar with the neural mechanisms that interact, this opens for targeted treatments towards relevant mechanisms in attention disorders. Thus, a better understanding of the mechanisms behind attention disorders may potentially have implications for approaches to rehabilitation and can hopefully lead to faster and more complete recovery. The present work suggests that the clinical field may benefit from future studies looking closer into interacting mechanisms of attention and cognitive resources as these may carry keys for potential advances in rehabilitation. This is also supported by previous research that suggests the functioning of non-spatial mechanisms is of relevance to the severity and prognosis of spatial attention deficits (Robertson et al., 1997; Hjaltason et al., 1996). Previous studies have even demonstrated that by increasing alertness levels in neglect patients their spatial symptoms ameliorate (Robertson et al., 1998). An increased understanding of the role of different attentional components and resource allocation in the neglect syndrome may be crucial for the rehabilitation process, as this knowledge may influence which processes can be singled out as appropriate targets for training and treatment.

The present findings inform us that oculomotor processes such as direction-specific saccade frequencies may be used to reveal neglect, even when it seems that the patient competently manages the task. A proper diagnosis or a clean bill of health may in some cases be imperative, for example before allowing the patient to drive a car. Furthermore, this information may be useful in monitoring the process of recovery. The fixation data of the current work further indicates that compensational fixation mechanisms may be at use in some neglect patients, as they show increased rates of fixations in the contralesional field compared to their ipsilesional field. Such compensational mechanisms have been detected in hemianopic patients before, and the present finding thus suggests that also neglect patients may learn to make use of such mechanisms to overcome their spatial attention deficits. Eventually, assessments of these mechanisms may inform us of the likely prognosis for spontaneous recovery or probable response to interventions. However, there is still considerable time before these measures can be utilized in this way.

With large variations in the extent of the damage from stroke, it is imperative to achieve detailed and accurate knowledge of the patient's pathology. This is important in order

to make accurate diagnoses, to predict with good probability the patient's prognosis of recovery, and also to set up an appropriate plan for training and rehabilitation procedures. Moreover it is important that family members of the patient are provided with realistic expectations of how their situation will develop in order for them to be able to assist with training, care and support in the best possible way.

The present work attempts also to separate which deficits may be related to the clinical condition of neglect and which may be caused by stroke in general. Notably, even though visual processing efficiency can be reduced in stroke patients regardless of whether they show symptoms of neglect, one should keep in mind that this cognitive change may still affect the attention and visual strategies of neglect patients. Knowledge of attention mechanisms in general may also have implications for diagnosis, prognosis, and treatment in other neuropsychological or psychiatric disorders where attention pathologies are apparent. Connecting the findings from research in different areas of attention pathology may broaden our knowledge of how attention works and also strengthen the support for specific theoretical ideas.

The recent advances in eye-tracking technologies open numerous possibilities. Eye-tracking has become a non-invasive method that can provide a host of valuable information. It is now even simpler to apply these measurements in a clinical setting, as calibration methods are simplified and demands on the patients are lessened (e.g., they may not need chinrests depending on the type of experiment and task). An important point, however, is that we need to develop a better understanding of what these measures represent so that we can identify which measures are more relevant and applicable in different settings and best utilize the available resources. The present work utilized the MOT task in combination with eye-tracking and pupillometry measures and thus provides an example of how attention may be measured by use of these procedures. Pupillary responses were used to reflect states of attention arousal in the participant. Eye-tracking revealed the functioning of the participants' oculomotor components and allowed for closer assessments of how they were utilizing their visual field and their visual processing resources. An advantage of eye-tracking and pupillometry measures is also that they provide efficient tools of data collection. In addition to the numerous types of measurement parameters that can be extracted from a data file, this technique produces a lot of data with great speed (there are often multiple fixations and saccades registered during each trial), therefore easily providing considerable statistical power.

While standard neglect tasks address spatial attention dysfunction, recently more emphasis is being placed on the non-spatial components of the neglect syndrome, suggesting that clinical assessments should include tests of various non-spatial attention components as well. While MOT was clearly able to provide a test of spatial attention, it additionally uncovered reduced functioning in the ipsilesional field. MOT thus provided a sensitive measure of both spatial and non-spatial attention deficits. Importantly, while the MOT task in general is a quite demanding task it can also be adjusted with a lower load than what was used in the present work by: shortening the tracking time, including fewer objects on the screen (fewer distractors), or adjusting the speed of movements. An advantage of the MOT task is that it covers several components of attention; divided, sustained, spatial, etc. Moreover, parameters reflecting such components may easily be adjusted (e.g., load, degree of distractions, tracking time, spatial aspects, bilateral or unilateral stimulation, size of stimuli, speed). The simplicity of the stimuli and task, and the variety of possible attention measures thus offers a reasonable potential for being developed into computerized cognitive assessment and training. In addition, compared to traditional, static, paper-and-pencil tasks, MOT provides ecological validity as it reflects the dynamic environment around us.

## **METHODOLOGICAL ISSUES AND LIMITATIONS**

Studies of brain damaged patients provide a unique opportunity to assess the relations between different aspects of attention functioning. Research with clinical groups may isolate certain components, helping to shed light on these mechanisms. It should be noted that this approach, as any other, is not free from confounds. It is rare to find an explicit processing deficit without the simultaneous expression of other deficits, and patient groups may vary greatly with regard to lesion locations and extensity, as well as the composition of cognitive damage resulting from the brain injury (Rorden & Karnath, 2004). In addition to variations in the clinical picture, the patients' health history and socioeconomic background are often different which may further complicate interpretation of the results. These elements may lead to much variation within groups, challenge the means of generalizability, and complicate isolating the distinct aspects of cognitive functioning, such as attention components. In addition, since inclusion of participants was not randomized, participation was voluntary, and Sunnaas patients may be different from the general stroke population (as enrollment of patients are decided on the basis of specific criteria), selection biases may have occurred leading the patient sample not to be representative for the stroke population in general. There

may also be further selection biases in the subgroups of patients. Despite the possible limitations, studies of brain-damaged patients still provide a valuable contribution to the sciences of cognitive and neuropsychology, and especially so in combination with recent technological advances.

The present work would have greatly benefited from the inclusion of a left hemisphere stroke patient group, providing a better view on lateralized components of attention. As only a right hemisphere stroke patient control group was included, we must be careful in generalizing the results from this group to the whole stroke population, as we cannot know for certain whether a right hemisphere stroke or a stroke in general would lead to the results found in this group.

The occurrence of neglect has been associated with large and extensive lesions (Husain & Rorden, 2003; Karnath, Fruhmann Berger, Küker, & Rorden, 2004). Unfortunately, we were not able to retrieve detailed information about the lesions of individual patients and accordingly, we could not conduct any analyses including lesion volume or detailed anatomical locations of injuries as factors. Thus, we cannot say whether the size of the stroke affected the results or point to specific locations of the right hemisphere being responsible for particular neural processes.

