Maastricht University

Bringing neglected space to light

Citation for published version (APA):

Middag - van Spanje, W. B. M. (2025). *Bringing neglected space to light: understanding and treating visuospatial attention deficits with non-invasive brain stimulation*. [Doctoral Thesis, Maastricht University]. Maastricht University. https://doi.org/10.26481/dis.20250603wm

Document status and date:
Published: 03/06/2025

DOI:
10.26481/dis.20250603wm

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 27 mei. 2025

Bringing Neglected Space to Light

Understanding and Treating
Visuospatial Attention Deficits
with Non-Invasive Brain Stimulation

Marij Middag-van Spanje

Legantur Academia
an imprint of Publishing House Legantur
Amersfoort, The Netherlands

© 2025 by Marij Middag-van Spanje

Published by Legantur Academia
an imprint of Publishing House Legantur, Amersfoort, The Netherlands

Printed in The Netherlands by IPSKAMP, Enschede

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means–for example, electronic, photocopy, recording–without the prior written permission of the publisher.

ISBN 978-90-90399-48-5
NUR 776

Bringing Neglected Space to Light

Understanding and Treating Visuospatial Attention Deficits with Non-Invasive Brain Stimulation

DISSERTATION

to obtain the degree of Doctor at Maastricht University,
on the authority of the Rector Magnificus, Prof. Dr. Pamela Habibović
in accordance with the decision of the Board of Deans,
to be defended in public on Tuesday, June 3rd 2025, at 13:00 hours

by Willemijn Berthine Mirjam Middag-van Spanje

Supervisors:
Prof. Dr. Teresa Schuhmann, *Maastricht University*
Prof. Dr. Caroline van Heugten, *Maastricht University*
Prof. Dr. Alexander Sack, *Maastricht University*

Assessment Committee

Chair:
Prof. Dr. Milene Bonte, *Maastricht University*

Members:
Prof. Dr. Arjan Blokland, *Maastricht University*
Prof. Dr. Monika Harvey, *University of Glasgow, Scotland, UK*
Prof. Dr. Anne Visser-Meily, *University Medical Center Utrecht*

Organization that contributed to the doctoral research:
InteraktContour

Table of contents

Chapter 1	General introduction	7
	Part I	
Chapter 2	Transcranial magnetic stimulation over posterior parietal cortex modulates alerting and executive control processes in attention	35
Chapter 3	State-dependence of therapeutic tACS: Preconditioning the brain with TMS reverses the oscillatory after effects of tACS on resting-state EEG	67
	Part II	
Chapter 4	Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients	109
Chapter 5	Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect	131
Chapter 6	Alpha transcranial alternating current stimulation as add-on to neglect training: A randomized trial	155
Chapter 7	Summary and general discussion	207
	Impact paragraph	235
	Samenvatting (summary in Dutch)	243
	Acknowledgments	251
	About the author	259
	List of publications	263

Chapter 1

General introduction

Visuospatial neglect is a neuropsychological syndrome commonly observed following unilateral stroke. At its core, visuospatial neglect is a deficit in lateralized attention and can have a range of consequences, as it affects an individual's ability to attend and respond to visual information in one side of space (Buxbaum et al., 2004; Corbetta & Shulman, 2011; Heilman et al., 2000; Kerkhoff, 2001).

In recent decades, a variety of rehabilitation methods has emerged to address the multifaceted challenges of people with visuospatial neglect. These encompass approaches focused on retraining impaired functions (restitution), leveraging remaining intact brain structures (compensation), or adapting to impairments by using external devices or modifications (substitution) (Kerkhoff, 2000; Ting et al., 2011; Zebhauser et al., 2019). Notably, non-invasive brain stimulation (NIBS) techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial electric stimulation (tES) have gained traction within this array of approaches.

The realm of NIBS stands as an area of profound scientific interest. Central to the concept of NIBS is the idea of externally modulating the intricate neural processes within the human brain, be it through magnetic fields or electrical currents. In fundamental research, the application of NIBS in the healthy brain has yielded significant insights into the neural mechanisms of human cognition and behavior. Moreover, the unique property of NIBS to non-invasively and safely alter neural activity and affect cognition and behavior, has raised interest in the possible clinical applications. In a variety of brain disorders, NIBS has already shown remarkable efficacy (Boes et al., 2018; Lefaucheur et al., 2020). One cannot help but wonder whether NIBS holds the promise of relief for individuals burdened by the consequences of brain damage, or specifically, of visuospatial neglect.

The objective of the research in this thesis is to better understand visuospatial attention and treat visuospatial neglect. Throughout the thesis, all studies explore NIBS techniques, whether as a research tool to influence visuospatial attention in healthy volunteers (**chapters 2 and 3**) or as a therapeutic intervention in patients suffering from visuospatial neglect (**chapters 4, 5, and 6**). To comprehend how NIBS operates in these studies, it is necessary to gain a background understanding of attentional processes in the healthy brain, including theories that explain how visuospatial neglect arises after brain damage, and the basic principles underlying NIBS techniques. This first chapter thus lays the groundwork for the subsequent chapters of this thesis.

Visuospatial attention: concepts and categories

The concept of visuospatial attention encompasses the ability to focus on specific elements in our visual environment while disregarding others (Carrasco, 2011). This selective attention allows for faster and more accurate processing of information within the attended regions (Carrasco, 2011; Posner, 2012).

Attention may operate through different systems. Overt attention involves the orienting of multiple body systems to enhance stimulus processing. For instance, deliberately turning one's trunk and gaze toward someone during a conversation exemplifies overt spatial attention (Posner & Rothbart, 2007). In contrast, covert attention involves the engagement of a singular system to focus on a particular stimulus without the accompaniment of physical movement. This is evident when directing attention toward a more intriguing conversation nearby while maintaining the appearance of paying attention to your conversational partner (i.e., without eye movement accompanying the movement of attention) (Posner & Rothbart, 2007).

Visuospatial attention can also be categorized into exogenous attention, a bottom-up attentional process, and endogenous attention, characterized by top-down attentional control. Exogenous attention functions automatically, responding to salient and unexpected stimuli in the environment (Corbetta & Shulman, 2002). It facilitates swift reactions to sudden or potentially hazardous events in the environment, enhancing immediate responses. Conversely, endogenous attention involves the deliberate and voluntary shifting of attention toward specific stimuli, facilitating focused, goal-directed processing amidst distractions (Corbetta & Shulman, 2002).

Besides exogenous and endogenous mechanisms that allow us to orient our focus in visual space, alerting and executive control also play crucial roles in attentional processes (Posner & Rothbart, 2007). The concept of alerting refers to the mechanisms the system puts in place when preparing for an anticipated stimulus, leading to quicker processing upon its arrival (Fan et al., 2009). Executive control manages the suppression of irrelevant stimuli, facilitating the selection of pertinent information and resolving conflicts among responses (Fan et al., 2009).

These three attention mechanisms – orienting, alerting, and executive control – have been widely studied using various computerized behavioral tasks. The orienting function has been traditionally studied by presenting stimuli preceded by symbolic cues designed to direct attention. Participants are required to rapidly and accurately identify the target's characteristics, such as its orientation. When the cue correctly predicts the upcoming stimulus location (i.e., valid trial), participants respond faster and/or more accurately compared to when the cue predicts incorrectly (i.e., invalid trial), suggesting that spatial attention improves the processing of information (Posner et al., 1980). The alertness level can be modulated experimentally by presenting a neutral cue that carries information about when, but not where, a stimulus will appear. For instance, a neutral cue, also referred to as an alerting or warning cue, may be a (visual) cue indicating directions both left and right. Contrasting performance in the neutral-cue condition with that in the no-cue condition, which lacks both spatial and temporal information, enables the isolation of alerting effects (Fan et al., 2005). Executive control can be assessed by introducing distractors alongside target stimuli, as they disrupt target identification and require inhibition. Performance is diminished when participants must resolve the conflict induced by the distractors, compared to trials where flanker stimuli do not induce conflict (Fan et al., 2002).

The most typical tasks used to measure spatial attention are the Posner cueing task, a classic paradigm to measure the orienting mechanism (Posner et al., 1980), and the attention network test (ANT), designed to measure all three attention components separately and in combination (Fan et al., 2002, 2005). Its updated version, the lateralized-ANT (LANT), measures attention components in each hemisphere, vital for understanding functional asymmetries in the brain (Greene et al., 2008).

Brain networks underlying visuospatial attention

The brain's attentional processes rely on intricate networks involving various brain regions as shown by a wealth of neuroimaging studies (e.g., Carrasco, 2011; Corbetta & Shulman, 2002; Petersen & Posner, 2012). Corbetta & Shulman's influential model highlights two interconnected networks governing spatial attentional control: the ventral attention network (VAN) and the dorsal attention network (DAN) (Corbetta & Shulman, 2011, 2002). The VAN is associated with exogenous attention and responds to unexpected yet behaviorally relevant stimuli, allowing for the reallocation of attention in visual space. The VAN is right-lateralized and consists of the temporoparietal junction and ventral frontal cortex. In contrast, the DAN is linked to endogenous attention and facilitates the voluntary directing of attention. The DAN is bilateral, including the frontal eye field and intraparietal sulcus.

The connections within and between (the nodes of) these attentional networks, along with the control they exert over the occipital cortex, facilitate enhanced processing within a specific part of the visual field or of a specific stimulus (Reynolds & Heeger, 2009). This is achieved by selectively recruiting the neurons responsible for processing the attended visual field or the properties of the targeted stimulus.

Furthermore, alerting mechanisms involve fronto-parietal cortical regions and thalamic regions (Fan et al., 2007). Executive control mechanisms engage a network including the anterior cingulate cortex, supplementary motor area, prefrontal and orbitofrontal cortices, portions of the basal ganglia, and the thalamus (Fernandez-Duque & Posner, 2001).

Despite advancements in cognitive neuroscience, including neuroimaging techniques providing valuable data on spatial brain activity correlations, they fall short in establishing the causal relevance of specific brain areas/networks in attention. Overcoming this limitation requires methodologies that directly manipulate brain activity, rather than those that solely observe neural activity change during behavioral tasks. The more recent utilization of brain stimulation techniques has proven notably useful in further unravelling causal structure-function relationships (Duecker & Sack, 2015).

Transcranial magnetic stimulation (TMS)

Brain stimulation techniques can be broadly categorized into invasive and non-invasive methods. Invasive approaches involve surgical intervention, whereby electrodes are implanted directly into the brain by opening the skull. Conversely, non-invasive brain stimulation (NIBS) entails the placement of electrodes or coil(s) externally on the scalp. NIBS methods hold significant importance in various fields of neuroscience and clinical applications due to its capability to modulate brain activity without the need for surgical procedures. Transcranial magnetic stimulation (TMS) stands out as a widely used, well-established, non-invasive research tool.

TMS operates by generating a magnetic field to transiently modulate brain activity (Barker et al., 1985; Robertson et al., 2003; Sack, 2006). The TMS machine consists of two main parts: the stimulator and the coil. The stimulator generates a strong electric current that is passed through a cable to the coil, which is made of wound copper wires. Positioned tangentially to the head, the coil emits brief magnetic pulses that penetrate the (intact) skull to induce an electric field in the underlying brain tissue. This electric field then interacts with the natural transmission of electric signals among neurons. Each TMS pulse reaches a depth of only a few centimeters beneath the stimulating coil, yet the functional consequences may extend beyond the stimulated site, impacting broader neuronal circuits (in cortical and subcortical brain areas) due to interconnections between brain areas (Robertson et al., 2003; Sack, 2006).

Various factors, including intensity and frequency of delivered pulses, play critical roles in determining the path, strength, and subsequent effects of stimulation in altering brain activity during TMS. Adjusting these parameters allows for a tailored approach in modulating brain activity based on the intended research or therapeutic goals. In TMS experiments, the intensity of stimulation is established based on the individual resting motor threshold (rMT) (Rossini et al., 1994). A single TMS pulse (spTMS) over the motor cortex triggers the activation of corticospinal circuits, resulting in an observable contralateral finger muscle twitch (Rothwell et al., 1999).

Notably, when multiple pulses are delivered, as in repetitive TMS (rTMS), neuroplastic ('lasting') effects on cortical excitability have been observed. The stimulation frequency or pattern of pulses determines the type of aftereffect on cortical excitability (Maeda et al., 2000; Robertson et al., 2003; Sack, 2006). Generally speaking, low-frequency protocols (i.e., pulses delivered at 1 Hz or lower) have been shown to have inhibitory neuroplastic effects, while high-frequency protocols (i.e., pulses delivered at 5 Hz or higher) have been shown to be excitatory (Maeda et al., 2000). These classical rTMS protocols, involving both high and low frequencies, typically require stimulation sessions lasting up to 40 minutes, with resultant aftereffects persisting for maximally 40 minutes (Thut & Pascual-Leone, 2010). TMS can also be applied using more complex patterns combining different frequencies, such as the case in theta burst stimulation (TBS) protocols. Theta burst patterns involve delivering a total of 600 pulses grouped in triplets at 50 Hz between pulses, with triplets repeated in a 5 Hz rhythm (Huang et al., 2005; Suppa et al., 2016). There are two categories of TBS protocols: intermittent TBS (iTBS), requiring only 3.5 minutes of stimulation, which has demonstrated excitatory effects lasting up to 60 minutes post-stimulation, and continuous TBS (cTBS), requiring merely 40 seconds of stimulation, with inhibitory effects persisting also up to 60 minutes (Huang et al., 2005; Suppa et al., 2016). Due to their abbreviated duration yet strong effects on cortical excitability changes, the TBS protocols have garnered widespread utilization in research and in clinical applications over the past two decades.

Inhibitory TMS protocols allow researchers to temporarily disrupt the efficiency of the targeted region and observe the resulting changes in cognitive performance, mimicking brain lesions in healthy participants (Sack, 2006). These inhibitory protocols have repeatedly been applied to parietal brain regions to disrupt performance on attention tasks, resembling the behavioral deficits seen in stroke patients with visuospatial neglect (for review, see Duecker & Sack, 2015; Sack, 2010). Unfortunately, nearly all of these studies focus on spatial orienting; the (in)voluntary allocation of attention to one location in visual space (Bien et al., 2012; Brighina et al., 2002; Cazzoli et al., 2009; Dambeck et al., 2006; Fierro et al., 2000; Hilgetag et al., 2001; Koch et al., 2005; Szczepanski & Kastner, 2013; Thut et al., 2005). This aspect of attention is important, but as explained above, it is only one small component of a larger, dynamic, intrinsically connected attention system.

Unilateral damage within the attention networks

Current functional-anatomical models agree that different brain networks play a crucial role in visuospatial attentional control, while highlighting a functional hemispheric asymmetry in their organization. Nevertheless, an ongoing debate exists regarding the contribution of each hemisphere to visuospatial attention (Duecker & Sack, 2015; Gallotto et al., 2020). This disagreement becomes especially evident in the various efforts to understand why attention deficits, such as visuospatial neglect after unilateral brain damage, are often more pronounced and prevalent following damage to the right hemisphere (Chen et al., 2015; Ringman et al., 2004; Ten Brink, Verwer, et al., 2017). Two prominent theories have emerged over the years, i.e., the hemispatial theory and the interhemispheric competition theory, each explaining this asymmetry but proposing opposing explanations regarding how attention can be impaired after unilateral brain damage (**Box 1**).

Dysfunction within the attention networks previously described, contributes significantly to the development of deficits in visuospatial attentional control. Visuospatial neglect arises subsequent to either focal damage (e.g., to frontal, parietal or subcortical structures like the thalamus) or damage to white matter tracts (Corbetta, 2014). Especially lesions that penetrate deeply into the white matter, particularly affecting the dorsal periventricular white matter containing fibers of the superior longitudinal fasciculus, worsen neglect (Corbetta, 2014). These fibers connect various frontal and parietal brain regions that are part of the networks responsible for attentional control. Thus, damage to the white matter, by disconnecting multiple nodes of the attention networks, causes more severe neglect than cortical damage (Corbetta, 2014). Also, as mentioned above, visuospatial neglect tends to be more common and severe after right hemispheric damage compared to left hemispheric damage (Chen et al., 2015; Ringman et al., 2004; Ten Brink, Verwer, et al., 2017). In the following paragraph, more background information on visuospatial neglect is provided.

Box 1 Hemispheric asymmetries in attentional control.

The hemispatial theory of attention (Heilman & Van Den Abell, 1980) suggests that the right hemisphere mediates attention shifts toward both sides of visual space, while the left hemisphere mediates attention shifts only toward the contralateral (right) side. Consequently, damage to the left hemisphere typically leads to mild deficits in processing stimuli from the contralateral (right) side, since the right hemisphere can compensate by attending to both visual fields. In contrast, if damage occurs in the right hemisphere, there is no functional compensation due to the lack of functional overlap. As a result, the ability to shift attention toward the left visual field is compromised, leading to visuospatial neglect of the left visual field subsequent to a right hemispheric lesion.

In contrast, the interhemispheric competition theory of attention (Kinsbourne, 1977), also known as the opponent processor model, posits that unilateral brain damage disrupts activity levels in both hemispheres rather than solely interfering with processing in the affected hemisphere. This theory argues that, normally, there exists an activity balance between the two hemispheres due to transcallosal inhibition, stating that the left hemisphere exhibits a stronger rightward bias than the right hemisphere's leftward bias. In visuospatial neglect patients, damage to either hemisphere leaves the unaffected hemisphere unopposed, resulting in an overactivated contralesional hemisphere, causing an ipsilesional attention bias. Damage to the left hemisphere results in mild deficits due to the relatively weak leftward bias of the right hemisphere, preserving the ability to shift attention to both visual fields. However, damage in the right hemisphere unleashes the strong rightward bias of the left hemisphere, causing left-sided visuospatial neglect.

In summary, the two theories present distinct viewpoints on how hemispheric imbalances contribute to the manifestation of visuospatial neglect; the hemispatial theory thereby supports the notion of a right hemispheric dominance, whereas the interhemispheric competition theory favors a left hemispheric dominance. However, both theories do highlight the significance of hemispheric biases in attention and clearly support the clinical observation that visuospatial neglect tends to be more frequent or severe following a lesion in the right hemisphere in comparison to a lesion in the left hemisphere.

Visuospatial neglect

Among neurological disorders, stroke emerges as the foremost global contributor to both disability-adjusted life years (DALYs) and mortality (Feigin et al., 2016). In The Netherlands, an estimated 40,000 individuals suffer from a cerebrovascular accident yearly, based on incidence data from 2019 to 2022 (Nivel Zorgregistraties Eerste Lijn, 2023). Following unilateral stroke, visuospatial neglect manifests as a prevalent syndrome, affecting approximately 50% of survivors with right hemispheric brain damage and 30% of those with left hemispheric brain damage (Chen et al., 2015). Typically, spontaneous neuronal recovery from visuospatial neglect occurs during the first three months following stroke onset (Nijboer et al., 2018). Yet, roughly 40% of individuals experiencing visuospatial neglect still exhibit the disorder one year post-stroke onset (Nijboer et al., 2013).

Neglect, also known as hemineglect or (hemi-)inattention, is a complex, heterogeneous syndrome, including a variety of clinically important deficits, such as spatial bias, failure of vigilance/arousal and sustained attention, and deficits of insight and body awareness (Corbetta, 2014). Neglect can be divided into sensory, (pre)motor, and representational (imaginary) neglect (Zebhauser et al., 2019), and can involve various clinical subtypes that differ in modality (visual, auditory, tactile, or olfactory), frame of reference (egocentric or allocentric), and region of space (personal, peripersonal, or extrapersonal) (Rode et al., 2017; Van der Stoep et al., 2013). This thesis focusses on visuospatial neglect, a form of sensory neglect that affects space-related behavior (Zebhauser et al., 2019). Visuospatial neglect is defined by diminished attentional processing toward visual stimuli located on the side opposite the cerebral damage, in the absence of elementary sensorimotor deficits (Buxbaum et al., 2004; Corbetta & Shulman, 2011; Heilman et al., 2000; Kerkhoff, 2001). Visuospatial neglect is henceforth referred to as 'neglect'.

Drawing from the illustration of the profound impact of neglect in a patient (**Box 2**), it becomes evident how the effects of neglect reverberate throughout every aspect of a patient’s daily life, from the simplest acts of self-care to more complex cognitive endeavors (Bosma et al., 2020; Buxbaum et al., 2004; Kerkhoff, 2001; Nijboer et al., 2013). Neglect alters a patient’s perception of the world in ways most people take for granted. A meal may appear half-consumed when only one side of the plate has been touched, and the act of dressing may involve putting on clothes in a disorganized or careless manner, overlooking one side entirely. Interactions with others can be affected, as the patient may fail to acknowledge the presence or conversation of individuals situated on their neglected side.

Box 2 The impact of neglect: a fictitious patient's daily struggle.

Every morning, as I navigate through my daily routine, I feel a sense of frustration like a persistent companion. It has already been five years since my stroke, yet I continue to grapple with the challenges of neglect. I frequently encounter obstacles, often unaware of what lies just beyond my sight. The damaged left door post serves as a reminder of my ongoing struggle. Simple tasks can become demanding, almost like a game of hide and seek played by my own mind. I find myself in a continuous battle with my own senses, a constant reminder of all that I have lost. My mood may dim as the day progresses as I know that, despite my best efforts, this elusive vision will keep me navigating a world that often feels divided.

Neuropsychological assessments of neglect commonly employ standardized paper-and-pencil tests like cancellation or bisection tasks (Spreij et al., 2020a; Spreij et al., 2020b; Ten Brink, 2017). In cancellations tasks, such as the bells task (Gauthier et al., 1989) or star cancellation task (Wilson et al., 1987), patients must cross out all target items (e.g., the letter "O") interspersed among non-targets (e.g., "H" and "P") on paper, with neglect inferred from the discrepancy in the number of missed targets between the left and right sides. Line bisection tasks require the patient to indicate the midpoint of presented horizontal lines, with substantial deviation from the center indicating neglect on the opposite side of space (Schenkenberg et al., 1980).

These conventional paper-and-pencil tests of neglect are easily and swiftly administered, making them suitable even for bed-bound patients or those with language impairments (Ten Brink, 2017). However, there are instances where patients exhibit neglect in daily activities despite performing well on these classic, clinical tests (Chen et al., 2015), especially among those in the chronic phase who have adopted compensatory strategies (Azouvi, 2017; Ten Brink, 2017). Several reasons contribute to this discrepancy. Firstly, the broad spectrum of neglect subtypes may not be fully captured by paper-and-pencil tasks that essentially focus on visual neglect in peripersonal space, potentially missing other subtypes (Chen et al., 2015; Ten Brink, 2017). Secondly, clinical tests may primarily depend on mechanisms that necessitate voluntary orienting of attention, while in everyday situations, automatic orienting is essential (Azouvi, 2017). Thirdly, detecting relevant stimuli in dynamic, real-world situations poses challenges, particularly when simultaneous events occur on both the affected and unaffected sides. This ‘attentional competition’ is typically minimized in classic, static neglect tasks (Ten Brink, 2017). Lastly, this discrepancy could simply be due to test-retest effects (Azouvi, 2017).

Neglect treatment

Interventions designed to ameliorate neglect include compensatory approaches such as optokinetic stimulation and limb activation, substitution strategies like prism adaptation, and restitution methods including pharmacological treatment and mental imagery (for more examples, see Zebhauser et al., 2019). The current standard treatment for neglect involves visual scanning training (Ten Brink, Van Kessel, et al., 2017), an intensive compensatory program aimed at improving viewing and searching behavior through top-down strategies (Pizzamiglio et al., 1992). Visual scanning training teaches patients to consciously attend to stimuli in the neglected visual field by making systematic eye movements. An essential assumption for the efficacy of this training relies on the premotor theory of attention. According to this theory, spatial attention is functionally equivalent to motor preparation, meaning that the planning of a goal directed action, such as an eye movement, is sufficient to cause a shift of spatial attention (Smith & Schenk, 2012). However, not all patients appear to benefit from the standard visual scanning training (Kerkhoff & Schenk, 2012). Various reasons have been suggested for its limited efficacy, such as the inability to reliably anticipate improvements in awareness of the deficit among individual patients and the potential influence of lesion site on the variability of training effects (Van Kessel et al., 2013).

In recent decades, stroke rehabilitation research has explored the potential of NIBS techniques in clinical studies, drawing inspiration from the theory of attention of Kinsbourne (1977). NIBS, as a rehabilitation tool, utilizes excitatory or inhibitory stimulation protocols to modulate unilateral cortical excitability, aiming to restore interhemispheric balance in stroke patients. In most NIBS studies, excitability-decreasing paradigms are applied to the hyperactive contralesional (intact) hemisphere to counteract the pathological attentional bias caused by the stroke. Methods include low-frequency repetitive transcranial magnetic stimulation (LF-rTMS), cTBS, and transcranial direct current stimulation (tDCS). Yet, although promising, reported clinical effects have remained small and heterogeneous, warranting no recommendations for the use of conventional rTMS in the treatment of neglect, and only level-C evidence (“possible efficacy”) for cTBS in the most recent European guidelines (Lefaucheur et al., 2020; Longley et al., 2021). Also, regarding tDCS, only evidence of very low quality suggests that there is an effect of tDCS for improving neglect (Elsner et al., 2020).

More recently, promising new avenues for neuromodulation with NIBS have opened up. Specifically, transcranial electric stimulation (tES) enables the targeting of oscillatory brain activity, instead of merely changing local cortical excitability. This is intriguing, as locally generated oscillations correlate with specific cognitive processes. The following paragraphs further introduce the concepts of oscillatory activity and tES.

Oscillatory activity underlying visuospatial attention

Brain oscillations play an important role in coordinating neuronal processing through the phasic modulation of neuronal firing (Jensen et al., 2014; Thut et al., 2012). Oscillatory brain activity reflects the synchronized firing of neurons in rhythmic patterns. It is detectable through the placement of electrodes on the scalp, a method employed by electroencephalography (EEG) to capture and interpret these neural signals. The electrodes, linked to an amplifier and analog-to-digital converter, relay the signals to a computer for display over time. EEG has an exceptional temporal resolution, enabling the detection of extremely small fluctuations in the electrical signals within milliseconds. Neural oscillations can be categorized into five frequency bands: delta (< 4 Hz), theta (4-6 Hz), alpha (7-13 Hz), beta (14-30 Hz), and gamma (> 30 Hz), naturally associated with distinct brain networks and cognitive processes (Başar et al., 2001; Thut & Miniussi, 2009). Besides varying in frequency, the electric signals also fluctuate in amplitude (strength/power), indicating the level of synchronized neuronal firing at a specific frequency.

The alpha rhythm, especially exhibited in parieto-occipital sites when eyes are closed, has historically been associated with a relaxed state (Berger, 1929). The alpha rhythm emerges when specific brain regions become inactive, such as when there is no visual input after closing the eyes. This association led the suggestion of referring to alpha oscillations as an 'idling rhythm' (Pfurtscheller et al., 1996). However, contemporary views propose that alpha activity mirrors an active inhibition in a given region rather than a passive consequence of information absence (Jensen et al., 2014; Klimesch et al., 2007).

Attention studies have repeatedly shown the involvement of posterior alpha activity in visuospatial attentional control; endogenous (voluntary) attention shifts toward one visual field correlate with alpha lateralization over posterior sites (Gould et al., 2011; Händel et al., 2011; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000). It is postulated that, contingent on where attention is shifted, parieto-occipital alpha oscillations increase in the ipsilateral hemisphere and decrease in the contralateral hemisphere (Jensen et al., 2014; Jensen & Mazaheri, 2010) (**Figure 1**).

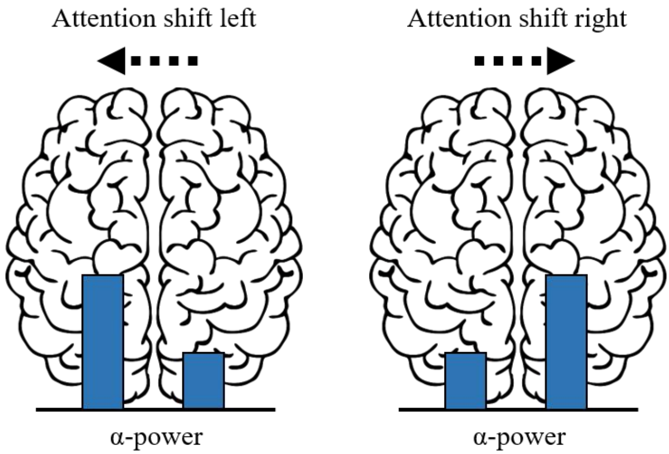

Figure 1 Biases in visuospatial attention are associated with an interhemispheric asymmetry in oscillatory alpha power in parieto-occipital regions. When attention is shifted to either hemifield, this is accompanied by alpha power increases on the same side as the focus of attention and alpha power decreases on the opposite side. This suggests that alpha oscillations might help inhibit distracting sensory information, enabling selective processing of relevant stimuli.

Transcranial electric stimulation (tES)

While TMS uses magnetic pulses for direct neuronal stimulation, tES stands as a distinct category among NIBS techniques, utilizing low-intensity electric stimulation (Antal, 2012; Herrmann et al., 2013; Paulus, 2011). TES employs a setup involving at least two electrodes attached to the head and linked to a battery, enabling the administration of an electric current directly to the scalp. This current then penetrates the skull and interacts with neural activity. While TMS is capable of evoking action potentials, thus resulting in pronounced local and remote effects, tES rather alters the local resting potential. TES methods encompass transcranial random noise stimulation (tRNS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS). The research presented in this thesis focuses on tACS.

TACS is capable of directly modulating the ongoing rhythmic brain activity by applying sinusoidal (alternating) currents that synchronize with the brain's natural rhythms (Thut et al., 2011). This phenomenon, termed entrainment – the temporal-locking process in which the signal or oscillation of one system aligns with the signal of another system – significantly enhances the coherence and power of these oscillations (Lakatos et al., 2019; Neuling et al., 2013; Zaehle et al., 2010). This aspect of tACS is particularly compelling given the fundamental role brain oscillations serve in supporting various sensory and cognitive processes in their associated brain networks, such as the above described role of alpha oscillatory activity in visuospatial attention. If indeed tACS could be used to modulate alpha power in patients with asymmetric attentional deficits like neglect, this could in turn modulate attention bias and lead to a reduction of neglect symptoms (**Figure 2**).

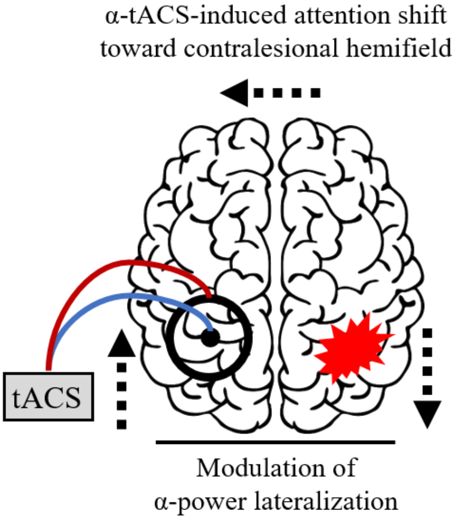

Figure 2 Example of anticipated effects of unilateral tACS in a patient with a right-sided stroke (with left-sided neglect; not shown in figure). TACS uses alternating electrical currents to increase the power of brain oscillations. If indeed alpha power is increased in the ipsilateral relative to the contralateral side of attention, we hypothesize that the attention bias toward the right hemifield seen in right-sided stroke patients can be corrected for by increasing alpha power in left posterior sites by tACS.

However, although EEG research uncovers associations between (the strength of) certain oscillations and specific cognitive processes, it does not establish the causal significance of these oscillations. Consequently, for tACS to serve as a potential treatment approach for patients with neglect, it is crucial to confirm that alpha oscillations are more than just an epiphenomenon and are indeed functionally relevant in visuospatial attentional control.

Researchers have recently addressed this in healthy individuals by directly modulating alpha oscillations using tACS – applied at alpha frequency – and observing the effects on attention performance (Kemmerer, De Graaf, et al., 2022; Kemmerer, Sack, et al., 2022; Schuhmann et al., 2019). This approach has yielded promising results, demonstrating the ability of tACS to modulate alpha power lateralization, concurrently influencing visuospatial attention. These findings strongly advocate for exploring the potential of employing this entrainment-based neuromodulation approach as an innovative treatment for patients with neglect, and have inspired us to further test alpha-tACS in neglect patients.

Outline of the thesis

As described above, numerous EEG studies suggest that biases in visuospatial attention are associated with an asymmetry in alpha power between hemispheres, particularly in posterior regions (Gallotto et al., 2020; Gould et al., 2011; Händel et al., 2011; Lasaponara et al., 2019; Newman et al., 2013; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000). Additionally, tACS at alpha frequency has been frequently utilized to modulate alpha power lateralization and/or visuospatial attention in healthy volunteers (Coldea et al., 2021; Kasten et al., 2020; Kemmerer, Sack, et al., 2022; Schuhmann et al., 2019; Van Schouwenburg et al., 2018; Veniero et al., 2017). However, to date, no studies have evaluated the effects of alpha-tACS in individuals with asymmetric attentional deficits like neglect due to stroke.

The first chapters of this thesis (**chapters 2 and 3**) introduce an innovative approach in evaluating treatment options that could be applied in rehabilitation, where inhibitory TMS (i.e., cTBS) is used to simulate neglect in healthy volunteers and alpha-tACS is subsequently used to ‘virtually treat’ these simulated patients. Thus, while we employ TMS to disrupt parietal cortex in order to induce (mild and transient) lateralized attention deficits, by means of tACS we specifically aim at treating attention deficits. Furthermore, as discussed previously, inhibitory protocols targeting parietal brain regions have frequently been utilized to mimic the attentional impairments observed in stroke patients with neglect. However, the majority of these studies concentrate solely on spatial orienting (Bien et al., 2012; Brighina et al., 2002; Cazzoli et al., 2009; Dambeck et al., 2006; Fierro et al., 2000; Hilgetag et al., 2001; Koch et al., 2005; Szczepanski & Kastner, 2013; Thut et al., 2005), neglecting the broader, interconnected dynamics of attention encompassing various components beyond spatial allocation. **Chapters 2 and 3** therefore aim to bridge this gap in literature, by investigating the causal contributions the parietal cortex makes to attention as a multifaceted process. This involves not only examining the spatial orienting component of attention but also considering alerting and executive control components.

The chapters that then follow (**chapters 4, 5, and 6**) focus on evaluating alpha-tACS as a therapeutic intervention in 'actual' patients suffering from neglect. In these chapters, we compiled a diverse set of tasks to assess neglect, encompassing both novel and traditional approaches, as previous research has identified cases where patients perform well on standard clinical tests yet demonstrate neglect in daily activities, particularly among those in the chronic phase (Azouvi, 2017; Ten Brink, 2017).

The outline of the thesis falls apart into two main sections and is thus as follows:

Is alpha-tACS effective in reducing neglect-like behavioral patterns in healthy participants that have undergone cTBS inducing neglect-like symptoms?
Part I includes **chapters 2 and 3**.

Is alpha-tACS effective in reducing neglect behavioral patterns after stroke?
Part II includes **chapters 4, 5, and 6**.

In **chapter 7**, the key findings are summarized, with discussions on theoretical and methodological implications. Recommendations for future research and clinical practice are also presented.

References

Antal, A. (2012). Physiological basis and methodological aspects of transcranial electric stimulation (tDCS, tACS, and tRNS). In C. Miniussi, W. Paulus, & M. Rossini (Eds.), *A reference book for transcranial brain stimulation*. Taylor and Francis Group.

Azouvi, P. (2017). The ecological assessment of unilateral neglect. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 186–190. https://doi.org/10.1016/j.rehab.2015.12.005

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *The Lancet*, *325*(8437), 1106–1107. https://doi.org/10.1016/S0140-6736(85)92413-4

Başar, E., Başar-Eroglu, C., Karakaş, S., & Schürmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *International Journal of Psychophysiology*, *39*(2–3), 241–248. https://doi.org/10.1016/S0167-8760(00)00145-8

Berger, H. (1929). Über das Elektrenkephalogramm des Menschen. *Archiv Für Psychiatrie Und Nervenkrankheiten*, *87*(1), 527–570. https://doi.org/10.1007/BF01797193

Bien, N., Goebel, R., & Sack, A. T. (2012). Extinguishing extinction: Hemispheric differences in the modulation of TMS-induced visual extinction by directing covert spatial attention. *Journal of Cognitive Neuroscience*, *24*(4), 809–818. https://doi.org/10.1162/jocn_a_00179

Boes, A. D., Kelly, M. S., Trapp, N. T., Stern, A. P., Press, D. Z., & Pascual-Leone, A. (2018). Noninvasive brain stimulation: Challenges and opportunities for a new clinical specialty. *Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 173–179. https://doi.org/10.1176/appi.neuropsych.17110262

Bosma, M. S., Nijboer, T. C. W., Caljouw, M. A. A., & Achterberg, W. P. (2020). Impact of visuospatial neglect post-stroke on daily activities, participation and informal caregiver burden: A systematic review. *Annals of Physical and Rehabilitation Medicine*, *63*(4), 344–358. https://doi.org/10.1016/j.rehab.2019.05.006

Brighina, F., Bisiach, E., Piazza, A., Oliveri, M., La Bua, V., Daniele, O., & Fierro, B. (2002). Perceptual and response bias in visuospatial neglect due to frontal and parietal repetitive transcranial magnetic stimulation in normal subjects. *NeuroReport*, *13*(18), 2571–2575. https://doi.org/10.1097/00001756-200212200-00038

Buxbaum, L., Ferraro, M., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., Frassinetti, F., & Coslett, H. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology*, *62*, 749–756. https://doi.org/10.1212/01.wnl.0000113730.73031.f4

Carrasco, M. (2011). Visual attention: The past 25 years. *Vision Research*, *51*(13), 1484–1525. https://doi.org/10.1016/j.visres.2011.04.012

Cazzoli, D., Müri, R. M., Hess, C. W., & Nyffeler, T. (2009). Horizontal and vertical dimensions of visual extinction: A theta burst stimulation study. *Neuroscience*, *164*(4), 1609–1614. https://doi.org/10.1016/j.neuroscience.2009.09.044

Chen, P., Chen, C. C., Hreha, K., Goedert, K. M., & Barrett, A. M. (2015). Kessler Foundation neglect assessment process uniquely measures spatial neglect during activities of daily living. *Archives of Physical Medicine and Rehabilitation*, *96*(5), 869-876.e1. https://doi.org/10.1016/j.apmr.2014.10.023

Coldea, A., Morand, S., Veniero, D., Harvey, M., & Thut, G. (2021). Parietal alpha tACS shows inconsistent effects on visuospatial attention. *PLOS ONE*, *16*(8), e0255424. https://doi.org/10.1371/journal.pone.0255424

Corbetta, M. (2014). Hemispatial neglect: Clinic, pathogenesis, and treatment. *Seminars in Neurology*, *34*(5), 514–523. https://doi.org/10.1055/s-0034-1396005

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215. https://doi.org/10.1038/nrn755

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, *34*, 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Topper, R., & Boroojerdi, B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, *1072*(1), 194–199. https://doi.org/10.1016/j.brainres.2005.05.075

Duecker, F., & Sack, A. T. (2015). The hybrid model of attentional control: New insights into hemispheric asymmetries inferred from TMS research. *Neuropsychologia*, *74*, 21–29. https://doi.org/10.1016/j.neuropsychologia.2014.11.023

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2020). Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. In *Cochrane Database of Systematic Reviews* (Vol. 2020, Issue 11). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD009645.pub4

Fan, J., Gu, X., Guise, K. G., Liu, X., Fossella, J., Wang, H., & Posner, M. I. (2009). Testing the behavioral interaction and integration of attentional networks. *Brain and Cognition*, *70*(2), 209–220. https://doi.org/10.1016/j.bandc.2009.02.002

Fan, J., Kolster, R., Ghajar, J., Suh, M., Knight, R. T., Sarkar, R., & Mccandliss, B. D. (2007). Response anticipation and response conflict: An event-related potential and functional magnetic resonance imaging study. *The Journal of Neuroscience*, *27*(9), 2272–2282. https://doi.org/10.1523/jneurosci.3470-06.2007

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*(3), 340–347. https://doi.org/10.1162/089892902317361886

Fan, J., Mccandliss, T. B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *NeuroImage*, *26*, 471–479. https://doi.org/10.1016/j.neuroimage.2005.02.004

Feigin, V. L., Roth, G. A., Naghavi, M., Parmar, P., Krishnamurthi, R., Chugh, S., Mensah, G. A., Norrving, B., Shiue, I., Ng, M., Estep, K., Cercy, K., Murray, C. J. L., & Forouzanfar, M. H. (2016). Global burden of stroke and risk factors in 188 countries, during 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *The Lancet Neurology*, *15*(9), 913–924. https://doi.org/10.1016/S1474-4422(16)30073-4

Fernandez-Duque, D., & Posner, M. I. (2001). Brain imaging of attentional networks in normal and pathological states. *Journal of Clinical and Experimental Neuropsychology*, *23*(01), 74–93. https://doi.org/10.1076/jcen.23.1.74.1217

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D., & Bisiach, E. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport*, *11*(7), 1519–1521.