Since none of the patients were tested in the acute phase after the stroke and anosognosia is more likely to occur during this phase, we did not include assessments of whether any patients suffered from this additional awareness deficit or to what degree this deficit was present in the individual. However, such an assessment could have been done using the Catherine Bergego Scale (CBS; Azouvi et al., 2003) and would have allowed for an investigation of whether any correlations were present between spatial distribution of fixations and anosognosia. If a patient suffered from anosognosia for neglect, one could argue that any attempt to compensate for problems with spatial attention would be unlikely, as the patient would not be aware of these problems.

Regarding eye-tracking measures, it should also be noted that since we have not included any measures of microsaccades in the current study, we cannot conclude whether or not there are differences between the groups in the number of smaller correctional saccades in left and right directions. Such differences could possibly reflect saccadic compensational strategies, for example attempting to overcome any challenges in orienting attention. However, the equipment used in the current work is not recommended for analyses on such measures. Future studies using more sophisticated equipment for investigating saccadic properties may possibly reveal signs of saccadic compensational strategies in neglect.

Concerning the pupillary findings of the present work, there are also a few issues that should be taken into account when interpreting the results. The findings that stroke patients, and neglect patients in particular, had reduced arousal responses could be explained by several means. Lowered arousal levels could for example reflect a lack of dedication to perform the task correctly. However, in order to ensure that some effort was invested in the task, we chose to include only trials with correct responses in our pupillary analyses. For the same reason, only conditions where all groups had accuracy scores significantly exceeding the chance level of 50% were included in the analyses, as there is an increased chance of getting false positives (guessing correctly without actually managing to track the targets) when accuracy scores approach chance level. Moreover the experiment presented trials of different conditions in an unpredictable order (left vs right hemispace conditions and yes vs no responses being presented in a pseudorandomized manner). Thus, as the patients showed quite high accuracy scores in some conditions (right hemispace and lower load conditions) it is also probable that they maintained attention to the task throughout the experiment. Thus, small pupillary changes would not indicate a lack of commitment, but impaired mechanisms of arousal regulation. Future studies could, by reducing the number of distractors, tracking speed and duration, possibly lower the task demands sufficiently so that neglect patients may also perform better in the left hemispace. This may allow for more detailed assessments of potential interactions between effects of load and hemispace in this group.

Finally, using relatively large size stimuli for the binocular rivalry task could have resulted in a higher incidence of piecemeal rivalry. Piecemeal rivalry may further lead to inaccurate reports if participants are not provided with clear task instructions. For example, a modest participant may report fewer alternations than what actually occurs. We thus took as much time as needed to instruct participants well, allowing them to ask questions and discuss their rivalry experience during test trials before starting with the experiment. A possible solution to avoid piecemeal rivalry, and also to avoid crosstalk that may occur due to poor filtration of colors through the glasses, is to present the task using a mirror arrangement with dual-monitors and a stereoscope.

## CONCLUSION

The three articles in the present work investigate the allocation of different forms of cognitive resources and components of attention in neglect patients, stroke patients without neglect symptoms, and healthy controls. Taken together, our findings confirm that in some neglect patients not only spatial attention deficits can be found, but also general problems with allocating and/or regulating attentional resources by adjusting the arousal levels in the brain. Reduced attention resources may also present a problem for right hemisphere stroke patients without neglect, though it appears that the ability to regulate arousal in accordance with task demands is more severely affected when the right hemisphere stroke has additionally led to the condition of spatial neglect. Our findings suggest that the consequences from right hemisphere stroke on attention functioning may be more serious in cases where neglect symptoms are evident, as performance on attention tasks can drop considerably even in the ipsilesional field.

In addition, perceptual processing may be affected from a stroke in general (at least a right hemisphere stroke), as alternation rates in binocular rivalry can be slower than what would be considered normal. Our findings further suggest that this problem can be magnified for someone suffering from neglect. Slow alternation rates suggest a slowing of neural processing mechanisms, which may reflect a reduction in the available neural processing resources. Thus, both arousal measures and rivalry dynamics are indicative of neglect involving problems with resource allocation.

The present results show that fixation rates may also reflect resource utilization in the processing of visual input. It is evident that a right hemisphere stroke in general may affect visual processing efficiency, increasing the need for more fixations (at least during specific attention demanding tasks) because less information is taken in with each fixation. Increases in fixation rates indicate that there is an ability to activate such compensation mechanisms, attempting to improve the efficiency of visual processing. There were no signs of a further increase in fixation frequencies when neglect symptoms were present. However, as performance was more reduced in neglect patients, the general strategy of increasing the fixation rate may have provided better compensation when there was no additional problem with spatial attention. In fact, within the population of neglect patients, it may be that this strategy is more successful in patients who exhibit less pronounced spatial symptoms, as they could also have the ability to distribute the additional fixations more advantageously by

directing them towards the problematic left visual field. Accordingly, while both right hemisphere stroke patients with and without neglect may have the ability to compensate for inefficient visual information uptake by increasing fixation rates, neglect patients may also depend on an ability to focus this resource investment towards their neglected field in order to benefit from this.

It should be emphasized that further research is needed to get a proper understanding of the significance and the potential implications of the functioning of different resource mechanisms in neglect. The present work contributes towards a broader understanding of the pathologies that may occur in neglect and of attention and its many interconnected and interacting mechanisms. We encourage future researchers to utilize eye-tracking and pupillary measurements in assessments of visual attention and in particular, in assessments of neglect. As we accentuate the focus on general, and hence non-spatial, mechanisms of cognitive resource allocation in the neglect syndrome, we hope to influence future approaches to clinical assessment and rehabilitation. A more complete understanding of the significance of such mechanisms in neglect may be beneficial in the development of tools for diagnosing attention pathologies, for predicting prognoses of recovery, as well as for training attention functioning.



## REFERENCES

- Adair, J. C., Williamson, D. J., Jacobs, D. H., Na, D. L., & Heilman, K. M. (1995). Neglect of radial and vertical space: importance of the retinotopic reference frame. *Journal of Neurology, Neurosurgery & Psychiatry*, Jun;58(6):724–728.
- Aliabadi, F., Borhani, K., Alizadeh, M., & Amiri, N. (2011). Visuo-spatial Attention in ADHD Children: Investigating the Asymmetry. *Iranian Rehabilitation Journal*, 9(13), 19-21.
- Allen, M. (2017). *The SAGE Encyclopedia of Communication Research Methods*. SAGE Publications, Inc. Los Angeles, p.666, ISBN: 978-1-4833-8143-5.
- Alnaes, D., Sneve, M. H., Espeseth, T., Endestad, T., de Pavert, S. H. P. V., & Laeng, B. (2014). Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. *Journal of Vision*, 14(4), 1-20. doi:Artn110.1167/14.4.1.
- Alvarez, G. A., & Franconeri, S. L. (2007). How many objects can you attentively track?: Evidence for a resource-limited tracking mechanism. *Journal of Vision*, 7(13), 1-10. doi:10.1167/7.13.14 .
- Anderson, B. (1996). A mathematical model of line bisection behaviour in neglect. *Brain*, 119: 841 – 850.
- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annual Review of Neuroscience*, 28:403-50, DOI: 10.1146/annurev.neuro.28.061604.135709.
- Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., & Tesio, L. (2003). Behavioral Assessment of Unilateral Neglect: Study of the Psychometric Properties of the Catherine Bergego Scale. *Archives of Physical Medicine & Rehabilitation*, Vol 84. doi:10.1053/apmr.2003.50062.
- Bailey, M. J., & Riddoch, M. J. (1999). Hemineglect. Part 1. The nature of hemineglect and its clinical assessment in stroke patients: an overview. *Physical Therapy Reviews*, 4:67-75.
- Bashinski, H. S., & Bacharach V. R. (1980). Enhancement of perceptual sensitivity as the result of selectively attending to spatial locations. *Perception & Psychophysics*, 1980,28 (3),241-248.
- Bartolomeo, P., & Chokron, S. (1999). Left unilateral neglect or right hyperattention? *Neurology*, 53, 2023–2027.
- Bartolomeo, P., & Chokron, S. (2002). Orienting of attention in left unilateral neglect. *Neuroscience and Biobehavioral Reviews*, 26(2), 217–234.
- Battelli, L., Cavanagh, P., Intriligator, J., Tramo, M. J., Henaff, M.-A., Michel, F., & Barton, J. J. S. (2001). Unilateral right parietal damage leads to bilateral deficit for high-level motion. *Neuron*, 32, 985–995.

- Baynes, K., Holtzman, J. D., & Volpe, B. (1986). Components of visual attention: Alterations in response patterns to visual stimuli following parietal lobe infarction. *Brain*, 109: 99-114.
- Beatty, J. (1982). Task-Evoked Pupillary Responses, Processing Load, and the Structure of Processing Resources. *Psychological Bulletin*, 91(2), 276-292. doi:Doi10.1037/0033-2909.91.2.276.
- Beatty, J., & Lucero-Wagoner, B. (2000). The pupillary system. In J. T. Cacioppo, L.G. Tassinary, G.G. Berntson (Eds.), *Handbook of Psychophysiology (2<sup>nd</sup> edition)*, Cambridge University Press. ISBN 62634X.
- Behan, M., & Wilson, M. (2008). State anxiety and visual attention: The role of the quiet eye period in aiming to a far target, *Journal of Sports Sciences*, 26:2, 207-215, DOI:10.1080/02640410701446919.
- Behrmann, M., Ghiselli-Crippa, T., Sweeney, J. A., Di Matteo, I., & Kass, R. (2002). Mechanisms Underlying Spatial Representation Revealed through Studies of Hemispatial Neglect. *Journal of Cognitive Neuroscience*, 14:2, 272–290.
- Behrmann, M., Ghiselli-Crippa, T., & Dimatteo, I. (2001). Impaired initiation but not execution of contralesional saccades in hemispatial neglect. *Behavioural Neurology*, 2001; 13: 39–60.
- Behrmann, M., & Moscovitch, M. (1994). Object-centered neglect in patients with unilateral neglect: Effects of left-right coordinates of objects. *Journal of Cognitive Neuroscience*, 6, 1-16.
- Behrmann, M., Watt, S., Black, S. E., & Barton, J. J. (1997). Impaired visual search in patients with unilateral neglect: An oculographic analysis. *Neuropsychologia*, 35, 1445–1458. doi:Doi10.1016/S0028-3932(97)00058-4.
- Beintema, J. A., van Loon, E. M., & van den Berg, A. V. (2005). Manipulating saccadic decision-rate distributions in visual search. *Journal of Vision*, 5, 150-164.
- Berlyne, D. E. (1960). *McGraw-Hill series in psychology. Conflict, arousal, and curiosity*. New York, NY, US: McGraw-Hill Book Company.
- Bissiach, E., & Luzzatti, C. (1978). Unilateral neglect of representational space. *Cortex*, 14, 129-133.
- Bonato, M. (2012). Neglect and extinction depend greatly on task demands: a review. *Frontiers in Human Neuroscience*, 6, 1-13, doi:10.3389/fnhum.2012.00195.
- Bonato, M., Priftis, K., Marenzi, R., Umiltà, C., & Zorzi, M. (2010). Increased attentional demands impair contralesional space awareness following stroke. *Neuropsychologia*, 48, 3934–3940.
- Bonneh, Y. S., Pavlovskaya, M., Ring, H., & Soroker, N. (2004). Abnormal binocular rivalry in unilateral neglect: evidence for a non-spatial mechanism of extinction. *NeuroReport*, 15(3), 473–477. <http://dx.doi.org/10.1097/01.wnr.0000109988.85243.c6>.

- Bosworth, R. G., Petrich, J. A., & Dobkins, K. R. (2012). Effects of spatial attention on motion discrimination are greater in the left than right visual field. *Vision Research*, 52(1):11-19. Doi: 10.1016/j.visres.2011.10.004.
- Bowen, A., McKenna, K., & Tallis, R. (1999). Reasons for the variability in the reported rate of occurrence of unilateral spatial neglect following stroke. *Stroke*, 30(6):1196-202.
- Bowers, D., & Heilman, K. M. (1980). Pseudoneglect: Effects of hemispace on a tactile line bisection task. *Neuropsychologia*, 18(4-5), 491-498. [http://dx.doi.org/10.1016/0028-3932\(80\)90151-7](http://dx.doi.org/10.1016/0028-3932(80)90151-7).
- Broadbent, D. E. (1958). *Perception and communication*. Oxford: Oxford University Press.
- Bundesen, C., & Habekost, T. (2008). *Principles of Visual Attention. Linking Mind and Brain*. New York, Oxford University Press. ISBN 978-0-10-857070-7.
- Cantor, J.B., Ashman, T., Gordon, W., Ginsberg, A., Engmann, C., Egan, M., ..., Flanagan, S. (2008). Fatigue after traumatic brain injury and its impact on participation and quality of life. *Journal of Head Trauma Rehabilitation*, 23(1):41-51.
- Carter, C. S., Krener, P., Chaderjian, M., Northcutt, C., & Wolfe, V. (1995). Asymmetrical visual-spatial attentional performance in ADHD: Evidence for a right hemispheric deficit. *Biological Psychiatry*, 37, 789–797.
- Chatterjee, A. (1994). Picturing unilateral spatial neglect: viewer versus object centred reference frames. *Journal of Neurology, Neurosurgery, and Psychiatry*, 57:1236-1240.
- Chatterjee, A., & Coslett, H. B. (2003). Neglect: Cognitive neuropsychological issues. In T. E. Feinberg & M. J. Farah (Eds.), *Behavioral Neurology and Neuropsychology (2nd edition)*. New York: McGraw Hill.
- Chelnokova, O., & Laeng, B. (2011). Three-dimensional information in face recognition: An eye-tracking study. *Journal of Vision*, 11.(13). ISSN 1534-7362. doi:10.1167/11.13.27.
- Cherney, L.R. (2002). Unilateral Neglect: A Disorder of Attention. *Seminars in Speech and Language*, 23(2), 117-128.
- Clarke, S., & Bindschaedler, C. (2014). Unilateral neglect and anosognosia, in M.E. Selzer, S. Clarke, L.G. Cohen, G. Kwakkel, and R.H. Miller (Eds.), *Textbook of Neural Repair and Rehabilitation (2nd edition)* (pp.463-477). Cambridge University Press.
- Clifford, C.W.G. (2009). Binocular rivalry. *Current Biology*, 19(22), 1022-1023.
- Corbetta, M., Kincade, M.J., Lewis, C., Snyder, A.Z., & Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature Neuroscience*, 8(11), 1603–1610. <http://dx.doi.org/10.1038/nn1574>.
- Corbetta, M., Akbudak, E., Conturo, T.E., Snyder, A.Z., Ollinger, J.M., Drury, H.A., ...Shulman, G.L. (1998). A Common Network of Functional Areas for Attention and Eye Movements. *Neuron*, Vol. 21, 761–773.