Gallotto, S., Duecker, F., Ten Oever, S., Schuhmann, T., De Graaf, T. A., & Sack, A. T. (2020). Relating alpha power modulations to competing visuospatial attention theories. *NeuroImage*, *207*, 1–10. https://doi.org/10.1016/j.neuroimage.2019.116429

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*, *11*(2), 49–54.

Gould, I. C., Rushworth, M. F., & Nobre, A. C. (2011). Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *Journal of Neurophysiology*, *105*(3), 1318–1326. https://doi.org/10.1152/jn.00653.2010

Greene, D. J., Barnea, A., Herzberg, K., Rassis, A., Neta, M., Raz, A., & Zaidel, E. (2008). Measuring attention in the hemispheres: The lateralized attention network test (LANT). *Brain and Cognition*, *66*(1), 21–31. https://doi.org/10.1016/j.bandc.2007.05.003

Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha oscillations correlate with the successful inhibition of unattended stimuli. *Journal of Cognitive Neuroscience*, *23*(9), 2494–2502. https://doi.org/10.1162/jocn.2010.21557

Heilman, K. M., Valenstein, E., & Watson, R. T. (2000). Neglect and related disorders. *Seminars in Neurology*, *20*(4), 463–470. https://doi.org/10.1055/s-2000-13179

Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention: The mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology*, *30*, 327–330.

Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00279

Hilgetag, C. C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced ‘virtual lesions’ of human parietal cortex. *Nature Neuroscience*, *4*(9), 953–957. https://doi.org/10.1038/nn0901-953

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*(2), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Frontiers in Human Neuroscience*, *4*, 1–8. https://doi.org/10.3389/fnhum.2010.00186

Jensen, O., Spaak, E., & Zumer, J. M. (2014). Human brain oscillations: From physiological mechanisms to analysis and cognition. In *Magnetoencephalography* (pp. 359–403). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-33045-2_17

Kasten, F. H., Wendeln, T., Stecher, H. I., & Herrmann, C. S. (2020). Hemisphere-specific, differential effects of lateralized, occipital–parietal α- versus γ-tACS on endogenous but not exogenous visual-spatial attention. *Scientific Reports*, *10*. https://doi.org/10.1038/s41598-020-68992-2

Kemmerer, S. K., De Graaf, T. A., Ten Oever, S., Erkens, M., De Weerd, P., & Sack, A. T. (2022). Parietal but not temporoparietal alpha-tACS modulates endogenous visuospatial attention. *Cortex*, *154*, 149–166. https://doi.org/10.1016/j.cortex.2022.01.021

Kemmerer, S. K., Sack, A. T., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Schuhmann, T. (2022). Frequency-specific transcranial neuromodulation of alpha power alters visuospatial attention performance. *Brain Research*, *1782*. https://doi.org/10.1016/j.brainres.2022.147834

Kerkhoff, G. (2000). Neurovisual rehabilitation: Recent developments and future directions. *Journal of Neurology, Neurosurgery & Psychiatry*, *68*(6), 691–706. https://doi.org/10.1136/jnnp.68.6.691

Kerkhoff, G. (2001). Spatial hemineglect in humans. *Progress in Neurobiology*, *63*, 1–27. https://doi.org/10.1016/s0301-0082(00)00028-9

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia*, *50*(6), 1072–1079. https://doi.org/10.1016/j.neuropsychologia.2012.01.024

Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. *Advances in Neurology*, *18*, 41–49.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Koch, G., Oliveri, M., Torriero, S., & Caltagirone, C. (2005). Modulation of excitatory and inhibitory circuits for visual awareness in the human right parietal cortex. *Experimental Brain Research*, *160*(4), 510–516. https://doi.org/10.1007/s00221-004-2039-2

Lakatos, P., Gross, J., & Thut, G. (2019). A new unifying account of the roles of neuronal entrainment. *Current Biology*, *29*, R890–R905. https://doi.org/10.1016/j.cub.2019.07.075

Lasaponara, S., Pinto, M., Aiello, M., Tomaiuolo, F., & Doricchi, F. (2019). The hemispheric distribution of a-band EEG activity during orienting of attention in patients with reduced awareness of the left side of space (spatial neglect). *Journal of Neuroscience*, *39*(22), 4332–4343. https://doi.org/10.1523/jneurosci.2206-18.2019

Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipović, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jääskeläinen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J. P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., … Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical Neurophysiology*, *131*(2), 474–528. https://doi.org/10.1016/j.clinph.2019.11.002

Longley, V., Hazelton, C., Heal, C., Pollock, A., Woodward-Nutt, K., Mitchell, C., Pobric, G., Vail, A., & Bowen, A. (2021). Non-pharmacological interventions for spatial neglect or inattention following stroke and other non-progressive brain injury. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003586.pub4

Maeda, F., Keenan, J. P., Tormos, J. M., Topka, H., & Pascual-Leone, A. (2000). Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiology*, *111*(5), 800–805. https://doi.org/10.1016/S1388-2457(99)00323-5

Neuling, T., Rach, S., & Herrmann, C. S. (2013). Orchestrating neuronal networks: Sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00161

Newman, D. P., O'Connell, R. G., & Bellgrove, M. A. (2013). Linking time-on-task, spatial bias and hemispheric activation asymmetry: A neural correlate of rightward attention drift. *Neuropsychologia*, *51*(7), 1215–1223. https://doi.org/10.1016/j.neuropsychologia.2013.03.027

Nijboer, T. C. W., Van de Port, I., Schepers, V., Post, M., & Visser-Meily, A. (2013). Predicting functional outcome after stroke: The influence of neglect on basic activities in daily living. *Frontiers in Human Neuroscience*, *7*, 1–6. https://doi.org/10.3389/fnhum.2013.00182

Nijboer, T. C. W., Winters, C., Kollen, B. J., & Kwakkel, G. (2018). Impact of clinical severity of stroke on the severity and recovery of visuospatial neglect. *PLoS ONE*, *13*(7). https://doi.org/10.1371/journal.pone.0198755

Nivel Zorgregistraties Eerste Lijn. (2023). *Zorg door de huisarts: Jaarcijfers 2022 en trendcijfers 2018-2022*. Nivel.

Paulus, W. (2011). Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychological Rehabilitation*, *21*(5), 602–617. https://doi.org/10.1080/09602011.2011.557292

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience*, *35*(1), 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Pfurtscheller, G., Stancák, A., & Neuper, Ch. (1996). Event-related synchronization (ERS) in the alpha band — an electrophysiological correlate of cortical idling: A review. *International Journal of Psychophysiology*, *24*(1–2), 39–46. https://doi.org/10.1016/S0167-8760(96)00066-9

Pizzamiglio, L., Antonucci, G., Judica, A., Montenero, P., Razzano, C., & Zoccolotti, P. (1992). Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral right brain damage. *Journal of Clinical and Experimental Neuropsychology*, *14*(6), 901–923. https://doi.org/10.1080/01688639208402543

Posner, M. I. (2012). Imaging attention networks. *NeuroImage*, *61*(2), 450–456. https://doi.org/10.1016/j.neuroimage.2011.12.040

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. https://doi.org/10.1146/annurev.psych.58.110405.085516

Posner, M. I., Snyder, C. R., & Davidson, B. J. (1980). Attention and the detection of signals. *Journal of Experimental Psychology*, *109*(2), 160–174.

Reynolds, J. H., & Heeger, D. J. (2009). The normalization model of attention. *Neuron*, *61*(2), 168–185. https://doi.org/10.1016/j.neuron.2009.01.002

Ringman, J. M., Saver, J. L., Woolson, R. F., Clarke, W. R., & Adams, H. P. (2004). Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. *Neurology*, *63*, 468–474. https://doi.org/https://doi.org/10.1212/01.WNL.0000133011.10689.CE

Robertson, E. M., Théoret, H., & Pascual-Leone, A. (2003). Studies in cognition: The problems solved and created by transcranial magnetic stimulation. *Journal of Cognitive Neuroscience*, *15*(7), 948–960. https://doi.org/10.1162/089892903770007344

Rode, G., Pagliari, C., Huchon, L., Rossetti, Y., & Pisella, L. (2017). Semiology of neglect: An update. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 177–185. https://doi.org/10.1016/j.rehab.2016.03.003

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., Dimitrijević, M. R., Hallett, M., Katayama, Y., Lücking, C. H., Maertens de Noordhout, A. L., Marsden, C. D., Murray, N. M. F., Rothwell, J. C., Swash, M., & Tomberg, C. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, *91*(2), 79–92. https://doi.org/10.1016/0013-4694(94)90029-9

Rothwell, J. C., Hallett, M., Berardelli, A., Eisen, A., Rossini, P., & Paulus, W. (1999). Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. *Electroencephalography and Clinical Neurophysiology. Supplement*, *52*, 97–103.

Sack, A. T. (2006). Transcranial magnetic stimulation, causal structure–function mapping and networks of functional relevance. *Current Opinion in Neurobiology*, *16*(5), 593–599. https://doi.org/10.1016/j.conb.2006.06.016

Sack, A. T. (2010). Using non-invasive brain interference as a tool for mimicking spatial neglect in healthy volunteers. *Restorative Neurology and Neuroscience*, *28*, 485–497. https://doi.org/10.3233/RNN-2010-0568

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W. R., & Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917–2926. https://doi.org/10.1111/j.1460-9568.2005.04482.x

Schenkenberg, T., Bradford, D., & Ajax, E. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509–517. https://doi.org/10.1212/wnl.30.5.509

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *PLoS ONE*, *14*(11), 1–25. https://doi.org/10.1371/journal.pone.0217729

Smith, D. T., & Schenk, T. (2012). The premotor theory of attention: Time to move on? *Neuropsychologia*, *50*(6), 1104–1114. https://doi.org/10.1016/j.neuropsychologia.2012.01.025

Spreij, L. A., Ten Brink, A. F., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2020a). Increasing cognitive demand in assessments of visuo-spatial neglect: Testing the concepts of static and dynamic tests. *Journal of Clinical and Experimental Neuropsychology*, *42*(7), 675–689. https://doi.org/10.1080/13803395.2020.1798881

Spreij, L. A., Ten Brink, A. F., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2020b). Simulated driving: The added value of dynamic testing in the assessment of visuo-spatial neglect after stroke. *Journal of Neuropsychology*, *14*(1), 28–45. https://doi.org/10.1111/jnp.12172

Suppa, A., Huang, Y.-Z., Funke, K., Ridding, M. C., Cheeran, B., Di Lazzaro, V., Ziemann, U., & Rothwell, J. C. (2016). Ten years of theta burst stimulation in humans: Established knowledge, unknowns and prospects. *Brain Stimulation*, *9*(3), 323–335. https://doi.org/10.1016/j.brs.2016.01.006

Szczepanski, S. M., & Kastner, S. (2013). Shifting attentional priorities: Control of spatial attention through hemispheric competition. *The Journal of Neuroscience*, *33*(12), 5411–5421. https://doi.org/10.1523/jneurosci.4089-12.2013

Ten Brink, A. F. (2017). *Visuospatial neglect after stroke: Heterogeneity, diagnosis and treatment*. Utrecht University, Ridderkerk.

Ten Brink, A. F., Van Kessel, M. E., & Nijboer, T. C. W. (2017). Neglect. In C. Van Heugten, D. Bertens, & J. Spikman (Eds.), *Richtlijn Neuropsychologische Revalidatie* (pp. 1–92). Nederlands Instituut van Psychologen. www.psynip.nl

Ten Brink, A. F., Verwer, J. H., Biesbroek, J. M., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2017). Differences between left- and right-sided neglect revisited: A large cohort study across multiple domains. *Journal of Clinical and Experimental Neuropsychology*, *39*(7), 707–723. https://doi.org/10.1080/13803395.2016.1262333

Thut, G., & Miniussi, C. (2009). New insights into rhythmic brain activity from TMS–EEG studies. *Trends in Cognitive Sciences*, *13*(4), 182–189. https://doi.org/10.1016/j.tics.2009.01.004

Thut, G., Miniussi, C., & Gross, J. (2012). The functional importance of rhythmic activity in the brain. *Current Biology*, *22*(16), R658–R663. https://doi.org/10.1016/j.cub.2012.06.061

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/jneurosci.0875-06.2006

Thut, G., Nietzel, A., & Pascual-Leone, A. (2005). Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. *Cerebral Cortex*, *15*(5), 628–638. https://doi.org/10.1093/cercor/bhh164

Thut, G., & Pascual-Leone, A. (2010). A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. *Brain Topography*, *22*(4), 219–232. https://doi.org/10.1007/s10548-009-0115-4

Thut, G., Schyns, P. G., & Gross, J. (2011). Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Frontiers in Psychology*, *2*. https://doi.org/10.3389/fpsyg.2011.00170

Ting, D. S. J., Pollock, A., Dutton, G. N., Doubal, F. N., Ting, D. S. W., Thompson, M., & Dhillon, B. (2011). Visual neglect following stroke: Current concepts and future focus. *Survey of Ophthalmology*, *56*(2), 114–134. https://doi.org/10.1016/j.survophthal.2010.08.001

Van der Stoep, N., Visser-Meily, J. M. A., Kappelle, L. J., De Kort, P. L. M., Huisman, K. D., Eijsackers, A. L. H., Kouwenhoven, M., Van der Stigchel, S., & Nijboer, T. C. W. (2013). Exploring near and far regions of space: Distance-specific visuospatial neglect after stroke. *Journal of Clinical and Experimental Neuropsychology*, *35*(8), 799–811. https://doi.org/10.1080/13803395.2013.824555

Van Kessel, M. E., Geurts, A. C. H., Brouwer, W. H., & Fasotti, L. (2013). Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task. *Frontiers in Human Neuroscience*, *7*, 1–11. https://doi.org/10.3389/fnhum.2013.00358

Van Schouwenburg, M. R., Sörensen, L. K. A., De Klerk, R., Reteig, L. C., & Slagter, H. A. (2018). No differential effects of two different alpha-band electrical stimulation protocols over fronto-parietal regions on spatial attention. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00433

Veniero, D., Benwell, C. S. Y., Ahrens, M. M., & Thut, G. (2017). Inconsistent effects of parietal α-tACS on pseudoneglect across two experiments: A failed internal replication. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.00952

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). Development of a behavioral test of visuospatial neglect. *Archives of Physical Medicine and Rehabilitation*, *68*(2), 98–102.

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience*, *20*(6), 1–6. https://doi.org/10.1523/jneurosci.20-06-j0002.2000

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE*, *5*(11), e13766. https://doi.org/10.1371/journal.pone.0013766

Zebhauser, P. T., Vernet, M., Unterburger, E., & Brem, A.-K. (2019). Visuospatial neglect - a theory-informed overview of current and emerging strategies and a systematic review on the therapeutic use of non-invasive brain stimulation. *Neuropsychology Review*, *29*(4), 397–420. https://doi.org/10.1007/s11065-019-09417-4

Part I

Is alpha-tACS effective in reducing neglect-like behavioral patterns in healthy participants that have undergone cTBS inducing neglect-like symptoms?

Chapter 2

Transcranial magnetic stimulation over posterior parietal cortex modulates alerting and executive control processes in attention

Corresponding manuscript:

Middag-van Spanje, M., Duecker, F., Gallotto, S., De Graaf, T. A., Van Heugten, C., Sack, A. T., & Schuhmann, T. (2022). Transcranial magnetic stimulation over posterior parietal cortex modulates alerting and executive control processes in attention. *European Journal of Neuroscience*, *56*(10), 5853–5868. https://doi.org/10.1111/ejn.15830

Abstract

Attention includes three different functional components: generating and maintaining an alert state (alerting), orienting to sensory events (orienting), and resolving conflicts between alternative actions (executive control). Neuroimaging and patient studies suggest that the posterior parietal cortex (PPC) is involved in all three attention components. Transcranial magnetic stimulation (TMS) has repeatedly been applied over the PPC to study its functional role for shifts and maintenance of visuospatial attention. Most TMS-PPC studies used only detection tasks or orienting paradigms to investigate TMS-PPC effects on attention processes, neglecting the alerting and executive control components of attention. The objective of the present study was to investigate the role of PPC in all three functional components of attention: alerting, orienting, and executive control. To this end, we disrupted PPC with TMS (continuous theta-burst stimulation), to modulate subsequent performance on the lateralized-attention network test, used to assess the three attention components separately. Our results revealed hemifield-specific effects on alerting and executive control functions, but we did not find stimulation effects on orienting performance. While this field of research and associated clinical development have been predominantly focused on orienting performance, our results suggest that parietal cortex and its modulation may affect other aspects of attention as well.

Introduction

Our world consists of a large amount of stimuli and as these stimuli exceed the capacity of our brain, we have to filter the input. Attention is the cognitive process that helps us to selectively concentrate on a certain aspect of information. It is a broad concept, often defined in terms of selection, suppression, and thus biasing of sensory inputs for preferred processing. The concept of attention can be divided into three different types of attention functions: alerting, orienting and executive control (Petersen & Posner, 2012) and these functions are regulated by three relatively distinct but highly connected and partially overlapping neural networks (Fan et al., 2009, 2005, 2002; Petersen & Posner, 2012).

Alerting is defined as generating and maintaining a vigilant state (Coull et al., 1999; Posner & Petersen, 1990) and is responsible for spreading attention over a broad area of space and a higher alert state allows faster processing of information, independently of its spatial location. Imaging studies show that voluntarily maintaining our level of alertness over time is controlled mostly by thalamic and right frontal and parietal regions, including the posterior parietal cortex (PPC; Fan, Kolster, et al., 2007; Pardo et al., 1991; Sturm et al., 2005, 1999; Sturm & Willmes, 2001). Alertness can also be modulated experimentally by presenting warning cues that indicate when, but not where, a stimulus will occur. This function is known as 'phasic alertness' and is associated with activity in left frontal-parietal areas and thalamus (Fan et al., 2005; Sturm & Willmes, 2001; Yanaka et al., 2010).

Orienting enables directional shifts of attention to a relevant spatial location (Fan et al., 2002). The influential functional-anatomical model of Corbetta and Shulman (2011) suggests two distinct but interacting networks being responsible for spatial attentional control. On the one hand, the bilateral dorsal fronto-parietal attention network is involved in shifts and maintenance of spatial attention and includes the PPC and frontal eye field. On the other hand, the right-lateralized ventral fronto-parietal attention network supports attentional re-orienting to unexpected events and includes the temporo-parietal junction and ventral frontal cortex (for reviews, see Corbetta & Shulman, 2011, 2002; Mesulam, 1999).

Executive control of attention reflects the individual's capacity to monitor and resolve conflict in the presence of competing information (Fan, Byrne, et al., 2007). Neuroimaging studies have shown activation of a network of brain areas in response to many forms of control, including task switching, inhibitory control, conflict resolution, novelty processing, and error detection (for reviews, see Bush et al., 2000; Carter et al., 1999; Posner & Rothbart, 1998). The areas usually activated include the anterior cingulate cortex and supplementary motor area, the orbitofrontal cortex, the dorsolateral prefrontal cortex, and portions of the basal ganglia and the thalamus (Fernandez-Duque & Posner, 2001), but it has been hypothesized that the PPC, which is known to be involved in alerting and orienting, also plays a role in the executive control of attention (Friedman-Hill et al., 2003; Lega et al., 2019; Marek & Dosenbach, 2018).

The abovementioned evidence for the regions and networks related to each of the three attention components, provided by brain imaging studies, is correlational in nature and limited in revealing causal relationships between task-dependent changes in brain activity and their respective behavioral consequences. Noninvasive brain stimulation (NIBS) techniques, in particular transcranial magnetic stimulation (TMS), have become important tools in showing causality between specific brain areas and attention processes (Bien et al., 2012; Duecker & Sack, 2015a; Silvanto et al., 2009; Szczepanski & Kastner, 2013).

In healthy volunteers, TMS has repeatedly been applied over the PPC to study its functional role in visuospatial attention. TMS over PPC has been shown to affect performance on attention tasks in various experimental designs, resembling the attention deficits observed in patients with spatial hemineglect (for review, see Duecker & Sack, 2015a), but the majority of these studies used only detection tasks or spatial orienting paradigms. Thus, previous TMS-PPC work almost exclusively addressed the 'orienting' component of attention, neglecting the alerting and executive control components of the framework as proposed by Petersen and Posner (2012) and particularly their potential interactions. This, in spite of the mentioned evidence from imaging studies implicating PPC in all three attention functions *and* in spite of evidence shown in behavioral studies for interactions among the three functions (Callejas et al., 2005, 2004; Chica et al., 2011; Fan et al., 2009; Posner & Petersen, 1990). For instance, in studies using a tone as alerting signal, the flanker-congruency effect (a measure of executive control) is larger on trials where an alerting signal has been previously presented, pointing to an inhibitory relationship between alerting and executive control (Callejas et al., 2005, 2004). Orienting has also shown to interact with executive control; more engagement in conflict resolution leads to an increase in benefit when one orients to the target position than when one orients to the location opposite to that of the target (Greene et al., 2008). These interactions further support the notion that the brain networks supporting the functions interact. Altogether, it is likely that TMS manipulation of PPC affects not only orienting, but also alerting and executive control.

In the current study, we were interested in the functional role of PPC in all three functional components of attention (alerting, orienting, and executive control). The lateralized-attention network test (LANT; Asanowicz et al., 2012; Fan et al., 2002; Greene et al., 2008) is a behavioral task that simultaneously assesses the efficiency of each of the proposed functional components of attention, as well as their possible interactions.

To investigate the role of PPC in the three functions of attention, and their interactions, within each hemifield, we applied a continuous theta-burst stimulation (cTBS) protocol (Huang et al., 2005) to the right PPC before participants performed the LANT and compared the behavioral effects to sham stimulation. Since it has been proposed that the PPC in each hemisphere biases attention toward the contralateral hemifield (Kinsbourne, 1977), we expected a reduction in alerting (Petersen & Posner, 2012), orienting (Duecker & Sack, 2015a), and executive control (Friedman-Hill et al., 2003; Lega et al., 2019) efficiency for the left hemifield, potentially accompanied by a shift of attentional resources toward the right hemifield.

Methods

Participants

Thirty-four volunteers (20 women; mean age = 22.79 years, SD = 3.71) from Maastricht University participated in this study in return for course credits or monetary compensation. All were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision, and had no psychiatric or neurological history, assessed by self-report. Participants were screened for TMS experimentation safety prior to each testing session. The research question and hypotheses remained unknown to the participants until the end of the experiment.

Procedure

This study presents data that were collected as part of a larger study that consisted of in total four sessions per participant. (More information on the procedure regarding the larger study can be found in the supplementary material.) The data reported here reflect LANT performance that was collected in two of those sessions; namely in a session in which (generally) inhibitory active TMS (cTBS) was applied, and in a session in which sham TMS was applied. Stimulation conditions were counterbalanced across participants. Experimental sessions were separated by at least four days (mean = 13 days between active and sham TMS sessions, SD = 7.1).

At the beginning of each session, participants practiced the LANT to get accustomed to the task (36 trials), during which they received feedback if they responded incorrectly or too slowly. The individual resting motor threshold was determined in the first testing session, and the same threshold value was used for the second session. A cap indicating the electrode positions of the international 10-20 electroencephalography (EEG) positioning system was used to mark the stimulation site P4 (right PPC). Then, participants were seated in front of the computer screen with the head supported by a chin rest. After calibration of the eye tracker, (active or sham) TMS was applied to the right parietal cortex, after which participants performed the LANT. EEG was recorded between TMS application and task administration (supplementary material), but time from the TMS ending and the start of the task never exceeded 5 minutes.

Task and stimuli

Alerting, orienting, and executive control were assessed by the LANT (**Figure 1**; Asanowicz et al., 2012; Greene et al., 2008). In each trial, participants first focused on a fixation point which was continuously displayed in the screen center. After 1400, 1600, or 1800 ms a cue was presented for 100 ms. The stimulus onset asynchrony between cue and target presentation onset was 600 ms, and the main stimulus was displayed for 200 ms. The trial ended after the participant's response or, in case no response was given, after 1200 ms.

The main stimulus comprised an array of five arrows arranged in a vertical line, presented at 7° eccentricity from the fixation point. The middle arrow was the target and pointed either up or down. The four other arrows flanked the target and pointed in a direction that was either congruent or incongruent with the target arrow. In the incongruent condition, participants had to overcome the conflict elicited by the distractor arrows. There were three cue conditions that preceded the target. A neutral cue was used to alert participants. An orienting cue was used to orient participants' attention and could be either valid (i.e., correctly indicating the location of the following target) or invalid. Therefore, the neutral (c.q., alerting) cue informed participants when the target would occur, whereas the orienting cue additionally (mis)informed them about the target location. A no-cue reference condition was also included. Central symbolic cues were used to prompt voluntary shifts of attention (**Figure 1**), although it should be noted that there is evidence that arrows can orient attention involuntarily to the location they are pointing at (Hommel et al., 2001) and therefore are not purely endogenous.

The target was displayed with an equal probability on the left or right side of the screen. This presentation to one or the other hemifield enabled lateralization effects to be measured. Participants were instructed to maintain central fixation throughout the task, and to indicate the direction of the target arrow as quickly and accurately as possible by pressing the up or down key on a standard keyboard with the right middle finger or index finger, respectively. Speed and accuracy of responses were measured. Participants received no feedback on their accuracy, except when they responded too slowly (RT > 1000 ms). This measure was taken in order to keep participants vigilant to the task.

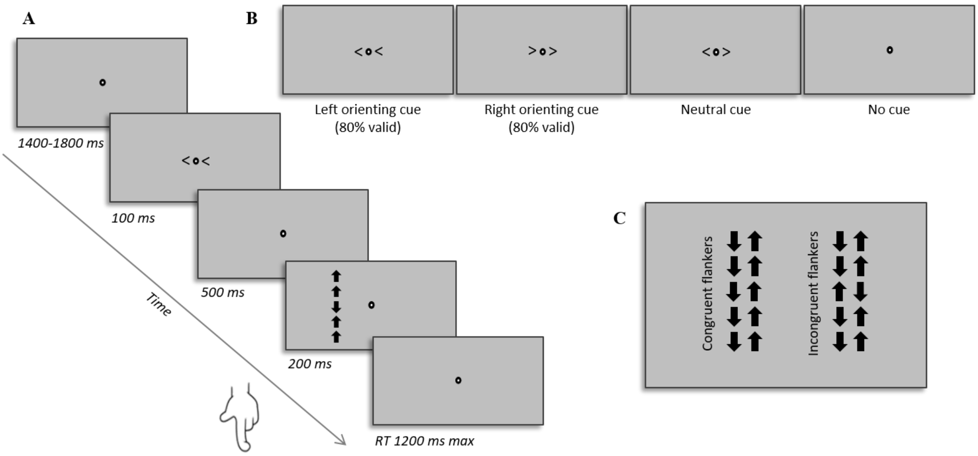

Figure 1 Experimental procedure for the lateralized-attention network test. (A) An example of the sequence of events for a trial with a valid spatial cue and incongruent flankers. **(B)** Cue conditions (left-orienting and right-orienting cue, neutral cue, and no cue). **(C)** Flanker types (congruent flankers and incongruent flankers).

The LANT consisted of 720 trials divided into five blocks of 144 trials each, presented in randomized order. On 400 trials, the target was preceded by an orienting cue that indicated the target's location with a probability of 80%. Thus, on 320 trials the orienting cue validly predicted the target location, while on 80 trials the orienting cue was misleading. The remaining 320 trials were evenly divided into neutral-cue (160) and no-cue (160) trials. Concerning the flanker arrows, on one half of the trials (360), the target was flanked by congruent flankers, and on the other half by incongruent flankers. We added four warm-up trials at the beginning of each block that were not considered in the analysis. Including short breaks between blocks, the total duration of the task was 35-40 minutes.

Stimuli were presented using the Presentation software package (NeuroBehavioural Systems, Albany, CA) on a Iiyama ProLite B2483HS monitor at 70 cm viewing distance. The video mode was 1920 × 1080 at 60 Hz, and background luminance was 100 cd/m2.

TMS protocol

TMS was applied with a MagPro R30 stimulator (MagVenture A/S, Farum, Denmark) and a figure-of-eight TMS coil (MC-B70; inner radius = 10 mm, outer radius = 50 mm). Pulses were biphasic, with an anterior-posterior followed by posterior-anterior current direction in the brain. The coil was placed tangentially to the scalp over the electrode position P4 (based on the international 10-20 system) with the handle in posterior direction orienting 45° away from the midline. The cTBS protocol consists of a total of 600 stimuli applied in bursts of three stimuli at twenty ms intervals (50 Hz), with bursts repeated at 200 ms intervals (5 Hz) (Huang et al., 2005). Stimuli were given at an intensity of 100% of the individual resting motor threshold (mean stimulation intensity = 33.9% of maximum stimulator output, SD = 5.3, 46.8 A/µs). Resting motor threshold was determined using single pulse TMS over the right motor cortex. It was defined as the lowest intensity that elicited an observable muscle twitch of the left index finger on three of six trials (Pridmore, Filho, Nahas, Liberatos, & George, 1998; Varnava, Stokes, & Chambers, 2011). During sham stimulation, the coil was held at 90° to the participant's skull, so that no pulses perturbed underlying cortex (Hilgetag et al., 2001).

Eye movement control

We performed video-based monocular eye tracking (EyeLink 1000 system, SR Research, Mississauga, Canada) to track gaze position of the participant's right eye at a sampling rate of 1000 Hz and with high sensitivity for automatic detection. The five-point (center, top, bottom, left, and right) calibration and validation procedure was used, while the participant's head was supported by a chin rest. The software automatically detected eye movements and blinks when the participant performed the task. This information later allowed us to discard all trials that were contaminated by eye movements (exceeding 2° of visual angle) or blinks (M = 7.1% of trials across conditions, SD = 6.4). The critical time window ranged from 100 ms before appearance of the cue until stimulus onset. This ensured that the participant did not overtly shift attention toward the target but merely performed covert shifts of spatial attention and that behavioral effects were not to be distorted by interruptions of central fixation.

Data analysis

We first inspected the individual data sets of sessions with sham TMS to detect strongly deviating performances in the absence of possible stimulation effects. One participant showed accuracies around chance level in all sham conditions, so we excluded this data set from further analyses. Besides excluding trials contaminated by eye blinks or eye movements, we also excluded trials in case of incorrect responses or misses. For each condition, trials were identified as outliers if the participant's reaction time (RT) deviated by more than 1.5 times the interquartile range (IQR) from Q1 and Q3. After application of these exclusion criteria, 84% of all trials remained for further analysis. We computed mean RTs for each condition, and the average amount of trials per smallest cell (invalid trials) was seventeen trials (SD = 2.5). The average amount of trials in the other conditions was 67 (SD = 9.7) in the valid trials, 33 (SD = 5.1) in the neutral trials, and 33.6 (SD = 4.9) in the no-cue trials. After computing mean RTs and scores of the three functions of attention (see formulae below), as a final pre-analysis step, we inspected the RTs and scores in sessions with sham TMS. We decided to exclude one more data set from further analyses due to extreme outliers in mean RTs and scores (> 3.0*IQR from Q1 and Q3) in multiple sham conditions, reducing the sample size to 32 participants.

To calculate scores of the attention functions we conducted three separate subtractions using mean RTs of trials in which participants responded correctly (Fan et al., 2002):

1. Alerting score = no cue – neutral cue
2. Orienting score = invalid cue – valid cue
3. Executive control score = incongruent flanker – congruent flanker

We divided our analyses in two parts:

1. *LANT performance in the sham condition*. We first focused only on task performance under baseline conditions (sham stimulation) to test whether experimental manipulation of attention was successful and whether we could

observe interactions among the three attention functions that previous behavior studies have found. To this end, we submitted mean RTs of the sham condition to a repeated measures ANOVA (RM ANOVA) with hemifield (left and right), cue (valid, neutral, invalid, and no cue), and congruency (congruent and incongruent) as within-subject factors. Also, we submitted the alerting, orienting, and executive control scores of the baseline conditions to three RM ANOVAs, one for each score. For the ANOVAs on alerting and orienting scores, congruency was included as a within-subject factor, and for the ANOVA on executive scores, cue was included as a within-subject factor. By doing so, we considered interactions between the three components.

2. *Stimulation effects*. Secondly, we performed analyses to evaluate the differential effects of TMS-PPC on alerting, orienting and executive control. We chose *not* to analyze mean RTs here anymore (as we extensively did for the sham data, allowing us to discuss and compare our results with observations of previous behavior studies) but to reduce the task conditions and *only* analyze the three scores (alerting, orienting and executive control). Thus, to evaluate the effects of TMS, we submitted each of the three scores to a RM ANOVA. We considered interactions between the three components by including congruency and cue as within-subject factors for the ANOVAs on alerting and orienting, and executive control, respectively.

All analyses were performed using IBM SPSS Statistics version 25. For all RM ANOVAs, we reported the multivariate test statistics (Pillai's trace). Follow-up analyses were conducted with paired t tests and Wilcoxon signed-rank tests were performed when data were not normally distributed (according to the Shapiro-Wilk test). When Wilcoxon signed-rank tests were performed, we reported z values. We used a significance level of $p < .05$.

Results

Overall accuracy in the sham and the active TMS condition yielded 93.05% (SD = 9.94) and 93.55% (SD = 9.76), respectively. Mean RTs of all conditions are given in **Table 1**.

Table 1 Mean reaction times (RTs, in ms) of correct responses and standard error (in brackets) for each experimental condition, for sham and active TMS conditions.

		Left hemifield		Right hemifield	
		Sham	Active	Sham	Active
Valid	Congruent	471.7 (10.0)	469.9 (8.3)	466.4 (10.5)	466.8 (8.6)
	Incongruent	521.0 (10.2)	529.3 (9.1)	530.3 (12.7)	531.3 (10.4)
Neutral	Congruent	473.2 (9.7)	473.9 (8.7)	470.0 (10.6)	466.7 (8.9)
	Incongruent	528.7 (10.5)	533.7 (9.0)	538.8 (13.5)	528.7 (10.2)
Invalid	Congruent	490.0 (11.0)	487.9 (8.9)	482.0 (12.3)	483.4 (10.4)
	Incongruent	539.6 (10.9)	546.1 (10.0)	547.4 (13.6)	544.1 (11.6)
No cue	Congruent	511.4 (10.1)	514.6 (8.9)	505.9 (11.3)	501.4 (8.9)
	Incongruent	563.6 (10.3)	562.7 (8.6)	562.3 (13.8)	559.4 (11.3)

LANT performance in the sham condition

We first focused on task performance under baseline conditions (sham stimulation). A RM ANOVA on mean RTs was performed with hemifield (left and right), cue (valid, neutral, invalid, and no cue), and congruency (congruent and incongruent) as within-subject factors. RTs differed between cue conditions ($F(3,29) = 63.034$, $p < .001$). Subsequently, we performed planned comparisons between the cue conditions. As expected, participants responded significantly faster in valid-cue as compared to neutral-cue trials ($t(31) = 3.018$, $p = .005$), neutral-cue as compared to invalid-cue trials ($z = 3.927$, $p < .001$, $r = .491$), and invalid-cue as compared to no-cue trials ($t(31) = 7.656$, $p < .001$). Also, to ensure that the alerting and orienting attention components we aimed to modulate with TMS were present in a normal (baseline/sham) condition, we performed two additional *t* tests. Participants reacted significantly faster in neutral-cue compared to no-cue trials, resulting in a significant score of alerting ($t(31) = 12.368$, $p < .001$), and in valid-cue compared to invalid-cue trials, resulting in a significant score of orienting ($z = 4.245$, $p < .001$, $r = .531$). We also found a main effect of congruency ($F(1,31) = 223.017$, $p < .001$), demonstrating significantly faster performance for congruent-flanker than for incongruent-flanker trials, resulting in a significant score of executive control. Both the observed cue and congruency effects supported our expected response patterns. No main effect of hemifield was found ($F(1,31) = .018$, $p = .894$).

There was also a significant interaction between hemifield and congruency ($F(1,31) = 7.630$, $p = .010$). Follow-up *t* tests showed that this interaction reflected a right hemifield advantage in congruent trials ($t(31) = 1.951$, $p = .060$), and a left hemifield advantage in incongruent trials ($t(31) = 1.148$, $p = .260$), both not significant. RTs in congruent trials were significantly faster than RTs in incongruent trials in both hemifields (left: $t(31) = 12.218$, *p*

< .001; right: $t(31) = 13.812$, $p < .001$). Lastly, a significant interaction between cue and congruency ($F(3,29) = 2.929$, $p = .050$) was found (**Figure 2**), so we conducted additional ANOVAs separately for alerting scores (no-cue minus neutral-cue trials), orienting scores (invalid-cue minus valid-cue trials), and executive scores (incongruent-flanker minus congruent-flanker trials) to test for possible relationships between the three functions of attention. These additional ANOVAs are reported in the three paragraphs below ('Alerting', 'Orienting' and 'Executive control'). Please note that these also still concern the baseline conditions (sham stimulation) only. No significant interactions were found between hemifield and cue ($F(3,29) = 2.184$, $p = .111$) nor between hemifield, cue, and congruency ($F(3,29) = 1.149$, $p = .346$).

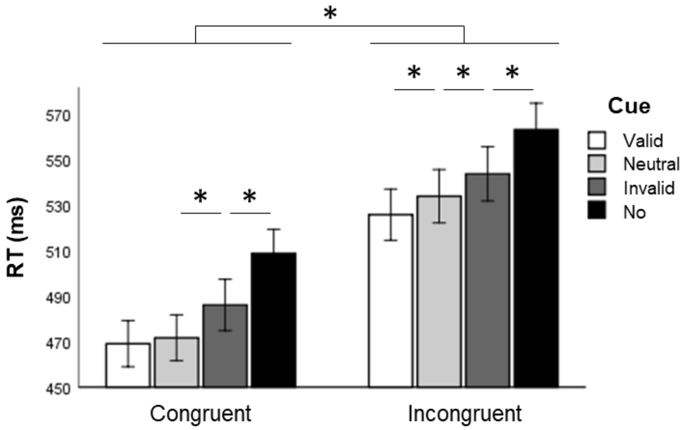

Figure 2 Reaction times (RT, in ms) per type of cue and congruency during sham stimulation, averaged over hemifields. Participants reacted significantly faster in neutral-cue compared to no-cue trials, in valid-cue compared to invalid-cue trials, and in congruent-flanker compared to incongruent-flanker trials. Thus, we efficiently measured the scores of alerting, orienting, and executive control, respectively. Asterisks (*) depict significant difference ($p < .05$). Error bars depict one standard error.

Alerting

A RM ANOVA on alerting scores was performed with hemifield (left and right) and congruency (congruent and incongruent) as within-subject factors. This showed a significant main effect of hemifield, with lower alerting scores in the right hemifield ($F(1,31) = 5.622$, $p = .024$), and a significant main effect of congruency, with lower alerting scores in incongruent trials ($F(1,31) = 4.607$, $p = .040$). The latter implies an interaction between alerting and executive control. No significant interaction between hemifield and congruency was found ($F(1,31) = 1.949$, $p = .173$).

Orienting

A RM ANOVA on orienting scores was performed with hemifield (left and right) and congruency (congruent and incongruent) as within-subject factors. No significant main effects of hemifield ($F(1,31) = .266$, $p = .610$) and congruency ($F(1,31) = .046$, $p = .831$) were found, nor an interaction between these factors ($F(1,31) = .029$, $p = .865$).

Executive control

We performed a RM ANOVA on executive scores with hemifield (left and right) and cue (valid, neutral, invalid, and no cue) as within-subject factors. This gave a significant main effect of hemifield, with lower executive scores (c.q., lower cost of conflict) in the left hemifield ($F(1,31) = 7.630$, $p = .010$), and a significant main effect of cue ($F(3,29) = 2.929$, $p = .050$). Follow-up *t* tests revealed significantly lower executive scores for valid-cue compared to neutral-cue trials ($t(31) = 2.602$, $p = .014$). Executive scores did not differ between neutral-cue and invalid-cue trials ($t(31) = 1.015$, $p = .318$) nor between invalid-cue and no-cue trials ($t(31) = .638$, $p = .528$). Noteworthy, significantly higher executive scores were found for neutral-cue trials compared to no-cue trials ($t(31) = 2.146$, $p = .040$), which again shows the interaction between alerting and executive control processes. Executive scores did not differ between valid-cue and invalid-cue trials (thus no interaction between orienting and executive control, $t(31) = .215$, $p = .831$). No significant interaction between hemifield and cue was found ($F(3,29) = 1.149$, $p = .346$).