- Corbetta, M., Patel, G., & Shulman, G.L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, 58:306–24.
- Corbetta, M., & Shulman, G.L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, 34:569–99, doi: 10.1146/annurev-neuro-061010-113731.
- Craighero, L., & Rizzolatti, G. (2005). The premotor theory of attention. In Laurent Itti, Geraint Rees & John K. Tsotsos (eds.), *Neurobiology of Attention*. Academic Press. pp. 181-186.
- Crick, F., & Koch, C. (1998). Consciousness and Neuroscience. *Cerebral Cortex*, 8(2):97–107.
- Cusack, R., Carlyon, R. P., & Robertson, I. H. (2000). Neglect between but not within auditory objects. *Journal of Cognitive Neuroscience*, 12, 1056–1065.
- Daini, R., Facchin, A., Bignotti, M., Lentini, C., Peverelli, M., O'Shea, R. P., & Molteni, F. (2010). Neuropsychological evidence of high-level processing in binocular rivalry. *Behavioural Neurology*, 23(4), 233–235. <http://dx.doi.org/10.3233/BEN-2010-0303>.
- Dobler, V. B., Anker, S., Gilmore, J., Robertson, I. H., Atkinson, J., & Manly, T. (2005). Asymmetric deterioration of spatial awareness with diminishing levels of alertness in normal children and children with ADHD. *Journal of Child Psychology and Psychiatry*, 46:11 (2005), pp 1230–1248. doi: 10.1111/j.1469-7610.2005.00421.x.
- Driver, J., & Mattingley, J.B. (1998). Parietal neglect and visual awareness. *Nature Neuroscience*, 1(1), 17-22.
- Dufour, A., Touzalin, P., & Candas, V. (2007). Time-on-task effect in pseudoneglect. *Experimental Brain Research*, 176:532–537. DOI 10.1007/s00221-006-0810-2.
- Duncan, J., Bundesen, C., Olson, A., Humphreys, G., Chavda, S., & Shibuya, H. (1999). Systematic analysis of deficits in visual attention. *Journal of Experimental Psychology-General*, 128(4), 450-478. doi:Doi10.1037/0096-3445.128.4.450.
- Egeth, H.E., Virzi, R.A., & Garbart, H. (1984). Searching for conjunctively defined targets. *Journal of Experimental Psychology: Human Perception and Performance*, 10, 32-39.
- Ferro, J.M., Mariano, G., & Madureira, S. (1999). Recovery from aphasia and neglect. *Cerebrovascular Diseases*, 9 Suppl 5:6-22.
- Field, A. (2009). *Discovering statistics using SPSS, (3<sup>rd</sup> edition)*, SAGE Publications Ltd, London, ISBN 978-1-84787-906-6.
- Fitzpatrick, D. (ed. unit II) (2004). Chapter 11. Central Visual Pathways. In D. Purves, G.J. Augustine, D. Fitzpatrick, W.C. Hall, A.S. LaMantia, J.O. McNamara, S.M. Williams, (Eds.), *Neuroscience, (3<sup>rd</sup> edition)*, (pp. 259-282). Sunderland (MA): Sinauer Associates. ISBN 0-87893-725-0.
- Geeraerts, S., Lafosse, C., Vandebussche E., & Verfaillie, K. (2005). A psychophysical study of visual extinction: ipsilesional distractor interference with contralesional orientation thresholds in visual hemineglect patients. *Neuropsychologia*, 43, 530–541.

- Girotti, F., Casazza, M., Musicco, M., & Avanzini, G. (1983). Oculomotor disorders in cortical lesions in man: The role of unilateral neglect. *Neuropsychologia*, 21, 543–553.
- Goldberg, J.H., & Kotval, X.P. (1999). Computer interface evaluation using eye movements: methods and constructs. *International Journal of Industrial Ergonomics*, 24 (6), 631-645.
- Granholm, E., Asarnow, R.F., Sarkin, A.J., & Dykes, K.L. (1996). Pupillary responses index cognitive resource limitations. *Psychophysiology*, 33, 457-461.
- Hafed, Z. M., & Clark, J. J. (2002). Microsaccades as an overt measure of covert attention shifts. *Vision Research*, 42:2533–2545. doi: 10.1016/S0042-6989(02)00263-8.
- Hall, W.C. (ed. unit III) (2004). Chapter 19. Eye Movements and Sensory Motor Integration. In D. Purves, G.J. Augustine, D. Fitzpatrick, W.C. Hall, A.S. LaMantia, J.O. McNamara, S.M. Williams (Eds.). *Neuroscience*, 3rd edition, (pp. 453-468). Sunderland (MA): Sinauer Associates. ISBN 0-87893-725-0.
- Halligan, P.W., Marshall, J.C., & Wade, D.T. (1989). Visuospatial neglect: Underlying factors and test sensitivity. *The Lancet*. October 14, 1989.
- Hartman-Maeir, A., & Katz, N. (1995). Validity of the Behavioral Inattention Test (BIT): Relationships With Functional Tasks. *The American Journal of Occupational Therapy*, 49(6), 507-516.
- Harwell, M.R., Rubinstein, E.N., Hayes, W.S., & Olds, C.C. (1992). Summarizing Monte Carlo results in methodological research: the one- and two-factor fixed effects ANOVA cases. *Journal of Educational Statistics*, 17: 315-339.
- Hawkins, H.L., Hillyard, S.A., Luck, S.J., Mouloua, M., Downing, C.J., & Woodward, D.P. (1990). Visual Attention Modulates Signal Detectability. *Journal of Experimental Psychology: Human Perception and Performance*, 16, 4, 802-811.
- Heilman, K.M., Bowers, D., Coslett, H.B., Whelan, H., & Watson, R.T. (1985). Directional hypokinesia, *Neurology*, 35, 855–859.
- Heilman, K.M., Schwartz, H.D., & Watson, R.T. (1978). Hypoarousal in patients with the neglect syndrome and emotional indifference, *Neurology*, (Minneapolis) 28: 229-232.
- Heilman, K.M., Valenstein, E., & Watson, R.T. (2000). Neglect and related disorders. *Seminars in Neurology*, 20(4), 463-470. doi:DOI10.1055/s-2000-13179.
- Heilman, K.M., & Valenstein, E. (1979). Mechanisms Underlying Hemispatial Neglect. *Annals of Neurology*, 5(2), 166-170. doi:10.1002/ana.410050210.
- Hess, E. H., & Polt, J. M. (1964). Pupil Size in Relation to Mental Activity during Simple Problem Solving. *Science*, 140, 1190-1192.  
<http://dx.doi.org/10.1126/science.143.3611.1190>.
- Hjaltason, H., Tegner, R., Tham, K., Levander, M., & Ericson, K. (1996). Sustained attention and awareness of disability in chronic neglect. *Neuropsychologia*, 34(12), 1229-1233. doi:Doi10.1016/0028-3932(96)00044-9.

- Hoffman, J. E. (1975). Hierarchical stages in the processing of visual information. *Perception & Psychophysics*, 18(5), 348-354.
- Hoffman, J. E., & Subramaniam, B. (1995). The role of visual attention in saccadic eye movements. *Perception & Psychophysics*, 57(6), 787-795.
- Holcombe, A., & Chen, W.-Y. (2013). Splitting attention reduces temporal resolution from 7 Hz for tracking one object to <3 Hz when tracking three. *Journal of Vision*, 13(1):12, 1–19, doi:10.1167/13.1.12.
- Holmqvist, K., Nyström, N., Andersson, R., Dewhurst, R., Jarodzka, H., & Van de Weijer, J. (Eds.) (2011). *Eye tracking: a comprehensive guide to methods and measures*, Oxford, UK: Oxford University Press.
- Husain, M. (2008). Hemispatial neglect. In G. Goldenberg, B.L. Miller (Eds.), *Handbook of Clinical Neurology*, Vol. 88 (3rd series) *Neuropsychology and behavioral neurology*. (pp. 359-372).
- Husain, M., Mannan, S., Hodgson, T., Wojciulik, E., Driver, J., & Kennard, C. (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. *Brain*, 124(5), 941-952.
- Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, 4(1), 26-36. doi:10.1038/nrn1005.
- Husain, M., Shapiro, K., Martin, J., & Kennard, C. (1997). Abnormal temporal dynamics of visual attention in spatial neglect patients. *Nature*, 385(6612), 154-156. doi:DOI10.1038/385154a0.
- Hyönä, J., Tommola, J., & Alaja, A.M. (1995). Pupil Dilation as a Measure of Processing Load in Simultaneous Interpretation and Other Language Tasks. *The Quarterly Journal of Experimental Psychology*, 48A (3),598-612.
- Indredavik, B., Salvesen, R., Næss, H., & Thorsvik, D. (2010). *Nasjonal retningslinje for behandling og rehabilitering ved hjerneslag*. Andvord Grafisk AS.
- Ishiai, S. (2006). What do eye-fixation patterns tell us about unilateral spatial neglect? *Restorative Neurology and Neuroscience*, 24, 261–271. IOS Press.
- Ishiai, S., Furukawa, T., & Tsukagoshi, H. (1987). Eye-fixation patterns in homonymous hemianopia and unilateral spatial neglect. *Neuropsychologia*, 25(4), 67-79.
- Jehkonen, M., Laihosalo, M., & Kettunen, J. (2006). Anosognosia after stroke: assessment, occurrence, subtypes and impact on functional outcome reviewed. *Acta Neurologica Scandinavica*, 114: 293–306.
- Jimenes-Buedo, M., & Miller, L.M. (2010). Why a Trade-Off? The Relationship between the External and Internal Validity of Experiments. *Theoria*, 69, 301-321.
- Jones, B.E., Halaris, A.E., McIlhany, M., & Moore, R.Y. (1977). Ascending projections of the locus coeruleus in the rat. I. Axonal transport in central noradrenaline neurons. *Brain Research*, 127, 1—21.

- Just, M. A., & Carpenter, P. A. (1976). Eye Fixations and Cognitive Processes. *Cognitive Psychology*, 8, 441-480.
- Just, M. A., & Carpenter, P. A. (1980). A theory of reading: From eye fixations to Comprehension. *Psychological Review*, 87(4), 329-354.
- Kahneman, D. (1973). *Attention and effort*. Englewood Cliffs, New Jersey: Prentice-Hall Inc.
- Kahneman, D. (2011). *Thinking, fast and slow*. London: Penguin Books. ISBN 978-0-141-03357-0.
- Kahneman, D., Tursky, B., Shapiro, D., & Crider, A. (1969). Pupillary, heart rate and skin resistance changes during a mental task. *Journal of Experimental Psychology*, 79, 164-167.
- Kahneman, D., & Beatty, J. (1966). Pupil diameter and load on memory. *Science*, 154, 1583-1585.
- Kang, M. S., & Blake, R. (2010). What causes alternations in dominance during binocular rivalry? *Attention, Perception, & Psychophysics*, 72(1), 179–186. <http://dx.doi.org/10.3758/APP.72.1.179>.
- Kaplan, R.F., Verfaellie, M., Meadows, M.E., Caplan, L.R., Pessin, M.S., & DeWitt, L.D. (1991). Changing Attentional Demands in Left Hemispatial Neglect. *Archives of Neurology*, 48, 1263-1266.
- Karnath, H.-O. (1988). Deficits of attention in acute and recovered visual hemi-neglect. *Neuropsychologia*, 26, 27-43.
- Karnath, H.O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature*, 411: 950-3. PMID 11418859 DOI: 10.1038/35082075.
- Karnath, H.-O., Fruhmann Berger, M., Küker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cerebral Cortex*, 14: 1164-1172.
- Karnath, H.-O., & Niemeier, M. (2002). Task-dependent differences in the exploratory behaviour of patients with spatial neglect. *Neuropsychologia*, 40: 1577-85. PMID 11985839 DOI: 10.1016/S0028-3932(02)00020-9.
- Karnath, H.-O., Niemeier, M., & Dichgans, J. (1998). Space exploration in neglect. *Brain*, 1998; 121: 2357–67.
- Karnath, H.O., Schenkel, P., & Fischer, B. (1991). Trunk orientation as the determining factor of the ‘contralateral’ deficit in the neglect syndrome and as the physical anchor of the internal representation of body orientation in space. *Brain*, 114, 1997–2014.
- Kasarskis, P., Stehwien, J., Hickox, J., Aretz, A., & Wickens, C.D. (2001). Comparison of expert and novice scan behaviors during VFR flight. *Paper presented at the 11th International Symposium on Aviation Psychology*. Columbus: The Ohio State University.