Stimulation effects

We then compared active TMS to sham TMS (as control condition) to systematically evaluate the effects of stimulation on alerting, orienting, and executive control scores. To this end, we submitted each of the scores to a RM ANOVA, with hemifield included as a within-subject factor in every analysis.

Effects on alerting

TMS effects on alerting were analyzed using a RM ANOVA on alerting scores with stimulation (active and sham), hemifield (left and right), and congruency (congruent and incongruent) as within-subject factors. The analysis revealed significant main effects of hemifield, with lower alerting scores in the right hemifield ($F(1,31) = 4.356$, $p = .045$), and congruency, with lower scores in the incongruent trials ($F(1,31) = 10.098$, $p = .003$). Although no main effect of stimulation was found ($F(1,31) = .080$, $p = .780$), nor any two-way interactions between the factors (all p values > .285), crucially, there was a significant three-way interaction between stimulation, hemifield, and congruency ($F(1,31) = 6.736$, $p = .014$). We then analyzed the alerting scores separately for the congruent and incongruent trials. In the congruent condition, there were no significant main effects (stimulation: $F(1,31) = .011$, $p = .918$; hemifield: $F(1,31) = 2.967$, $p = .095$) nor an interaction between stimulation and hemifield ($F(1,31) = 1.228$, $p = .276$; **Figure 3A**). In the incongruent condition, also, no main effects were found (stimulation: $F(1,31) = .078$, $p = .781$; hemifield: $F(1,31) = 1.061$, $p = .311$), but importantly, the interaction between stimulation and hemifield remained significant ($F(1,31) = 9.178$, $p = .005$; **Figure 3B**). Follow-up t tests revealed that there was a left hemifield advantage in sham TMS but not in active TMS (left vs. right in sham: $t(31) = 2{,}454$, $p = .020$; left vs. right in active: $t(31) = .603$, $p = .551$). Also, alerting scores did not differ in active TMS compared to sham TMS, for neither hemifields (left: $t(31) = 1.827$, $p = .077$; right: $t(31) = 1.910$, $p = .065$).

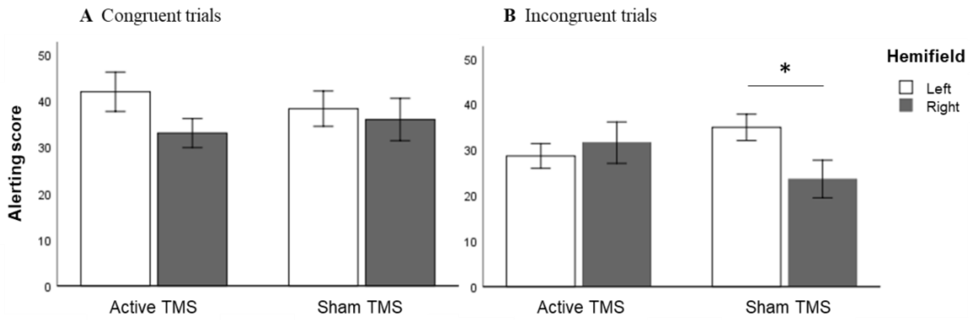

Figure 3 Latency estimates of alerting for congruent-flanker and incongruent-flanker trials. A significant three-way interaction between stimulation, hemifield, and congruency was found for the alerting effect. **(A)** In the congruent condition, no significant main effects or interactions were found. **(B)** In the incongruent condition, stimulation interacted with hemifield (significant stimulation*hemifield interaction). There was a left hemifield advantage in sham TMS (significant p value left vs. right in sham), but not in active TMS. Also, comparing active TMS versus sham TMS: There was a decrease of alerting efficiency in the left hemifield and an increase of alerting efficiency in the right hemifield (both comparisons not significant). Asterisks (*) depict significant difference ($p < .05$). Error bars depict one standard error.

Effects on orienting

TMS effects on orienting were analyzed using a RM ANOVA on orienting scores with stimulation (active and sham), hemifield (left and right), and congruency (congruent and incongruent) as within-subject factors. The statistics revealed no significant main effects (stimulation: $F(1,31) = .062$, $p = .805$; hemifield: $F(1,31) = .714$, $p = .405$; congruency: $F(1,31) = .013$, $p = .909$) nor interactions (all p values > .628) (**Figure 4**).

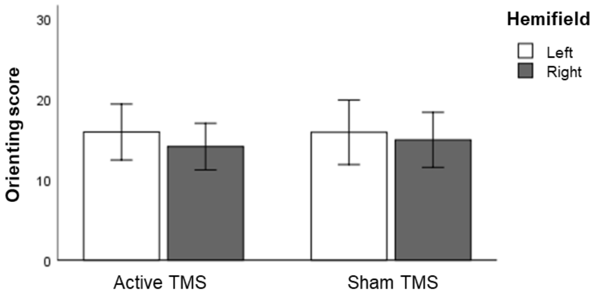

Figure 4 Latency estimates of orienting, averaged over congruent and incongruent trials. No significant main effects or interactions were found. Error bars depict one standard error.

Effects on executive control

TMS effects on executive control were analyzed using a RM ANOVA on executive scores with stimulation (active and sham), hemifield (left and right), and cue (valid, neutral, invalid and no cue) as within-subject factors. The analysis revealed a significant main effect of hemifield, with generally lower cost of conflict in the left hemifield ($F(1,31) = 4.165$, $p = .050$), and a significant main effect of cue ($F(3,29) = 4.200$, $p = .014$), due to generally higher cost of conflict in neutral-cue compared to no-cue trials ($p = .003$). No main effect of stimulation was found ($F(1,31) = .056$, $p = .815$), but critically, there was a significant interaction between stimulation and hemifield ($F(1,31) = 4.188$, $p = .049$; **Figure 5**). Follow-up t tests revealed that there was a significantly lower cost of conflict in the left compared to the right hemifield in sham TMS but not in active TMS (left vs. right in sham: $t(31) = 2.762$, $p = .010$; left vs. right in active: $t(31) = 1.102$, $p = .279$). Follow-up t tests also showed that executive scores did not differ in active TMS compared to sham TMS, for neither hemifields (left: $z = 1.459$, $p = 0.145$, $r = 0.182$; right: $t(31) = .735$, $p = .468$). Other interactions were non-significant (all p values of > .108).

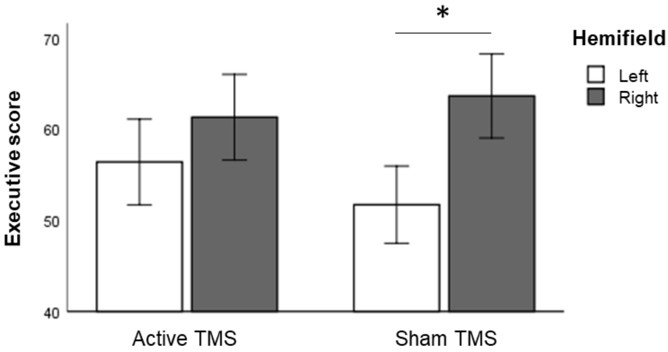

Figure 5 Latency estimates of executive control, averaged over all cue levels. A significant interaction between stimulation and hemifield was found for the executive control effect. There was a significant difference between the left and the right hemifield in sham TMS (significantly lower executive score for left compared to right hemifield in sham TMS) but not in active TMS. Also, comparing active TMS versus sham TMS: We found a reduced executive control efficiency in the left hemifield (i.e., higher cost of conflict, not significant) and an improved efficiency of resolving conflict processes in the right hemifield (i.e., lower cost of conflict, not significant). Asterisks (*) depict significant difference ($p < .05$). Error bars depict one standard error.

Effects on the alerting-executive control interaction

Although stimulation did not interact with cue in the previous section ('Effects on executive control'), we were interested to find out whether TMS affected the alerting-executive control interaction since the executive control score depended on cue type (neutral vs. no cue) in the sham condition. To this end, we used a RM ANOVA on executive scores with stimulation (active and sham), hemifield (left and right), and cue (neutral and no cue) as within-subject factors. We found a significant main effect of cue, with higher cost of conflict in neutral-cue trials ($F(1,31) = 10.098$, $p = .003$). No significant other main effects (stimulation: $F(1,31) = .432$, $p = .516$; hemifield: $F(1,31) = 2.891$, $p = .099$) nor two-way interactions were found (all p values of > .496), but critically, there was a significant interaction between stimulation, hemifield and cue ($F(1,31) = 6.736$, $p = .014$).

To further investigate this significant three-way interaction, we reduced the conditions by subtracting the executive scores of the sham TMS condition from the active TMS condition, giving us the stimulation-induced changes in the executive score as dependent variable (**Figure 6**). We used a RM ANOVA on this new measure with hemifield (left and right) and cue (neutral and no cue) as within-subject factors. We found no significant main effects (hemifield: $F(1,31) = .302$, $p = .586$; cue: $F(1,31) < .001$, $p = .995$), nor a significant interaction between hemifield and cue ($F(1,31) = 3.994$, $p = .055$; **Figure 6**).

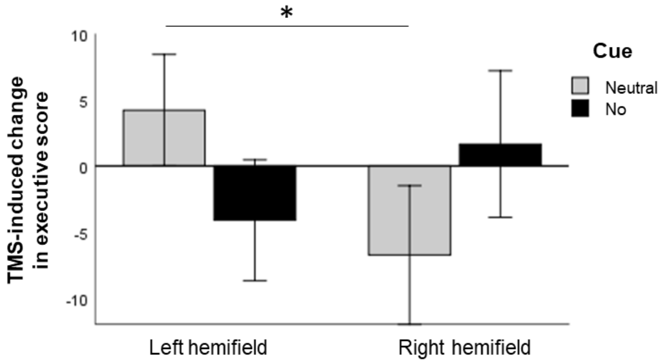

Figure 6 TMS-induced change in executive score, shown separately for neutral-cue and no-cue trials. A higher executive score reflects a higher cost of conflict in the active TMS condition compared to the sham TMS condition. A non-significant two-way interaction between hemifield and cue was found. Asterisks (*) depict significant difference ($p < .05$). Error bars depict one standard error.

Discussion

The objective of the present study was to investigate the role of PPC in the three functional components of attention as proposed by the framework of Petersen and Posner (2012; alerting, orienting, and executive control) in both hemifields. To this end, we applied a cTBS protocol to disrupt right PPC in 32 healthy volunteers and subsequently used the LANT to assess behavioral performance.

LANT performance in the sham condition

The behavioral outcomes under baseline conditions showed that we successfully replicated previously reported effects of cues and flanker arrows on RTs in our implementation of the LANT. We observed the typical pattern of RTs across cueing and flanker conditions; participants responded faster to targets as cues became increasingly informative, and responded slower to targets that created conflict.

Similar to Greene and colleagues (2008), we found no significant main effect of hemifield. However, we did find a significant interaction between hemifield and congruency. When hemifield differences were analyzed separately for the congruent-flanker and the incongruent-flanker trials, the asymmetry turned out to be near significant in the congruent trials only. Responses were faster on right than on left congruent trials. This finding may be explained by the Simon effect because participants had to respond with their right hand. The Simon effect is the well-known phenomenon that people are faster when responding to stimuli that are in the same relative location as the response, even though the location information is irrelevant to the actual task (Simon & Rudell, 1967). In the incongruent trials, however, we saw faster responses on left compared to right trials, although this difference was not significant. Asanowicz and colleagues (2012) also found a left hemifield advantage in the incongruent-flanker trials and suggest this may indicate the right hemisphere's dominance in resolution of conflict.

We also found an interaction between cue and congruency. Significantly faster responses were observed when cued in the correct direction than responses to neutral cues, but this finding was only found in trials that created conflict (incongruent trials). In congruent trials, responses to validly cued trials were not significantly faster than responses to neutral cues (**Figure 2**). This is in line with the findings of Greene and colleagues (2008), who also found a higher facilitative effect of valid cues in incongruent trials as compared to congruent trials. Further, we corroborated previous evidence (Asanowicz et al., 2012; Callejas et al., 2005, 2004; Chica et al., 2011; Lupiáñez & Funes, 2005), by showing that valid orienting cues improve resolution of conflict (lower cost of conflict in valid-cue trials as compared to neutral-cue trials). This indicates that when attention is oriented to the target location there is a reduced interference from incongruent flankers.

The current study brought interesting findings on the relationship between alerting and executive control. In line with the finding of Greene and colleagues (2008), the alerting effect was less in incongruent trials. This suggests that the longer time that is needed to respond to targets in incongruent (more difficult) trials, cancels out the advantage of having been alerted by an alerting (c.q., neutral) cue. Or, in other words, how Greene and colleagues (2008, p.30) put it: "the more one is engaged in conflict resolution processing, the less benefit will be gained from a temporally alerting cue". In accordance with previous studies (Callejas et al., 2005, 2004), we found a higher cost of conflict in neutral-cue trials as compared to no-cue trials, demonstrating an inhibitory relationship between alerting and executive control processes. This inhibitory influence between alerting and executive control has previously been described by Posner (1994). Posner proposed that the anterior cingulate cortex, which has shown to be associated with the executive control network, is inhibited when the alerting network is highly activated, to prevent the system from engaging in higher level processing in order to promote a fast response to the stimulus rather than concentrating on control functions.

To conclude, our findings on LANT performance under baseline conditions are in agreement with previous work and provide evidence on the behavioral level that different aspects of attention interact. In the following section we discuss how stimulation affected the performance of each of the three attention functions and their interactions.

Stimulation effects

Until now, to our knowledge only two previous studies have investigated effects of repetitive TMS protocols on the performance of all three attention functions, thereby giving a broader perspective on attention by also quantifying alerting and executive control functioning, next to the classical effects on orienting (Xu et al., 2016, 2013). However, these studies did not take hemifield-specific effects into consideration, presenting targets above and below fixation. This limitation is particularly relevant here, because attentional biases are generally hemifield-specific and NIBS to attention-related regions in a single hemisphere have repeatedly been shown to have hemifield-specific effects on task performance (Duecker et al., 2017; Duecker & Sack, 2015a). Thus, for studies that implement a hemisphere-specific neuromodulation approach, hemispheric contributions are elementary and outcome measures should aim to capture lateralization of attention processes.

In the current study, we compared active TMS to sham TMS to investigate the role of PPC in the three functions of attention (alerting, orienting, and executive control), and their interactions, within each hemifield. Since it has been proposed that the PPC in each hemisphere biases attention toward the contralateral hemifield, we expected hemifield-specific effects after applying TMS over right PPC, and more specifically, a rightward shift of attention. The pattern of effects we found on alerting and executive control seems to be in line with this expectation, but the effect on orienting is in contrast to previous TMS studies that have used Posner, line bisection or extinction paradigms (Bien et al., 2012; Brighina et al., 2002; Cazzoli et al., 2009; Dambeck et al., 2006; Fierro et al., 2000; Hilgetag et al., 2001; Koch et al., 2005; Szczepanski & Kastner, 2013; Thut et al., 2005).

Effects on alerting

Alerting was defined as performance in the no-cue condition minus performance in the neutral-cue condition. We found a significant interaction between brain stimulation and hemifield on incongruent trials. Follow-up analyses showed a significant left hemifield advantage in sham TMS but not in active TMS. Compared to sham, active TMS reduced alerting performance in the left hemifield and enhanced performance in the right hemifield (note that these are interpretations based on the descriptives following the significant interaction term, rather than on the pairwise follow-up comparisons). Thus, by applying TMS over right PPC, we found the expected rightward shift of alerting attention.

Previous studies have suggested that the alerting system is controlled mostly by right frontal and right parietal lobes (Fan et al., 2002; see also references in Introduction). Indeed, in our study the left hemifield advantage in the sham condition indicates a right hemisphere dominance, and, in their LANT study, Greene and colleagues (2008) too suggest that alerting is dominated by the right hemisphere. However, Asanowicz and colleagues (2012) did not find a visual field asymmetry for the alerting effect and they give several interesting interpretations of this lack of asymmetry which we believe can be tested with TMS. For instance, fMRI studies have reported a greater involvement of the *left* hemisphere in the processing of alerting cues (Coull et al., 2001, 2000; Fan et al., 2005), and several authors suggest that this discrepancy may result from differential specialization of the hemispheres, namely, more engagement of the left hemisphere in phasic alertness, and superiority of the right hemisphere in tonic alertness (Coull et al., 2000; Okubo & Nicholls, 2008; Posner, 2008). To shed more light on the organization and laterality of the alerting network, it seems promising to further investigate the effects on alerting functioning in left and right hemifields by applying TMS over left PPC and to compare this with right PPC stimulation.

Effects on orienting

We found no stimulation effects on orienting, which was defined as performance in the invalid-cue condition minus performance in the valid-cue condition. This is in contrast to several previous studies investigating spatial orienting effects of TMS over parietal cortex. For instance, Thut and colleagues (2005) found a general impairment of target detection following leftward cues and an enhancement in the right hemifield following rightward cues after low-frequency TMS over right PPC. This resembles the general finding of contralateral disruption seen in other experimental paradigms, using line bisection tasks and visual extinction tasks, applying TMS over PPC (line bisection tasks: Brighina et al., 2002; Fierro et al., 2000; Szczepanski & Kastner, 2013; visual extinction tasks: Bien et al., 2012; Cazzoli et al., 2009; Dambeck et al., 2006; Hilgetag et al., 2001; Koch et al., 2005).

There are several potential explanations for the absence of a TMS effect on orienting. Perhaps the selection of the stimulation site based on the international 10-20 EEG positioning system was suboptimal compared to, for example, (f)MRI-guided localization (Sack et al., 2009), and therefore did not lead to the expected TMS-induced orienting effects. In the absence of individual fMRI data, we cannot rule out that TMS coil positioning was suboptimal, thus leading to weak or no effects in a subset of participants. However, many previous studies used the 10-20 system, just like we did here and reported positive results. Somewhat surprisingly, we recently even failed to find an effect on orienting after cTBS to right PPC with fMRI-guided localization (Gallotto et al., 2022).

It thus seems that other factors may be at play. The absence of effects on orienting performance could be explained by the fact that the task required participants to maintain relatively high levels of sustained attention throughout the task. In the current study we used a lateralized flanker-type task (a small target needs to be differentiated among flankers), whereas in previous studies that have used TMS in investigating functional asymmetries between the left and right hemisphere with regard to spatial attentional control, single lateralized targets were used that had to be detected by participants. Also, compared to Greene and colleagues (2008) and Asanowicz and colleagues (2012), our design was more intensely lateralized (target stimuli at 7° eccentricity in our study, 1° in Greene et al., 2008, and 5° in Asanowicz et al., 2012). It is important to note that all these aspects might have put more demands on attentional resources and might have required higher levels of sustained attention (i.e., tonic alertness). Since it has been shown that the alerting system ‘co-activates’ the parietal cortex involved in spatial orienting (Fernandez-Duque & Posner, 2001; Posner & Petersen, 1990; Robertson et al., 1998), high levels of voluntary, sustained attention may have eliminated a possible induced orienting deficit. That orienting deficits can be successfully treated with self-instructional or computerized training methods that focus on improving intrinsic/sustained alertness (Robertson et al., 1995; Sturm et al., 1997; Sturm & Willmes, 2001) further supports the idea that non-spatial aspects of attentional mechanisms, such as alerting, can have modulatory effects on the orienting system (Chica et al., 2011; Fernandez-Doque & Posner, 2001; Sturm et al., 2005). It may therefore be the case that orienting performance on the LANT is more robust against TMS modulation.

It is also plausible that the stimulation on the right PPC was not enough to interfere with the task. In previous studies, in general, exogenous orienting tasks (eliciting bottom-up mechanisms) are used (e.g., Bien et al., 2012), while in this study an endogenous task (with a top-down component) was used. Given that top-down orienting is implemented in a bilateral network (Corbetta & Shulman, 2011, 2002), stimulation of the right PPC may not have been enough to interfere with the task. However, for exogenous orienting, which is more right lateralized (Corbetta & Shulman, 2011, 2002), the stimulation of the right PPC would have more consistent effects.

Effects on executive control

As for alerting, there was a significant interaction between brain stimulation and hemifield. We observed a significantly lower cost of conflict in the left compared to the right hemifield in sham TMS, but not in active TMS. Furthermore, regarding the alerting-executive control interaction that was present in the sham data, we found that TMS influenced this relationship in a hemifield-specific way. The significant interaction between stimulation, hemifield, and cue (neutral vs. no cue) reflected an increased cost of conflict due to active TMS compared to sham TMS in the left compared to the right hemifield (significant for the neutral cue, c.q., alerting cue, trials only). Thus, by applying TMS over right PPC, we found the expected rightward shift of executive control. As for alerting, this conclusion should be read with caution because difference scores did not reach significance in active versus sham TMS, for neither hemifields.

Executive control resolves conflict among competing stimuli (Fan et al., 2002). In the LANT, it is assessed by the flanker task. Although the anterior cingulate cortex and the dorsolateral prefrontal cortex are usually associated with the executive control system (Botvinick et al., 2001; Bush et al., 2000), there is evidence that links parietal cortex to executive control. Firstly, a study found that a patient with bilateral posterior parietal lesions was impaired at filtering out distractors (Friedman-Hill et al., 2003) suggesting that the PPC plays a role in the top-down filtering of irrelevant visual information. Furthermore, neuroimaging and patient studies support the theory that several largely non-overlapping networks – including a fronto-parietal control network with areas of the PPC – are involved in cognitive control, in which conflict resolution is an essential feature (for review, see Marek & Dosenbach, 2018).

In sum, it is not inconceivable that the behavioral consequences of the stimulation in our study were caused by direct effects by directly hitting the areas of the executive system. Our observed effects on executive control suggest not only a correlational relationship but causality between the PPC and executive control.

Limitation

Our study could be criticized for the specific implementation of the sham stimulation. Instead of a purpose-built sham TMS coil, we simply tilted the coil by 90° so that the magnetic field was not directed toward the brain. While this approach has been widely used by the TMS community, it can be criticized for multiple reasons. For example, the auditory and somatosensory effects of TMS may not be perfectly matched as the TMS pulse may feel weaker, and the sound may be different. In this context, it seems worthwhile to point out that all control strategies come with their unique disadvantages (Duecker & Sack, 2015b). However, our tilted TMS coil approach is widely accepted as it does mimic sound and sensation (the latter better than a placebo TMS coil). The clicking sound and feeling the weight of the coil on the head of the tilt-sham approach are known to be well-matched with active TMS (Duecker & Sack, 2015b). But most importantly, we want to highlight that TMS in our study was not applied during the execution of the task, but rather well before the task started, and therefore we consider it unlikely that our observed behavioral effects after (active or sham) TMS were produced by the clicking or bone-conducted sound of the TMS coil or sensations on the head. This would be more of a risk when stimulation is given during the execution of a task.

While sham TMS may account for a general placebo (expectation) effect and may also control for direct sensory-driven behavioral or cognitive changes (clicking and somatosensation), only a control site can test the site-specificity of our TMS findings and in this sense test how specific these effects are to, for example, parietal cortex. Indeed, in the absence of a control site, no claims can be made about the specific role of PPC and the site-specificity of our findings. However, this was not the gist of our study. Instead, our study aims to build upon this established and often replicated functional relevance of PPC for attention, now directly comparing three different aspects of attention – orienting, alerting, and executive control. Our main gist is therefore the task-specificity of these TMS over PPC effects, not site-specificity. Therefore, we decided for a sham control rather than a control site.

Conclusion

Neuroimaging evidence from previous studies implicated PPC in neural networks sub serving three different types of attention functions: alerting, orienting and executive control. By assessing them separately one can assess differential effects of TMS-PPC on these functional components of attention. Our results clearly demonstrate differential brain stimulation effects on two of these components: alerting and executive control. For both these components, TMS over right PPC led to the expected rightward shift (based on the descriptives following the significant interactions). We want to stress here again that the use of flankers made our task clearly different from prior TMS-PPC studies. This perhaps made orienting performance on the LANT more robust against TMS modulation and may explain why we did not find a direct stimulation effect on orienting. But the demonstrated effects on attention mechanisms of alerting and executive control, rather than the previously revealed role in spatial orienting, emphasize the multifaceted functional contributions of PPC to a range of attention mechanisms. In turn, this implies that future research would benefit from a more inclusive approach, moving from isolated studies of specific aspects of attention to a more integrated approach designed to reveal the intrinsic interplay between attention processes at the behavioral and the neuronal level.

References

Asanowicz D., Marzecova A., Jaskowski P., & Wolski P. (2012). Hemispheric asymmetry in the efficiency of attentional networks. *Brain and Cognition, 79*, 117–128. https://doi.org/10.1016/j.bandc.2012.02.014

Bien N., Goebel R., & Sack A. T. (2012). Extinguishing extinction: hemispheric differences in the modulation of TMS-induced visual extinction by directing covert spatial attention. *Journal of Cognitive Neuroscience*, *24*(4), 809–818. https://doi.org/10.1162/jocn_a_00179

Botvinick M. M., Braver T. S., Barch D. M., Carter C. S., & Cohen J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, *108*, 624–652. https://doi.org/10.1037/0033-295x.108.3.624

Brighina F., Bisiach E., Piazza A., Oliveri M., LaBua V., Daniele O., & Fierro B. (2002). Perceptual and response bias in visuospatial neglect due to frontal and parietal repetitive transcranial magnetic stimulation in normal subjects. *Neuroreport*, *13*(18), 2571–2575. https://doi.org/10.1097/00001756-200212200-00038

Bush G., Luu P., & Posner M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*, 215–222. https://doi.org/10.1016/S1364-6613(00)01483-2

Callejas A., Lupiáñez J., Funes M. J., & Tudela P. (2005). Modulations among the alerting, orienting and executive control networks. *Experimental Brain Research*, *167*(1), 27-37. https://doi.org/10.1007/s00221-005-2365-z

Callejas A., Lupiañez J., & Tudela P. (2004). The three attentional networks: On their independence and interactions. *Brain and Cognition*, *54*(3), 225-227. https://doi.org/10.1016/j.bandc.2004.02.012

Carter C. S., Botvinick M. M., & Cohen J. D. (1999). The contribution of the anterior cingulate cortex to executive processes in cognition. *Reviews in the Neurosciences*, *10*, 49–57. https://doi.org/10.1515/revneuro.1999.10.1.49

Cazzoli D., Müri R., Hess C., & Nyffeler T. (2009). Horizontal and vertical dimensions of visual extinction: a theta burst stimulation study. *Neuroscience*, *164*(4), 1609–1614. https://doi.org/10.1016/j.neuroscience.2009.09.044

Chica A. B., Thiebaut de Schotten M., Toba M., Malhotra P., Lupiáñez J., & Bartolomeo P. (2011). Attention networks and their interactions after right-hemisphere damage. *Cortex*, *48*(6), 654-63. https://doi.org/10.1016/j.cortex.2011.01.009

Corbetta M., & Shulman G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience, 34*(1), 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Corbetta M., & Shulman G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*, 201–215. https://doi.org/10.1038/nrn755

Coull J. T., Buchel C., Friston K. J., & Frith C. D. (1999). Noradrenergically mediated plasticity in a human attentional neuronal network. *NeuroImage*, *10*(6), 705e715. https://doi.org/10.1006/nimg.1999.0513

Coull J. T., Frith C. D., Buchel C., & Nobre A. C. (2000). Orienting attention in time: behavioural and neuroanatomical distinction between exogenous and endogenous shifts. *Neuropsychologia, 38*(6), 808–819. https://doi.org/10.1016/s0028-3932(99)00132-3

Coull J. T., Nobre A. C., & Frith C. D. (2001). The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. *Cerebral Cortex*, *11*(1), 73–84. https://doi.org/10.1093/cercor/11.1.73

Dambeck N., Sparing R., Meister I. G., Wienemann M., Weidemann J., Topper R., & Boroojerdi B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, *1072*(1), 194-199. https://doi.org/10.1016/j.brainres.2005.05.075

Duecker F., & Sack A. T. (2015a). The hybrid model of attentional control: New insights into hemispheric asymmetries inferred from TMS research. *Neuropsychologia*, *74*, 21-29. https://doi.org/10.1016/j.neuropsychologia.2014.11.023

Duecker F., & Sack A. T. (2015b). Rethinking the role of sham TMS. *Frontiers in Psychology*, *6*, 1-5. https://doi.org/10.3389/fpsyg.2015.00210

Duecker F., Schuhmann T., Bien N., Jacobs C., & Sack A. T. (2017). Moving beyond attentional biases: Shifting the interhemispheric balance between left and right posterior parietal cortex modulates attentional control processes. *Journal of Cognitive Neuroscience*, *29*(7), 1267-1278. https://doi.org/10.1162/jocn_a_01119

Fan J., Byrne J., Worden M. S., Guise K. G., McCandliss B. D., Fossella J., & Posner M. I. (2007) The relation of brain oscillations to attentional networks. *The Journal of Neuroscience*, *27*(23), 6197–6206. https://doi.org/10.1523/JNEUROSCI.1833-07.2007

Fan J., Gu X., Guise K. G., Liu X., Fossella J., Wang H., & Posner M. I. (2009). Testing the behavioral interaction and integration of attentional networks. *Brain and Cognition*, *70*(2), 209-220. https://doi.org/10.1016/j.bandc.2009.02.002

Fan J., Kolster R., Ghajar J., Suh M., Knight R. T., Sarkar R., & McCandliss B. D. (2007). Response anticipation and response conflict: An event-related potential and functional magnetic resonance imaging study. *The Journal of Neuroscience, 27*(9), 2272-2282. https://doi.org/10.1523/jneurosci.3470-06.2007

Fan J., McCandliss B. D., Fossella J., Flombaum J. I., & Posner M. I. (2005). The activation of attentional networks. *Neuroimage*, *26*(2), 471–479. https://doi.org/10.1016/j.neuroimage.2005.02.004

Fan J., McCandliss B. D., Sommer T., Raz A., & Posner M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*(3), 340-347. https://doi.org/10.1162/089892902317361886

Fernandez-Duque D., & Posner M. I. (2001). Brain imaging of attentional networks in normal and pathological states. *Journal of Clinical and Experimental Neuropsychology*, *23*(1), 74-93. https://doi.org/10.1076/jcen.23.1.74.1217

Fierro B., Brighina F., Oliveri M., Piazza A., LaBua V., Buffa D., & Bisiach E. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport*, *11*(7), 1519–1521. https://doi.org/10.1097/00001756-200005150-00030

Friedman-Hill S. R., Robertson L. C., Desimone R., & Ungerleider L. G. (2003). Posterior parietal cortex and the filtering of distractors. *Proceedings of the National Academy of Sciences of the USA*, *100*(7), 4263-4268. https://doi.org/10.1073/pnas.0730772100

Gallotto S., Schuhmann T., Duecker F., Middag-van Spanje M., De Graaf T., & Sack A. T. (2022). Concurrent frontal and parietal network TMS for modulating attention. *iScience*, *25*(3), 103962. https://doi.org/10.1016/j.isci.2022.103962

Greene D. J., Barnea A., Herzberg K., Rassis A., Neta M., Raz A., & Zaidel E. (2008). Measuring attention in the hemispheres: The lateralized attention network test (LANT). *Brain and Cognition*, *66*, 21–31. https://doi.org/.1016/j.bandc.2007.05.003

Hilgetag C. C., Théoret H., & Pascual-Leone A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nature Neuroscience*, *4*(9), 953-957. https://doi.org/10.1038/nn0901-953

Hommel B., Pratt J., Colzato L., & Godijn R. (2001). Symbolic control of visual attention. *Psychological Science*, *12*(5), 360–365. https://doi.org/10.1111/1467-9280.00367

Huang Y. Z., Edwards M. J., Rounis E., Bhatia K. P., & Rothwell J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45,* 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Kinsbourne M. (1977). Hemi-neglect and hemisphere rivalry. *Advances in Neurology*, *18,* 41–49.

Koch G., Oliveri M., Torriero S., & Caltagirone C. (2005). Modulation of excitatory and inhibitory circuits for visual awareness in the human right parietal cortex. *Experimental Brain Research*, *160*(4), 510–516. https://doi.org/10.1007/s00221-004-2039-2

Lega C., Ferrante O., Marini F., Santandrea E., Cattaneo L., & Chelazzi L. (2019). Probing the neural mechanisms for distractor filtering and their history-contingent modulation by means of TMS. *The Journal of Neuroscience, 39*(38), 7591–7603. https://doi.org/10.1523/JNEUROSCI.2740-18.2019

Lupiáñez J., & Funes M. J. (2005). Peripheral spatial cues modulate spatial congruency effects: Analysing the ‘‘locus’’ of the cueing modulation. *European Journal of Cognitive Psychology*, *17*(5), 727–752. https://doi.org/10.1080/09541440540000103

Marek S., & Dosenbach, N. U. F. (2018). The frontoparietal network: function, electrophysiology, and importance of individual precision mapping. *Dialogues in clinical neuroscience, 20*(2), 133-140. https://doi.org/10.31887/DCNS.2018.20.2/smarek

Mesulam M. M. (1999). Spatial attention and neglect: Parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philosophical*

Transactions of the Royal Society of London. Series B, Biological Sciences, *354*(1387), 1325–1346. https://doi.org/10.1098/rstb.1999.0482

Okubo M., & Nicholls M. E. R. (2008). Hemispheric asymmetries for temporal information processing: Transient detection versus sustained monitoring. *Brain and Cognition*, *66*(2), 168–175. https://doi.org/10.1016/j.bandc.2007.07.002

Oldfield R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, *9*, 97-113. https://doi.org/10.1016/0028-3932(71)90067-4

Pardo J. V., Fox P. T., & Raichle M. E. (1991). Localization of a human system for sustained attention by positron emission tomography. *Nature, 349,* 61–64. https://doi.org/10.1038/349061a0

Petersen S. E., & Posner M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience, 35*, 73-89. https://doi.org/10.1146/annurev-neuro-062111-150525

Posner M. I. (2008). Measuring alertness. *Annals of the New York Academy of Sciences*, *1129,* 193–199. https://doi.org/10.1196/annals.1417.011

Posner M. I. (1994). Attention: the mechanisms of consciousness. *Proceedings of the National Academy of Sciences of the USA, 97*, 7398–7403. https://doi.org/10.1073/pnas.91.16.7398

Posner M. I., & Petersen S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13,* 25-42. https://doi.org/10.1146/annurev-neuro-062111-150525

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. https://doi.org/10.1146/annurev.psych.58.110405.085516

Posner M. I., & Rothbart M. K. (1998). Attention, self-regulation and consciousness. *Philosophical Transactions of the Philosophical Society of London Series B. Biological Sciences*, *353*, 1915-1927. https://doi.org/10.1098/rstb.1998.0344

Pridmore S., Filho J. A. F., Nahas Z., Liberatos C., & George M. S. (1998). Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *The Journal of ECT*, *14*(1), 25-27. https://doi.org/10.1097/00124509-199803000-00004

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. https://doi.org/10.1038/25993

Robertson I. H., Tegner R., Tham K., Lo A., & Nimmo-Smith I. (1995). Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology*, *17*(3), 416-430. https://doi.org/10.1080/01688639508405133

Sack A. T., Cohen Kadosh R., Schuhmann T., Moerel M., Walsh V., & Goebel R. (2009). Optimizing functional accuracy of TMS in cognitive studies: A comparison of methods. *Journal of Cognitive Neuroscience*, *21*(2), 207–221. https://doi.org/10.1162/jocn.2009.21126

Silvanto J., Muggleton N., Lavie N., & Walsh V. (2009). The perceptual and functional consequences of parietal top–down modulation on the visual cortex. *Cerebral Cortex*, *19*, 327–330. https://doi.org/10.1093/cercor/bhn091

Simon J. R., & Rudell A. P. (1967). Auditory S-R compatibility: The effect of an irrelevant cue on information processing. *Journal of Applied Psychology*, *51*, 300-304. https://doi.org/10.1037/h0020586

Sturm W., De Simone A., Krause B. J., Specht K., Hesselmann V., Radermacher I., et al. (1999). Functional anatomy of intrinsic alertness: Evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia*, *37*(7), 797–805. https://doi.org/10.1016/s0028-3932(98)00141-9

Sturm W., Schmenk B., Fimm B., Specht K., Weis S., Thron A., et al. (2005). Spatial attention: More than intrinsic alerting? Experimental Brain Research. *Experimentelle Hirnforschung. Expérimentation Cérébrale*, *171*(1), 16–25. https://doi.org/10.1007/s00221-005-0253-1

Sturm W., & Willmes K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage*, *14*(1), S76–S84. https://doi.org/10.1006/nimg.2001.0839

Sturm W., Willmes K., & Orgass B. (1997). Do specific attention deficits need specific training? *Neuropsychological Rehabilitation*, *7*(2), 81-103. https://doi.org/10.1080/713755526

Szczepanski S. M., & Kastner S. (2013). Shifting attentional priorities: Control of spatial attention through hemispheric competition. *Journal of Neuroscience*, *33*(12), 5411–5421. https://doi.org/10.1523/JNEUROSCI.4089-12.2013

Thut G., Nietzel A., & Pascual-Leone A. (2005). Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. *Cereb. Cortex*, *15*(5), 628–638. https://doi.org/10.1093/cercor/bhh164

Varnava A., Stokes M. G., & Chambers C. D. (2011). Reliability of the 'observation of movement' method for determining motor threshold using transcranial magnetic stimulation. *Journal of Neuroscience Methods*, *201*(2), 327-332. https://doi.org/10.1016/j.jneumeth.2011.08.016

Verleger R., Smigasiewicz K., & Möller F. (2011). Mechanisms underlying the left visual-field advantage in the dual stream RSVP task: Evidence from N2pc, P3, and distractor-evoked VEPs. *Psychophysiology*, *48*(8), 1096–1106. https://doi.org/10.1111/j.1469-8986.2011.01176.x

Xu G. Q., Lan Y., Huang D., Chen S., Chen L., Zeng J., & Pei Z. (2013). The study on the frontoparietal networks by continuous theta burst stimulation in health human subjects. *Behavioural Brain Research*, *240*, 60-68. https://doi.org/10.1016/j.bbr.2012.11.015

Xu G. Q., Lan Y., Zhang Q., Liu D. X., He X. F., & Lin T. (2016). 1-Hz repetitive transcranial magnetic stimulation over the posterior parietal cortex modulates spatial attention. *Frontiers in Human Neuroscience*, *10*, 38. https://doi.org/10.3389/fnhum.2016.00038

Yanaka H. T., Saito D. N., Uchiyama Y., & Sadato N. (2010). Neural substrates of phasic alertness: A functional magnetic resonance imaging study. *Neuroscience Research*, *68*(1), 51–58. https://doi.org/10.1016/j.neures.2010.05.005

Supplementary material

To be transparent about the greater experimental context of this research report, in this paragraph we describe additional details of the procedure. In both sessions, in addition to (active or sham) TMS, participants received *placebo* transcranial alternating current stimulation (tACS) to left parietal cortex, and brain activity (electroencephalography, EEG) was recorded. TACS and EEG electrodes were attached to the participant's head using the 10-20 system. Sham tACS was applied to P3 (left PPC) at individual alpha frequency, with intensity set to 1.5 mA peak-to-peak, and consisted of a brief ramping up and immediate ramping down. Sham tACS was delivered during task performance; task duration was between 40-45 minutes. EEG leads were applied to P5, PO3, PO4, P6, left mastoid (A1, online reference), right mastoid (A2, offline reference), and forehead (ground). EEG was recorded three times in each session; before and after (active or sham) TMS and after (sham) tACS (at the end of the session). Participants were required to relax and keep eyes closed during three minutes of EEG recording.

EMBARGOED

Chapter 3

State-dependence of therapeutic tACS: Preconditioning the brain with TMS reverses the oscillatory after effects of tACS on resting-state EEG

Corresponding manuscript:

Middag-van Spanje, M., Duecker, F., Sack, A. T., & Schuhmann, T. *(in preparation)*. State-dependence of therapeutic tACS: Preconditioning the brain with TMS reverses the oscillatory after effects of tACS on resting-state EEG.

Part II

Is alpha-tACS effective in reducing neglect behavioral patterns after stroke?

Chapter 4

Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients

Corresponding manuscript:

Schuhmann, T., Duecker, F., **Middag-van Spanje, M.**, Gallotto, S., Van Heugten, C., Schrijnemaekers, A. C., Van Oostenbrugge, R., & Sack, A. T. (2022). Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. *International Journal of Clinical and Health Psychology*, *22*(3). https://doi.org/10.1016/j.ijchp.2022.100326

Abstract

Non-invasive brain stimulation techniques such as transcranial alternating current stimulation (tACS) may help alleviate attention deficits in stroke patients with hemispatial neglect by modulating oscillatory brain activity. We applied high-definition (HD-)tACS at alpha frequency over the contralesional hemisphere to support unilateral oscillatory alpha activity and correct for the pathologically altered attention bias in neglect patients. We performed a within-subject, placebo-controlled study in which sixteen subacute stroke patients with hemispatial neglect underwent 10 Hz (alpha) as well as sham (placebo) stimulation targeting the contralesional posterior parietal cortex. Attentional bias was measured with a computerized visual detection paradigm and two standard paper-and-pencil neglect tests. We revealed a significant shift of attentional resources after alpha-HD-tACS, but not sham tACS, toward the ipsilateral and thus contralesional hemifield leading to a reduction in neglect symptoms, measured with a computerized visual detection paradigm and a widely used standard paper and pencil neglect test. We showed a significant alpha-HD-tACS-induced shift of attentional resources toward the contralesional hemifield, thus leading to a reduction in neglect symptoms. Importantly, HD-tACS effects persisted after the stimulation itself had ended. This tACS protocol, based on intrinsic oscillatory processes, may be an effective and well-tolerated treatment option for neglect.