- Kastner, S., & Ungerleider, L.G. (2000). Mechanisms of Visual Attention in the Human Cortex. *Annual Review of Neuroscience*, 23:315-341.
- Kim, M. S., & Cave, K. R. (1999). Top-down and bottom-up attentional control: On the nature of interference from a salient distractor. *Perception & Psychophysics*, 61(6), 1009-1023. doi:10.3758/bf03207609.
- Kim, M., Schwartz, R. L., & Heilman, K. M. (1999). Pupillographic findings in neglect. *Journal of Neurology, Neurosurgery & Psychiatry*, 67, 82–85.
- Kinsbourne, M. (1970). A Model for the Mechanism of Unilateral Neglect of Space. *Transactions of the American Neurological Association*, 95: 143-146.
- Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. In E. A. Weinstein & R. P. Friedland (Eds.), *Hemi-inattention and hemisphere specialization* (Advances in neurology, pp. 41–49). New York: Raven.
- Kinsbourne, M. (1987). Mechanisms of unilateral neglect. In: M Jeannerod (ed.), *Neurophysiological and Neuropsychological Aspects of Unilateral Neglect*. Amsterdam: Elsevier Science, 69 – 86.
- Kinsbourne, M. (2006). From unilateral neglect to the brain basis of consciousness. *Cortex*, 42(6), 869-874.
- Koch, C., & Ullman, S. (1985). Shifts in selective visual attention: Towards the underlying neural circuitry. *Human Neurobiology*, 4, 219-227.
- Krieber, M., Bartl-Pokorny, K. D., Pokorny, F. B., Einspieler, C., Langmann, A., Körner, C., ... Marschik, P. B. (2016). The Relation between Reading Skills and Eye Movement Patterns in Adolescent Readers: Evidence from a Regular Orthography. *PLoS ONE*, 11(1): e0145934. <https://doi.org/10.1371/journal.pone.0145934>
- Kristjansson, A., & Vuilleumier, P. (2010). Disruption of spatial memory in visual search in the left visual field in patients with hemispacial neglect. *Vision Research*, 50 (14), 1426-1435.
- Ladavas, E. (1987). Is the hemispacial deficit produced by right parietal lobe damage associated with retinal or gravitational coordinates? *Brain*, 110, 167—180.
- Laeng, B., Brennen, T., & Espeseth, T. (2002). Fast responses to neglected targets in visual search reflect pre-attentive processes: an exploration of response times in visual neglect. *Neuropsychologia*, 40(9), 1622-1636. [https://doi.org/10.1016/S0028-3932\(01\)00230-5](https://doi.org/10.1016/S0028-3932(01)00230-5).
- Laeng, B., Brennen, T., Johannessen, K., Holmen, K., & Elvestad, R. (2002). Multiple reference frames in neglect: an investigation of the object-centred frame and the dissociation between “near” and “far” from the body by use of a mirror. *Cortex*, 38, 511-528.
- Laeng, B., Sirois, S., & Gredeback, G. (2012). Pupillometry: A Window to the Preconscious? *Perspectives on Psychological Science*, 7(1), 18-27. doi:10.1177/1745691611427305.

- Leopold, D.A., & Logothetis, N.K. (1999). Multistable phenomena: Changing views in perception. *Trends in Cognitive Sciences*, 3(7), 254-264. doi: 10.1016/s1364-6613(99)01332-7.
- Lindell, A.B., Jalas, M.J., Tenovuo, O., Brunila, T., Voeten, M.J.M., & Hämäläinen, H. (2007). Clinical Assessment of Hemispatial Neglect: Evaluation of Different Measures and Dimensions, *The Clinical Neuropsychologist*, 21:3, 479-497, DOI: 10.1080/13854040600630061.
- Lix, L.M., Keselman, J.C., & Keselman, H.J. (1996). Consequences of assumption violations revisited: A quantitative review of alternatives to the one-way analysis of variance F test. *Review of Educational Research*, 66: 579-619.
- Logothetis, N.K., Leopold, D.A., & Sheinberg, D.L. (1996). What is rivaling during binocular rivalry? *Nature*, 380, 621-624.
- Makovski, T., Vazquez, G.A., & Jiang, Y.V. (2008). Visual learning in multiple-object tracking. *PLoS One*, 3(5), e2228. doi: 10.1371/journal.pone.0002228.
- Manly, T., Dobler, V.B., Dodds, C.M., & George, M.A. (2005). Rightward shift in spatial awareness with declining alertness. *Neuropsychologia*, 43, 1721-1728. doi:10.1016/j.neuropsychologia.2005.02.009.
- Martinez-Conde, S., Macknik, S.L., & Hubel, D.H. (2000). Microsaccadic eye movements and firing of single cells in the striate cortex of macaque monkeys. *Nature Neuroscience*, 3, 251-258.
- Massironi, M., Antonucci, G., Pizzamiglio, L., Vitale, M., & Zoccolotti, P. (1988). The Wundt-Jastrow illusion in the study of spatial hemi-inattention. *Neuropsychologia*, 26:161-6.
- Mesulam, M. M. (1981). A Cortical Network for Directed Attention and Unilateral Neglect. *Annals of Neurology*, 10, 309-325. <http://dx.doi.org/10.1002/ana.410100402>.
- Morrow, L. A., & Ratcliff, G. (1988). The disengagement of covert attention and the neglect syndrome. *Psychobiology*, 16(3), 261-269.
- Niemeier, M., & Karnath, H. O. (2003). Stimulus-driven and voluntary saccades are coded in different coordinate systems. *Current Biology*, 13:585-589.
- Nijboer, T. C., Kollen, B. J., & Kwakkel, G. (2013). Time course of visuospatial neglect early after stroke: a longitudinal cohort study. *Cortex*, 49(8), 2021-2027.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, 9, 97-113.
- Orfei, M. D., Robinson, R. G., Prigatano, G. P., Starkstein, S., Rüsç, N., & Bria, P. (2007). Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: A systematic review of the literature. *Brain*, 130(12): 3075-3090.

- Orquin, J. L., & Holmqvist, K. (2017). Threats to the validity of eye-movement research in psychology. *Behavior Research Methods*, 1-12. <https://doi.org/10.3758/s13428-017-0998-z>.
- Paffen, C. L., & Alais, D. (2011). Attentional modulation of binocular rivalry. *Frontiers in Human Neuroscience*, 5, 105. <http://dx.doi.org/10.3389/fnhum.2011.00105>.
- Parton, A., Malhotra, P., & Husain, M. (2004). Hemispatial Neglect. *Journal of Neurology, Neurosurgery & Psychiatry*, 75: 13-21. PMID:14707298 PMC1757480.
- Peavler, W. S. (1974). Pupil size, information overload, and performance differences. *Psychophysiology*, 11 (5), 559-566.
- Petersen, S. E., & Posner, M. I. (2012). The Attention System of the Human Brain: 20 Years After. *Annual Review of Neuroscience*, 35: 73–89. doi:10.1146/annurev-neuro-062111-150525.
- Ponsford, J. L., Ziino, C., Parcell, D. L., Shekleton, J. A., Roper, M., Redman, J. R., ... Rajaratnam, S. M. W. (2012). Fatigue and sleep disturbance following traumatic brain injury – Their nature, causes and potential treatments. *Journal of Head Trauma Rehabilitation*, 27(3):224-33.
- Posner, M. I. (1980). Orienting of attention. *The Quarterly Journal of Experimental Psychology*, 32: 1, 3-25. DOI: 10.1080/00335558008248231.
- Posner, M. I. (2008). Measuring Alertness. *Annals of the New York Academy of sciences*, 1129: 193–199. doi: 10.1196/annals.1417.011.
- Posner, M.I., & Rothbart, M.K. (2007). Research on Attention Networks as a Model for the Integration of Psychological Science. *Annual Review of Psychology*, 58:1–23.
- Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience*, 4(7), 1863-1874.
- Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1987). How do the parietal lobes direct covert attention? *Neuropsychologia*, 25, 135-145. Pergamon Journals Ltd.
- Posner, M. I., & Petersen, S. E. (1990). The Attention System of the Human Brain. *Annual Review of Neuroscience*, 13, 25-42. doi:10.1146/annurev.neuro.13.1.25.
- Pouget, A., & Driver, J. (2000). Relating unilateral neglect to the neural coding of space. *Current Opinion in Neurobiology*, 10:242–249.
- Pritchard, R.M., Heron, W., & Hebb, D.O. (1960). Visual Perception Approached by the Method of Stabilized Images. *Canadian Journal of Psychology*, 14, 67–77.
- Rayner, K. (1998). Eye Movements in Reading and Information Processing: 20 Years of Research. *Psychological Bulletin*, 124, 3, 372-422.
- Raz, A., & Buhle, J. (2006). Typologies of attentional networks. *Nature Reviews Neuroscience*, 7(5), 367-379. doi:DOI10.1038/nrn1903.

- Rees, G., Wojciulik, E., Clarke, K., Husain, M., Frith, C., & Driver, J. (2000). Unconscious activation of visual cortex in the damaged right hemisphere of a parietal patient with extinction. *Brain*, 123 (8), 1624-1633.
- Reingold, E. M., & Charness, N. (2005). Perception in chess: Evidence from eye movements. In G. Underwood (ed.), *Cognitive Processes in Eye Guidance* (pp. 325- 354). Oxford: Oxford University Press.
- Reingold, E. M., Charness, N., Pomplun, M., & Stampe, D. M. (2001). Visual span in expert chess players: Evidence from eye movements. *Psychological Science*, 12, 48–55.
- Rizzolatti, G., Riggio, L., Dascola, I., & Umiltà, C. (1987). Reorienting attention across the horizontal and vertical meridians – Evidence in favor of a premotor theory of attention. *Neuropsychologia*, 25(1A), 31L 40.
- Rizzolatti, G., Riggio, L., & Sheliga, B. M. (1994). Space and selective attention. In *Attention and performance XV*, 15, 231–265).
- Robertson, I. H. (2001). Do we need the "lateral" in unilateral neglect? Spatially nonselective attention deficits in unilateral neglect and their implications for rehabilitation. *Neuroimage*, 14, 85-90.
- Robertson, I. H., & Frasca R. (1992). Attentional Load and Visual Neglect, *International Journal of Neuroscience*, 62:1-2, 45-56, DOI: 10.3109/00207459108999756.
- Robertson, I. H., Manly, T., Beschin, N., Daini, R., Haeske-Dewick, H., Hömberg, V., ... Weber, E. (1997). Auditory sustained attention is a marker of unilateral spatial neglect. *Neuropsychologia*, 35, 1527–1532.
- Robertson, I. H., Mattingley, J. B., Rorden, C., & Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature*, 395(6698), 169-172. doi:10.1038/25993.
- Rorden, C., & Karnath, H.-O. (2004). Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nature Reviews Neuroscience*, 5, 813-819.
- Rucci, M., & Poletti M. (2015). Control and function of fixational eye movements. *Annual Review of Vision Science*, 1:499–518, 2015.
- Samuelsson, H., Hjelmquist, E., Jensen, C., Ekholm, S., & Blomstrand, C. (1998). Nonlateralized Attentional Deficits: An Important Component Behind Persisting Visuospatial Neglect? *Journal of Clinical and Experimental Neuropsychology*, 20:1, 73-88.
- Sabrin, H. W., & Kertesz, A. E. (1983). The effect of imposed fixational eye movements on binocular rivalry. *Perception & Psychophysics*, 34 (2), 155-157.
- Scholl, B. J. (2009). What have we learned about attention from multiple-object tracking (and vice versa)? In D. Dedrick & L. Trick (Eds.), *Computation, cognition, and Pylyshyn*. Cambridge, MA: MIT Press (pp. 49–77).