Introduction

Each year more than twelve million people worldwide suffer from the devastating consequences of a new stroke, including severe cognitive deficits in attention and memory (Feigin et al., 2022). Among these cognitive deficits, visuospatial hemineglect is a common and disabling problem and is marked by the inability to attend to the contralesional side of space (Buxbaum et al., 2004; Osawa & Maeshima, 2021). These pronounced spatial attention deficits in hemineglect have a substantial negative impact on stroke patients' everyday life and are a strong predictor of poor functional recovery (Di Monaco et al., 2011; Stone et al., 1992). Current rehabilitation options include a number of cognitive trainings, such as visual scanning training (VST), prism adaptation, or limb activation training. However, although the VST is generally advised as a preferred treatment option (Ten Brink et al., 2016) and implemented in many rehabilitation centers, recent randomized controlled trials find only limited clinical benefits (Azouvi et al., 2017; Fasotti & Van Kessel, 2013). To achieve higher clinical benefit, new treatment options have to be explored, possibly aiming at a neuromodulation of brain structures involved in visuospatial processing.

Fundamental neuroscientific research has started to unravel the functional organization and brain network communication underlying the control of spatial attention in the healthy brain (Morishima et al., 2009; Ruff et al., 2008; Sack et al., 2007), linking spatial attention bias to cortical excitability (Klimesch et al., 2007, 1998) and oscillatory activity in posterior parietal cortices (Fiebelkorn & Kastner, 2019). Modulating unilateral cortical excitability by noninvasive brain stimulation (NIBS) to create (or restore) an imbalance between competing hemispheres that suppress each other via interhemispheric inhibition, has shown to significantly affect spatial attention performance in a hemifield-specific way (Battelli et al., 2009; Bien et al., 2012; Dambeck et al., 2006; Hilgetag et al., 2001; Sack et al., 2002). Several small-scale clinical trials have tried to exploit this link between cortical excitability and attentional bias in patients with visuospatial neglect. In these studies, NIBS is applied to counteract the pathological attentional bias caused by the stroke through decreasing cortical excitability within the contralesional, i.e., unaffected, posterior parietal cortex, expecting to reduce its hyper-excitability and to thereby restore the interhemispheric balance. Unfortunately, although promising, reported clinical effects have remained rather small and heterogeneous (Koch et al., 2012; Lefaucheur et al., 2020, 2014; Longley et al., 2021).

NIBS protocols are not limited to modulating cortical excitability, but can also be tuned to influence oscillatory brain activity. Specifically, intrinsic brain oscillations can be amplified by alternating currents using transcranial alternating current stimulation (tACS) with the appropriate frequency, leading to entrainment and/or resonance effects (Lakatos et al., 2019). In the context of attention, oscillatory activity in the alpha range (8-12 Hz) over the posterior parietal cortex has been linked to attentional bias and attentional orienting (Thut et al., 2006; Worden et al., 2000). Mechanistically, it is often argued that alpha oscillations are crucial for gating information flow between different regions within a brain network by functional inhibition (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Accordingly, shifting attention to the right hemifield is accompanied by alpha power decreases in the left hemisphere (release from inhibition) and alpha power increases in the right hemisphere (inhibiting the unattended left hemifield). Modulating this alpha power lateralization, instead of merely changing local cortical excitability, may therefore be a promising new and mechanistically different approach to correct for a pathological spatial attention bias after stroke using NIBS. Yet, until today, no study has tested this oscillation-based NIBS intervention in stroke patients suffering from visuospatial neglect to evaluate its feasibility and clinical efficacy.

Here, we present a proof-of-concept study for the use of high-definition (HD-)tACS in subacute stroke patients with visuospatial neglect aimed at reducing the visuospatial attention bias. To this end, we applied both sham and active HD-tACS at alpha frequency over the contralesional posterior parietal cortex in two different sessions. Based on the fundamental neuroscientific insights obtained in healthy volunteers outlined above, we expected an alpha-tACS-induced shift of attentional resources toward the ipsilateral and thus contralesional hemifield leading to a reduction in neglect symptoms measured with a novel computerized visual detection task and two widely used standard paper and pencil neglect tasks.

Methods

Study design

We performed a single center, within-subject, placebo-controlled study. Each patient underwent 10 Hz (alpha) as well as sham (placebo) stimulation in two separate HD-tACS sessions. The order of sessions was counterbalanced and the two sessions were performed on two different days with at least one-day inter-session interval. In both sessions, patients had to perform three different tasks, administered before (baseline), during, and immediately after HD-tACS. Patients gave written informed consent before participating in this experiment, in accordance with the 2008 Declaration of Helsinki and with the approval of the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (METC MUMC, registration number METC143030), The Netherlands.

Participants

We recruited seventeen subacute stroke patients from Adelante Rehabilitation center, Hoensbroek, The Netherlands in the period of October 2015 to April 2017. Patients with a recent clinically diagnosed first and/or recurrent stroke (ischemic or intracerebral haemorrhagic lesion) were considered eligible. Patients had to fulfil the inclusion criteria of having visuospatial neglect symptoms (either left- or right-sided neglect) based on clinical judgment and of having sufficient communication skills to understand the researcher's instructions. Patients were excluded if they had dementia and/or cochlear implants. Demographics (age, gender) and stroke-related characteristics (time since stroke, stroke type, stroke side) were collected from the patients' medical records. Sixteen of the patients were right-handed, one patient was left-handed. Independence in activities of daily living (ADL) was assessed using the Barthel index (Collin et al., 1988) within two weeks after having been admitted to the rehabilitation center. Barthel scores ranged from 0 (completely dependent) up to 20 (completely independent).

Transcranial alternating current stimulation

HD-tACS was performed using a small circular (diameter: 2.1cm, thickness: 2mm) and a large rubber ring (outer diameter: 11 cm; inner diameter: 9 cm, thickness: 2 mm) tACS electrode (NeuroConn, Ilmenau, Germany) that were both placed onto the contralesional posterior parietal cortex, with the small electrode positioned over P3 or P4 (based on the international 10-20 EEG system) and the large electrode centered on it. This ring electrode montage enables a higher spatial focality as compared to standard rectangular electrodes (Datta et al., 2008) (**Figure 1**). Conductive gel (ten20 paste, Weaver and Company, Aurora, CO, USA) was applied between skin and electrodes to reduce the impedance to below 10 kΩ. Stimulation frequency and intensity were respectively set to 10 Hz and 1.5 mA peak to peak, phase offset was set to 0 and 100 cycles were used for ramping up. The control intervention consisted of sham stimulation and included ramping up and then immediately ramping down with each 100 cycles. This way, the patient feels the ramp-up and ramp-down events (which are the most noticeable in TES), but does not receive a significant dose of TES (Paulus et al., 2013). Unlike for TMS, this placebo/sham condition is indistinguishable from active HD-tACS for participants, ensuring successful blinding. Stimulation in both conditions lasted for maximally 30 minutes.

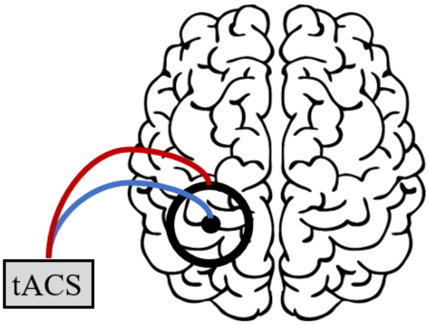

Figure 1 Schematic figure of the HD-tACS set-up. HD-tACS was performed using a small circular (diameter: 2.1 cm, thickness: 2 mm) and a large rubber ring (outer diameter: 11 cm; inner diameter: 9 cm, thickness: 2 mm) tACS electrode (NeuroConn, Ilmenau, Germany) that were both placed onto the contralesional posterior parietal cortex, with the small electrode positioned over P3 or P4 (based on the international 10-20 EEG system) and the large electrode centered on it.

Primary outcome: computerized visual detection task (CVDT)

The CVDT measures perceptual sensitivity and attentional selection in each hemifield separately, but also in the context of competition between visual stimuli in both hemifields. It is a simple and sensitive assessment of unilateral neglect and extinction (Bien et al., 2012; Duecker et al., 2017; Schuhmann et al., 2019). During the task, patients were seated in front of a computer screen at a distance of 57 cm. They were asked to fixate on the center of the screen, marked with a bull's-eye. Gabor patches (spatial frequency = 1.5 cycles per degree, envelope standard deviation = 0.75°, random orientation) were presented to the left, right, and bilateral sides of the screen at 14° eccentricity. Stimuli were shown for 100 ms and stimulus size was 10°. Patients had to verbally indicate whether they saw the stimulus appearing on the left, right, or both sides of the fixation bull's-eye. For each trial, the stimulus position, contrast level, and response were recorded.

For each of the three locations (left, right, and bilateral) independently, the contrast of the stimuli was adaptively changed on a trial-by-trial basis using the QUEST staircase algorithm (Watson & Pelli, 1983), as implemented in the Psychophysics Toolbox extension (Brainard, 1997) for MATLAB (The MathWorks, Inc., Natick, MA). We supplied the following parameters: prior mean was based on a short calibration procedure (see below), prior standard deviation = 1, beta = 3.5, gamma = 0.01, delta = 0.01, and aim performance = 0.5 (50% detection rate). The next contrast value was requested with QuestQuantile, and we obtained final detection threshold estimates with QuestMean.

Participants initially performed a short calibration procedure to obtain a first estimate of the individual detection threshold, which was used as a prior for the Bayesian staircase procedure. During this calibration, bilateral stimuli were presented on the screen, matching the positions used during the experimental task, and participants adjusted the contrast level of the stimuli until they could barely see them. At the beginning of the experimental task, two warm-up trials with high-contrast stimuli were included for each condition (left, right, and bilateral) that were easy to detect and not part of the staircase procedure. Then, participants completed three randomly interleaved staircases (left, right, and bilateral) with 40 trials each. The overall duration of this task never exceeded ten minutes.

Stimuli were presented on a Dell Latitude E6540 laptop. The video mode was 1920 × 1080 at 60 Hz, and background luminance was 105.55 cd/m2. The Presentation software package (NeuroBehavioural Systems, Albany, CA) was used to control stimulus presentation and recording of behavioral responses, interfacing with MATLAB for running QUEST functions.

Secondary outcomes

We administered two neuropsychological paper-and-pencil tasks to assess the presence and severity of visuospatial neglect. The bells task (BT) is a cancellation task which directly reflects the basic direction-specific deficit in visual searching (exploratory deficit) that is so characteristic of neglect patients' clinical behavior (Ferber & Karnath, 2001). The test consists of an A4 sheet of paper with 315 black objects printed on it. Of the 315 objects, 35 are target items (bells) and the other 280 are distractor objects (houses, horses, etc.).

Although the objects appear to be presented in random order, they are distributed equally into seven columns across the A4 sheet with five targets and 40 distractors per column. Patients were seated such that the center of the sheet was aligned to their midsagittal plane and instructed to circle all target items as quickly as possible. The total number of omitted targets was recorded, ranging from 0 to 35. The spatial distribution of the omitted targets determines the direction and severity of the visual neglect.

We also used the line bisection task (LBT), which is a quick quantitative assessment of the presence and severity of unilateral spatial neglect (Schenkenberg et al., 1980). Line bisection necessitates correct perception of the size of a single stimulus, and a displacement of the bisection mark toward the ipsilesional side is interpreted as a symptom of neglect (Ferber & Karnath, 2001). The LBT requires patients to place a mark through the center of a series of twelve horizontal lines on a page placed in front of them. The test was scored by measuring the deviation in millimeters of the patient's bisection mark from the true center of the line. Deviations were scored positive for marks placed on the ipsilesional side of the center of the line and scored negative for marks placed on the contralesional side of the line-center (potential score range: -590 to +590 mm). Trials with omitted lines were scored as if patients put the mark all the way to the right or left side (in case of right or left hemisphere damage, resp.).

Data analysis

Detection performance of the CVDT was tested in three conditions (ipsilesional stimulus, contralesional stimulus, and bilateral stimulus), with the unilateral conditions directly relating to neglect symptoms, and the bilateral condition relating to extinction symptoms. Task performance was initially defined as detection thresholds for the three stimulus conditions. However, detection thresholds could not be used in some patients because they had so severe deficits that parameters were outside the test range and thus unreliable. The number of correct hits could be used as an alternative but this ignores the fact that contrast levels varied on a trial by trial basis, thus failing to take task difficulty into account. Hits were therefore weighted by the contrast level, according to the following formula: x = log10(max_contrast) / log10(trial_contrast). This measure accounts for the logarithmic nature of contrast detection, and makes trials count more when the contrast was low. This results in a potential scoring range of 0 to 76.49 weighted hits per condition. To illustrate, trials detected at maximum contrast received a score of 1, whereas trials with a relatively low contrast level of 10% received a score of 2.

Performance in visual search as measured by the BT was tested in two conditions (contralesional side and ipsilesional side). To derive performance in the contralesional side, we calculated the average of missed targets in the three far-most contralesional columns, and to derive performance in the ipsilesional side, we calculated the average of missed targets in the three far-most ipsilesional columns.

Performance of the LBT was defined as the deviation of the patient's bisection mark from the true center of the line. The relative deviation was used to analyze the LBT data and was derived by means of the formula: x = deviation score / true half line length * 100. Relative deviation scores were then averaged across all twelve lines.

To quantify the patients' spatial attention deficits, we analyzed the baseline measurements (before stimulation) of both sessions (active and sham HD-tACS sessions averaged) per task. In the results we report our findings per task; always first showing the patients' spatial attention deficits (sensitivity of the task), followed by the inference analyses performed using IBM SPSS Statistics version 25. For all repeated measures (RM) ANOVAs, we reported the multivariate test statistics (Pillai's trace). Follow-up analyses were conducted with paired t tests. Significance was determined at $p < .05$.

Results

We recruited seventeen subacute stroke patients from Adelante Rehabilitation center. One patient decided to stop participating after one session and was not included in the analyses. The final study sample comprised of sixteen patients, aged 37 to 76 years (M = 57.8 years, SD = 9.7). Time since stroke ranged from 39 to 127 days (M = 87.4 days, SD = 24.6). Patient characteristics are shown in **Table 1**. All patients included in the analyses were right-handed.

Table 1 Patient characteristics (*n* = 16).

Characteristics	**Outcome**
Gender: males, *n* (%)	12 (75.0)
Age in years, mean ± SD (range)	57.8 ± 9.7 (37.1 – 76.1)
Time since stroke in days[a], mean ± SD (range)	87.4 ± 24.6 (39.0 – 127.0)
Stroke type: *n* (%)	
Ischemic	10 (62.5)
Haemorrhagic	6 (37.5)
Stroke side: right, *n* (%)	15 (93.8)
Barthel index[b], mean ± SD (range)	8.3 ± 7.1 (1.0 – 20.0)

[a] Time between stroke and baseline measurement of first session. [b] Scores 1-20, higher score means higher degree of independence.

Computerized visual detection task

Out of the sixteen patients, one patient was not able to perform the CVDT, and two patients displayed very high variability and were identified as statistical outliers (> 3.0*IQR from Q1 and Q3). We here report the results of thirteen patients. All analyses of the CVDT were conducted on weighted hits. A RM ANOVA of the baseline measurements averaged over both sessions, with spatial location (contralesional, bilateral, ipsilesional) as within-participant factor showed a significant effect of spatial location ($F(2,11) = 54.049$, $p < .00001$, $\eta_p^2 = .908$). Follow-up analyses showed a significant difference between contralesional and ipsilesional stimuli ($t(12) = 8.289$, $p < .00001$) and between bilateral and ipsilesional stimuli ($t(12) = 7.115$, $p < .0001$), demonstrating the strong attention deficits of the neglect patients in detecting stimuli in the contralesional hemifield. There was no significant difference between contralesional and bilateral stimuli ($t(12) = .176$, $p = .864$), indicating that performance in both conditions was equally impaired.

The CVDT data was then split up to test the three hypotheses. First, we assessed the effect of unilateral HD-tACS stimulation over the contralesional parietal cortex on performance in the contralesional hemifield and expected an improvement in visual detection in active compared to sham tACS. Including only trials with stimuli in the contralesional hemifield, we performed a RM ANOVA with HD-tACS (active, sham) and time (baseline, during stimulation, after stimulation) as within-participant factors, revealing no main effects of HD-tACS ($F(1,12) = 1.724$, $p = .214$, $\eta_p^2 = .126$) or Time ($F(2,11) = .729$, $p = .504$, $\eta_p^2 = .117$). However, the interaction between HD-tACS and time was significant ($F(2,11) = 8.895$, $p = .005$, $\eta_p^2 = .618$), indicating that the difference between detection performance before, during, and after stimulation was significantly different between the active alpha HD-tACS and the sham alpha HD-tACS stimulation conditions (**Figure 2A**).

Regarding differences in performance between active and sham HD-tACS sessions, performance was equal at baseline ($t(12) = .975$, $p = .349$), but during stimulation performance was significantly improved in the active compared to the sham session ($t(12) = 4.472$, $p = .001$). This improvement was not significant after stimulation ($t(12) = 1.566$, $p = .143$).

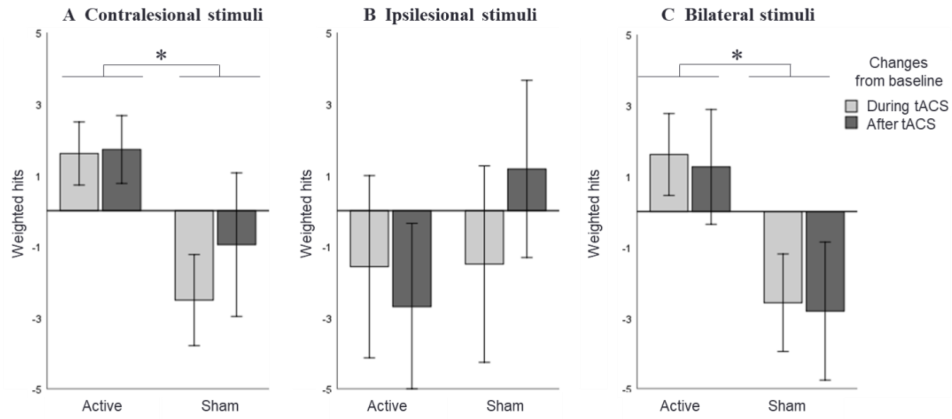

Figure 2 Computerized visual detection task: baseline corrected weighted hits (A) in contralesional hemifield, (B) in ipsilesional hemifield, and (C) when stimuli compete in both hemifields, for active and sham HD-tACS. A positive value indicates an improvement in detection performance over time (from baseline). A negative value indicates decreased performance compared to baseline, presumably due to increasing fatigue. Error bars depict one standard error. Asterisks (*) depict significant difference ($p < .05$).

We then assessed the effect of unilateral HD-tACS stimulation on performance in the ipsilesional hemifield and expected no (or a negative) effect in visual detection performance in active compared to sham tACS. Including only trials with stimuli in the ipsilesional hemifield, a RM ANOVA with HD-tACS (active, sham) and time (baseline, during stimulation, after stimulation) as within-participant factors showed no main effect of HD-tACS ($F(1,12) = .901$, $p = .361$, $\eta_p^2 = .070$), or time ($F(2,11) = .409$, $p = .674$, $\eta_p^2 = .069$), or interaction between these factors ($F(2,11) = 1.084$, $p = .372$, $\eta_p^2 = .165$) on the performance on the ipsilateral hemifield (**Figure 2B**).

Lastly, we assessed the effect of unilateral HD-tACS on performance when visual stimuli compete during bilateral presentation and expected an improvement in visual detection performance in active compared to sham sessions. Including only trials with bilateral stimuli, a RM ANOVA analyzing the performance on the bilateral trials, with HD-tACS (active, sham) and time (baseline, during stimulation, after stimulation) as within-participant factors again revealed no main effect of time ($F(2,11) = .106$, $p = .901$, $\eta_p^2 = .019$), but a significant main effect of HD-tACS ($F(1,12) = 5.179$, $p = .042$, $\eta_p^2 = .301$) and a significant interaction between HD-tACS and time ($F(2,11) = 24.895$, $p < .0001$, $\eta_p^2 = .819$). Follow-up analyses revealed no difference at baseline between the two stimulations ($t(12) = .281$, $p = .783$), but during the stimulation itself, performance was significantly improved in the active compared to the sham session ($t(12) = 3.209$, $p = .008$) and this difference was still present after stimulation ($t(12) = 3.325$, $p = .006$). Thus, HD-tACS affected performance during bilateral presentation of stimuli during and after the stimulation (**Figure 2C**).

Bells task

One patient was identified as statistical outlier (> 3.0*IQR from Q1 and Q3), thus the data presented here includes fifteen patients. To quantify the patients' spatial attention deficits on the BT a paired-samples *t* test on baseline measurements averaged over both sessions revealed a significantly higher average of omitted targets in the contralesional side compared to the ipsilesional side ($t(14) = 2.870$, $p = .012$).

A RM ANOVA including only the number of missed bells in the contralesional side with HD-tACS (active, sham) and time (baseline, during stimulation, after stimulation) as within-participant factors did not reveal a main effect of HD-tACS ($F(1,14) = .215$, $p = .650$, $\eta_p^2 = .015$) nor time ($F(2,13) = .038$, $p = .963$, $\eta_p^2 = .006$), but it did reveal an interaction between HD-tACS and time ($F(2,13) = 5.347$, $p = .020$, $\eta_p^2 = .451$). Since baseline differences between active and sham sessions ($t(14) = 2.578$, $p = .022$) were found, we further explored the interaction by analyzing changes from baseline. A RM ANOVA on change scores, with HD-tACS (active, sham) and time (during stimulation, after stimulation) as within-participant factors showed a main effect of HD-tACS ($F(1,14) = 7.261$, $p = .017$, $\eta_p^2 = .342$), but not time ($F(1,14) = .021$, $p = .887$, $\eta_p^2 = .001$) nor an interaction between HD-tACS and time ($F(1,14) = .015$, $p = .905$). The average number of misses in the contralesional side was lower during and after stimulation in the active sessions as compared to the sham sessions (**Figure 3A**).

A RM ANOVA including only the number of missed bells in the ipsilesional side with HD-tACS (active, sham) and time (baseline, during stimulation, after stimulation) as within-participant factors revealed no main effects (HD-tACS: $F(1,14) = .009$, $p = .925$, η_p^2

= .001; time: $F(2,13) = 2.836$, $p = .095$, $\eta_p^2 = .304$) nor an interaction ($F(2,13) = .064$, $p = .939$, $\eta_p^2 = .010$). This implies that HD-tACS had no effect on the performance in the ipsilesional side (**Figure 3B**).

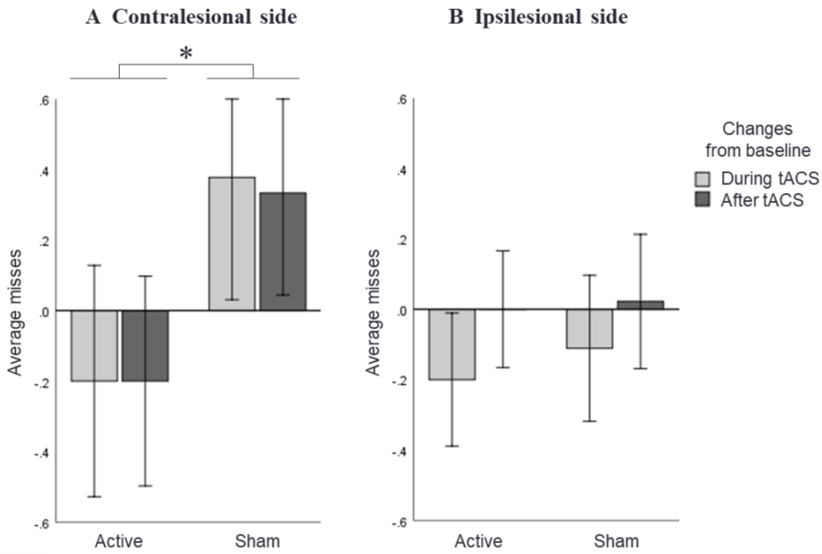

Figure 3 Bells task: baseline corrected average misses (A) in contralesional side and (B) in ipsilesional side, for active and sham HD-tACS. A negative value indicates an improvement in performance in visual search over time (from baseline). A positive value indicates decreased performance compared to baseline, presumably due to increasing fatigue. Error bars depict one standard error. Asterisks (*) depict significant differences ($p < .05$).

Line bisection task

No patients were identified as statistical outliers (> 3.0*IQR from Q1 and Q3), and the data reported below is based on sixteen patients. Baseline performance on the LBT averaged over both sessions revealed a displacement of the bisection mark to the ipsilesional side, compared to 0 ($t(15) = 3.610$, $p = .003$). A RM ANOVA with HD-tACS (active, sham) and time (baseline, during stimulation, after stimulation) as within-participant factors revealed no main effects of HD-tACS ($F(1,15) = .055$, $p = .818$, $\eta_p^2 = .004$) nor time ($F(2,14) = 2.170$, $p = .151$, $\eta_p^2 = .237$) nor an interaction between HD-tACS and time ($F(2,14) = .254$, $p = .779$, $\eta_p^2 = .035$) (**Figure 4**). This implies that tACS had no effect on the visual bias in the LBT.

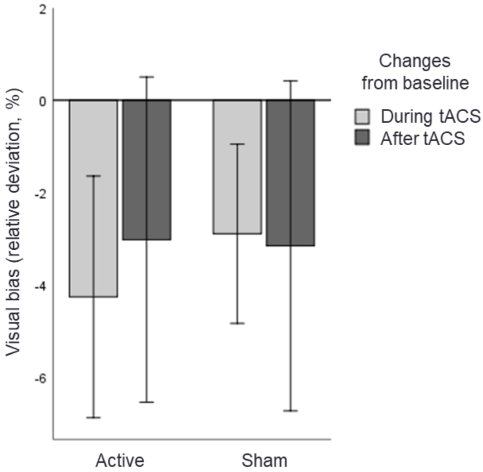

Figure 4 Line bisection task: baseline corrected visual bias for active and sham HD-tACS. A negative value indicates that, compared to baseline, the bisection mark was placed less toward the ipsilesional side of space and more toward the contralesional (affected) side of space. Error bars depict one standard error.

Discussion

This study aimed to alleviate attention deficits in hemineglect patients by using noninvasive transcranial brain stimulation to target functionally relevant oscillatory activity as a critical mechanism of attentional control. To this end, we applied high-definition transcranial alternating current stimulation (HD-tACS) at alpha frequency to the contralesional posterior parietal cortex of seventeen hemineglect patients to modulate alpha power lateralization and to consequently correct their pathologically altered spatial attention bias. Compared to sham stimulation, patients significantly improved in allocating their attentional resources toward the contralesional hemifield leading to a reduction in neglect symptoms measured with a novel computerized visual detection paradigm (CVDT) and a widely used standard paper and pencil neglect task (bells task, BT), but not on the line bisection task (LBT). This effect could be seen in the unilateral/contralesional as well as the bilateral condition (measured with the CVDT), where performance depends on the contralesional and ipsilesional hemifield. Interestingly, the effects in the bilateral condition of the CVDT as well as the amount of misses in the BT in the contralesional side outlasted the stimulation time, meaning that the effect of the brain stimulation was still visible after stimulation. These results are the first proof-of-concept demonstration that this oscillatory-based transcranial stimulation approach is feasible, tolerable, and potentially clinically effective in treating hemineglect after stroke.

Our HD-tACS approach continues a recent trend toward directly targeting the biological basis for stroke-related impairments by non-invasive brain stimulation (NIBS). Previous studies aiming to reduce local cortical excitability in the contralesional hemisphere of patients with visuospatial neglect have produced some promising results, but the overall small and heterogeneous clinical effects at present only warrant a level-C recommendation according to the most recent European guidelines. Our hope is that improvements of efficacy can be made by tuning the brain stimulation protocol to the fundamental properties of network communication supported by oscillatory activity within and between functional brain networks.

This is exactly the mechanism based on which the here presented novel oscillation-based NIBS approach was developed. Instead of changing local cortical excitability, we aimed to entrain alpha oscillatory activity in the posterior parietal cortices to gate top-down selective information flow by functional inhibition (Jensen & Mazaheri, 2010; Klimesch et al., 2007). The oscillatory alpha band has been shown to be causally linked to such inhibitory gating with shifting attention to the right hemifield being accompanied by alpha power decreases in the left hemisphere (release from inhibition) and alpha power increases in the right hemisphere (inhibiting the unattended left hemifield).

We here show that modulating this alpha power lateralization with HD-tACS in neglect patients holds the potential to correct for a pathological spatial attention bias after stroke. Importantly, while classical excitability-based brain stimulation protocols often also achieve ipsilateral attention improvement but at the costs of contralateral attention impairments (shifting the balance toward the neglected side of space), our approach of enhancing alpha oscillatory activity in the left hemisphere did not negatively affect performance in the contralateral, i.e., ipsilesional hemifield as a consequence of the revealed significant performance improvement in the contralesional (neglected) hemifield. From a clinical standpoint, this novel brain stimulation approach may therefore be more beneficial and desirable as compared to the current standard of decreasing unilateral excitability levels.

Interestingly, alpha-HD-tACS differentially affected the different paradigms used to assess attentional performances in our patient sample. The absence of effects on the LBT is somewhat unexpected, and likely due to compensatory strategies patients learned during cognitive training. This compensatory effect in the LBT has been reported previously (Keller et al., 2005).

A second possible explanation is that a deviation in line bisection is not fundamentally related to spatial neglect, but may also arise from disturbances of other sensory and cognitive processes, such as hemianopia (Ferber & Karnath, 2001). Our tACS-therapy targets attentional processes in the brain and does not treat visual deficits. It may well be that some neglect patients in our sample also suffered from visual field deficits, since visual neglect and visual field deficits commonly co-occur after unilateral brain damage such as stroke (Halligan, 1999). In a study that compared the accuracy of the LBT and cancellation tests (including the BT) in detecting spatial neglect, cancellation tests proved to be far superior, suggesting they reflect spatial neglect symptomatology more distinctly (Ferber & Karnath, 2001). This demonstrates that carefully selected tasks are very relevant to reveal attention deficits. Even though the BT worked as intended in our current study, we believe adaptive testing as used here during our CVDT is very promising as it allows assessment across the entire spectrum of neglect severity (at least in the ideal case).

We were able to show immediate stimulation effects, but also effects outlasting the stimulation itself. This not only suggests that our approach does qualify for a clinical treatment protocol aimed at achieving longer lasting after-effects, but also indicates that the task-specific effects we find are not confounded by the stimulation itself. It should be noted that the current study only included sixteen patients, and future studies with more patients are recommended. Future studies could also include electroencephalography (EEG), not only to measure and show potential changes in oscillations after stimulation, but also to individualize the stimulation parameters themselves. We were able to show in a healthy population group that stimulation at the individual frequency, compared to stimulation at flanker frequencies lead to larger alpha lateralization after stimulation (Kemmerer et al., 2022). The oscillatory-based approach described thus allows personalizing the treatment protocol by stimulating based on individual oscillatory frequency parameters (Zaehle et al., 2010) but it also allows extending to different frequency bands. In addition, HD-tACS has shown to be a very well tolerated, feasible, low-cost and portable technique, which therefore lends itself perfectly to be amended by cognitive training and even used in a home-setting (at-home use with remote supervision). Based on this proof-of-concept, a larger randomized controlled clinical trial is needed to evaluate the clinical efficacy of many repeated treatment sessions over the course of rehabilitation to hopefully induce long-lasting changes, which has already been demonstrated in psychiatric disorders, such as depression.

Conclusion

Administering HD-tACS at alpha frequency over the contralesional hemisphere improves spatial attention deficits in subacute stroke patients. Oscillatory-based tACS might be a promising therapeutic tool in patients with attentional deficits.

References

Azouvi, P., Jacquin-Courtois, S., & Luauté, J. (2017). Rehabilitation of unilateral neglect: Evidence-based medicine. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 191–197. https://doi.org/10.1016/j.rehab.2016.10.006

Battelli, L., Alvarez, G. A., Carlson, T., & Pascual-Leone, A. (2009). The role of the parietal lobe in visual extinction studied with transcranial magnetic stimulation. *Journal of Cognitive Neuroscience*, *21*(10), 1946–1955. https://doi.org/10.1162/jocn.2008.21149

Bien, N., Goebel, R., & Sack, A. T. (2012). Extinguishing extinction: Hemispheric differences in the modulation of TMS-induced visual extinction by directing covert spatial attention. *Journal of Cognitive Neuroscience*, *24*(4), 809–818. https://doi.org/10.1162/jocn_a_00179

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*, *10*(4), 433–436. https://doi.org/10.1017/CBO9781107415324.004

Buxbaum, L., Ferraro, M., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., Frassinetti, F., & Coslett, H. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology*, *62*, 749–756. https://doi.org/10.1212/01.wnl.0000113730.73031.f4

Collin, C., Wade, D. T., Davies, S., & Horne, V. (1988). The Barthel ADL index: A reliability study. *Disability and Rehabilitation*, *10*(2), 61–63. https://doi.org/10.3109/09638288809164103

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Topper, R., & Boroojerdi, B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, *1072*(1), 194–199. https://doi.org/10.1016/j.brainres.2005.05.075

Datta, A., Elwassif, M., Battaglia, F., & Bikson, M. (2008). Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. *Journal of Neural Engineering*, *5*(2), 163–174. https://doi.org/10.1088/1741-2560/5/2/007

Di Monaco, M., Schintu, S., Dotta, M., Barba, S., Tappero, R., & Gindri, P. (2011). Severity of unilateral spatial neglect is an independent predictor of functional outcome after acute inpatient rehabilitation in individuals with right hemispheric stroke. *Archives of Physical Medicine and Rehabilitation*, *92*(8), 1250–1256. https://doi.org/10.1016/j.apmr.2011.03.018

Duecker, F., Schuhmann, T., Bien, N., Jacobs, C., & Sack, A. T. (2017). Moving beyond attentional biases: Shifting the interhemispheric balance between left and right posterior parietal cortex modulates attentional control processes. *Journal of Cognitive Neuroscience*, *29*(7), 1267–1278. https://doi.org/10.1162/jocn_a_01119

Fasotti, L., & Van Kessel, M. (2013). Novel insights in the rehabilitation of neglect. *Frontiers in Human Neuroscience*, *7*, 1–8. https://doi.org/10.3389/fnhum.2013.00780

Feigin, V. L., Brainin, M., Norrving, B., Martins, S., Sacco, R. L., Hacke, W., Fisher, M., Pandian, J., & Lindsay, P. (2022). World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. *International Journal of Stroke*, *17*(1), 18–29. https://doi.org/10.1177/17474930211065917

Ferber, S., & Karnath, H.-O. (2001). How to assess spatial neglect - Line bisection or cancellation tasks? *Journal of Clinical and Experimental Neuropsychology*, *23*(5), 599–607. https://doi.org/10.1076/jcen.23.5.599.1243

Fiebelkorn, I. C., & Kastner, S. (2019). A rhythmic theory of attention. *Trends in Cognitive Sciences*, *23*(2). https://doi.org/10.1016/j.tics.2018.11.009

Halligan, P. W. (1999). Hemianopia and visual neglect: A question of balance? *Journal of Neurology Neurosurgery and Psychiatry*, *67*(5), 565–566. https://doi.org/10.1136/jnnp.67.5.565

Hilgetag, C. C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nature Neuroscience*, *4*(9), 953–957. https://doi.org/10.1038/nn0901-953

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Frontiers in Human Neuroscience*, *4*. https://doi.org/10.3389/fnhum.2010.00186

Keller, I., Schindler, I., Kerkhoff, G., Rosen, F. Von, & Golz, D. (2005). Visuospatial neglect in near and far space: Dissociation between line bisection and letter cancellation. *Neuropsychologia*, *43*(5), 724–731. https://doi.org/10.1016/j.neuropsychologia.2004.08.003

Kemmerer, S. K., Sack, A. T., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Schuhmann, T. (2022). Frequency-specific transcranial neuromodulation of alpha power alters visuospatial attention performance. *Brain Research*, *1782*. https://doi.org/10.1016/j.brainres.2022.147834

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., & Schwaiger, J. (1998). Induced alpha band power changes in the human EEG and attention. *Neuroscience Letters*, *244*(2), 73–76. https://doi.org/10.1016/S0304-3940(98)00122-0

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Koch, G., Bonnì, S., Giacobbe, V., Bucchi, G., Basile, B., Lupo, F., Versace, V., Bozzali, M., & Caltagirone, C. (2012). Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. *Neurology*, *78*(1), 24–30. https://doi.org/10.1212/WNL.0b013e31823ed08f

Lakatos, P., Gross, J., & Thut, G. (2019). A new unifying account of the roles of neuronal entrainment. In *Current Biology* (Vol. 29, Issue 18, pp. R890–R905). Cell Press. https://doi.org/10.1016/j.cub.2019.07.075

Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipović, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jääskeläinen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J. P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., … Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). In *Clinical Neurophysiology* (Vol. 131, Issue 2, pp. 474–528). Elsevier Ireland Ltd. https://doi.org/10.1016/j.clinph.2019.11.002

Lefaucheur, J. P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., Cantello, R. M., Cincotta, M., de Carvalho, M., de Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S. R., Hummel, F. C., Jääskeläinen, S. K., Kimiskidis, V. K., Koch, G., Langguth, B., Nyffeler, T., … Garcia-

Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*, *125*, 2150–2206. https://doi.org/10.1016/j.clinph.2014.05.021

Longley, V., Hazelton, C., Heal, C., Pollock, A., Woodward-Nutt, K., Mitchell, C., Pobric, G., Vail, A., & Bowen, A. (2021). Non-pharmacological interventions for spatial neglect or inattention following stroke and other non-progressive brain injury. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003586.pub4

Morishima, Y., Akaishi, R., Yamada, Y., Okuda, J., Toma, K., & Sakai, K. (2009). Task-specific signal transmission from prefrontal cortex in visual selective attention. *Nature Neuroscience*, *12*(1), 85–91. https://doi.org/10.1038/nn.2237

Osawa, A., & Maeshima, S. (2021). Unilateral spatial neglect due to stroke. In S. Dehkharghani (Ed.), *Stroke*. Exon Publications. https://doi.org/10.36255/exonpublications.stroke.2021

Paulus, W., Antal, A., & Nitsche, M. A. (2013). Physiological basis and methodological aspects of transcranial electric stimulation (tDCS, tACS, and tRNS). In C. Miniussi, W. Paulus, & P. Rossini (Eds.), *Transcranial Brain Stimulation* (pp. 93–111). CRC Press.

Ruff, C. C., Bestmann, S., Blankenburg, F., Bjoertomt, O., Josephs, O., Weiskopf, N., Deichmann, R., & Driver, J. (2008). Distinct causal influences of parietal versus frontal areas on human visual cortex: Evidence from concurrent TMS-fMRI. *Cerebral Cortex*, *18*(4), 817–827. https://doi.org/10.1093/cercor/bhm128

Sack, A. T., Hubl, D., Prvulovic, D., Formisano, E., Jandl, M., Zanella, F., Maurer, K., Goebel, R., Dierks, T., & Linden, D. (2002). The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Cognitive Brain Research*, *13*(1), 85–93. https://doi.org/10.1016/S0926-6410(01)00087-8

Sack, A. T., Kohler, A., Bestmann, S., Linden, D. E. J., Dechent, P., Goebel, R., & Baudewig, J. (2007). Imaging the brain activity changes underlying impaired visuospatial judgments: Simultaneous fMRI, TMS, and behavioral studies. *Cerebral Cortex*, *17*(12), 2841–2852. https://doi.org/10.1093/cercor/bhm013

Schenkenberg, T., Bradford, D., & Ajax, E. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509–517. https://doi.org/10.1212/wnl.30.5.509

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *PLoS ONE*, *14*(11), 1–25. https://doi.org/10.1371/journal.pone.0217729

Stone, S., Patel, P., Greenwood, R., & Halligan, P. (1992). Measuring visual neglect in acute stroke and predicting its recovery: The visual neglect recovery index. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(6), 431–436. https://doi.org/10.1136/jnnp.55.6.431

Ten Brink, T., Nijboer, T., & Visser-Meily, A. (2016). De behandeling van neglect, een aandachtstoornis. *Nederlands Tijdschrift Der Geneeskunde*, *160*(D393).

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/JNEUROSCI.0875-06.2006

Watson, A. B., & Pelli, D. G. (1983). QUEST: A Bayesian adaptive psychometric method. *Perception & Psychophysics*, *33*(2), 113–120. https://doi.org/10.3758/BF03202828

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience*, *20*(6), 1–6. https://doi.org/10.1523/jneurosci.20-06-j0002.2000

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE*, *5*(11), e13766. https://doi.org/10.1371/journal.pone.0013766

Chapter 5

Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect

Corresponding manuscript:

Middag-van Spanje, M., Schuhmann, T., Nijboer, T. C. W., Van der Werf, O., Sack, A. T., & Van Heugten, C. (2022). Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect. *BMC Neurology, 22*(1). https://doi.org/10.1186/s12883-022-02932-7

Abstract

A frequent post stroke disorder in lateralized attention is visuospatial neglect (VSN). As VSN has a strong negative impact on recovery in general and independence during daily life, optimal treatment is deemed urgent. Next to traditional stroke treatment, non-invasive brain stimulation offers the potential to facilitate stroke recovery as a complementary approach. In the present study, visual scanning training (VST; the current conventional treatment) will be combined with transcranial alternating current stimulation (tACS) to evaluate the additive effects of repeated sessions of tACS in combination with six weeks VST rehabilitation. In this double-blind randomized placebo-controlled intervention study (RCT), we will compare the effects of active tACS plus VST to sham (placebo) tACS plus VST, both encompassing eighteen VST sessions, 40 minutes each, during six weeks. Chronic stroke patients with VSN (> six months post-stroke onset) are considered eligible for study participation. In total 22 patients are needed for the study. The primary outcome is change in performance on a cancellation task. Secondary outcomes are changes in performance on a visual detection task, two line bisection tasks, and three measures to assess changes in activities of daily living. Assessment is at baseline, directly after the first and ninth training session, after the last training session (post training), and one week and three months after termination of the training (follow-up). If effective, a tACS-VST rehabilitation program could be implemented as a treatment option for VSN.

Introduction

Visuospatial neglect (VSN) is a common syndrome after unilateral stroke; 25-30% of all stroke patients have VSN (Appelros et al., 2002; Buxbaum et al., 2004). VSN patients show a failure or slowness to report, respond or orient to events and stimuli located in the contralesional side of space (Buxbaum et al., 2004; Heilman et al., 2000). It is thought that the brain damage causes impairment of the brain's spatial attention mechanisms, resulting in VSN (Corbetta & Shulman, 2011; Heilman & Van Den Abell, 1980). VSN patients show slower and more attenuated motor recovery patterns (Nijboer et al., 2014) and need more help in activities of daily living (ADL) compared to stroke patients without VSN (Nijboer, Van de Port, et al., 2013). Moreover, VSN negatively influences participation in society, increases caregiver burden (Bosma et al., 2020) and is negatively related to life satisfaction (Verhoeven et al., 2011). These findings show the considerable impact of VSN on daily life and stress the importance of adequate treatment.

Over the past decades, many therapeutic interventions aiming to improve VSN have been developed and evaluated (for overview, see Azouvi et al., 2017) ranging from treatments using top-down strategies such as mental imagery training (Smania et al., 1997), to bottom-up methods such as prism adaptation (Rossetti et al., 1998; Ten Brink, Visser-Meily et al., 2017), and from sustained attention training (Robertson et al., 1995), to non-invasive brain stimulation (NIBS) techniques (Jacquin-Courtois, 2015). Currently, the standard treatment for VSN is a visual scanning training (VST), an intensive compensatory training with emphasis on top-down strategies designed to improve viewing and searching behavior (Pizzamiglio et al., 1992). However, generalization of the effects of VST to everyday life is insufficiently established (Azouvi et al., 2017; Ten Brink, Van Kessel et al., 2017) and there exists a large variability in patients' benefits from VST (Van Kessel et al., 2013). It is unclear why some patients benefit from the training while others do not. One reason could be that top-down methods such as VST may be limited as they solicit the attentional abilities, which may be hampered by lack of awareness of the spatial neglect behavior (Azouvi et al., 2017; Van Kessel et al., 2013). The heterogeneity of VSN, with high variability of symptoms within and between patients, may also play a role in the variability of responsiveness to interventions for neglect (Ten Brink, Visser-Meily et al., 2017). Because neglect is a multifaceted disorder, it is suggested that the best treatment might involve a combination of different methods to improve their overall effectiveness (Azouvi et al., 2017; Fasotti & Van Kessel, 2013; Jacquin-Courtois, 2015; Kerkhoff & Schenk, 2012; Saevarsson et al., 2011; Ten Brink, Visser-Meily et al., 2017).

NIBS offers a completely different strategy to facilitate recovery, not by means of a behavioral approach submitting the patient to a program of standardized behavioral tasks that require a voluntary (attentional) effort by the patient to follow a therapist's instructions (such as VST), but by directly inducing neuroplastic changes in the patient's brain, hoping to positively affect cognitive functioning. For example, brain stimulation protocols can be tuned to modulate oscillatory brain activity (for review, see Abd Hamid et al., 2015). This is particularly interesting in the field of neglect rehabilitation, as oscillatory activity in the alpha range (8-12 Hz) in posterior parietal cortices has been linked to spatial attention bias in healthy subjects (Gould et al., 2011; Händel et al., 2011; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000). In our recent studies, we showed that transcranial alternating current stimulation (tACS), applied at alpha frequency, can be used to influence visuospatial attention performance in healthy participants (Schuhmann et al., 2019) and in sub-acute VSN patients (Schuhmann et al., 2022) in a single session.

To our knowledge, no study has yet reported the combined impact of this oscillatory-based NIBS approach and conventional neglect therapy on rehabilitation outcome. The overall aim of the current study is therefore to evaluate the effects of repeated sessions of tACS in combination with six weeks VST rehabilitation. Our primary research question is: Does VST complemented with active tACS improve neglect-related symptoms to a larger extent compared to VST with sham (placebo) tACS post training compared to baseline? Secondary questions are: 1) whether long-lasting effects occur, 2) whether effects already occur earlier during the six weeks training, and 3) whether effects generalize to daily life situations.

Methods

Design

This study is a double-blind randomized placebo-controlled intervention study (RCT; **Figure 1**). We will compare the effects of active tACS to sham (control) tACS, both combined with conventional rehabilitation (VST). Irrespective of the intervention group, *all* patients will receive VST during the (active or sham) stimulation.

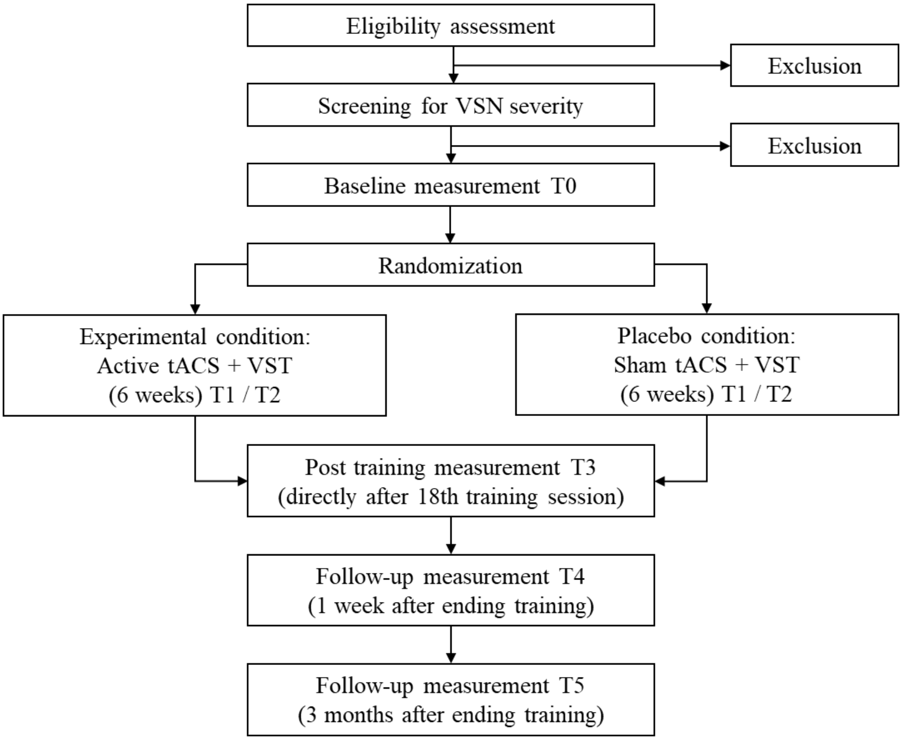

Figure 1 Study flow chart.

This study is conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, Korea, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study is approved by the Medical-Ethical Committee azM/UM of Maastricht University (NL70256.068.19 / METC 19-047) and registered in ClinicalTrials.gov (Non-Invasive Brain Stimulation as an Innovative Treatment for Chronic Neglect Patients (NibsNeglect), NCT05466487).

Patient sample – inclusion and exclusion criteria

Patients with a clinically diagnosed, chronic stroke and with signs of neglect symptoms (based on clinical judgment), will be considered eligible for our study. Patients will be recruited by psychologists of healthcare organizations in The Netherlands that are specialized in supporting and treating people with acquired brain injury (InteraktContour, De Hoogstraat Revalidatie, Heliomare, De Noorderbrug, Esdégé-Reigersdaal). The inclusion of participants started in September 2020 and data will be collected until September 2023.

Inclusion criteria are: 1) neurologically objectified stroke (first or recurrent, ischemic or intracerebral or subarachnoid haemorrhagic lesion); 2) stroke occurred when patient was 18-80 years of age; 3) chronic stroke (> six months post-stroke onset); 4) sufficient comprehension and communication skills to benefit from training (based on clinical judgment); and lastly 5), a screening containing four neuropsychological tests will be performed to evaluate the current severity of the neglect, since the diagnosis of neglect may have been established months or even years ago in our sample of chronic stroke patients.

Exclusion criteria are: 1) currently engaging in cognitive rehabilitation treatment or neglect treatment; 2) physically or mentally unable to participate (based on clinical judgment); 3) hemianopia (based on clinical judgment); 4) severe communicative disability, as task descriptions need to be understood; 5) local scalp injuries; 6) eczema on scalp or psoriasis; 7) diagnosed (neuro)psychiatric or neurodegenerative diseases; 8) current alcohol and/or drug abuse; and 9) pregnancy, due to tACS safety considerations (5-9).

Procedure, neglect screening, outcome measures and baseline descriptors

Patients are allowed to proceed in the study when they show neglect on minimally one of the four screening tasks, on the basis of standard norms: bells task (BT) (Gauthier et al., 1989), balloons-subtest B (BB) (Edgeworth et al., 1998), Schenkenberg line bisection task (SLBT) (Schenkenberg et al., 1980), and McIntosh line bisection task (MLBT) (McIntosh et al., 2017, 2005). Patients who show neglect during screening will be randomly assigned to either the experimental (active tACS) or placebo (sham tACS) condition, and will receive VST training for six weeks. Enrolled patients will be tested six times on an array of tasks: before the training (T0; baseline), after the first (T1), ninth (T2), and eighteenth (T3) training session, as well as one week (T4) and three months (T5) after termination of the training (**Figure 1**). The star cancellation task (SCT), computerized visual detection task (CVDT), MLBT-digitized (MLBT-d), and SLBT will be assessed during all six testing-time points in the study (T0-T5). The baking tray task (BTT), Catherine Bergego scale (CBS), and subjective neglect questionnaire (SNQ) will be administered at four testing-time points (T0, T2, T4, and T5).

Screening tasks

Bells task (BT)

This cancellation task will be presented on an A4 paper and consists of 35 target items (bells), interspersed among 280 distractor objects (Gauthier et al., 1989). Patients will be instructed to mark all bells. Four or more omissions are considered as indicative for VSN (Van Kessel et al., 2013).

Balloons-subtest B (BB)

The scores of subtest B of the balloons test (Edgeworth et al., 1998) will be used to calculate a total score (total number of targets cancelled) and a laterality score (number of targets cancelled on the left side of the page expressed as a percentage of the total number of targets cancelled). Subtest B consists of an A3 paper with twenty targets (circles) and 180 distractors (balloons). A total score of less than 17 *and* a laterality score of less than 45% is indicative of left VSN.

Schenkenberg line bisection task (SLBT)

The SLBT consists of twenty horizontal lines, varying from ten to twenty cm in length (average fifteen cm), at three different positions (left, middle, right) on a landscape-oriented A4 sheet (Schenkenberg et al., 1980). Patients will be asked to mark their perceived midpoint of every line. The following formula will be used to calculate the relative deviation score:

$$deviation = \frac{(bisection\ mark - true\ center)}{true\ center} * 100\%$$

Where values are always measured from the left end of the line. The relative deviation scores will then be averaged across all twenty lines to generate the summary score, and across the three line positions to generate the left, middle, and right average score, respectively. VSN is indicated when the average bisection mark deviates more than 10% from the true center (Schenkenberg et al., 1980).

McIntosh line bisection task (MLBT)

The MLBT provides a simple measure of lateral asymmetry, the endpoint weightings bias (EWB) (McIntosh et al., 2005, 2017). The EWB is a different approach to line bisection to diagnose VSN. Compared to classical line bisection tests, the EWB is a more theoretically neutral and parsimonious approach, based on the weight one distributes to both of the endpoints of the line, rather than using the deviation from the midpoint. The MLBT consists of 32 horizontal lines (width: 3 mm), each presented individually on an A4 sheet. The patient is asked to mark the subjective midpoint of each line. There are eight repetitions of each of four unique lines (lines A, B, C, D), presented in a fixed-random order (McIntosh et al., 2017, 2005). We refer to McIntosh and colleagues (2017) for the arrangement of the four lines. Each response is coded as a horizontal coordinate relative to the center of the page. The analysis then focuses on how this response position varies from trial-to-trial as a consequence of changes in the left endpoint (lines A & C vs B & D) and changes in the right endpoint (lines A & B vs C & D). Thus, the left endpoint weighting (dPL), the right endpoint weighting (dPR), and the bias toward one of the two endpoints (EWB) are derived as follows:

$$dPL = \frac{(P_{mean} \text{ in line A and C}) - (P_{mean} \text{ in line B and D})}{40}$$

$$dPR = \frac{(P_{mean} \text{ in line C and D}) - (P_{mean} \text{ in line A and B})}{40}$$

$$EWB = dPR - dPL$$

Where dPL and dPR are expressed as a proportion of the endpoint change (40 mm), and range from 0 to 1. Perfect performance would yield symmetrical right and left endpoint weightings of 0.5, and an EWB-value of 0. An EWB-value above 0 indicates a greater influence of the right endpoint (over the left), and would be a sign for left-sided neglect. To define cut-off scores for the MLBT, we administered the task to healthy controls (*n* = 46, female = 47.7%, age = 57.8 years, SD = 9.2). This yielded a mean EWB of -.0217 (SD = .0546). Scores of 2 SD's above and below the mean are considered to exceed normal range, leading to upper and lower cut-offs for left and right neglect respectively, of +0.09 and −0.13. Study protocol was approved by the ethical committee of the Faculty of Psychology and Neuroscience at Maastricht University (ERCPN number: 177_03_03_2017_S32).

Primary outcome measure: star cancellation task (SCT)

The SCT is developed to detect the presence of VSN in the near extra personal space in patients with stroke, and consists of 52 large stars, thirteen letters, and ten short words interspersed with 56 smaller stars (Wilson et al., 1987). In our study, the SCT will be presented on a laptop screen (screen size: 14 inch). The patient is instructed to mark all targets by touching the screen with the finger (small stars). After each touch, a small circle appears at the touched location and remains on the screen. Two small stars in the center are used for demonstration. To determine the severity of the VSN, quality of search (QoS) for the left and right visual fields will be derived. This score combines speed and accuracy in a single measure, and is calculated using the equation as shown below (Dalmaijer et al., 2014). A high score reflects a combination of a high number of cancelled targets, and a high cancellation speed.

$$QoS = \frac{{N_{cor}}^2}{N_{tar} \cdot t_{tot}}$$

Where N_{cor} is the number of cancelled targets (correct responses), N_{tar} is the total number of targets, and t_{tot} is the total time spent.

The SCT, as well as the CVDT and the MLBT-d (see subsection ‘Secondary outcome measures’), will be administered on the same touch screen laptop as will be used for the training (HP EliteBook x360 1040 G5 Notebook; screen size: 14 inch). PsychoPy will be used to control stimulus presentation and recording of behavioral responses.

Secondary outcome measures

Computerized visual detection task (CVDT)

The CVDT measures perceptual sensitivity and attentional selection in each hemifield (Bien et al., 2012; Duecker et al., 2017; Schuhmann et al., 2022, 2019). During the task, the patient is seated in front of the laptop screen at 52 cm distance. The patient is asked to fixate on the fixation cross at the center of the screen. Gabor patches (spatial frequency = 1.5 cycles per degree, envelope standard deviation = 7.5°, random orientation) are presented to the left, right, and bilateral sides of the screen at 14° eccentricity. Stimuli are shown for 100 ms and stimulus size is 10°. The patient is instructed to indicate the position of the stimulus (left, bilateral, or right) by pressing the <, ∨, or > key, respectively. For each trial, the stimulus position, contrast level, and response are recorded. Video mode is 1280 × 720 at 60 Hz.

For each of the three locations (left, bilateral, right) independently, the contrast of the stimuli is adaptively changed on a trial-by-trial basis. The following parameters are used: prior grating contrast = 1, prior standard deviation = 0.5, beta = 3.5, gamma = 0.01, delta = 0.01, and aim performance = 0.5 (50% detection rate). At the beginning of the task, nine practice trials are presented (i.e., three for each condition; left, bilateral, right) for the patient to become familiar with the task. The stimuli are at maximum contrast, are not part of the staircase procedure, and are not saved. After each practice trial, short written feedback is given (‘Correct’, ‘Wrong’) in the center of the screen. Then, in the actual task, three randomly interleaved staircases are included (left, right, bilateral), with 40 trials each. Correct hits will be weighted by the contrast level, according to the following formula:

$$weighted\ hits = \frac{\log_{10} contrast_{max}}{\log_{10} contrast_{trial}}$$

Where $contrast_{max}$ is 100% (Schuhmann et al., 2022). This variable accounts for the logarithmic nature of contrast detection, and makes trials count more when the contrast was low. To illustrate, trials detected at maximum contrast receive a score of 1, whereas trials detected at minimal contrast level of 10% receive a score of 2. Performance of the CVDT will be the sum of weighted hits per condition (ipsilesional stimulus, contralesional stimulus, bilateral stimulus), resulting in a score of 0 to 76.49 per condition.

McIntosh line bisection task-digitized (MLBT-d)

A digitized version of the above described MLBT (subsection ‘Screening tasks’) is also used as study outcome measure. Each of the 32 lines of the MLBT-d are presented individually on a laptop screen. The patient is asked to mark the subjective midpoint of each line by touching the screen with the finger.

Schenkenberg line bisection task (SLBT)

In addition to the MLBT(-d), which is still a novel method for administering and analyzing line bisection, we will administer the SLBT, which is a simple line bisection task, widely used in the diagnosis and study of VSN (Schenkenberg et al., 1980). A description of the SLBT is already given in subsection ‘Screening tasks’.

Baking tray task (BTT)

The patient is asked to distribute sixteen cubes of 3.5 cm as evenly as possible over a 75 x 100 cm board (as if spreading out buns on a baking tray) (Tham, 1996). The entire board will be scanned using the Microsoft Lens iOS app. Coordinates of all cubes will be manually identified using a custom Python script. An average positive x-coordinate indicates a rightward bias.

Catherine Bergego scale (CBS)

The CBS is an observation scale for VSN in ADL (Azouvi et al., 2003; Ten Brink et al., 2013) and will be filled out by a therapist or proxy (partner or caregiver). Neglect severity will be scored for each of ten items, resulting in a total score of 0 (no neglect) to 30 (severe neglect).

Subjective neglect questionnaire (SNQ)

The SNQ is a nineteen-item questionnaire that will be administered to patients and proxies, asking them to rate the presence of common problems associated with neglect (Towle & Lincoln, 1991). Each item will be scored on a five-point scale according to the frequency of the occurrence of the difficulty (ranging from at most once a month to at least once a day). The minimum score of 19 indicates no reported problems, the maximum score is 95 (Van Kessel et al., 2013).

Baseline descriptors

The following data will be collected: demographics (age, gender, handedness, educational level), stroke characteristics (time post-stroke, lesion side, stroke type (ischemic, intracerebral or subarachnoid haemorrhage) and stroke history (first-ever or recurrent)), and global cognitive functioning (Montreal Cognitive Assessment; MoCA version 8.1; Nasreddine et al., 2005).

Randomization, blinding and treatment allocation

Participants will be randomly assigned to either the active tACS plus VST group *or* the sham tACS plus VST group. We will apply minimization, a method of adaptive stratified sampling, to prevent imbalances of potential confounders between the active and sham group. This will be achieved using MinimPy, an open-source customizable minimization program for allocation of patients to parallel groups in clinical trials (Saghaei & Saghaei, 2011). Patients will be stratified according to the following factors: age (18-59/60-80), gender (male/female), and having had previous neglect treatment (yes/no). The software will automatically send an e-mail with the randomization results to a not-closely involved and only unblinded research assistant. This assistant will then pick a five-digit code from the list of codes provided in the NeuroConn DC Stimulator user manual (neuroConn GMBH) that either initiates the preprogrammed active stimulation protocol or the sham protocol. The unblinded assistant will assign this unique code to the enrolled patient in question and will send the code to the blinded researchers. The unblinded assistant will further not be involved in the study, so will play no further role in inclusion, testing or analyses. The blinded researchers will perform the intervention and administer the outcome measurements, independently of the unblinded assistant. Patients will also be blinded to treatment allocation.

Intervention

The intervention (VST with active or sham ACS) will be offered by the researchers at the patients' homes. In every training session, the patients will perform the VST on a touch screen laptop (HP EliteBook x360 1040 G5 Notebook; screen size: 14 inch), whilst also receiving the (active or sham) stimulation. The VST lasts as long as the stimulation is applied (40 minutes). In total, patients will receive eighteen training sessions in six weeks (three sessions per week).

VST

All patients will receive computerized VST. The aim of the conventional VST is to train VSN patients to actively explore and consciously pay attention to stimuli on the contralesional side (Pizzamiglio et al., 1992). The conventional VST is similar to our digitized version. Patients' visual search is systematically guided by contralesional cues (e.g., a visual stimulus of reference on the left) and by the researcher's feedback (Pizzamiglio et al., 1992).

Our VST program consists of several digitalized, evidence-based training tasks: 1) digit detection; 2) copying of line drawings on a dot matrix; 3) figure description; 4) reading training (tasks 1-4 based on Pizzamiglio et al., 1992); 5) fill-out objects (based on Priftis et al., 2013); 6) figure search (based on cancellation tasks, e.g., Gauthier et al., 1989; Weintraub & Mesulam, 1985); 7) congruent movement training (Elshout et al., 2019); and 8) eye-movement training ('standard VST' in Elshout et al., 2019).

Active tACS

The experimental group will receive active tACS during each session of the VST. To understand how tACS can correct for the attentional bias seen in VSN patients, in the next paragraph we elaborate on the rationale of our study.

Previous electroencephalography studies with healthy participants have linked attention shifts to alpha power in posterior parietal cortices (Gould et al., 2011; Händel et al., 2011; Sauseng et al., 2005; Thut et al., 2006). To specify, increased alpha power reflects suppression of incoming sensory information. Thus, shifting attention to the right hemifield is accompanied by alpha power increases in the right hemisphere (inhibiting the unattended left hemifield) and alpha power decreases in the left hemisphere (release from inhibition). Interesting for the field of neglect rehabilitation is that previous studies have shown that tACS can increase the power of the alpha frequency (Neuling et al., 2013; Zaehle et al., 2010). If indeed alpha power is increased in the ipsilateral relative to the contralateral side of attention, we hypothesize that the bias in visuospatial attention seen in neglect patients can be corrected for by boosting the alpha power in the contralesional parietal cortex by tACS.

Therefore, in the current study a small circular (diameter: 2.1 cm, thickness: 2 mm) and a large rubber ring (outer diameter: 11 cm; inner diameter: 9 cm, thickness: 2 mm) tACS electrode (NeuroConn, Ilmenau, Germany) will be placed onto the contralesional parietal cortex, with the small electrode positioned over P3 or P4 (based on the international 10-20 EEG system) and the large electrode centered around it. This ring electrode montage enables a higher spatial focality as compared to standard rectangular electrodes (Datta et al., 2008). TACS ring electrodes will be attached to the patient's head with conductive gel (ten20 paste, Weaver and Company, Aurora, CO, USA). The conductive gel will be used to reduce the impedance between skin and electrodes to below 10 kΩ.

Stimulation frequency and peak-to-peak intensity will be set to 10 Hz and 1.5 milliampere (mA), phase offset will be set to 0 and 100 cycles (10 s) will be used for ramping up. At the start of the VST, the tACS will be started. When the training is finished, after maximally 40 minutes, the tACS will be switched off.

Sham tACS

The placebo group will receive sham tACS, using the same device and electrodes positioned over the same location (P3 or P4), which is an inactive form of stimulation during which the patient believes they are being stimulated normally. We will implement sham tACS by ramping down the current immediately after the ramp-up period. This way, the patient feels the ramp up and ramp down (which are the most noticeable in transcranial current stimulation), but does not receive a significant dose of transcranial current stimulation (Paulus et al., 2013).

Sample size estimates

To our knowledge, we are the first to combine an oscillatory-based transcranial brain stimulation protocol (10-Hz tACS) with conventional neglect treatment (VST). Other forms of NIBS (repetitive transcranial magnetic stimulation, rTMS; theta burst stimulation, TBS; transcranial direct current stimulation, tDCS) have indeed been used in combination with neglect treatment previously, but there, however, the rationale was to improve neglect based on conventional theoretical models, which prescribe 're-balancing' activity between the hemispheres, via excitatory stimulation of the under-active injured hemisphere, or inhibition of the hyperactive intact hemisphere, or a combination of both. Since the current study is a conceptually novel approach, we estimated the necessary sample size based on the results of previous neglect studies that combined neglect treatment with NIBS that aimed at such re-balancing in repeated sessions. The review of Van Lieshout and colleagues (2019) reports four such RCT's for which effect sizes are known or could be calculated. Cohen's *d* ranged from 1.07-5.27 in two rTMS studies (Kim et al., 2013; Yang et al., 2015), 1.48-7.14 in two TBS studies (Fu et al., 2015; Yang et al., 2015), and 1.50-2.35 in one tDCS study (Bang & Bong, 2015). In summary, all of the studies showed large effect sizes. Since these previous studies all took place in (sub-)acute patients, in which spontaneous neurological recovery can still occur (Nijboer, Kollen, et al., 2013), we choose an effect size of .80, which is lower than the previously reported range of effect sizes, but which is still commonly considered as a large effect size.

In our study, we will compare the SCT test score before and after the six-week training period. To calculate the required sample size of our study population, we made use of G*Power (version 3.1) (Faul et al., 2007). To find an effect size of d = .80 (Cohen's f = .40), we calculated parameters for a repeated measures ANOVA with a 2x2 design (within-between interaction, two groups, and two testing sessions), a power of .80 and an alpha of .05, which yielded a total required sample size of sixteen patients (eight per group). This is a conservative estimate, as mixed linear modeling, the method we will use to analyze our data, is more powerful than repeated measures ANOVA (Goedert et al., 2013). We choose to set this to 22 patients (eleven per group) because patients may dropout due to the relatively long training period of six weeks (dropout estimated at 25%). The abovementioned RCT's included a comparable number of patients per group (approximately ten per group) and reported significant effects and large effect sizes, so we too expect that our design will have sufficient power, which we confirm with our a priori sample size calculation.

Statistical analyses

The background characteristics of the patients will be described by using descriptive statistics. Baseline characteristics of the intervention and control group will be compared to detect differences at the start of the trial. Linear mixed model regression analyses with random effects for intercept and slope will be used to test for change in the primary and secondary outcome measures both within and between group. The predictors of theoretical interest are the effects of time and group and the interaction between time and group (fixed effects). Baseline score of the outcome measure, time since stroke, gender, and age will be introduced as potential fixed covariates. This is regardless whether or not these variables differ between groups, to enhance the fit of the model. *Post hoc* contrasts will be performed for the interaction between time and group to test differences in treatment effects by intervention group allocation. The intention-to-treat principle is used by including all patients as randomized in the analyses, regardless of whether they received the complete program (dropout, non-adherence). Significance is set to $p < .05$ (two-sided). Analyses will be performed in IBM SPSS Statistics version 26.

Data monitoring committee

No data monitoring committee was set up for this research.

Discussion

One of the most important aspects of tACS is its ability to achieve cortical (brain activity) changes (even outlasting the stimulation) and to be able to put the brain in a state in which the effects of standard treatment can be bigger and/or longer-lasting. Modification of brain activity, by means of cortical stimulation, may improve the patient’s ability to relearn or acquire new strategies for carrying out a behavioral task, by facilitating local activity or by inhibiting maladaptive competing activity from other brain areas (Miniussi et al., 2008). Previous studies have shown that NIBS during or before a learning process may yield behavioral improvements that are more robust and stable (O’Shea et al., 2017; Pascual-Leone, 2006; Rossi & Rossini, 2004). Highly relevant in the context of tACS, is that the effect of tACS depends on the state of the brain (Feurra et al., 2019, 2013; Silvanto et al., 2008), and this state-dependence further offers currently unexplored options such as combining tACS with cognitive-behavioral interventions for synergistic augmentation.

Another strength of this study is that the use of digitized tests and training tasks will allow for a highly precise and detailed data collection, which opens the possibility to assess (subtle) progression on innovative outcome measures during training. Other strengths concern the study design (i.e., randomized and double-blind design), and range of outcome measures (i.e., ADL measures, follow-up assessments).

In the current study, the intervention (VST and active/sham tACS) will be offered by the research team. If proven effective, an exploration of the implementation of a tACS-VST rehabilitation program in chronic stroke care will be necessary, after which tACS-VST could be implemented as a treatment option for VSN.

References

Abd Hamid, A. I., Gall, C., Speck, O., Antal, A., & Sabel, B. A. (2015). Effects of alternating current stimulation on the healthy and diseased brain. *Frontiers in Neuroscience*, *9*(OCT). https://doi.org/10.3389/fnins.2015.00391

Appelros, P., Karlsson, G. M., Seiger, A., & Nydevik, I. (2002). Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. *Journal of Rehabilitation Medicine*, *34*, 215–220.

Azouvi, P., Jacquin-Courtois, S., & Luauté, J. (2017). Rehabilitation of unilateral neglect: Evidence-based medicine. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 191–197. https://doi.org/10.1016/j.rehab.2016.10.006

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 and Rehabilitation*, *84*, 51–57. https://doi.org/10.1053/apmr.2003.50062

Bang, D.-H., & Bong, S.-Y. (2015). Effect of combination of transcranial direct current stimulation and feedback training on visuospatial neglect in patients with subacute stroke: A pilot randomized controlled trial. *Journal of Physical Therapy Science*, *27*(9), 2759–2761. https://doi.org/10.1589/jpts.27.2759

Bien, N., Goebel, R., & Sack, A. T. (2012). Extinguishing extinction: Hemispheric differences in the modulation of TMS-induced visual extinction by directing covert spatial attention. *Journal of Cognitive Neuroscience*, *24*(4), 809–818. https://doi.org/10.1162/jocn_a_00179

Bosma, M. S., Nijboer, T. C. W., Caljouw, M. A. A., & Achterberg, W. P. (2020). Impact of visuospatial neglect post-stroke on daily activities, participation and informal caregiver burden: A systematic review. *Annals of Physical and Rehabilitation Medicine*, *63*(4), 344–358. https://doi.org/10.1016/j.rehab.2019.05.006

Buxbaum, L., Ferraro, M., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., Frassinetti, F., & Coslett, H. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology*, *62*, 749–756. https://doi.org/10.1212/01.wnl.0000113730.73031.f4

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, *34*, 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Dalmaijer, E. S., Van der Stigchel, S., Nijboer, T. C. W., Cornelissen, T. H. W., & Husain, M. (2014). CancellationTools: All-in-one software for administration and analysis of cancellation tasks. *Behavior Research Methods*, *47*(4), 1065–1075. https://doi.org/10.3758/s13428-014-0522-7

Datta, A., Elwassif, M., Battaglia, F., & Bikson, M. (2008). Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. *Journal of Neural Engineering*, *5*(2), 163–174. https://doi.org/10.1088/1741-2560/5/2/007

Duecker, F., Schuhmann, T., Bien, N., Jacobs, C., & Sack, A. T. (2017). Moving beyond attentional biases: Shifting the interhemispheric balance between left and right posterior parietal cortex modulates attentional control processes. *Journal of Cognitive Neuroscience*, *29*(7), 1267–1278. https://doi.org/10.1162/jocn_a_01119

Edgeworth, J. A., MacMillan, T. M., & Robertson, I. H. (1998). *The balloons test manual*. Thames Valley Test Company.

Elshout, J. A., Nijboer, T. C. W., & Van der Stigchel, S. (2019). Is congruent movement training more effective than standard visual scanning therapy to ameliorate symptoms of visuospatial neglect? Study protocol of a randomised control trial. *BMJ Open*, *9*(12). https://doi.org/10.1136/bmjopen-2019-031884

Fasotti, L., & Van Kessel, M. (2013). Novel insights in the rehabilitation of neglect. *Frontiers in Human Neuroscience*, *7*, 1–8. https://doi.org/10.3389/fnhum.2013.00780

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/BF03193146

Feurra, M., Blagoveshchensky, E., Nikulin, V. V., Nazarova, M., Lebedeva, A., Pozdeeva, D., Yurevich, M., & Rossi, S. (2019). State-dependent effects of transcranial oscillatory currents on the motor system during action observation. *Scientific Reports*, *9*(1), 1–11. https://doi.org/10.1038/s41598-019-49166-1

Feurra, M., Pasqualetti, P., Bianco, G., Santarnecchi, E., Rossi, A., & Rossi, S. (2013). State-dependent effects of transcranial oscillatory currents on the motor system: What you think matters. *Journal of Neuroscience*, *33*(44), 17483–17489. https://doi.org/10.1523/JNEUROSCI.1414-13.2013

Fu, W., Song, W., Zhang, Y., Yang, Y., Huo, S., Zhang, R., & Wang, M. (2015). Long-term effects of continuous theta-burst stimulation in visuospatial neglect. *Journal of International Medical Research*, *43*(2), 196–203. https://doi.org/10.1177/0300060513498663

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*, *11*(2), 49–54.

Goedert, K. M., Boston, R. C., & Barrett, A. M. (2013). Advancing the science of spatial neglect rehabilitation: An improved statistical approach with mixed linear modeling. *Frontiers in Human Neuroscience*, *7*(MAY). https://doi.org/10.3389/fnhum.2013.00211

Gould, I. C., Rushworth, M. F., & Nobre, A. C. (2011). Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *Journal of Neurophysiology*, *105*(3), 1318–1326. https://doi.org/10.1152/jn.00653.2010

Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha oscillations correlate with the successful inhibition of unattended stimuli. *Journal of Cognitive Neuroscience*, *23*(9), 2494–2502. https://doi.org/10.1162/jocn.2010.21557

Heilman, K. M., Valenstein, E., & Watson, R. T. (2000). Neglect and related disorders. *Seminars in Neurology*, *20*(4), 463–470. https://doi.org/10.1055/s-2000-13179

Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention: The mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology*, *30*, 327–330.

Jacquin-Courtois, S. (2015). Hemi-spatial neglect rehabilitation using non-invasive brain stimulation: Or how to modulate the disconnection syndrome? *Annals of Physical and Rehabilitation Medicine*, *58*(4), 251–258. https://doi.org/10.1016/j.rehab.2015.07.388

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia*, *50*(6), 1072–1079. https://doi.org/10.1016/j.neuropsychologia.2012.01.024

Kim, B. R., Chun, M. H., Kim, D. Y., & Lee, S. J. (2013). Effect of high- and low-frequency repetitive transcranial magnetic stimulation on visuospatial neglect in patients with acute stroke: A double-blind, sham-controlled trial. *Archives of Physical Medicine and Rehabilitation*, *94*(5), 803–807. https://doi.org/10.1016/j.apmr.2012.12.016

McIntosh, R. D., Ietswaart, M., & Milner, A. D. (2017). Weight and see: Line bisection in neglect reliably measures the allocation of attention, but not the perception of length. *Neuropsychologia*, *106*, 146–158. https://doi.org/10.1016/j.neuropsychologia.2017.09.014

McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research*, *25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., Oliveri, M., Pascual-Leone, A., Paulus, W., Priori, A., & Walsh, V. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimulation*, *1*, 326–336. https://doi.org/10.1016/j.brs.2008.07.002

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Neuling, T., Rach, S., & Herrmann, C. S. (2013). Orchestrating neuronal networks: Sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00161

Nijboer, T. C. W., Kollen, B. J., & Kwakkel, G. (2013). Time course of visuospatial neglect early after stroke: A longitudinal cohort study. *Cortex*, *49*(8), 2021–2027. https://doi.org/10.1016/j.cortex.2012.11.006

Nijboer, T. C. W., Kollen, B. J., & Kwakkel, G. (2014). The impact of recovery of visuo-spatial neglect on motor recovery of the upper paretic limb after stroke. *PLoS ONE*, *9*(6). https://doi.org/10.1371/journal.pone.0100584

Nijboer, T. C. W., Van de Port, I., Schepers, V., Post, M., & Visser-Meily, A. (2013). Predicting functional outcome after stroke: The influence of neglect on basic activities in daily living. *Frontiers in Human Neuroscience*, *7*, 1–6. https://doi.org/10.3389/fnhum.2013.00182

O'Shea, J., Revol, P., Cousijn, H., Near, J., Petitet, P., Jacquin-Courtois, S., Johansen-Berg, H., Rode, G., & Rossetti, Y. (2017). Induced sensorimotor cortex plasticity remediates chronic treatment-resistant visual neglect. *ELife*, *6*, 1–38. https://doi.org/10.7554/eLife.26602.001

Pascual-Leone, A. (2006). Disrupting the brain to guide plasticity and improve behavior. In A. R. Moller (Ed.), *Progress in Brain Research* (Vol. 157, pp. 315–331). Elsevier. https://doi.org/10.1016/S0079-6123(06)57019-0

Paulus, W., Antal, A., & Nitsche, M. A. (2013). Physiological basis and methodological aspects of transcranial electric stimulation (tDCS, tACS, and tRNS). In C. Miniussi, W. Paulus, & P. Rossini (Eds.), *Transcranial Brain Stimulation* (pp. 93–111). CRC Press.

Pizzamiglio, L., Antonucci, G., Judica, A., Montenero, P., Razzano, C., & Zoccolotti, P. (1992). Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral right brain damage. *Journal of Clinical and Experimental Neuropsychology*, *14*(6), 901–923. https://doi.org/10.1080/01688639208402543

Priftis, K., Passarini, L., Pilosio, C., Meneghello, F., & Pitteri, M. (2013). Visual scanning training, limb activation treatment, and prism adaptation for rehabilitating left neglect: Who is the winner? *Frontiers in Human Neuroscience*, *7*, 1–12. https://doi.org/10.3389/fnhum.2013.00360

Robertson, I. H., Tegnér, R., Tham, K., Lo, A., & Nimmo-Smith, I. (1995). Sustained attention training for unilateral neglect: Theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology*, *17*(3), 416–430. https://doi.org/10.1080/01688639508405133

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., & Perenin, M.-T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature*, *395*, 166–169. https://www.nature.com/articles/25988

Rossi, S., & Rossini, P. M. (2004). TMS in cognitive plasticity and the potential for rehabilitation. *Trends in Cognitive Sciences*, *8*(6), 273–279. https://doi.org/10.1016/j.tics.2004.04.012

Saevarsson, S., Halsband, U., & Kristjánsson, Á. (2011). Designing rehabilitation programs for neglect: Could 2 be more than 1+1? *Applied Neuropsychology*, *18*(2), 95–106. https://doi.org/10.1080/09084282.2010.547774

Saghaei, M., & Saghaei, S. (2011). Implementation of an open-source customizable minimization program for allocation of patients to parallel groups in clinical trials. *Journal of Biomedical Science and Engineering*, *04*(11), 734–739. https://doi.org/10.4236/jbise.2011.411090

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W. R., & Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917–2926. https://doi.org/10.1111/j.1460-9568.2005.04482.x

Schenkenberg, T., Bradford, D., & Ajax, E. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509–517. https://doi.org/10.1212/wnl.30.5.509

Schuhmann, T., Duecker, F., Middag-van Spanje, M., Gallotto, S., Van Heugten, C., Schrijnemaekers, A. C., Van Oostenbrugge, R., & Sack, A. T. (2022). Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. *International Journal of Clinical and Health Psychology*, *22*(3). https://doi.org/10.1016/j.ijchp.2022.100326

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *PLoS ONE*, *14*(11), 1–25. https://doi.org/10.1371/journal.pone.0217729

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences*, *12*(12), 447–454. https://doi.org/10.1016/j.tics.2008.09.004

Smania, N., Bazoli, F., Piva, D., & Guidetti, G. (1997). Visuomotor imagery and rehabilitation of neglect. *Archives of Physical Medicine and Rehabilitation*, *78*, 430–436.