- Schwarz, L. A., & Luo, L. (2015). Organization of the Locus Coeruleus-Norepinephrine System. *Current Biology*, 25, 1051–1056.
- Sekitani, T. (2001). Anaglyph Maker (Version 1.08) [for Windows 98/Me/NT/2000/XP/VISTA/7] created with C++Builder5, Copyright 2001–2004 Takashi Sekitani, All Rights Reserved.
- Serences, J. T., & Kastner, S. Chapter 4. (2014). A Multi-level account of selective attention. In Nobre A.C., & Kastner, S. (Eds.), *The Oxford Handbook of Attention*, (p.76-104). Oxford University Press. ISBN: 978-0-19-967511-1.
- Shelton, P. A., Bowers, D., Heilman, K. M. (1990). Peripersonal and vertical neglect. *Brain*, 113, 191-205.
- Sheppard, D. M., Bradshaw, J. L., Mattingley, J. B., & Lee, P. (1999). Effects of stimulant medication on the lateralization of line bisection judgments of children with attention deficit hyperactivity disorder. *Journal of Neurology, Neurosurgery and Psychiatry*, 66, 57–63.
- Singh, V., Rana, R. K., & Singhal R. (2013). Analysis of repeated measurement data in the clinical trials. *Journal of Ayurveda & Integrative Medicine*, 4(2), 77-81.
- Stangor, C. (2014). *Research Methods for the Behavioral Sciences*, (5<sup>th</sup> ed.). Stamford, CT: Cengage Learning. ISBN-13: 978-1285077024.
- Stevens, C., & Bavelier, D. (2012). The role of selective attention on academic foundations: A cognitive neuroscience perspective. *Developmental Cognitive Neuroscience*, 2, 30–48.
- Stone, S. P., Halligan, P. W., & Greenwood, R. J. (1993). The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age & Ageing*, 22:46–52.
- Sturm, W., de Simone, A., Krause, B. J., Specht, K., Hesselmann, V., Radermacher, I., ... Willmes, K. (1999). Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia*, 37(7), 797-805. doi:Doi10.1016/S0028-3932(98)00141-9.
- Sturm, W., & Willmes, K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage*, 14(1), 76-S84. doi:DOI10.1006/nimg.2001.0839.
- Sunderland, A., Wade, D., & Langton-Hewer, R. (1987). The natural history of visual neglect after stroke: indications from two assessment methods. *International Disability Studies*, 9:55-61.
- Tipper, S. P., & Behrmann, M. (1996). Object-Centered Not Scene-Based Visual Neglect. *Journal of Experimental Psychology: Human Perception and Performance*, 22(5), 1261-1278.
- Tong, F., & Engel, S. A. (2001). Interocular rivalry revealed in the human cortical blind-spot representation. *Nature*, 411, 195-199.

- Tong, F., Nakayama, K., Vaughan, J. T., & Kanwisher, N. (1998). Binocular rivalry and visual awareness in human extrastriate cortex. *Neuron*, 21(4), 753–759.
- Treisman, A. M. (1964). Selective attention in man. *British Medical Bulletin*, 20(1), 12-16.
- Treisman, A. M., & Gelade, G. (1980). A Feature-Integration Theory of Attention. *Cognitive psychology*, 12, 97-136.
- Tucha, O., Mecklinger, L., Laufkötter, R., Klein, H. E., Walitza, S., & Lange, K. W. (2006a). Methylphenidate-induced improvements of various measures of attention in adults with Attention Deficit Hyperactivity Disorder. *Journal of Neural Transmission*, 113: 1575–1592. DOI 10.1007/s00702-005-0437-7.
- Tucha, O., Prell, S., Mecklinger, L., Bormann-Kischkel, C., Küber, S., Linder, M., ... Lange, K. W. (2006b). Effects of methylphenidate on multiple components of attention in children with attention deficit hyperactivity disorder. *Psychopharmacology*, 185: 315–326. DOI 10.1007/s00213-006-0318-2.
- Umiltà, C. (2001). Mechanisms of Attention. In B. Rapp (Ed.), *The Handbook of Cognitive Neuropsychology: What Deficits Reveal about the Human Mind*. (p. 135-158) Psychology Press.
- van Dam, L. C. J., & van Ee, R. (2006). Retinal image shifts, but not eye movements per se, cause alternations in awareness during binocular rivalry. *Journal of Vision*, 6, 1172–1179. doi: 10.1167/6.11.3.
- Vallar, G. (1998). Spatial hemineglect in humans. *Trends in Cognitive Sciences*, 2, (3), 1-23.
- Vallines, I., & Greenlee, M. W. (2006). "Saccadic Suppression of Retinotopically Localized Blood Oxygen Level-Dependent Responses in Human Primary Visual Area V1". *Journal of Neuroscience*, 26 (22): 5965–5969. doi:10.1523/JNEUROSCI.0817-06.2006. PMID 16738238.
- Vecera, S.P., & Rizzo, M. (2003). Spatial attention: normal processes and their breakdown. *Neurologic Clinics of North America*, 21, 575–607. doi:10.1016/S0733-8619(02)00103-2.
- Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., & Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. *Brain*, 133, 880-894. doi:10.1093/brain/awp305.
- Vocat, R., Staub, F., Stroppini, T., & Vuilleumier, P. (2010). Anosognosia for hemiplegia: a clinical-anatomical prospective study. *Brain*, 133; 3578–3597. doi:10.1093/brain/awq297.
- Wahn, B., Ferris, D.P., Hairston, W.D., & König, P. (2016). Pupil Sizes Scale with Attentional Load and Task Experience in a Multiple Object Tracking Task. *PLoS ONE*, 11(12): e0168087. doi:10.1371/journal.pone.0168087.
- Walker, R., Findlay, J.M., Young, A.W., & Welch J. (1991). Disentangling neglect and hemianopia. *Neuropsychologia*, 29 (10), 1019-1027.

- Wallis, W. D., & George, J. C. (2011). Latin Squares. In Kenneth Rosen (series editor), *Discrete Mathematics and its Applications: Introduction to Combinatorics* (p. 207-229). CRC Press, Boca Raton, ISBN 13: 978-1-4398-0623-4 (Ebook-PDF).
- Watson, R. T., Miller, B. D., & Heilman, K. M. (1977). Evoked Potential in Neglect. *Archives of Neurology*, 34, 224-227.
- Wechsler, D. (1997). *Wechsler Adult Intelligence Scale III*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D. (1999). *Manual for the Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.
- Weintraub, S., & Mesulam, M. M. (1987). Right cerebral dominance in spatial attention: further evidence based on ipsilateral neglect. *Archives of Neurology*, 44, 621–625.
- Williams, A. M., Singer, R. N., & Frelich, S. G. (2002). Quiet Eye Duration, Expertise, and Task Complexity in Near and Far Aiming Tasks. *Journal of Motor Behavior*, 34 (2), 197–207.
- Wilson, B., Cockburn, J., & Halligan, P. (1987). "Development of a behavioral test of visuospatial neglect." *Archives of Physical Medicine & Rehabilitation*, 68: 98-9102.
- World Medical Association. (2013). WMA declaration of Helsinki: Ethical principles for medical research involving human subjects. Retrieved from <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- Worringham, C.J. (1991). The integration of “Noise” into the structure of movements. In J. Requin & G.E. Stelmach (Eds.), *Tutorials in motor neuroscience*, (pp. 59-75). Dordrecht, The Netherlands. Kluwer Academic Publishers.
- Yokoyama, K., Jennings, R., Ackles, P., Hood, P., & Boller, F. (1987). Lack of heart rate changes during an attention-demanding task after right hemisphere lesions. *Neurology*, 37: 624-630.
- Zaretskaya, N., Thielscher, A., Logothetis, N.K., & Bartels, A. (2010). Disrupting parietal function prolongs dominance durations in binocular rivalry. *Current Biology*, 20(23), 2106–2111. <http://dx.doi.org/10.1016/j.cub.2010.10.046>.

## **ARTICLES I-III**