Ten Brink, A. F., Van Kessel, M. E., & Nijboer, T. C. W. (2017). Neglect. In C. Van Heugten, D. Bertens, & J. Spikman (Eds.), *Richtlijn Neuropsychologische Revalidatie* (pp. 1–92). Nederlands Instituut van Psychologen. www.psynip.nl

Ten Brink, A. F., Visser-Meily, J. M. A., Schut, M. J., Kouwenhoven, M., Eijsackers, A. L. H., & Nijboer, T. C. W. (2017). Prism adaptation in rehabilitation? No additional effects of prism adaptation on neglect recovery in the subacute phase poststroke: A randomized controlled trial. *Neurorehabilitation and Neural Repair*, *31*(12), 1017–1028. https://doi.org/10.1177/1545968317744277

Ten Brink, A., Nijboer, T., Van Beekum, L., Van Dijk, J., Peeters, R., Post, M., & Visser, J. (2013). De Nederlandse Catherine Bergego schaal: Een bruikbaar en valide instrument in de CVA-zorg. *Wetenschappelijk Tijdschrift Voor Ergotherapie*, *6*(3), 27–36.

Tham, K. (1996). The Baking Tray Task: A test of spatial neglect. *Neuropsychological Rehabilitation*, *6*(1), 19–26. https://doi.org/10.1080/713755496

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/jneurosci.0875-06.2006

Towle, D., & Lincoln, N. B. (1991). Development of a questionnaire for detecting everyday problems in stroke patients with unilateral visual neglect. *Clinical Rehabilitation*, *5*, 135–140. https://doi.org/10.1177/026921559100500208

Van Kessel, M. E., Geurts, A. C. H., Brouwer, W. H., & Fasotti, L. (2013). Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task. *Frontiers in Human Neuroscience*, *7*, 1–11. https://doi.org/10.3389/fnhum.2013.00358

Van Lieshout, E. C. C., Van Hooijdonk, R. F., Dijkhuizen, R. M., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2019). The effect of noninvasive brain stimulation on poststroke cognitive function: A systematic review. *Neurorehabilitation and Neural Repair*, *33*(5), 355–374. https://doi.org/10.1177/1545968319834900

Verhoeven, C. L. M., Post, M. W. M., Schiemanck, S. K., Van Zandvoort, M. J. E., Vrancken, P. H., & Van Heugten, C. M. (2011). Is cognitive functioning 1 year poststroke related to quality of life domain? *Journal of Stroke and Cerebrovascular Diseases*, *20*(5), 450–458. https://doi.org/10.1016/j.jstrokecerebrovasdis.2010.02.018

Weintraub, S., & Mesulam, M.-M. (1985). Mental state assessment of young and elderly adults in behavioral neurology. In M.-M. Mesulam (Ed.), *Principles of behavioral neurology* (pp. 71–123). F.A. Davis company.

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). Development of a behavioral test of visuospatial neglect. *Archives of Physical Medicine and Rehabilitation*, *68*(2), 98–102.

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience*, *20*(6), 1–6. https://doi.org/10.1523/jneurosci.20-06-j0002.2000

Yang, W., Liu, T. T., Song, X. Bin, Zhang, Y., Li, Z. H., Cui, Z. H., Hao, Q., Liu, H. L., Lei, C. L., & Liu, J. (2015). Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. *Journal of the Neurological Sciences*, *359*(1–2), 219–225. https://doi.org/10.1016/j.jns.2015.08.1541

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE*, *5*(11), e13766. https://doi.org/10.1371/journal.pone.0013766

Chapter 6

Alpha transcranial alternating current stimulation as add-on to neglect training: A randomized trial

Corresponding manuscript:

Middag-van Spanje, M., Nijboer, T. C. W., Schepers, J., Van Heugten, C., Sack, A. T., & Schuhmann, T. (2024). Alpha transcranial alternating current stimulation as add-on to neglect training: A randomized trial. *Brain Communications, 6*(5). https://doi.org/10.1093/braincomms/fcae287

Abstract

Visuospatial neglect (VSN) is a common and debilitating condition following unilateral stroke, significantly impacting cognitive functioning and daily life. There is an urgent need for effective treatments that can provide clinically relevant and sustained benefits. In addition to traditional stroke treatment, non-invasive brain stimulation, such as transcranial alternating current stimulation (tACS), shows promise as a complementary approach to enhance stroke recovery. In the current study, we aimed to evaluate the additive effects of multi-session tACS at alpha frequency when combined with visual scanning training (VST) in chronic stroke patients with VSN. In this double-blind randomized controlled trial, we compared the effects of active tACS at alpha frequency to sham (placebo) tACS, both combined with VST. Both groups received eighteen 40-minute training sessions over a six-week period. A total of 22 chronic VSN patients participated in the study (active group n = 12, sham group n = 10). The median age was 61.0 years, with a median time since stroke of 36.1 months. We assessed the patients at six time-points: at baseline, after the first, ninth and eighteenth training sessions, as well as one week and three months following the completion of the combined neuromodulation intervention. The primary outcome measure was the change in performance on a visual search task, specifically the star cancellation task. Secondary outcomes included performance on a visual detection task, two line bisection tasks, and three tasks evaluating VSN in daily living. We found significantly improved visual search (primary outcome) and visual detection performance in the neglected side in the active tACS group, compared to the sham tACS group. We did not observe stimulation effects on line bisection performance nor in daily living. Time effects were observed on all but one outcome measures. Multi-session tACS combined with VST may be a more effective treatment for chronic VSN than VST alone. These findings provide valuable insights into novel strategies for stroke recovery, even long after the injury, with the aim of enhancing cognitive rehabilitation outcomes and improving the overall quality of life for individuals affected by this condition.

Introduction

Visuospatial attention allows us to select and prioritize input from specific locations in space of our visual environment. In patients with visuospatial neglect (VSN), lateralized spatial attention processes are disrupted, usually due to unilateral stroke, leading to the inability to attend and respond to the contralesional side of space (Buxbaum et al., 2004; Heilman et al., 2000). While spontaneous neuronal recovery occurs in many VSN patients (Nijboer et al., 2018), up to 40% of patients continue to experience neglect symptoms even up to 1 year post-stroke (Nijboer et al., 2013). VSN is a strong predictor of poor functional recovery and significantly impairs activities of daily living (ADL) (Bosma et al., 2023; Di Monaco et al., 2011; Embrechts et al., 2021; Stone et al., 1992). As such, adequate treatment of neglect is of utmost importance.

In recent decades, a wide range of rehabilitation methods has emerged to attenuate neglect symptoms, spanning from those that enhance awareness of neglect behavior through a top-down approach to those involving a low-level bottom-up approach with many trials and few therapeutic-guided cueing (Azouvi et al., 2017). Current neglect treatment guidelines primarily recommend behavioral compensation-based approaches such as visual scanning training (VST) (Pizzamiglio et al., 1992), aimed at improving viewing and searching behavior through top-down strategies (Van Kessel et al., 2013); yet, the supporting evidence for these methods remains limited (Azouvi et al., 2017; Kerkhoff & Schenk, 2012; Longley et al., 2021). However, it should be noted that the review by Longley and colleagues (2021) ignores crossover design studies thereby not giving a full picture of all existing studies. In past years, noninvasive brain stimulation (NIBS) techniques have been explored as a potential rehabilitation tool aimed at directly modulating brain network activity implicated in visuospatial processing. NIBS techniques in rehabilitation treatment are often based on the interhemispheric rivalry model proposed by Kinsbourne (1977), typically utilizing inhibitory stimulation protocols to reduce contralesional cortical excitability and restore interhemispheric balance in VSN patients. Yet, while promising, reported clinical effects of these NIBS interventions for VSN have remained small and heterogeneous (Elsner et al., 2020; Lefaucheur et al., 2020; Longley et al., 2021).

Recently, researchers have focused on NIBS techniques that utilize oscillatory-based neural entrainment, capable of modulating the intrinsic brain rhythms associated with brain network communication. Transcranial alternating current stimulation (tACS) has gained attention for its ability to entrain or synchronize neural oscillations. This entrainment significantly enhances the coherence and power of these oscillations, thereby influencing associated network communications, cognitive processes and behavior (Lakatos et al., 2019; Wischnewski et al., 2023).

To comprehend the association between oscillatory frequencies and cognitive processes, neuroimaging techniques such as electroencephalography (EEG) have proven invaluable. In the realm of attention, EEG studies in healthy participants have shown that posterior oscillatory activity within the alpha range (8-12 Hz) is crucially involved in the mechanisms underlying the control of visuospatial attention (Gould et al., 2011; Händel et al., 2011; Sauseng et al., 2005; Schuhmann et al., 2019; Thut et al., 2006; Worden et al., 2000). Voluntary shifts of attention toward one visual field are associated with oscillatory alpha lateralization in parieto-occipital areas. For example, shifting attention to the right hemifield is accompanied by alpha power decreases in the left hemisphere and alpha power increases in the right hemisphere. The successful tACS-induced modulation of alpha power lateralization in healthy individuals including corresponding improvements in visuospatial attention (Kasten et al., 2020; Kemmerer, Sack, et al., 2022; Radecke et al., 2023; Schuhmann et al., 2019), indicate that such an entrainment-based neuromodulation approach may also represent a novel treatment approach for patients suffering from asymmetric attentional deficits like VSN. It must be mentioned here that several other previous experiments have reported no or inconsistent effects (Coldea et al., 2021; Van Schouwenburg et al., 2018; Veniero et al., 2017).

We recently put this oscillation-based NIBS intervention to the test in subacute stroke patients suffering from VSN, and were able to reduce the spatial attention bias with tACS at alpha frequency targeting the contralesional posterior parietal cortex in a single session (Schuhmann et al., 2022). Besides immediate stimulation effects, we were also able to show that effects were outlasting the stimulation itself, suggesting that our approach qualifies for a clinical treatment protocol aimed at achieving longer lasting and sustainable clinically relevant improvements. It is likely that long-term benefits would require a multi-session multi-day protocol, like is demonstrated in depression treatment with rTMS (Perera et al., 2016), but to this day the cumulative effects of multi-session tACS remain largely unknown as extended human trials with tACS are lacking (Wischnewski et al., 2023).

Importantly, when designing clinical protocols using neuromodulation techniques, one should consider that one of the most compelling aspects of tACS is its capacity to support neuroplasticity. As such, it induces a brain state at which the effects of other treatments are facilitated, potentially amplifying both the magnitude and duration of its benefits (Wischnewski et al., 2023). The impact of tACS on the local neural entrainment is contingent upon the state of the brain (Kasten & Herrmann, 2022; Neuling et al., 2013), as brain networks tend to be more responsive when they are already in an active state. For example when the targeted brain rhythm is already task-engaged and the frequency and phase of endogenous and exogenous oscillations align (Nguyen et al., 2018; Wischnewski et al., 2023). Thus, neuronal plasticity induced by stimulation could be stronger when patients are currently active in a spatial training task. Therefore, to prime the brain for optimal learning conditions and to optimize the outcomes of the treatment, it is important that required attentional networks are activated through attention task performance (VST), executed concurrently with the application of tACS.

In the current study, we therefore combined tACS at alpha frequency with VST rehabilitation in a multi-session protocol, offered three times a week for six weeks (eighteen sessions). The overall aim was to evaluate the additive effects of multi-session (active) tACS in combination with VST, compared to multi-session sham (placebo) tACS with VST, in chronic VSN patients. Effects were measured on a cancellation task (primary outcome), a visual detection task, two line bisection tasks, and on three measures assessing VSN behavior in basic ADL. Based on our previous work, we expected to achieve a synergistic effect in which tACS strengthens the efficacy of other neurobehavioral interventions, such as VST, and potentially lead to long-lasting benefits (Wischnewski et al., 2023).

Materials and methods

Study design

A double-blind randomized placebo-controlled intervention study with an allocation ratio of 1:1 was conducted. We compared the effects of active tACS to sham tACS, both combined with VST. Written informed consent was obtained from each participant by the researcher before participation. The study was approved by the Medical-Ethical Committee azM/UM of Maastricht University (NL70256.068.19 / METC 19-047) and is registered at ClinicalTrials.gov (NCT05466487). More specific information of the methodology of the study can be obtained from our protocol paper published earlier (Middag-van Spanje et al., 2022). At the time of registration (July 2022), thirteen out of 22 patients had already participated in the study.

Participants

Chronic stroke patients, as defined by stroke occurrence more than six months ago, with VSN were considered eligible for our study. Patients were recruited by psychologists of healthcare organizations in The Netherlands that are specialized in supporting and treating people with acquired brain injury. Recruitment of participants started in September 2020 and data collection ended in March 2023.

Inclusion criteria were: 1) neurologically objectified stroke (first or recurrent, ischemic or intracerebral or subarachnoid haemorrhagic lesion); 2) stroke occurred at 18-80 years of age; 3) at least six months ago; 4) sufficient ability to comprehend and communicate as assessed by a psychologist; and 5) presence of VSN as confirmed with a screening (see screening tests and associated cut-off criteria in **Supplementary Table 1**). Exclusion criteria were: 1) current engagement in cognitive rehabilitation treatment or other neglect treatment to avoid potential cross-contamination; 2) physically or mentally unable to participate as assessed by a psychologist; 3) presence of hemianopia based on clinical judgment; 4) severe communicative disability as task descriptions need to be understood; 5) local scalp injuries; 6) eczema on scalp or psoriasis; 7) diagnosed (neuro)psychiatric or neurodegenerative diseases; 8) current alcohol and/or drug abuse; and 9) pregnancy. Excluding patients with hemianopia means that it is possible that there was a stronger focus on more restricted middle cerebral artery strokes, primarily located outside the temporal lobe (due to the presence of the optic radiations there; Rodrigues et al., 2022) and the inferior parts of the parietal lobe.

We determined the required sample size based on the results of previous studies that combined VSN treatment with NIBS in repeated sessions (Bang & Bong, 2015; Fu et al., 2015; Kim et al., 2013; Yang et al., 2015). Following an a priori power analysis with effect size of d = .80 and power of .80, and taking into consideration a drop-out estimated at 25%, a total sample size of 22 patients was necessary (Middag-van Spanje et al., 2022).

Interventions

Transcranial alternating current stimulation

The experimental group received active tACS and the placebo group received sham tACS using a DC-stimulator plus (NeuroConn, Ilmenau, Germany). A small circular tACS electrode was placed onto the contralesional parietal cortex (either P3 or P4, according to the international 10-20 system), and a large ring electrode was centered around it. TACS ring electrodes were attached to the patient's head with conductive gel (ten20 paste, Weaver and Company, Aurora, CO, USA). The gel was used to reduce the impedance between skin and electrodes to below 10 kΩ. Stimulation frequency and peak-to-peak intensity was set to 10 Hz and 1.5 mA, phase offset was set to 0 and 100 cycles was used for ramping up. **Figure 1** illustrates the size and position of the electrodes on the scalp as well as a current simulation for the electrode montage.

At the start of every first VST task in a session, the tACS device was turned on. When the VST ended, after maximally 40 minutes, the tACS was switched off. For sham tACS, we used the same electrode montage and stimulation frequency as for active tACS, but the current was immediately ramped down after the ramp-up period.

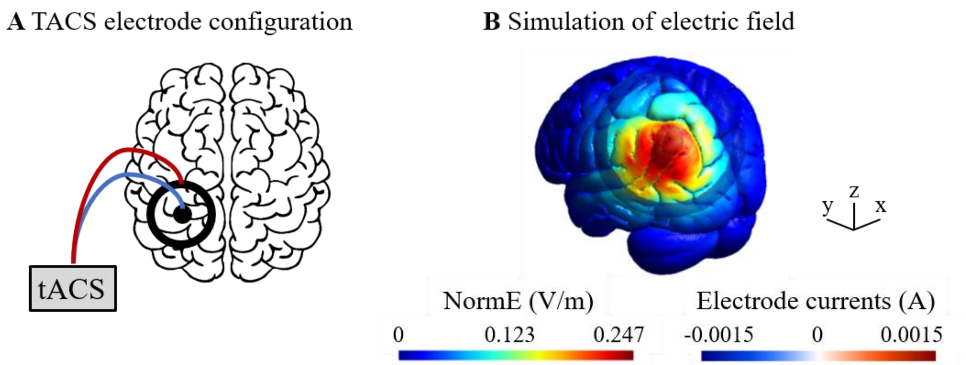

Figure 1 TACS electrode montage and simulation of the electric field. **(A)** A small circular tACS electrode (diameter: 2.1 cm, thickness: 2 mm) was placed onto the contralesional parietal cortex (either P3 or P4, according to the international 10-20 system), and a large ring electrode (outer diameter: 11 cm; inner diameter: 9 cm, thickness: 2 mm) was centered around it. **(B)** Simulation of the electric field in a standard head model (MNI 152 space). The software SimNIBS was used to run the simulation. Abbreviations: A, ampere; normE, norm electric field; tACS, transcranial alternating current stimulation; V/m, volt per meter.

Visual scanning training

In every session, patients performed the VST on a touchscreen laptop (HP EliteBook x360 1040 G5 Notebook; screen size: 14 inch). The aim of the VST was to train patients to actively explore and consciously pay attention to stimuli on the contralesional side (Middag-van Spanje et al., 2022; Pizzamiglio et al., 1992). The VST program comprised eight evidence-based training tasks (Middag-van Spanje et al., 2022). In these tasks, while predominantly employing top-down techniques relying on a voluntary effort from the patient, bottom-up elements such as exogenous cues were also integrated if the patient showed difficulty in initiating head and eye movements. Each session featured a variable combination of three to five tasks, depending on the patient's speed and performance. Tasks were designed with multiple levels of difficulty, ensuring task difficulty aligned with the patient's level of performance, as individuals varied substantially in their capabilities and neglect severity. This allowed for individualized sessions, with different tasks to be conducted in each session, ultimately ensuring that all tasks were covered over multiple sessions.

Primary outcome measure: star cancellation task (SCT)

The SCT consisted of 52 large stars, thirteen letters, and ten short words interspersed with 56 smaller stars (Wilson et al., 1987), presented on a laptop screen. The patient was instructed to mark all targets (small stars) by touching the screen with the finger. The quality of search (QoS) score combines accuracy and speed in a single measure (i.e., optimal accuracy/speed search ratio; see formula in **Supplementary Table 2**) (Dalmaijer et al., 2014). A high score reflects a combination of a high number of crossed out targets and a high cancellation speed (Dalmaijer et al., 2014).

Secondary outcome measures

Computerized visual detection task (CVDT)

The CVDT measures perceptual sensitivity and attentional selection in each hemifield (Bien et al., 2012; Duecker et al., 2017; Schuhmann et al., 2022, 2019). The patient was asked to fixate on the fixation cross at the center of the laptop screen. Gabor patches were presented to the left, right and bilateral sides of the screen (40 trials per location) and the patient had to indicate the location of the stimulus by pressing the <, >, or ∨ key, respectively. For each of the three locations independently, the contrast of the stimuli was adaptively changed on a trial-by-trial basis. For (offline) analysis, correct hits were weighted by the contrast level (see formula in **Supplementary Table 2**) and performance of the CVDT was the sum of weighted hits per condition (ipsilesional, contralesional, bilateral), resulting in a score of 0 to 76.49 per condition. As we expected attention deficits in the contralesional hemifield

(Schuhmann et al., 2022), our primary focus was directed toward the analyses of the contralesional and bilateral conditions and we only briefly reported on the ipsilesional condition. In the bilateral condition, the score depends on performance in both contralesional and ipsilesional hemifields.

McIntosh line bisection task-digitized (MLBT-d)

The MLBT-d was used to measure the so-called endpoint weightings bias (EWB), a measure of lateral asymmetry (McIntosh et al., 2017, 2005). There were eight repetitions of each of four unique lines, presented in a fixed-random order on the laptop screen. The patient was instructed to mark the subjective midpoint of each line by touching the screen with the finger. The analysis then focuses on how this response position varies from trial-to-trial as a consequence of changes in the left endpoint and changes in the right endpoint (see formulas in **Supplementary Table 2**). An EWB value above 0 indicates a greater influence of the right endpoint (over the left), and would be a sign for left-sided neglect.

Schenkenberg line bisection task (SLBT)

The SLBT consisted of twenty horizontal lines, varying from ten to twenty cm in length, at three different positions (left, middle, right) on a landscape-oriented A4 sheet (Schenkenberg et al., 1980). The patient was asked to mark their perceived midpoint of each line. The relative deviation scores were then calculated (see formula in **Supplementary Table 2**) and were averaged per line position to generate the left, middle, and right average scores. We analyzed only the lines positioned on the contralesional side as we expected worst performance there.

Daily living tasks

Baking tray task (BTT)

The patient was asked to distribute sixteen cubes of 3.5 cm as evenly as possible over a 75 x 100 cm board (as if spreading out buns on a baking tray) (Tham, 1996). The entire board was scanned using the Microsoft Lens iOS app. Coordinates of all cubes were manually identified using a custom Python script. An average positive x-coordinate indicates a rightward bias.

Catherine Bergego scale (CBS)

The CBS is a ten-item observation scale for measuring VSN severity in ADL, and results in a total score of 0 (no neglect) to 30 (severe neglect) (Azouvi et al., 2003; Ten Brink et al., 2013). The CBS was filled out by the patient's therapist or proxy (partner or caregiver), but we only considered data from forms completed by therapists, as intended. In case < 50% of the items of the CBS were observed, the total score was considered not reliable and therefore a missing value.

Subjective neglect questionnaire (SNQ)

The SNQ is a nineteen-item questionnaire for measuring the presence of common problems associated with VSN (Towle & Lincoln, 1991). The SNQ is scored on a five-point scale according to the frequency of the occurrence of the difficulty, resulting in a score of 19 (no reported problems) to 95 (many/frequently reported problems) (Van Kessel et al., 2013). The SNQ was administered to patients and proxies, but our analysis was based exclusively on forms completed by patients, as intended. In case < 50% of the items of the SNQ were filled out, the total score was considered not reliable and therefore a missing value.

Demographic and injury characteristics

Baseline descriptors were collected, including demographics (age, gender, and educational level), stroke characteristics (time post-stroke onset, stroke history, stroke type, and lesion side), and global cognitive functioning as measured by the Montreal Cognitive Assessment (MoCA version 8.1; Nasreddine et al., 2005).

Procedure

Eligible patients who met the inclusion criteria were identified by psychologists. After informed consent was given, baseline measurements were performed. Included patients were then randomly assigned to either the experimental or placebo group and received eighteen training sessions spread over six weeks (i.e., three sessions per week). The training sessions (including tACS and VST) were offered by the researchers at the patients' homes. The researchers tested the patients six times on an array of tasks: at baseline (T0), after the first (T1), ninth (T2), and eighteenth (T3) training session, as well as one week (T4) and three months (T5) after termination of the training. The SCT, CVDT, MLBT-d, and SLBT were assessed during all six assessments in the study (T0-T5). The BTT, CBS, and SNQ were administered at four assessments (T0, T2, T4, and T5). The SCT, CVDT, and MLBT-d were presented on the same touchscreen laptop as was used for the training. PsychoPy was used to control stimulus presentation and recording of behavioral responses.

Blinding, randomization and treatment allocation

Researchers, therapists and patients were blinded to treatment allocation. We applied minimization as randomization method, using MinimPy (Saghaei & Saghaei, 2011). Patients were stratified according to age, gender, and having had previous neglect treatment. To double-blind the tACS protocols, the ‘study mode’ of the NeuroConn DC Stimulator (neuroConn GMBH) was implemented using five-digit codes that either initiated the preprogrammed active stimulation protocol or the sham protocol. There was only one unblinded research assistant who assigned a unique code to every enrolled patient and sent the code to the (blinded) researchers who then carried out all other study procedures (including the interventions and assessments). The unblinded research assistant was not further involved in the study. Blinding was removed after data analysis was finalized.

Statistical analyses

Chi-square ($\chi 2$) and nonparametric Mann-Whitney tests were used to compare demographic and stroke-related characteristics between both groups. Baseline performance on neglect outcome variables was compared with a *t* test or Mann-Whitney test where appropriate, to detect differences at the start of the trial. To study any associations between the outcome variables, we conducted correlation analyses at T0 and at T5.

To test for change in the primary and secondary outcome measures both within and between groups, linear mixed model regression analysis was used, with a spatial power covariance structure to account for (time-decaying) residual covariance between repeated measures and a random intercept for patients. The predictors of interest were the effects of time and the interaction between time and group (fixed effects). We tested linear, quadratic, and cubic effects of time, although conceptually the latter was not expected to be plausible. Gender, age, and time since stroke were introduced as potential fixed covariates. A maximum likelihood estimation was used in the process of model selection. We started by focusing on potential removal of higher order interactions between group and time, and higher order effects of time, and finally the covariates. Terms were removed from the model if $p > .05$. The coefficients (and their tests) of the final model are reported per outcome measure, based on restricted maximum likelihood estimation. Supplementary *post hoc* contrasts with Bonferroni correction were performed to probe the interaction between time and group by testing differences between groups at specific time-points. As the actual time-points (in days) of measurement vary between patients, we used the mean number of days (across participants) since baseline (T0) to determine the time-points of interest.

The intention-to-treat principle was used by including all patients as randomized in the analyses, regardless of whether they received the complete program. In the context of mixed-model analysis, it is important to note there is no case-wise deletion, but all available data is incorporated. Alpha was set to .05. Analyses were performed in IBM SPSS Statistics version 26. Besides the correlation analyses, other analyses were preregistered (Middag-van Spanje et al., 2022).

Results

Patient characteristics

A total of 125 VSN patients were recruited by the healthcare organizations (**Figure 2**). Forty-two patients were screened for inclusion, of whom 22 were included in the study. **Supplementary Table 3** depicts the patients' performances on each screening test on the basis of which they were admitted to the study. The median age of the study sample was 61.0 years and 72.7% ($n = 16$) was male. Of the 22 included patients, ten were randomly assigned to the sham group and twelve to the active tACS group (**Table 1**). Three patients in the active tACS group terminated participation prematurely as a result of illness ($n = 2$) or mismatched expectations of the program ($n = 1$), and two patients in the sham group did not perform assessments at T1, both due to fatigue. **Figure 2** depicts the remaining number of patients included in each assessment.

The two groups were not significantly different with respect to demographic and stroke-related characteristics (all p values > .165, **Table 1**). Also, baseline scores on neglect outcome variables were comparable between groups, except for the BTT scores where patients in the active tACS group scored significantly lower (i.e., better performance) at baseline compared to patients in the sham group. Raw mean scores for all assessments (T0-

T5) are shown in **Supplementary Table 4**. Results of the correlation analyses between the outcome variables are shown in **Supplementary Table 5**.

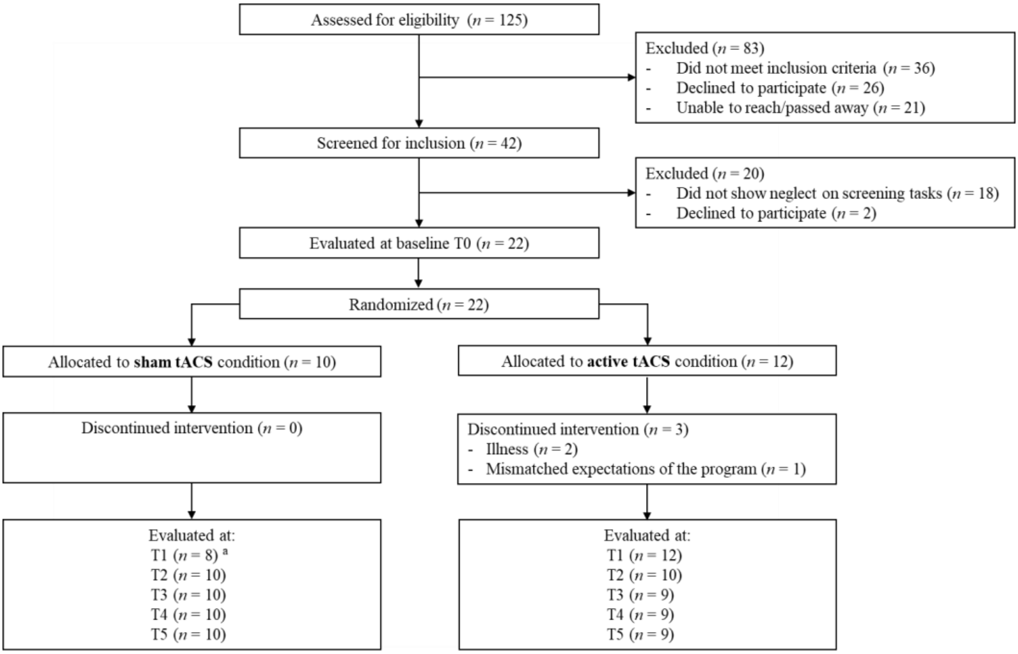

Figure 2 Patient flow through the study. Assessments took place before the training (T0, baseline), after the first (T1), ninth (T2), and eighteenth (T3) training session, as well as one week (T4) and three months (T5) after the end of the training. [a] Two patients did not perform assessments at T1, due to fatigue. Abbreviation: tACS, transcranial alternating current stimulation.

Table 1 Baseline demographic, and stroke- and neglect-related characteristics.

	Sham tACS		Active tACS		Comparison
	n	Median (IQR)	*n*	Median (IQR)	
Demographics					
Age, years	10	61.00 (12.50)	12	61.00 (20.50)	U = 52.00, z = -0.528, p = 0.597
Gender, % male	10	70	12	75	p = 1.000 [a]
Educational level, Verhage (0-7)	10	6.00 (1.25)	12	4.50 (2.00)	U = 40.50, z = -1.389, p = 0.165
Stroke characteristics					
Time post-stroke onset, months	10	31.80 (55.82)	12	39.88 (116.86)	U = 52.00, z = -0.528, p = 0.598
Stroke history, % first ever	10	80	12	67	p = 0.646 [a]
Stroke type, %					$\chi 2$ = 0.76, df = 2, p = 0.683
Ischemic	10	60	12	75	
Intracerebral hemorrhage	10	20	12	17	
Subarachnoid hemorrhage	10	20	12	8	
Stroke side, % right	10	100	12	100	N/A
Neglect side, % left	10	100	12	100	N/A
MoCA (0-30)	10	23.50 (4.75)	12	24.00 (5.50)	U = 42.50, z = -1.163, p = 0.245
Neglect characteristics					
Previous neglect treatment, % yes	10	80	12	83	p = 1.000 [a]
Neglect variables at baseline					
SCT					
Misses on contralesional side of screen	10	2.50 (19)	12	1.50 (3)	U = 49.50, z = -0.707, p = 0.479
CVDT, weighted hits					
Contralesional condition	10	6.50 (21.48)	11	10.00 (15.01)	U = 53.00, z = -0.141, p = 0.887
Bilateral condition	10	0.50 (11.48)	11	5.00 (10.90)	U = 35.00, z = 1.437, p = 0.151
SNQ (19-95)	10	34.03 (14.50)	11	29.86 (32.99)	U = 40.00, z = -1.06, p = 0.29
	n	Mean (SD)	*n*	Mean (SD)	
SCT					
QoS for contralesional side of screen	10	0.44 (0.32)	12	0.67 (0.47)	$t(20)$ = 1.293, p = 0.211
MLBT-d, EWB	10	0.25 (0.18)	12	0.23 (0.18)	$t(20)$ = 0.34, p = 0.735
SLBT, % deviation of contralesional lines	10	23.93 (20.39)	12	21.30 (14.67)	$t(20)$ = 0.35, p = 0.729
BTT, mean x-coordinate	10	0.13 (0.11)	11	0.02 (0.08)	$t(19)$ = 2.72, p = 0.014
CBS (0-30)	7	10.98 (9.13)	6	10.46 (6.94)	$t(11)$ = 0.112, p = 0.913

[a] Fisher's exact test (two-tailed) is reported when assumptions of $\chi 2$ have been violated. Abbreviations: BTT, baking tray task; CBS, Catherine Bergego scale; CVDT, computerized visual detection task; EWB, endpoint weightings bias; IQR, interquartile range; MLBT-d, McIntosh line bisection task-

digitized; MoCA, Montreal Cognitive Assessment; N/A, not applicable; QoS, quality of search; SCT, star cancellation task; SLBT, Schenkenberg line bisection task; SNQ, subjective neglect questionnaire.

Primary outcome: QoS (SCT)

We derived the QoS score for the contralesional side of the screen. The final regression model (**Table 2**) included a linear interaction between group and time ($F(1, 96) = 5.527$, $p = .021$), but not a quadratic ($F(1, 98) = .158$, $p = .692$) nor a cubic ($F(1, 99) = 2.756$, $p = .100$) group by time interaction. The significant group by time interaction indicates that the time effect was significantly different between the active group and the sham group (**Figure 3**). To conduct supplementary contrast tests of mean treatment differences at specific time-points, the mean number of days (across participants) since baseline was used to determine the time-points (in days) of interest: day 0 (baseline), day 4, day 24, day 46, day 53, and day 138. These contrasts showed a significant higher mean QoS at day 138 in the active tACS group compared to sham ($t(33) = 2.532$, $p = .016$; p values at all other time points were $\geq .092$). As can be seen in **Figure 3**, both groups showed initial improvement in QoS performance (day 0 – day 53); but in the sham group, this was followed by a decline in scores (day 53 – day 138). Although further enhancement stagnated, overall, the active group showed significantly more improvement compared to the sham group.

For the sake of completeness, we conducted a second analysis for the ipsilesional side of the screen, revealing no group by time interaction (p values for linear, quadratic, and cubic functions $\geq .655$). This outcome aligns with the underlying theory of our interventional approach, which predicts that contralesional stimulation does not affect (or negatively affects) performance in the ipsilesional side compared to sham stimulation. The final model is depicted in **Supplementary Table 6**.

Note that **Figures 3 and 4** plot model-predicted means, and not observed means, since the actual time-points (days) of measurement vary between patients (i.e., unbalanced longitudinal data).

Table 2 Final model of fixed-effect predictors and covariates for predicting primary and secondary outcomes.

Predictor	β [a]	SE_{β}	95% CI lower bound	95% CI higher bound	*p* value
QoS, contralesional side of screen (SCT) across T0 to T5 (*n* = 22)					
Time	0.001	0.001	2.84E-04	0.003	0.016
Group	-0.161	0.155	-0.482	0.160	0.310
Group x Time	-0.002	0.001	-0.004	-3.12E-04	0.021
Weighted hits, contralesional condition (CVDT) across T0 to T5 (*n* = 21)					
Time	0.032	0.018	-0.005	0.069	0.088
Group	-1.370	3.322	-8.257	5.517	0.684
Group x Time	-0.074	0.026	-0.126	-0.023	0.005
Gender	-9.420	3.482	-16.747	-2.094	0.015
Weighted hits, bilateral condition (CVDT) across T0 to T5 (*n* = 21)					
Time	0.198	0.050	0.098	0.297	< .001
Time x Time	-0.001	3.22E-04	-0.002	-3.06E-04	0.005
Group	-2.130	4.621	-11.750	7.490	0.650
Group x Time	-0.071	0.027	-0.124	-0.017	0.010
Gender	-14.148	4.977	-24.581	-3.715	0.011
EWB (MLBT-d) across T0 to T5 (*n* = 22)					
Time	-0.002	0.001	-0.003	-2.92E-04	0.018
Time x Time	1.08E-05	4.51E-06	1.77E-06	1.99E-05	0.020
Relative deviation on contralesional lines (SLBT) across T0 to T5 (*n* = 22)					
Time	-0.047	0.020	-0.088	-0.007	0.023
Mean x-coordinate (BTT) at T0, T2, T4, and T5 (*n* = 21)					
Group	0.078	0.030	0.014	0.142	0.019
CBS at T0, T2, T4, and T5 (*n* = 13)					
Time	-0.134	0.051	-0.239	-0.030	0.014
Time x Time	0.001	3.47E-04	3.89E-05	0.001	0.040
SNQ at T0, T2, T4, and T5 (*n* = 22)					
Time	-0.233	0.066	-0.366	-0.101	0.001
Time x Time	0.001	4.39E-04	4.93E-04	0.002	0.003

[a] β coefficients are shown in reference to the active group. Abbreviations: BTT, baking tray task; CBS, Catherine Bergego scale; CI, confidence interval; CVDT, computerized visual detection task; EWB, endpoint weightings bias; MLBT-d, McIntosh line bisection task-digitized; QoS, quality of search; SCT, star cancellation task; SLBT, Schenkenberg line bisection task; SNQ, subjective neglect questionnaire.

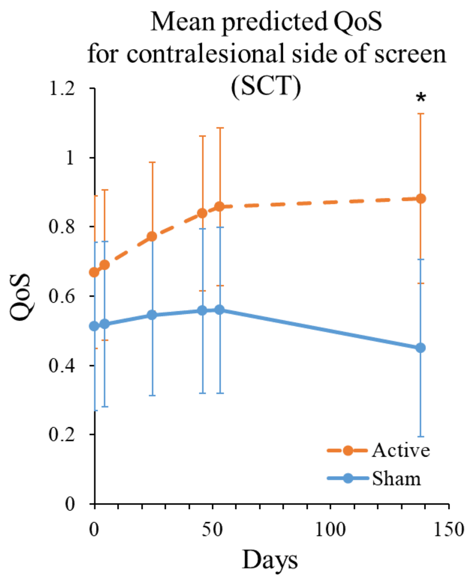

Figure 3 Mean model-predicted QoS scores for the contralesional side of the screen. Linear mixed regression analysis including *post hoc* contrasts with Bonferroni correction was performed to probe the interaction between time and group by testing for a difference between active and sham tACS groups at specific time-points. Predicted scores are based on the model that includes linear and quadratic group by time interaction terms. 95% confidence intervals for the mean in the active group (dashed orange line) and the mean in the sham group (solid blue line) are included at the time-points of interest at which the active versus sham contrasts were tested. Higher scores indicate less severe neglect. Asterisks (*) depict significant difference ($p < .05$). At day 138, the active tACS group showed a significantly higher mean QoS score compared to sham ($t(36) = 2.463$, $p = .019$). Please note that these test statistics deviate slightly from the test statistics as mentioned in the text, as the predicted scores shown here are based on the regression model that includes linear and quadratic group by time interaction terms, whereas in the text the comparison is based on the final regression model including only a linear group by time interaction term. Abbreviations: QoS, quality of search; SCT, star cancellation task.

Secondary outcomes

Sum of weighted hits (CVDT)

One patient of the active tACS group displayed a very high variability of weighted hits scores and was identified as statistical outlier (> 3.0*IQR from Q1 and Q3), thus the data presented here includes a total sample of 21 patients. As expected, the baseline scores were significantly lower (i.e., worse performance) of the contralesional and bilateral stimulus conditions compared to baseline scores of the ipsilesional condition (contralesional vs. ipsilesional: $Z = 4.02$, $p < .001$; bilateral vs. ipsilesional: $Z = 3.980$, $p < .001$).

The final model of the contralesional condition (**Table 2**) included a linear group by time interaction ($F(1, 52) = 8.493$, $p = .005$), but not a quadratic ($F(1, 44) = 3.760$, $p = .059$) nor a cubic ($F(1, 78) = .913$, $p = .342$) group by time interaction. Furthermore, only gender was included as a covariate ($F(1, 18) = 7.319$, $p = .015$). The significant group by time interaction indicates that the time effect was different between the active and sham group (**Figure 4A**); there was a positive linear effect of time in the active group ($p = .088$), and a negative linear effect of time in the sham group ($p = .020$). Follow-up contrasts showed a significant higher mean visual detection performance at day 138 in the active compared to the sham group ($t(40) = 2.933$, $p = .006$; p values at all other time-points were $\geq .108$).

The final model of the bilateral condition (**Table 2**) included a linear group by time interaction ($F(1, 68) = 6.940$, $p = .010$), but not a quadratic ($F(1, 60) = .086$, $p = .770$) nor a cubic ($F(1, 82) = 1.194$, $p = .278$) group by time interaction. Also, there was a negative quadratic effect of time ($F(1, 55) = 8.739$, $p = .005$), and gender was included as a covariate ($F(1, 19) = 8.082$, $p = .011$). The significant group by time interaction indicates that the time effect was different between the active and sham group. There was an initial improvement in both groups (day 0 – day 53; **Figure 4B**), but in the sham group this was followed by a decline in scores (day 53 – day 138). Additional contrasts showed significant better mean performance at day 138 in the active compared to the sham group ($t(32) = 2.283$, $p = .029$; p values at all other time-points were $\geq .208$).

For the sake of completeness, we conducted a final analysis for the ipsilesional condition, revealing no group by time interaction (p values for linear, quadratic, and cubic functions $\geq .459$). Again, this outcome aligns with the underlying theory of our interventional approach, which predicts that contralesional stimulation does not affect (or negatively affects) visual detection performance in the ipsilesional hemifield compared to sham stimulation. The final model is depicted in **Supplementary Table 6**.

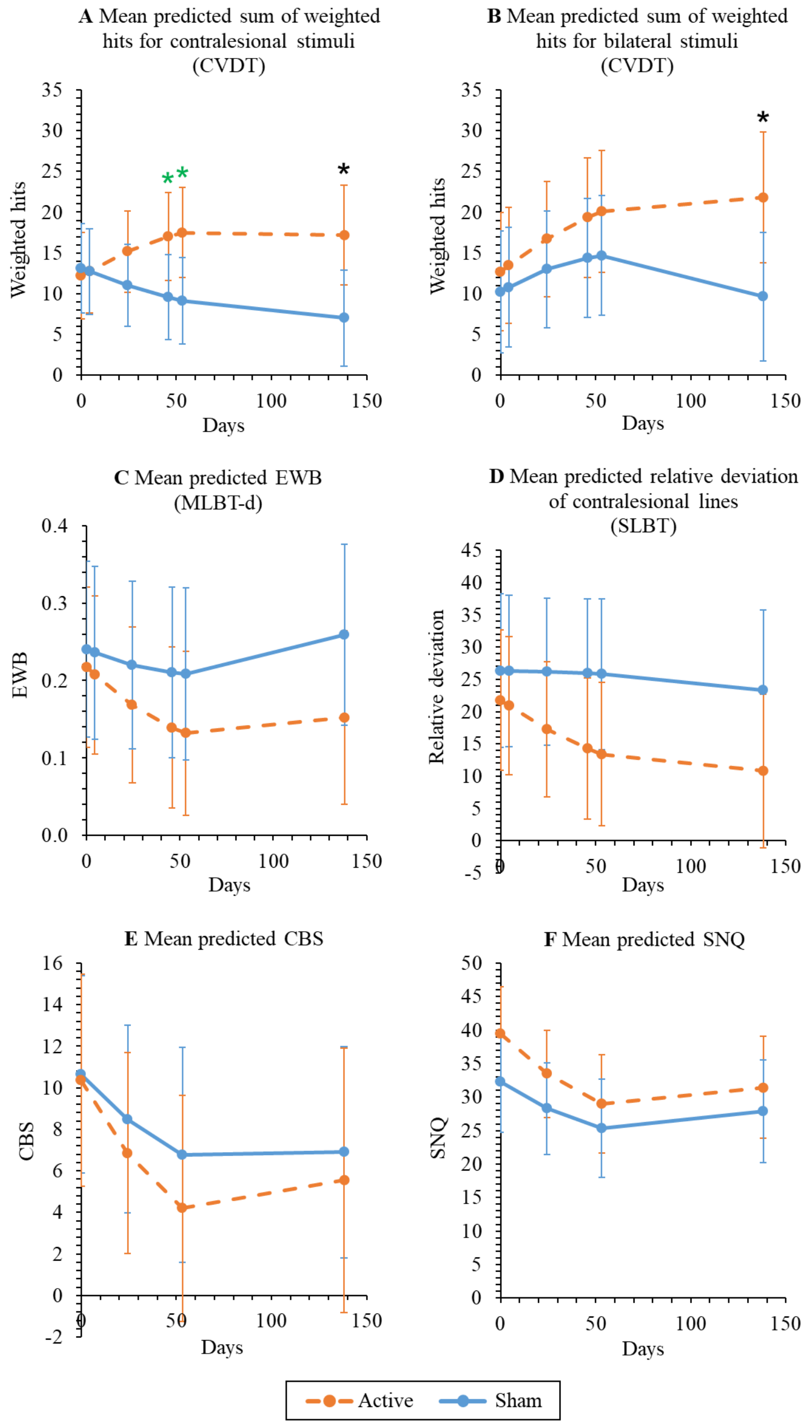

Figure 4 Mean model-predicted scores of secondary outcomes. Linear mixed regression analysis including *post hoc* contrasts with Bonferroni correction was performed to probe the interaction

between time and group by testing for a difference between active and sham tACS groups at specific time-points. Predicted scores of **(A)** sum of weighted hits for contralesional stimuli, **(B)** sum of weighted hits for bilateral stimuli, **(C)** EWB, **(D)** relative deviation of contralesional lines, **(E)** CBS, and **(F)** SNQ, are based on the models that include linear and quadratic group by time interaction terms. 95% confidence intervals for the mean in the active group (dashed orange line) and the mean in the sham group (solid blue line) are included at the time-points of interest at which the active versus sham contrasts were tested. Neglect is less severe when scores are higher (CVDT), or closer to zero (EWB, SLBT), or lower (CBS, SNQ). Asterisks (*) depict significant difference (p < .05). The active tACS group showed a significantly higher mean visual detection performance in the contralesional condition of the CVDT **(A)** at day 46 (t(25) = 2.146, p = .042), at day 53 (t(27) = 2.343, p = .027), and at day 138 (t(43) = 2.514, p = .016), as well as in the bilateral condition of the CVDT **(B)** at day 138 (t(34) = 2.288, p = .028). Please note that test statistics presented here deviate slightly from the test statistics as mentioned in the text, as the predicted scores shown here are based on the regression model that includes linear and quadratic group by time interaction terms, whereas in the text the comparisons are based on the final regression models including only a linear group by time interaction term. Asterisks in green (*) only apply to the regression model that includes both linear and quadratic group by time interaction terms, but do not apply to the regression model that includes only a linear group by time interaction term. Abbreviations: CBS, Catherine Bergego scale; CVDT, computerized visual detection task; EWB, endpoint weightings bias; MLBT-d, McIntosh line bisection task-digitized; SLBT, Schenkenberg line bisection task; SNQ, subjective neglect questionnaire.

EWB (MLBT-d)

The final model of the EWB (**Table 2**) did not include any group by time interaction (linear: F(1, 78) = 2.610, p = .110; quadratic: F(1, 58) = .314, p = .577; cubic: F(1, 88) = 3.354, p = .070). The final model included not only a linear main effect of time (F(1, 50) = 5.954, p = .018), but also a quadratic main effect of time (F(1, 54) = 5.744, p = .020). **Figure 4C** shows that, over the course of six weeks training and one-week follow-up (day 0 – day 53), regardless of whether tACS was involved or not, patients showed less bias toward the right endpoints of the lines; however, subsequent to that period (day 53 – day 138), any further improvement stagnated (active group) or even reversed (sham group).

Relative deviation (SLBT)

As expected, the baseline relative deviation was significantly higher (i.e., worse performance) of the lines positioned contralesional compared to lines either positioned in the middle or ipsilesional (contralesional vs. middle: Z = 3.652, p < .001; contralesional vs. ipsilesional: t(21) = 4.205, p < .001). The final model of the contralesional lines (**Table 2**) included no group by time interaction (linear: F(1, 82) = 1.730, p = .192; quadratic: F(1, 68) = 1.751, p = .190; cubic: F(1, 92) = 2.529, p = .115), and included only a linear main effect of time (F(1, 81) = 5.348, p = .023). This means that, over the course of time (day 0 – day

138), regardless of whether patients received tACS, patients showed less bias toward the ipsilesional side of the lines (**Figure 4D**).

Mean x-coordinate (BTT)

One patient of the active tACS group did not understand the instructions of the BTT, and was excluded from the BTT analyses. The final model (**Table 2**) did not include a group by time interaction (linear: $F(1, 58) = .487$, $p = .488$; quadratic: $F(1, 56) = 2.431$, $p = .125$; cubic: $F(1, 57) = .479$, $p = .492$), indicating that patterns of effects over time were similar for both groups. Furthermore, no time effect was found (linear, quadratic, and cubic; all p values $> .602$).

CBS

In eight out of 22 patients (36%), there was no therapist involved in the patient's care to fill out the CBS. Of the remaining fourteen patients (64%), there were seven forms that were not reliable (i.e., < five valid items), four missing forms due to practical concerns (such as therapist on leave or employed elsewhere), and five missing forms due to dropout. This eventually led to a sample size of thirteen patients (59%; seven sham group, six active group), with a mean number of filled out forms per patient of 3.08 (SD = 1.12).

The final model for the CBS (**Table 2**) did not include a group by time interaction (linear: $F(1, 27) = .063$, $p = .804$; quadratic: $F(1, 28) = .417$, $p = .524$; cubic: $F(1, 28) = .183$, $p = .672$), indicating that the time effect was similar for both groups (**Figure 4E**). There was, however, evidence not only for a linear main effect of time ($F(1, 26) = 6.948$, $p = .014$), but also a quadratic main effect of time ($F(1, 26) = 4.706$, $p = .040$). Over the course of six weeks training, regardless of whether tACS was involved or not, patients showed less VSN behavior in daily life activities (day 0 – day 53); however, subsequent to that period, any further enhancement in effects seemed to stagnate (day 53 – day 138; **Figure 4E**).

SNQ

Besides the eight forms that were missing due to the three patients that terminated participation prematurely (dropouts), there was only one form that was not reliable (i.e., < 10 valid items). Thus, sample size remained at 22, with a mean number of filled out forms per patient of 3.59 (SD = .96).

The final model for the SNQ (**Table 2**) did not include a group by time interaction (linear: $F(1, 55) = .494$, $p = .485$; quadratic: $F(1, 54) = .341$, $p = .562$; cubic: $F(1, 54) = .002$,

p = .965), indicating that the time effect was similar for both groups (**Figure 4F**). As was seen for the CBS, there was evidence not only for a linear main effect of time ($F(1, 53) = 12.741$, $p = .001$), but also a quadratic main effect of time ($F(1, 52) = 9.989$, $p = .003$). **Figure 4F** shows that, during the training trajectory of six weeks, regardless of stimulation group, patients experienced less problems due to VSN in their daily lives (day 0 – day 53); however, this initial phase of progress was followed by a plateau in effects (day 53 – day 138).

Discussion

This study evaluated the additive effects of multi-session transcranial alternating current stimulation (tACS) at alpha frequency, combined with visual scanning training (VST), on alleviating attention deficits in chronic stroke patients suffering from visuospatial neglect (VSN). We found that patients receiving active tACS with VST showed a significantly stronger improvement in their visual search performance on the contralesional side measured with a computerized cancellation task (SCT, primary outcome measure), as compared to patients receiving sham (placebo) stimulation with VST. Additionally, our novel tACS approach resulted in significantly stronger improvements in the allocation of attention toward the contralesional side measured with a computerized visual detection paradigm (CVDT), also compared to sham stimulation. Furthermore, although no differences in performance were found between active and sham tACS on the line bisection tasks (MLBT-d and SLBT) and the measures of neglect behavior in basic activities of daily living (ADL; BTT, CBS and SNQ), significant time-dependent improvements were observed, emphasizing the potential for recovery through rehabilitation in the later phases following a stroke.

Our findings closely parallel those of our prior single-session tACS study in subacute stroke patients (Schuhmann et al., 2022). There too, improvements were found specific to active tACS on a cancellation task (bells task) and the same visual detection task, but not on a line bisection task. The repeatedly observed divergent effects are likely due to the varying cognitive demands of distinct tasks. For example, cancellation tasks require visual search and tap into a different type of cognitive process than line bisection tasks (Ferber & Karnath, 2001; Van der Stigchel & Nijboer, 2017). Cancellation tasks may therefore better correspond with the skills and cognitive processes trained by VST, and, consequently, are more likely to capture the accurate underlying cognitive process.

Our current results are the first to show that multi-session tACS complemented with VST leads to long-term benefits of up to three months post treatment. Stimulation effects were seen in quality of search (QoS) on the contralesional side and in visual detection in the contralesional and bilateral conditions. The bilateral condition directly relates to the visual extinction phenomenon, a neurological syndrome closely associated with VSN. Extinction is characterized by the failure to process or attend to a contralesional event when a second competing stimulus is simultaneously presented in the ipsilesional hemifield (Riddoch et al., 2009; Vossel et al., 2011). These results suggest that our tACS therapy enhances perception in the neglected side, also/even in the presence of distractors in the non-neglected side. Additionally, this enhancement of attention in the neglected side was not accompanied by an impairment of attention in the non-neglected side, because stimulation did not affect performance in the ipsilesional side/condition of the SCT and CVDT, as may be the case when simply reducing cortical excitability of the contralesional hemisphere using conventional NIBS approaches (Dambeck et al., 2006; Hilgetag et al., 2001).

No tACS effects were found on questionnaires/tasks requiring more dynamic interactions (i.e., ADL-related measures: BTT, CBS and SNQ). This may be because ADL measures do not, typically, assess the ‘efficiency’ with which daily life activities are carried out, but merely measure the severity or frequency of occurrence of neglect-related behavior. In this sense, these measures are different from the SCT and CVDT where a time component or time restriction is included, and are less capable of detecting changes in performance efficiency, such as a better quality or effectiveness of the process to perform a daily life activity (e.g., less steps needed) or less time needed to complete an activity. Another explanation for the lack of a generalization effect could be the digitalized format of the VSN training. Possibly, training on a computer screen does not affect daily life tasks. Nonetheless, significant time-dependent improvements were observed on the CBS and SNQ, irrespective of stimulation group, suggesting that patients implemented the acquired visual scanning strategies of the VST in daily life. The digitized VST brings advantages as it is easily usable on a touchscreen and adapts to the patient’s performance ability. Also, the training program encompasses a variety of engaging tasks and provides data-driven feedback, ensuring a varied and stimulating experience to foster commitment and adherence among patients. Results of the CBS should, however, be interpreted with caution as sample size was reduced to a mere thirteen patients (59% of 22), reducing statistical power and increasing the likelihood of Type II errors.

The lack of stimulation effects on measures of ADL could have (also) been caused by the large performance variability seen in our patient sample. Patients were included based on the presence of VSN symptoms on several conventional, paper-and-pencil neglect tests (not including any measure of ADL), which, evidently, does not necessarily imply that they (also) suffered from neglect in dynamic daily living situations. Indeed, dissociations have been found between patients who displayed symptoms of VSN on conventional, static measures but not on measures of daily functioning, and vice versa (Azouvi et al., 2017; Huisman et al., 2013; Spreij et al., 2020).

Overall, assessing the transfer of treatment effects to daily life remains a considerable challenge. For instance, tools used to evaluate ADL can be significantly influenced by other VSN-related issues; motor deficits, for instance, have demonstrated notable effects on measures like the Barthel Index or Functional Independence Measure (Azouvi et al., 2017). Additionally, both the quantity and duration of treatment sessions can influence effectiveness. There remains a gap in the literature regarding systematic exploration of the optimal combination of treatment intensity and duration necessary for effective transfer of treatment effects to daily life (Azouvi et al., 2017; Kerkhoff & Schenk, 2012).

Shortcomings and strengths

A limitation is the study's response rate of 17.6% (22 included patients out of 125 eligible patients), which may raise concerns about the generalizability of findings to the broader neglect population. The low response rate may have been the result of the rather strict criteria that we use for research purposes while the clinical stroke population is much more diverse. Also, some patients were deceased or were unreachable since their discharge from rehabilitation.

A second limitation regards the novel approach for administering and analyzing the line bisection task (i.e., 'endpoint weightings analysis') that has recently been proposed by McIntosh and colleagues (2017, 2005). The endpoint weightings bias (EWB), representing the lateral attentional bias, has proven to be more sensitive to right-sided brain damage than the 'classical' bisection error, and relates more strongly to cancellation and copying measures (McIntosh et al., 2017). However, also on this new, more sensitive measure we did not observe tACS effects in the current study. We speculate that the means of assessment employed in this study may not have been the optimal choice; the 'touch' of the finger on a touchscreen laptop may have resulted in a less precise bisection mark compared to when the mark would be placed with pencil on paper (as was done in McIntosh et al., 2017) or even with pencil on touchscreen laptop or tablet.

While we did not explicitly assess patients' ability to distinguish between active and sham tACS, it is important to note that tACS does not generate audible signals and somatosensory sensations during active stimulation (Herrmann et al., 2013). Furthermore, we included a ramp-up period in both conditions so patients could (potentially) perceive the onset of stimulation; however, in the sham condition, this was followed by a ramp-down phase after a brief interval. Blinding effectiveness has previously been demonstrated in comparable studies involving healthy volunteers, utilizing identical tACS devices and stimulation parameters (Kemmerer, De Graaf, et al., 2022; Kemmerer, Sack, et al., 2022; Schuhmann et al., 2019).

Several important strengths of this study are in reference to the double-blind, randomized controlled study design. All patients, researchers, and therapists were blinded to treatment allocation, and the outcomes of the assessments did not affect therapists in any way. Furthermore, we used minimization as randomization method, to ensure balance across important patient characteristics that could have affected the study outcomes. Lastly, we adopted an interdisciplinary approach where brain-based NIBS is combined with behavior-based rehabilitation techniques combined with function-based and clinically relevant outcome measures, both in the short term and the long term.

Future research and clinical applications

The combined tACS-VST approach should be further tested in a rehabilitation setting, with subacute patients, and explore patterns of recovery within specific patient profiles. For instance, VSN involves different clinical subtypes that vary in frame of reference (egocentric and allocentric), sensory modality (visual, auditory, haptic and tactile), and region of space (personal, peripersonal and extrapersonal) (Corbetta, 2014; Rode et al., 2017; Van der Stoep et al., 2013), and different clinical subtypes have been associated with different lesion sites (Karnath & Rorden, 2012; Molenberghs et al., 2012). Evaluating at subgroup level, or even at individual level, with due consideration for distinct clinical subtypes and lesion location, will bring to light which patients are likely to benefit (most) from the treatment. Also, it is necessary to explore the most cost-effective setting for implementing the intervention. For example, although VST is traditionally offered in the clinical setting, our digitized VST program, in combination with a portable, low-cost tACS, would lend well to be used in a home-setting (Perera et al., 2023).

As our VST composed of both bottom-up and top-down strategies, it remains unclear what component of the training induces the strongest neuronal plasticity when combined with tACS. Determining the most influential element, whether it is the strengthening of exogenous orienting toward external cues (associated with the ventral attention network; Corbetta & Shulman, 2011, 2002) or the enhancement of systematic learning by top-down mechanisms (linked to endogenous attention regulated by the dorsal attention network; Corbetta & Shulman, 2011, 2002), warrants further exploration.

Regarding optimization of the tACS protocol itself, significant efforts have been made toward individualized stimulation parameters (e.g., personalized stimulation montage/location, dose, and waveform) using individual brain morphology (with computational head modeling) and neuroimaging (with EEG and fMRI) (Wischnewski et al., 2023). For example, we demonstrated in healthy individuals that stimulation at intrinsic individual frequencies, compared to stimulation at flanker frequencies leads to larger alpha power lateralization after stimulation (Kemmerer, Sack, et al., 2022). Personalizing tACS frequencies to individual brain rhythms could indeed improve tACS efficacy in a healthy population group (Zaehle et al., 2010), yet how such approach would be most effectively implemented to work in clinical populations where brain rhythms are disrupted after brain damage (Lasaponara et al., 2019, 2018), is clearly less straightforward and should be addressed through forthcoming research.

Conclusion

In conclusion, multi-session tACS at alpha frequency complemented with VST, led to significantly stronger improvement in visual search performance and more enhanced perception in the neglected side in chronic stroke patients with VSN up to three months post treatment, compared to sham tACS with VST. While we did not find additive effects of stimulation on other measures (line bisection and ADL), it is noteworthy that time-dependent improvements on all but one of these measures were observed, regardless of stimulation group. Future research should focus on specific clinical neglect profiles to account for the heterogeneous nature of the neglect syndrome, and create stimulation protocols customized for VSN patient groups to allow enhanced tACS efficacy, that ultimately transfers to beneficial effects in patients' daily living.

Acknowledgments

We would like to thank all patients who participated in this study and all therapists of the healthcare organizations who helped recruit patients and fill-out questionnaires throughout the study. In particular, we thank Dianne de Wilde for help with patient inclusion, and all students who helped with training and data collection.

References

Azouvi, P., Jacquin-Courtois, S., & Luauté, J. (2017). Rehabilitation of unilateral neglect: Evidence-based medicine. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 191–197. https://doi.org/10.1016/j.rehab.2016.10.006

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 and Rehabilitation*, *84*, 51–57. https://doi.org/10.1053/apmr.2003.50062

Bang, D.-H., & Bong, S.-Y. (2015). Effect of combination of transcranial direct current stimulation and feedback training on visuospatial neglect in patients with subacute stroke: A pilot randomized controlled trial. *Journal of Physical Therapy Science*, *27*(9), 2759–2761. https://doi.org/10.1589/jpts.27.2759

Bien, N., Goebel, R., & Sack, A. T. (2012). Extinguishing extinction: Hemispheric differences in the modulation of TMS-induced visual extinction by directing covert spatial attention. *Journal of Cognitive Neuroscience*, *24*(4), 809–818. https://doi.org/10.1162/jocn_a_00179

Bosma, M. S., Caljouw, M. A. A., Achterberg, W. P., & Nijboer, T. C. W. (2023). Prevalence, severity and impact of visuospatial neglect in geriatric stroke rehabilitation: A cross-sectional study. *Journal of the American Medical Directors Association*, *24*(11), 1798–1805. https://doi.org/10.1016/j.jamda.2023.06.038

Buxbaum, L., Ferraro, M., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., Frassinetti, F., & Coslett, H. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology*, *62*, 749–756. https://doi.org/10.1212/01.wnl.0000113730.73031.f4

Coldea, A., Morand, S., Veniero, D., Harvey, M., & Thut, G. (2021). Parietal alpha tACS shows inconsistent effects on visuospatial attention. *PLOS ONE*, *16*(8), e0255424. https://doi.org/10.1371/journal.pone.0255424

Corbetta, M. (2014). Hemispatial neglect: Clinic, pathogenesis, and treatment. *Seminars in Neurology*, *34*(5), 514–523. https://doi.org/10.1055/s-0034-1396005

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215. https://doi.org/10.1038/nrn755

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, *34*, 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Dalmaijer, E. S., Van der Stigchel, S., Nijboer, T. C. W., Cornelissen, T. H. W., & Husain, M. (2014). CancellationTools: All-in-one software for administration and analysis of cancellation tasks. *Behavior Research Methods*, *47*(4), 1065–1075. https://doi.org/10.3758/s13428-014-0522-7

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Topper, R., & Boroojerdi, B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, *1072*(1), 194–199. https://doi.org/10.1016/j.brainres.2005.05.075

Di Monaco, M., Schintu, S., Dotta, M., Barba, S., Tappero, R., & Gindri, P. (2011). Severity of unilateral spatial neglect is an independent predictor of functional outcome after acute inpatient rehabilitation in individuals with right hemispheric stroke. *Archives of Physical Medicine and Rehabilitation*, *92*(8), 1250–1256. https://doi.org/10.1016/j.apmr.2011.03.018

Duecker, F., Schuhmann, T., Bien, N., Jacobs, C., & Sack, A. T. (2017). Moving beyond attentional biases: Shifting the interhemispheric balance between left and right posterior parietal cortex modulates attentional control processes. *Journal of Cognitive Neuroscience*, *29*(7), 1267–1278. https://doi.org/10.1162/jocn_a_01119

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2020). Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. In *Cochrane Database of Systematic Reviews* (Vol. 2020, Issue 11). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD009645.pub4

Embrechts, E., Van Criekinge, T., Schröder, J., Nijboer, T., Lafosse, C., Truijen, S., & Saeys, W. (2021). The association between visuospatial neglect and balance and mobility post-stroke onset: A systematic review. *Annals of Physical and Rehabilitation Medicine*, *64*(4), 101449. https://doi.org/10.1016/j.rehab.2020.10.003

Ferber, S., & Karnath, H.-O. (2001). How to assess spatial neglect - Line bisection or cancellation tasks? *Journal of Clinical and Experimental Neuropsychology*, *23*(5), 599–607. https://doi.org/10.1076/jcen.23.5.599.1243

Fu, W., Song, W., Zhang, Y., Yang, Y., Huo, S., Zhang, R., & Wang, M. (2015). Long-term effects of continuous theta-burst stimulation in visuospatial neglect. *Journal of International Medical Research*, *43*(2), 196–203. https://doi.org/10.1177/0300060513498663

Gould, I. C., Rushworth, M. F., & Nobre, A. C. (2011). Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *Journal of Neurophysiology*, *105*(3), 1318–1326. https://doi.org/10.1152/jn.00653.2010

Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha oscillations correlate with the successful inhibition of unattended stimuli. *Journal of Cognitive Neuroscience*, *23*(9), 2494–2502. https://doi.org/10.1162/jocn.2010.21557

Heilman, K. M., Valenstein, E., & Watson, R. T. (2000). Neglect and related disorders. *Seminars in Neurology*, *20*(4), 463–470. https://doi.org/10.1055/s-2000-13179

Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00279

Hilgetag, C. C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced ‘virtual lesions’ of human parietal cortex. *Nature Neuroscience*, *4*(9), 953–957. https://doi.org/10.1038/nn0901-953

Huisman, K., Visser-Meily, A., Eijsackers, A., & Nijboer, T. (2013). Hoe kan de diagnostiek van visueel neglect verbeterd worden? *Tijdschrift Voor Neuropsychologie*, *8*(3), 134–140.

Karnath, H. O., & Rorden, C. (2012). The anatomy of spatial neglect. *Neuropsychologia, 50*(6), 1010–1017. https://doi.org/10.1016/j.neuropsychologia.2011.06.027

Kasten, F. H., & Herrmann, C. S. (2022). The hidden brain-state dynamics of tACS aftereffects. *NeuroImage*, *264,* 119713. https://doi.org/10.1016/j.neuroimage.2022.119713

Kasten, F. H., Wendeln, T., Stecher, H. I., & Herrmann, C. S. (2020). Hemisphere-specific, differential effects of lateralized, occipital–parietal α- versus γ-tACS on endogenous but not exogenous visual-spatial attention. *Scientific Reports*, *10*. https://doi.org/10.1038/s41598-020-68992-2

Kemmerer, S. K., De Graaf, T. A., Ten Oever, S., Erkens, M., De Weerd, P., & Sack, A. T. (2022). Parietal but not temporoparietal alpha-tACS modulates endogenous visuospatial attention. *Cortex*, *154*, 149–166. https://doi.org/10.1016/j.cortex.2022.01.021

Kemmerer, S. K., Sack, A. T., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Schuhmann, T. (2022). Frequency-specific transcranial neuromodulation of alpha power alters visuospatial attention performance. *Brain Research*, *1782*, 147834. https://doi.org/10.1016/j.brainres.2022.147834

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia*, *50*(6), 1072–1079. https://doi.org/10.1016/j.neuropsychologia.2012.01.024

Kim, B. R., Chun, M. H., Kim, D. Y., & Lee, S. J. (2013). Effect of high- and low-frequency repetitive transcranial magnetic stimulation on visuospatial neglect in patients with acute stroke: A double-blind, sham-controlled trial. *Archives of Physical Medicine and Rehabilitation*, *94*(5), 803–807. https://doi.org/10.1016/j.apmr.2012.12.016

Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. *Advances in Neurology*, *18*, 41–49.

Lakatos, P., Gross, J., & Thut, G. (2019). A new unifying account of the roles of neuronal entrainment. *Current Biology*, *29*, R890–R905. https://doi.org/10.1016/j.cub.2019.07.075

Lasaponara, S., D'Onofrio, M., Pinto, M., Dragone, A., Menicagli, D., Bueti, D., De Lucia, M., Tomaiuolo, F., & Doricchi, F. (2018). EEG correlates of preparatory orienting, contextual updating, and inhibition of sensory processing in left spatial neglect. *Journal of Neuroscience*, *38*(15), 3792–3808. https://doi.org/10.1523/JNEUROSCI.2817-17.2018

Lasaponara, S., Pinto, M., Aiello, M., Tomaiuolo, F., & Doricchi, F. (2019). The hemispheric distribution of a-band EEG activity during orienting of attention in patients with reduced awareness of the left side of space (spatial neglect). *Journal of Neuroscience*, *39*(22), 4332–4343. https://doi.org/10.1523/jneurosci.2206-18.2019

Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipović, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jääskeläinen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J. P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., … Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical Neurophysiology*, *131*(2), 474–528. https://doi.org/10.1016/j.clinph.2019.11.002

Longley, V., Hazelton, C., Heal, C., Pollock, A., Woodward-Nutt, K., Mitchell, C., Pobric, G., Vail, A., & Bowen, A. (2021). Non-pharmacological interventions for spatial neglect or inattention following stroke and other non-progressive brain injury. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003586.pub4

McIntosh, R. D., Ietswaart, M., & Milner, A. D. (2017). Weight and see: Line bisection in neglect reliably measures the allocation of attention, but not the perception of length. *Neuropsychologia*, *106*, 146–158. https://doi.org/10.1016/j.neuropsychologia.2017.09.014

McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research*, *25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

Middag-van Spanje, M., Schuhmann, T., Nijboer, T., Van der Werf, O., Sack, A. T., & Van Heugten, C. (2022). Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect. *BMC Neurology*, *22*(1). https://doi.org/10.1186/s12883-022-02932-7

Molenberghs, P., Sale, M. V., & Mattingley, J. B. (2012). Is there a critical lesion site for unilateral spatial neglect? A meta-analysis using activation likelihood estimation. *Frontiers in Human Neuroscience*, *March*. https://doi.org/10.3389/fnhum.2012.00078

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Neuling, T., Rach, S., & Herrmann, C. S. (2013). Orchestrating neuronal networks: Sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00161

Nguyen, J., Deng, Y., & Reinhart, R. M. G. (2018). Brain-state determines learning improvements after transcranial alternating-current stimulation to frontal cortex. *Brain Stimulation*, *11*(4), 723–726. https://doi.org/10.1016/j.brs.2018.02.008

Nijboer, T. C. W., Van de Port, I., Schepers, V., Post, M., & Visser-Meily, A. (2013). Predicting functional outcome after stroke: The influence of neglect on basic activities in daily living. *Frontiers in Human Neuroscience*, *7*, 1–6. https://doi.org/10.3389/fnhum.2013.00182

Nijboer, T. C. W., Winters, C., Kollen, B. J., & Kwakkel, G. (2018). Impact of clinical severity of stroke on the severity and recovery of visuospatial neglect. *PLoS ONE*, *13*(7). https://doi.org/10.1371/journal.pone.0198755

Perera, M. P. N., Bailey, N. W., Murphy, O. W., Mallawaarachchi, S., Sullivan, C., Hill, A. T., & Fitzgerald, P. B. (2023). Home-based individualized alpha transcranial alternating current stimulation improves symptoms of obsessive-compulsive disorder: Preliminary evidence from a randomized, sham-controlled clinical trial. *Depression and Anxiety*, *2023*, 1–11. https://doi.org/10.1155/2023/9958884

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. (2016). The Clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimulation*, *9*(3), 336–346. https://doi.org/10.1016/j.brs.2016.03.010

Pizzamiglio, L., Antonucci, G., Judica, A., Montenero, P., Razzano, C., & Zoccolotti, P. (1992). Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral right brain damage. *Journal of Clinical and Experimental Neuropsychology*, *14*(6), 901–923. https://doi.org/10.1080/01688639208402543

Radecke, J.-O., Fiene, M., Misselhorn, J., Herrmann, C. S., Engel, A. K., Wolters, C. H., & Schneider, T. R. (2023). Personalized alpha-tACS targeting left posterior parietal cortex modulates visuo-spatial attention and posterior evoked EEG activity. *Brain Stimulation*, *16*(4), 1047–1061. https://doi.org/10.1016/j.brs.2023.06.013

Riddoch, M. J., Rappaport, S. J., & Humphreys, G. W. (2009). Extinction: a window into attentional competition. In *Progress in Brain Research* (Vol. 176, pp. 149–159). https://doi.org/10.1016/S0079-6123(09)17619-7

Rode, G., Pagliari, C., Huchon, L., Rossetti, Y., & Pisella, L. (2017). Semiology of neglect: An update. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 177–185. https://doi.org/10.1016/j.rehab.2016.03.003

Rodrigues, E. M., Isolan, G. R., Becker, L. G., Dini, L. I., Vaz, M. A. S., & Frigeri, T. M. (2022). Anatomy of the optic radiations from the white matter fiber dissection perspective: A literature review applied to practical anatomical dissection. *Surgical Neurology International*, *13*, 309. https://doi.org/10.25259/SNI_1157_2021

Saghaei, M., & Saghaei, S. (2011). Implementation of an open-source customizable minimization program for allocation of patients to parallel groups in clinical trials. *Journal of Biomedical Science and Engineering*, *04*(11), 734–739. https://doi.org/10.4236/jbise.2011.411090

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W. R., & Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917–2926. https://doi.org/10.1111/j.1460-9568.2005.04482.x

Schenkenberg, T., Bradford, D., & Ajax, E. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509–517. https://doi.org/10.1212/wnl.30.5.509

Schuhmann, T., Duecker, F., Middag-van Spanje, M., Gallotto, S., Van Heugten, C., Schrijnemaekers, A. C., Van Oostenbrugge, R., & Sack, A. T. (2022). Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. *International Journal of Clinical and Health Psychology*, *22*(3). https://doi.org/10.1016/j.ijchp.2022.100326

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *PLoS ONE*, *14*(11), 1–25. https://doi.org/10.1371/journal.pone.0217729

Spreij, L. A., Ten Brink, A. F., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2020). Increasing cognitive demand in assessments of visuo-spatial neglect: Testing the concepts of static and dynamic tests.

Journal of Clinical and Experimental Neuropsychology, *42*(7), 675–689. https://doi.org/10.1080/13803395.2020.1798881

Stone, S., Patel, P., Greenwood, R., & Halligan, P. (1992). Measuring visual neglect in acute stroke and predicting its recovery: The visual neglect recovery index. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(6), 431–436. https://doi.org/10.1136/jnnp.55.6.431

Ten Brink, A., Nijboer, T., Van Beekum, L., Van Dijk, J., Peeters, R., Post, M., & Visser, J. (2013). De Nederlandse Catherine Bergego schaal: Een bruikbaar en valide instrument in de CVA-zorg. *Wetenschappelijk Tijdschrift Voor Ergotherapie*, *6*(3), 27–36.

Tham, K. (1996). The Baking Tray Task: A test of spatial neglect. *Neuropsychological Rehabilitation*, *6*(1), 19–26. https://doi.org/10.1080/713755496

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/jneurosci.0875-06.2006

Towle, D., & Lincoln, N. B. (1991). Development of a questionnaire for detecting everyday problems in stroke patients with unilateral visual neglect. *Clinical Rehabilitation*, *5*, 135–140. https://doi.org/10.1177/026921559100500208

Van der Stigchel, S., & Nijboer, T. C. W. (2017). Temporal order judgements as a sensitive measure of the spatial bias in patients with visuospatial neglect. *Journal of Neuropsychology*, *12*(3), 427–441. https://doi.org/10.1111/jnp.12118

Van der Stoep, N., Visser-Meily, J. M. A., Kappelle, L. J., De Kort, P. L. M., Huisman, K. D., Eijsackers, A. L. H., Kouwenhoven, M., Van der Stigchel, S., & Nijboer, T. C. W. (2013). Exploring near and far regions of space: Distance-specific visuospatial neglect after stroke. *Journal of Clinical and Experimental Neuropsychology*, *35*(8), 799–811. https://doi.org/10.1080/13803395.2013.824555

Van Kessel, M. E., Geurts, A. C. H., Brouwer, W. H., & Fasotti, L. (2013). Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task. *Frontiers in Human Neuroscience, 7*, 1–11. https://doi.org/10.3389/fnhum.2013.00358

Van Schouwenburg, M. R., Sörensen, L. K. A., de Klerk, R., Reteig, L. C., & Slagter, H. A. (2018). No differential effects of two different alpha-band electrical stimulation protocols over fronto-parietal regions on spatial attention. *Frontiers in Neuroscience, 12*. https://doi.org/10.3389/fnins.2018.00433

Veniero, D., Benwell, C. S. Y., Ahrens, M. M., & Thut, G. (2017). Inconsistent effects of parietal α-tACS on pseudoneglect across two experiments: A failed internal replication. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.00952

Vossel, S., Eschenbeck, P., Weiss, P. H., Weidner, R., Saliger, J., Karbe, H., & Fink, G. R. (2011). Visual extinction in relation to visuospatial neglect after right-hemispheric stroke: Quantitative assessment and statistical lesion-symptom mapping. *Journal of Neurology, Neurosurgery and Psychiatry, 82*(8), 862–868. https://doi.org/10.1136/jnnp.2010.224261

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). Development of a behavioral test of visuospatial neglect. *Archives of Physical Medicine and Rehabilitation*, *68*(2), 98–102.

Wischnewski, M., Alekseichuk, I., & Opitz, A. (2023). Neurocognitive, physiological, and biophysical effects of transcranial alternating current stimulation. *Trends in Cognitive Sciences*, *27*(2), 189–205. https://doi.org/10.1016/j.tics.2022.11.013

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience*, *20*(6), 1–6. https://doi.org/10.1523/jneurosci.20-06-j0002.2000

Yang, W., Liu, T. T., Song, X. Bin, Zhang, Y., Li, Z. H., Cui, Z. H., Hao, Q., Liu, H. L., Lei, C. L., & Liu, J. (2015). Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. *Journal of the Neurological Sciences*, *359*(1–2), 219–225. https://doi.org/10.1016/j.jns.2015.08.1541

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE*, *5*(11), e13766. https://doi.org/10.1371/journal.pone.0013766

Supplementary material

Supplementary Table 1 Cut-off criterion per screening test.

Screening test	Cut-off criterion
BT[1]	Four or more total omissions and an asymmetry of 3 or more between left and right hemifields.
BB[2]	Total score of less than 17 and a laterality of less than 45 percent.
SLBT[3]	Bisection mark deviations of 10% or more.
MLBT[4–6]	EWB of more than 0.09 and less than −0.13 for left and right VSN, respectively.

Patients were included if performance deviated from normal range on minimally one of the four following screening tests (all administered on paper): BT, BB, SLBT, MLBT. More detail about the screening tests can be found in the protocol publication.[6] Abbreviations: BB, balloons-subtest B; BT, bells task; EWB, endpoint weightings bias; MLBT, McIntosh line bisection task; SLBT, Schenkenberg line bisection task; VSN, visuospatial neglect.

References Supplementary Table 1

[1] Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*, *11*(2), 49–54.

[2] Edgeworth, J. A., MacMillan, T. M., & Robertson, I. H. (1998). *The balloons test manual*. Thames Valley Test Company.

[3] Schenkenberg, T., Bradford, D., & Ajax, E. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509–517. https://doi.org/10.1212/wnl.30.5.509

[4] McIntosh, R. D., Ietswaart, M., & Milner, A. D. (2017). Weight and see: Line bisection in neglect reliably measures the allocation of attention, but not the perception of length. *Neuropsychologia*, *106*, 146–158. https://doi.org/10.1016/j.neuropsychologia.2017.09.014

[5] McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research*, *25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

[6] Middag-van Spanje, M., Schuhmann, T., Nijboer, T., Van der Werf, O., Sack, A. T., & Van Heugten, C. (2022). Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect. *BMC Neurology*, *22*(1). https://doi.org/10.1186/s12883-022-02932-7

Supplementary Table 2 Formula(s) per outcome measure.

Outcome measure	Formula
SCT[1]	$QoS = \frac{{N_{cor}}^{2}}{N_{tar} \cdot t_{tot}}$ Where: QoS is the quality of search score; N_{cor} is the number of cancelled targets (correct responses); N_{tar} is the total number of targets; t_{tot} is the total time spent.
CVDT[2]	$weighted\ hits = \frac{\log_{10} contrast_{max}}{\log_{10} contrast_{trial}}$ Where: $contrast_{max}$ is 100%.
MLBT-d[3-5]	The lines have the following lengths and spatial positions in relation to the midpoint of the screen: Line A (-40 mm to 40 mm), Line B (-80 mm to +40 mm), Line C (-40 mm to +80 mm) and Line D (-80 mm to +80 mm). The center of the laptop screen is aligned with the patient's vertical body midline. The screen presents a single line at a time to the patient, who is instructed to bisect the line by marking a position (P). In the endpoint weightings analysis, the position of the patient's response and of the left and right endpoints are coded as horizontal coordinates relative to the midline of the screen. The analysis then focuses on how this response position varies from trial-to-trial as a consequence of changes in the left endpoint (lines A & C vs B & D) and changes in the right endpoint (lines A & B vs C & D). Perfect performance would yield symmetrical right and left endpoint weightings of 0.5, and an EWB value of 0. $dPL = \frac{(P_{mean} \text{ in line A and C}) - (P_{mean} \text{ in line B and D})}{40}$ $dPR = \frac{(P_{mean} \text{ in line C and D}) - (P_{mean} \text{ in line A and B})}{40}$ $EWB = dPR - dPL$ Where: P is the position of the patient's response; dPL is the left endpoint weighting; dPR is the right endpoint weighting; dPL and dPR are expressed as a proportion of the endpoint change (40 mm), and range from 0 to 1; EWB is the endpoint weightings bias (i.e., bias toward one of the two endpoints).
SLBT[6]	$deviation = \frac{(bisection\ mark - true\ center)}{true\ center} * 100\%$ Where: values are always measured from the left end of the line.

Abbreviations: CVDT, computerized visual detection task; MLBT-d, McIntosh line bisection task-digitized; SCT, star cancellation task; SLBT, Schenkenberg line bisection task.

References Supplementary Table 2

[1] Dalmaijer, E. S., Van der Stigchel, S., Nijboer, T. C. W., Cornelissen, T. H. W., & Husain, M. (2014). CancellationTools: All-in-one software for administration and analysis of cancellation tasks. *Behavior Research Methods*, *47*(4), 1065–1075. https://doi.org/10.3758/s13428-014-0522-7

[2] Schuhmann, T., Duecker, F., Middag-van Spanje, M., Gallotto, S., Van Heugten, C., Schrijnemaekers, A. C., Van Oostenbrugge, R., & Sack, A. T. (2022). Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. *International Journal of Clinical and Health Psychology*, *22*(3). https://doi.org/10.1016/j.ijchp.2022.100326

[3] McIntosh, R. D., Ietswaart, M., & Milner, A. D. (2017). Weight and see: Line bisection in neglect reliably measures the allocation of attention, but not the perception of length. *Neuropsychologia*, *106*, 146–158. https://doi.org/10.1016/j.neuropsychologia.2017.09.014

[4] McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research*, *25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

[5] Middag-van Spanje, M., Schuhmann, T., Nijboer, T., Van der Werf, O., Sack, A. T., & Van Heugten, C. (2022). Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect. *BMC Neurology*, *22*(1). https://doi.org/10.1186/s12883-022-02932-7

[6] Schenkenberg, T., Bradford, D., & Ajax, E. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology*, *30*(5), 509–517. https://doi.org/10.1212/wnl.30.5.509

Supplementary Table 3 Overview of performance per screening test of included patients (*n* = 22).

Patient	BT	BB	SLBT	MLBT
1	1	1	1	1
2	1	1	1	1
3	0	0	1^{X}	1
4	0	0	1	1
5	0	0	0	1
6	1	1	1^{BL}	missing
7	0	1^{BL}	1	1
8	missing	0	1	1
9	0	0	1	1
10	1	0	1	0
11	0	1	1^{X}	1^{R}
12	1^{BL}	1	1	1
13	1^{BL}	1^{R}	1	1
14	1	1	missing	1
15	1	0	1	1
16	1	1^{BL}	1	0
17	0	0	1^{X}	0
18	1	1	1	0
19	1	1	1^{BL}	1
20	1	0	1	1
21	0	0	1	0
22	0	1	1^{BL}	1

1 = scoring above cut-off, implying an indication of VSN; 0 = scoring below cut-off, implying no indication of VSN. Grey cells imply a right-sided bias to an extent that is indicative of left-sided VSN, on the basis of which patients were included in the study. Please note that only included patients (with right-hemispheric lesions) are shown in this table. Although we also screened patients with left-hemispheric lesions, none scored above cut-off, thus only patients with right-hemispheric lesions were included in the study. On average, mild VSN was detected on conventional neuropsychological tests, known for their notorious insensitivity in measuring VSN during the chronic phase. **BT and BB**: Lateralized omissions were calculated for the BT and BB. Distribution of omissions is indicated with superscript R in case of a right-sided distribution to an extent that is indicative of right-sided VSN, and with superscript BL in case of a bilateral distribution. **SLBT and MLBT**: The relative deviation score and EWB were calculated for the SLBT and MLBT, respectively. Bias is indicated with a superscript

X in case the bisection mark was placed ipsilesional (indeed implying right-sided bias) but – unusually – *not on the left lines*. (One would generally expect most bias on left-sided lines in left-sided VSN. Relative deviation on left lines is used as a secondary outcome measure of the SLBT in this study.) Furthermore, superscript R indicates that the bisection mark was placed contralesional implying right-sided VSN, and superscript BL indicates that both ipsilesional and contralesional biases were shown. Abbreviations: BB, balloons-subtest B; BT, bells task; MLBT, McIntosh line bisection task; SLBT, Schenkenberg line bisection task; VSN, visuospatial neglect.

Supplementary Table 4 Mean (SD) neglect scores per assessment.

	T0 Baseline		T1 After 1st session		T2 After 9th session		T3 After 18th session		T4 1-week follow-up		T5 3-month follow-up	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
SCT, QoS contralesional												
Active	12	0.67 (0.47)	12	0.71 (0.46)	10	0.73 (0.39)	9	0.82 (0.50)	9	0.96 (0.67)	9	0.90 (0.52)
Sham	10	0.44 (0.32)	8	0.63 (0.25)	10	0.60 (0.28)	10	0.52 (0.23)	10	0.56 (0.37)	10	0.45 (0.21)
CVDT, weighted hits contralesional												
Active	11	11.38 (11.05)	11	9.91 (10.20)	9	11.53 (10.77)	8	14.56 (11.51)	8	16.51 (11.92)	8	15.21 (8.00)
Sham	10	11.14 (11.19)	8	10.74 (10.49)	10	9.69 (8.63)	9	8.14 (6.81)	10	7.12 (7.77)	9	5.22 (4.69)
CVDT, weighted hits bilateral												
Active	11	9.41 (10.96)	11	11.41 (12.24)	9	11.16 (14.37)	8	16.99 (17.57)	8	18.49 (16.49)	8	18.87 (16.76)
Sham	10	6.34 (11.03)	8	9.96 (11.32)	10	11.69 (12.75)	9	12.67 (12.90)	10	11.08 (14.05)	9	7.84 (8.52)
MLBT-d, EWB												
Active	12	0.23 (0.18)	12	0.22 (0.18)	10	0.14 (0.10)	9	0.10 (0.14)	9	0.12 (0.12)	9	0.12 (0.14)
Sham	10	0.25 (0.18)	9	0.16 (0.13)	10	0.23 (0.19)	10	0.22 (0.17)	10	0.21 (0.22)	10	0.26 (0.24)
SLBT, % deviation on contralesional lines												
Active	12	21.30 (14.67)	12	22.21 (18.38)	10	16.26 (9.85)	9	21.51 (16.73)	9	8.94 (6.18)	9	11.61 (5.31)
Sham	10	23.93 (20.39)	8	28.32 (26.62)	10	32.72 (30.60)	10	24.97 (21.62)	10	22.04 (19.67)	10	23.80 (24.63)
BTT, average x-coordinate												
Active	11	0.02 (0.08)	-	-	9	0.02 (0.06)	-	-	8	0.04 (0.09)	8	0.02 (0.12)
Sham	10	0.13 (0.11)	-	-	10	0.13 (0.19)	-	-	10	0.06 (0.07)	10	0.10 (0.07)
CBS												
Active	6	10.46 (6.94)	-	-	5	5.98 (4.06)	-	-	4	3.61 (3.06)	3	4.07 (5.25)
Sham	7	10.98 (9.13)	-	-	5	7.57 (3.76)	-	-	4	5.44 (6.35)	6	5.83 (4.79)
SNQ												
Active	11	40.30 (17.18)	-	-	9	29.28 (9.46)	-	-	9	28.83 (12.20)	9	28.79 (8.75)
Sham	10	33.52 (13.70)	-	-	10	25.57 (4.43)	-	-	10	26.98 (8.78)	10	27.67 (10.40)

Abbreviations: BTT, baking tray task; CBS, Catherine Bergego scale; CVDT, computerized visual detection task; EWB, endpoint weightings bias; MLBT-d, McIntosh line bisection task-digitized; QoS, quality of search; SCT, star cancellation task; SD, standard deviation; SLBT, Schenkenberg line bisection task; SNQ, subjective neglect questionnaire.

Supplementary Table 5 Correlation analysis between the values of the neglect tests across patients at T0 (A) and at T5 (B).

A. Pearson correlations across patients at T0

		QoS (contralesional; SCT)	Weighted hits (contralesional; CVDT)	Weighted hits (bilateral; CVDT)	EWB (MLBT-d)	Relative deviation (SLBT)	Mean x-coordinate (BTT)	CBS	SNQ
QoS (contralesional; SCT)	Pearson Correlation	1							
	Sig. (2-tailed)								
	N	22							
Weighted hits (contralesional; CVDT)	Pearson Correlation	0.379	1						
	Sig. (2-tailed)	0.091							
	N	21	21						
Weighted hits (bilateral; CVDT)	Pearson Correlation	0.414	0.768	1					
	Sig. (2-tailed)	0.062	**< 0.001**						
	N	21	21	21					
EWB (MLBT-d)	Pearson Correlation	-0.300	-0.517	-0.508	1				
	Sig. (2-tailed)	0.176	**0.016**	**0.019**					
	N	22	21	21	22				
Relative deviation (SLBT)	Pearson Correlation	-0.215	-0.325	-0.333	0.430	1			
	Sig. (2-tailed)	0.336	0.151	0.140	**0.046**				
	N	22	21	21	22	22			
Mean x-coordinate (BTT)	Pearson Correlation	-0.382	-0.311	-0.323	0.329	0.478	1		
	Sig. (2-tailed)	0.088	0.182	0.164	0.145	**0.028**			
	N	21	20	20	21	21	21		
CBS	Pearson Correlation	-0.669	-0.465	-0.469	0.522	0.169	0.184	1	
	Sig. (2-tailed)	**0.012**	0.109	0.106	0.067	0.581	0.547		
	N	13	13	13	13	13	13	13	
SNQ	Pearson Correlation	-0.261	-0.346	-0.235	0.384	0.142	0.324	0.222	1
	Sig. (2-tailed)	0.254	0.136	0.318	0.085	0.539	0.163	0.487	
	N	21	20	20	21	21	20	12	21

B. Pearson correlations across patients at T5

		QoS (contralesional; SCT)	Weighted hits (contralesional; CVDT)	Weighted hits (bilateral; CVDT)	EWB (MLBT-d)	Relative deviation (SLBT)	Mean x-coordinate (BTT)	CBS	SNQ
QoS (contralesional; SCT)	Pearson Correlation	1							
	Sig. (2-tailed)								
	N	19							
Weighted hits (contralesional; CVDT)	Pearson Correlation	0.527	1						
	Sig. (2-tailed)	**0.030**							
	N	17	17						
Weighted hits (bilateral; CVDT)	Pearson Correlation	0.263	0.696	1					
	Sig. (2-tailed)	0.307	**0.002**						
	N	17	17	17					
EWB (MLBT-d)	Pearson Correlation	-0.373	-0.261	-0.365	1				
	Sig. (2-tailed)	0.116	0.312	0.150					
	N	19	17	17	19				
Relative deviation (SLBT)	Pearson Correlation	-0.283	-0.509	-0.459	0.458	1			
	Sig. (2-tailed)	0.241	**0.037**	0.064	**0.048**				
	N	19	17	17	19	19			
Mean x-coordinate (BTT)	Pearson Correlation	-0.605	-0.494	-0.248	0.271	0.272	1		
	Sig. (2-tailed)	**0.008**	0.052	0.355	0.276	0.275			
	N	18	16	16	18	18	18		
CBS	Pearson Correlation	-0.520	-0.085	0.111	-0.006	0.261	-0.006	1	
	Sig. (2-tailed)	0.152	0.828	0.775	0.987	0.498	0.987		
	N	9	9	9	9	9	9	9	
SNQ	Pearson Correlation	-0.109	0.030	0.479	0.264	-0.061	-0.112	0.619	1
	Sig. (2-tailed)	0.657	0.908	0.052	0.275	0.806	0.657	0.075	
	N	19	17	17	19	19	18	9	19

A. At T0, the primary outcome variable (QoS; contralesional side; SCT) correlated significantly with the CBS score (-0.669, p = 0.012). A negative correlation between the SCT and CBS is to be expected as a higher QoS and a lower CBS indicate better performance. **B.** At T5, QoS correlated significantly with the weighted hits (contralesional condition; CVDT) (0.527, p = 0.030) and the mean x-coordinate (BTT) (-0.605, p = 0.008). A negative correlation between the SCT and BTT is to be expected as a higher QoS and a lower (i.e., closer to 0) mean x-coordinate indicate better performance. Abbreviations: BTT, baking tray task; CBS, Catherine Bergego scale; CVDT, computerized visual detection task; EWB, endpoint weightings bias; MLBT-d, McIntosh line bisection task-digitized; QoS, quality of search; SCT, star cancellation task; SLBT, Schenkenberg line bisection task; SNQ, subjective neglect questionnaire.

Supplementary Table 6 Final models of fixed-effect predictors for predicting performance in the ipsilesional side of the star cancellation task and the ipsilesional condition of the computerized visual detection task.

Predictor	β [1]	SE_{β}	95% CI lower bound	95% CI higher bound	*p* value
QoS, ipsilesional side of screen (SCT) across T0 to T5 (*n* = 22)					
Age	-0.014	0.007	-0.027	-1.18E-04	0.048
Weighted hits, ipsilesional condition (CVDT) across T0 to T5 (*n* = 21)					
Time	0.443	0.206	0.034	0.852	0.034
Time x Time	-0.013	0.005	-0.023	-0.002	0.016
Time x Time x Time	6.56E-05	2.72E-05	1.15E-05	1.20E-04	0.018

[1] β coefficients are shown in reference to the active group. Abbreviations: CI, confidence interval; CVDT, computerized visual detection task; QoS, quality of search; SCT, star cancellation task.

Supplementary Table 7 SPSS syntax that is generated and used in this work for statistical analyses of primary and secondary outcomes.

Quality of search, contralesional side of screen (SCT)

```
* We started by focusing on potential removal of higher order interactions between group and time, and higher
order effects of time, and finally the covariates. Initial model:

MIXED Left_QoS BY Gender Group WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke
  Group Group*Time_continuous Group*Time_continuous*Time_continuous
Group*Time_continuous*Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).

* Final model:

MIXED Left_QoS BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous Group Group*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).
```

* With use of the final model, we performed supplementary *post hoc* contrasts with Bonferroni correction to probe the (significant) interaction between time and group by testing differences between groups at specific time-points. The syntax presented below is an example and shows the code to calculate contrasts at day = 0 (baseline). In the same way, we calculated contrasts at the other five time-points of interest, using the mean number of days (across participants) since day 0 (i.e., day 4.35, day 24.45, day 45.74, day 53.16 and day 138.16).

```
MIXED Left_QoS BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous Group Group*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI) WITH(time_continuous=0.00).
```

* We also performed contrasts with the aim of building the graph (see Fig. 3 in the manuscript). To this end, we used the model that included both linear *and* quadratic group by time interaction terms. The syntax presented below is an example and shows the code to calculate contrasts at day = 0 (baseline) for the primary outcome measure. In the same way, we calculated contrasts at the other five time-points of interest, as well as for building the graphs of the secondary outcome measures (see Fig. 4 in the manuscript).

```
MIXED Left_QoS BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous Time_continuous*Time_continuous Group Group*Time_continuous
Group*Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI) WITH(time_continuous=0.00).
```

Sum of weighted hits, contralesional condition (CVDT)

* Initial model:

```
MIXED CVDT_WH_left BY Group Gender WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Group Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke Group*Time_continuous
Group*Time_continuous*Time_continuous Group*Time_continuous*Time_continuous*Time_continuous  |
SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI).
```

* Final model:

```
MIXED CVDT_WH_left BY Group Gender WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Group Gender Time_continuous Group*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI).
```

* Note that the table output gives simple effects. We therefore used ‘Transform’ -> ‘Recode into same variables’ to recode the groups, and ran the final model again, giving us the β and *p* values of the linear effect of time for the other group.

* To perform *post hoc* contrasts at the six time-points of interest, the syntax line 'WITH(time_continuous=…)' was added to the final model. See above for an example of the syntax for the primary outcome measure.

Sum of weighted hits, bilateral condition (CVDT)

* Initial model:

```
MIXED CVDT_WH_bilat BY Group Gender WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Group Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke Group*Time_continuous
Group*Time_continuous*Time_continuous Group*Time_continuous*Time_continuous*Time_continuous |
SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI).
```

* Final model:

```
MIXED CVDT_WH_bilat BY Group Gender WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Group Gender Time_continuous Time_continuous*Time_continuous Group*Time_continuous |
SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI).
```

* To perform *post hoc* contrasts at the six time-points of interest, the syntax line 'WITH(time_continuous=…)' was added to the final model. See above for an example of the syntax for the primary outcome measure.

Endpoint weighting bias (MLBT-d)

* Initial model:

```
MIXED EWB BY Gender Group WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke Group
Group*Time_continuous Group*Time_continuous*Time_continuous
Group*Time_continuous*Time_continuous*Time_continuous  | SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
```

```
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).

* Final model:

MIXED EWB BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL).
```

Relative deviation on contralesional lines (SLBT)

```
* Initial model:

MIXED SLBT_left BY Gender Group WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke Group
Group*Time_continuous Group*Time_continuous*Time_continuous
Group*Time_continuous*Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).

* Final model:

MIXED SLBT_left BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /REPEATED=Time | SUBJECT(Subject) COVTYPE(SP_POWER) SPCOORDS(Time_continuous)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).
```

Mean x-coordinate (BTT)

```
* Initial model:
```

```
MIXED BTT_mean_X BY Gender Group WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Gender Age Months_since_stroke Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Group Group*Time_continuous
Group*Time_continuous*Time_continuous Group*Time_continuous*Time_continuous*Time_continuous |
SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).

* Final model:

MIXED BTT_mean_X BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Group | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).
```

CBS

```
* Initial model:

MIXED CBS_therapist_valids5 BY Gender Group WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke Group
Group*Time_continuous Group*Time_continuous*Time_continuous
Group*Time_continuous*Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).

* Final model:

MIXED CBS_therapist_valids5 BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
```

```
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL).
```

SNQ

```
* Initial model:

MIXED SNQ_patient BY Gender Group WITH Time_continuous Age Months_since_stroke
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Gender Time_continuous Time_continuous*Time_continuous
Time_continuous*Time_continuous*Time_continuous Age Months_since_stroke Group
Group*Time_continuous Group*Time_continuous*Time_continuous
Group*Time_continuous*Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=ML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Gender) COMPARE ADJ(BONFERRONI)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).

* Final model:

MIXED SNQ_patient BY Group WITH Time_continuous
  /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
    SINGULAR(0.000000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE)
PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=Time_continuous Time_continuous*Time_continuous | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Subject) COVTYPE(ID)
  /SAVE=FIXPRED PRED
  /EMMEANS=TABLES(OVERALL)
  /EMMEANS=TABLES(Group) COMPARE ADJ(BONFERRONI).
```

Chapter 7

Summary and general discussion

The objective of the research in this thesis was to enhance our understanding of visuospatial attention and treatment of neglect, a debilitating syndrome commonly observed after unilateral stroke, characterized by diminished attentional processing toward one side of space. Over the past two decades, numerous electroencephalography (EEG) studies in healthy volunteers have indicated that biases in visuospatial attention correlate with an asymmetry in oscillatory alpha power between the hemispheres, particularly in the posterior brain regions (Gallotto et al., 2020; Gould et al., 2011; Händel et al., 2011; Lasaponara et al., 2019; Newman et al., 2013; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000). Transcranial alternating current stimulation (tACS) has the capability to directly modulate ongoing rhythmic brain activity by applying sinusoidal currents that synchronize with the brain's natural rhythms. Consequently, tACS administered at the alpha frequency has often been used to modulate the lateralization of alpha power and/or visuospatial attention (Coldea et al., 2021; Kasten et al., 2020; Kemmerer, Sack, et al., 2022; Schuhmann et al., 2019; Van Schouwenburg et al., 2018; Veniero et al., 2017). Notably, all of these previous studies have been conducted exclusively with healthy individuals, and no studies have yet evaluated the effects of alpha-tACS in individuals experiencing asymmetric attentional deficits such as neglect due to stroke.

In this thesis, non-invasive brain stimulation (NIBS) techniques were used in multiple studies, utilizing them either as research tool to influence visuospatial attention in healthy individuals (**part I; chapters 2 and 3**) or as therapeutic intervention for patients with neglect (**part II; chapters 4, 5, and 6**). In this concluding chapter, key findings are summarized, theoretical and methodological considerations are discussed, and suggestions for future research and clinical practice are provided.

Part I

Part I of this thesis (**chapters 2 and 3**) presented a novel method for evaluating treatment options that could be applied in rehabilitation. Transcranial magnetic stimulation (TMS) was used to induce neglect-like behavioral patterns in healthy volunteers, followed by the application of tACS at individual alpha frequency (IAF) to 'virtually treat' these simulated neglect patients. We used the continuous theta burst stimulation (cTBS) protocol, known for its capacity to inhibit brain activity (Huang et al., 2005), to disrupt the right posterior parietal cortex (PPC). Despite its brief stimulation duration of only 40 seconds, cTBS induces sustained effects that can last up to 60 minutes post-stimulation (Huang et al., 2005; Suppa et al., 2016). We took advantage of this timeframe to apply alpha-tACS targeting the *left* PPC. Effects were measured both on the behavioral level, using the lateralized-attention network test (LANT) (Greene et al., 2008) to investigate the three functional components of attention (alerting, orienting, and executive control) as proposed by the framework of Petersen & Posner (2012), and on the neuronal level, using EEG.

Is alpha-tACS effective in reducing neglect-like behavioral patterns in healthy participants that have undergone cTBS inducing neglect-like symptoms?

In **chapter 2**, we first aimed to confirm whether cTBS over right PPC led to contralateral (left) neglect-like symptoms in healthy volunteers. As it has been suggested that parietal regions within the dorsal attention network engage in inter-hemispheric competition, where each hemisphere biases attention toward the contralateral visual field (Duecker & Sack, 2015), we anticipated hemifield-specific effects following TMS application over the right PPC, specifically a rightward shift of attention. The pattern of effects we found on alerting and executive control were in line with this expectation, but the absence of a TMS effect on orienting contrasted with previous TMS-PPC studies using Posner, line bisection, or extinction paradigms (Bien et al., 2012; Brighina et al., 2002; Cazzoli et al., 2009; Dambeck et al., 2006; Fierro et al., 2000; Hilgetag et al., 2001; Koch et al., 2005; Szczepanski & Kastner, 2013; Thut et al., 2005; Wang, De Graaf, Tanner, et al., 2023).

Our central argument for the absence of an orienting effect was that the use of flankers differentiated our task from previous TMS-PPC studies. The lateralized flanker-type LANT required participants to maintain high levels of sustained attention (i.e., the ability to maintain a certain level of arousal and alertness which requires mental effort and also top–down control of attention; Sturm & Willmes, 2001). Since previous research shows that the alerting system ‘co-activates’ the parietal cortex involved in spatial orienting (Fernandez-Duque & Posner, 2001; Posner & Petersen, 1990; Robertson et al., 1998), high levels of sustained attention may have made the orienting performance on the LANT more resistant to TMS modulation.

In **Chapter 3**, we explored the neural effects of TMS. As expected, TMS over right PPC resulted in a more pronounced rightward lateralization of oscillatory alpha power immediately after stimulation compared to the sham condition. Neural aftereffects had dissipated at the final resting-state EEG (rsEEG) measurement (around 40-45 minutes post-TMS), which was not surprising. Furthermore, while there was no TMS-induced electrophysiological lateralization of theta power at the group level, the change in orienting bias after TMS showed a significant dependency on the magnitude of theta power lateralization. We therefore suggested that the absence of a TMS behavioral effect on orienting bias (**chapter 2**) may have pointed toward a cause of inter-individual variability in our study. Previous studies have indeed shown that TBS-induced neuromodulation, though popular, exhibit considerable variability between and within individuals (Boucher et al., 2021; Corp et al., 2020; Jannati et al., 2019; McCalley et al., 2021; Sack et al., 2023), arising from factors such as measurement methods and biological differences.

Subsequent to TMS, alpha-tACS to left PPC did not affect any of three functions of attention (**chapter 3**). The absence of behavioral effects could have been due to the lower strength of the tACS-induced electric field compared to TMS, suggesting that a single tACS session at 1.5 mA might be insufficient for recovery of the (TMS-induced) lesion. Stronger intensities or multi-session protocols might be necessary for greater efficacy (Mohsen et al., 2019; Perera et al., 2016; Wischnewski et al., 2023). However, our further analyses investigating tACS effects on oscillatory alpha power indicated a stronger alternative explanation for our observations (**chapter 3**). The expected leftward lateralization of alpha power was found, but only when tACS was preceded by sham TMS, thus in the non-lesioned (healthy) brain. Surprisingly, preconditioning the brain with TMS reversed the oscillatory aftereffects of tACS on rsEEG, resulting in significant *rightward* alpha power lateralization after left tACS. Our findings add to existing research showing that TMS can alter brain activity, affecting both local and remote areas, and even reverse the intended changes of subsequent brain stimulation protocols (Sack et al., 2023).

The importance of a holistic approach in attention research

Attention and its neural correlates cannot be captured by a single concept. Instead, attentional phenomena are comprised of distinct yet interconnected neurocognitive mechanisms. Posner & Petersen (1990) identified three components of attention: alerting, orienting, and executive control. Earlier behavioral and fMRI research indicated that these attentional networks function independently (Fan et al., 2002, 2005; Fernandez-Duque & Posner, 1997). However, more recent studies involving behavioral, imaging, and patient data (Bartolomeo et al., 2012; Callejas et al., 2004, 2005; Chica et al., 2011; Fan et al., 2009; Posner & Petersen, 1990) suggest that these networks are interconnected and interact closely, with one modulating the other's efficiency to achieve optimal performance in complex situations (Chica et al., 2011). For example, studies have provided evidence on how the alerting network can modulate the orienting system and the orienting bias seen in neglect (Chica et al., 2011; Fernandez-Duque & Posner, 2001; Husain & Nachev, 2007; Husain & Rorden, 2003; Robertson et al., 1995; Sturm et al., 2006). Additionally, damage to specific anatomical regions, along with large-scale dysfunction across networks of brain regions, results in the heterogeneous manifestations of neglect (Corbetta, 2014), involving different clinical subtypes that cannot be fully explained by a single spatial deficit (Rode et al., 2017). In research, it is therefore essential to consider the entire system, including the interdependencies among its various components, rather than focusing on isolated parts. Yet, in TMS research, the majority of attention studies that have used inhibitory protocols to examine the functional relevance of parietal brain regions in attention, have concentrated solely on spatial orienting.

Considering the above, in our own TMS studies (**chapters 2 and 3**), we chose to use a task that could capture all three attention components separately and in combination (LANT) (Fan et al., 2005, 2002; Greene et al., 2008). While we observed no TMS effect on orienting, our findings did reveal significant stimulation effects on (phasic) alerting and executive control. These stimulation effects further emphasize the multifaceted functional contributions of the PPC beyond its traditionally recognized role in spatial orienting.

Also under baseline conditions (thus, with sham stimulation), LANT performance yielded interesting insights into the interplay between the three components of attention. For instance, the facilitative effect of orienting toward the target location was more pronounced in the presence of distracting information (flankers), compared to situations with no distractors – although in these former situations reduced benefits were gained when being in a state of high (phasic) alertness. Moreover, distracting information was less disruptive when attention was effectively oriented toward the target location. Our baseline findings showed remarkable alignment with those of earlier studies (Asanowicz et al., 2012; Callejas et al., 2004, 2005; Chica et al., 2011; Greene et al., 2008; Lupiáñez & Funes, 2005; Posner, 1994).

The multifaceted contributions of the PPC to attention mechanisms suggest that future TMS-attention research would benefit from a more integrated or holistic approach. Uncovering these functional dynamics of the brain not only significantly contributes to the scientific community but also informs applied sciences and holds substantial clinical implications. For instance, enhancing alertness through self-instructional or computerized training programs, has been shown to help patients compensate for deficits in the posterior orienting system and is beneficial in reducing neglect (Chica et al., 2011; Robertson et al., 1995; Sturm et al., 1997; Sturm & Willmes, 2001).

The findings of our own attention studies may contribute to this long-established body of knowledge, further advancing clinical research and practice. If distractors do indeed hinder the facilitative effects of alertness (**chapter 2**), it would be worthwhile to investigate whether alertness training aimed at addressing orienting deficits, is more effective in distraction-free, controlled settings. This idea is supported not only by our own findings, which demonstrate an inhibitory relationship between alerting and executive control processes (**chapter 2**), but also by early work of Posner (1994). Posner suggests that the anterior cingulate cortex, associated with the executive control network, is inhibited when the alerting network is highly active. This inhibition prevents the system from engaging in higher-level processing, thus promoting a rapid response to stimuli rather than focusing on control functions. A final example how fundamental research could enhance clinical work; if distracting stimuli are indeed less disruptive when attention is oriented toward the target location (**chapter 2**), it could be tested if (elements of) programs designed for training orienting performance might also be beneficial for patients with executive control deficits. Although often overlooked, patients with neglect frequently experience concurrent space-related executive dysfunctions (Zebhauser et al., 2019).

Part I summary

In sum, **part I** of this thesis (**chapters 2 and 3**) introduced an innovative approach in evaluating treatment options that could be applied in rehabilitation. By demonstrating cTBS effects on alerting and executive control in healthy individuals, rather than its previously recognized role in spatial orienting, the study in **chapter 2** emphasized the multifaceted functional contributions of the PPC to various attention mechanisms. This study also yielded interesting insights into the interplay between the three components of attention, as well as confirmed findings from previous attention research, and showed how our findings may further advance clinical research and practice. **Chapter 3** showed that subsequent application of alpha-tACS was however not effective in reducing neglect-like behavioral patterns, most likely because prior TMS reversed the oscillatory effects of tACS on rsEEG, pointing toward the important concept of state-dependence of brain stimulation effects.

Part II

Part II (**chapters 4, 5, and 6**) focused on evaluating alpha-tACS as a therapeutic approach in 'actual' patients with neglect. In **chapter 4**, we presented a proof-of-concept study that evaluated the (clinical) effectiveness of single-session tACS in subacute stroke patients with neglect. **Chapter 5** detailed the rationale and study protocol of a randomized controlled trial, the results of which are presented in **chapter 6**. This trial investigated if multi-session tACS as add-on to rehabilitation (visual scanning training; VST), yielded additional treatment effects compared to VST alone. We evaluated these effects in chronic stroke patients with neglect, employing sensitive, digitized testing aiming to capture neglect severity at the symptom level, alongside assessments of neglect-like behavior in daily activity.

Is alpha-tACS effective in reducing neglect behavioral patterns after stroke?

In both patient studies (**chapters 4 and 6**), we observed improvements in performance on the contralesional (i.e., neglected) side specific to active tACS in a cancellation task and a visual detection task. Remarkably, in both studies, the enhancement of attention on the neglected side was not accompanied by an impairment of attention on the non-neglected side, as stimulation did not affect visual search and visual detection in the ipsilesional side/condition of the cancellation and visual detection tasks, respectively. This is contrary to the effects that may be seen when reducing cortical excitability in the contralesional hemisphere using conventional NIBS approaches (Dambeck et al., 2006; Hilgetag et al., 2001; Wang, De Graaf, Williams, et al., 2023) – although it must be noted that, in the auditory domain, unihemispheric alpha-tACS caused a disruption in spatial attention contralaterally to the stimulated hemisphere (Deng et al., 2019; Wöstmann et al., 2018). In addition, our findings in **chapter 6** are the first to show that multi-session tACS complemented with VST leads to long-term benefits in chronic neglect patients, lasting up to three months post-treatment, highlighting the potential for recovery through rehabilitation in the later stages following a stroke.

Interestingly, in both studies, no effect of stimulation was seen on the line bisection tasks. These (repeatedly) divergent effects likely stem from varying cognitive demands of each task. For example, cancellation tasks involve visual search and engage different cognitive processes compared to line bisection tasks (Ferber & Karnath, 2001; Van der Stigchel & Nijboer, 2017). The line bisection task, as utilized in our studies, focusses more on basic perceptual processes and less on systematic searching. While locating the endpoints of the line involves some eye movements to the left and right, the emphasis shifts away from the systematic search strategies typically required for visual search or cancellation tasks. In these latter tasks, the importance of extensive and efficient visual scanning is more pronounced. Consequently, in **chapter 6**, where we evaluated the additive effects of multi-session alpha-tACS, combined with VST, cancellation tasks were better aligned with the skills and cognitive processes trained by VST, making them more likely to capture the true underlying cognitive improvements. Although line bisection has long been an important clinical and experimental task for the study of neglect, bisection deviation has indeed repeatedly been shown to relate only weakly to core measures of neglect (see list of studies in McIntosh et al., 2017).

Lastly, no differences in performance were found between active and sham tACS in measures of neglect behavior in basic activities of daily living (ADL; BTT, CBS and SNQ) (**chapter 6**). Despite this, significant time-dependent improvements were observed on two of these measures (CBS and SNQ), regardless of stimulation group, suggesting that patients effectively implemented the visual scanning strategies through VST in their daily lives.

The challenge of transferring treatment effects to daily life

Assessing the transfer of treatment effects to daily life remains a considerable challenge. A number of factors may explain why we found no additive effects of the stimulation on ADL-related tasks (**chapter 6**), varying from issues related to the method of measurement and analysis (e.g., CBS analysis most likely suffered from insufficient power because of the limited sample size), and the format of the scanning training.

First of all, ADL measures typically assess the severity or frequency of neglect-related behavior rather than the efficiency of performing daily life activities. Unlike the cancellation task and visual detection task, which include a time component or time restriction, tools used to evaluate ADL are less capable of detecting improvements in performance efficiency, such as completing activities with fewer steps or in less time. Also, ADL measures can be significantly affected by other neglect-related issues. For example, motor deficits have shown considerable impact on measures such as the Barthel Index and the Functional Independence Measure (Azouvi et al., 2017).

The lack of stimulation effects on ADL measures may have been further influenced by the large performance variability within our patient sample. Neglect includes different clinical subtypes, for example, varying by frame of reference and region of space (Corbetta, 2014; Rode et al., 2017; Van der Stoep et al., 2013). In our study, patients were included if they showed abnormal performance on at least one of the screening tests, which comprised only conventional paper-and-pencil tests and did not assess ADL. Consequently, not all patients showed neglect on all outcome measures and, importantly, inclusion did not necessarily mean that they experienced neglect in dynamic daily-living situations. There have indeed been cases where patients show symptoms of neglect on conventional, static tests but not on daily functioning measures, and vice versa (Azouvi et al., 2017; Huisman et al., 2013; Spreij et al., 2020). Given the complexity and heterogeneity of neglect, stratifying patients could provide more insight into which groups might benefit most from the intervention. For example, it might be useful to ask patients about the specific difficulties they face most to individualize outcome measures, ensuring that the assessments capture the real-world impact of neglect on their daily lives. Standard measures and screenings were used in our patient studies, which did not focus on individual issues. Because patients had varying levels of impairment and improvement potential, not every patient could have improved on each measure and each patient could have improved on (a combination of) different measures. By personalizing the approach – tailoring analyses and creating subgroups based on where patients score poorly – we could improve our understanding of treatment effects. In our patient studies (**chapters 4, 5, and 6**), our aim was not to group patients, and statistical limitations made analyzing smaller subgroups unfeasible. However, examining patterns of recovery within specific patient profiles is an important next step and should be a focus of future research.

The conventional approach to neglect treatment mainly involves VST (Van Heugten et al., 2017). VST is often only administered manually using pen and paper, resulting in variations in protocols across different rehabilitation centers and a lack of standardized structure. Although the digitized VST offers a range of advantages – such as being user-friendly on a touchscreen, adapting to patient performance, enabling self-administration with minimal therapist interaction, convenient data storage, giving room for many (extra) sensitive measures of cognitive functioning, in between assessment points, providing engaging tasks, and delivering automatic data-driven feedback to foster patient commitment and adherence – the digital format may have been another factor contributing to the lack of generalization effects. It is possible that training on a computer or laptop screen does not effectively translate to improvements in non-trained activities and daily life tasks. There is ample evidence that computerized cognitive training programs do not show far transfer (Cavedoni et al., 2022; Van Heugten, 2017). A future study could therefore combine tACS with a more ecologically valid form of scanning training than chosen in this study with emphasis on generalization to daily life functioning.

In particular, interest in virtual reality (VR) therapies has grown substantially over the past two decades (Salatino et al., 2023). VR has been defined as “an advanced form of human-computer interface that allows the user to ‘interact’ with and become ‘immersed’ in a computer-generated environment in a naturalistic fashion” (Schultheis & Rizzo, 2001). In a recent review (Salatino et al., 2023), VR-based treatments have proven effective for the rehabilitation of neglect regardless of the immersion level. Notably, benefits were also observed in daily living activities in most of the studies investigating transfer effects in ecological tasks. Another emerging technology is augmented reality (AR), or mixed reality, that could also offer promising solutions for neglect rehabilitation (Bakker et al., 2020). AR facilitates more natural interactions with the environment by superimposing computer-generated images on top of it. An advantage of an AR-based VST program is that it allows patients to practice visual scanning in familiar settings, and to do so with greater intensity and frequency than in a natural environment, potentially making the transition to the real-world easier (Bakker et al., 2020). Given that AR development is still in its early stages, more research is needed to determine if patients internalize the scanning behavior and apply it beyond the context of the AR intervention. Additionally, it would be particularly interesting to investigate if combining VR- or AR-based VST with alpha-tACS would result in (even) better outcomes. As VR or AR as well as a portable tACS all lend well to be used in a home-setting, this combination of interventions offers a promising approach for accessible, home-based rehabilitation. Home-based interventions are especially crucial in the later phases of stroke recovery, when patients return home while still experiencing significant disabilities (Van Heugten et al., 2020), and need to maintain and consolidate the positive outcomes achieved through rehabilitation training in the clinical setting (Cavedoni et al., 2022).

Part II summary

Part II of this thesis (**chapters 4, 5, and 6**) focused on evaluating the use of alpha-tACS as a therapeutic intervention for patients with neglect following a stroke. **Chapter 4** presented the first proof-of-concept evidence that this oscillatory-based transcranial stimulation method could be clinically effective in treating neglect in subacute stroke patients. Building on this initial study, in **chapter 5** we designed a larger randomized controlled clinical trial to assess the clinical efficacy of multiple treatment sessions throughout rehabilitation, aiming to achieve long-term benefits. In **chapter 6**, we described the results of this study, which again showed task-specific improvements in performance on the contralesional (neglected) side, specifically associated with active tACS. This study, which involved patients with chronic neglect, demonstrated sustained improvements up to three months post-treatment, underscoring the potential for recovery through rehabilitation even in the later stages following a stroke. The consistent findings across both patient studies highlight the robustness and reliability of our results. However, we did not observe additional benefits of the stimulation on ADL tasks.

Methodological considerations

The studies in this thesis employed various study designs, measurement techniques, and analysis methods. Specifically, the studies in **chapters 2, 3, and 4** used a within-subject, single-blinded design, while the randomized controlled trial (RCT) in **chapters 5 and 6** adopted a between-subject, double-blind design. RCTs are considered the gold standard in clinical research due to their ability to minimize bias and establish causality (Bouter et al., 2006). The double-blind design further strengthens the validity of the findings by reducing the risk of placebo effects and observer bias (Bouter et al., 2006). The studies in this thesis assessed effects across different populations, including healthy individuals, sub-acute and chronic stroke patients, and also included therapist evaluations regarding neglect severity in patients.

Although throughout the thesis we did not explicitly assess the participants' ability to distinguish between active and sham tACS, it is noteworthy that tACS does not typically generate audible signals or somatosensory sensations during active stimulation (Herrmann et al., 2013). To enhance blinding, we included a ramp-up period in both active and sham conditions; in the sham condition, this was followed by a ramp-down phase after a brief interval. The effectiveness of this blinding approach has been demonstrated in similar studies with healthy volunteers using identical tACS devices and stimulation parameters (Kemmerer, De Graaf, et al., 2022; Kemmerer, Sack, et al., 2022; Schuhmann et al., 2019).

In **chapters 5 and 6**, we adopted an interdisciplinary approach, combining brain-based NIBS with behavior-based rehabilitation techniques. The digitized VST was developed specifically for the chronic stroke population living at home, with tasks that could be adjusted to match each patient's abilities and level of neglect. This made it possible to provide personalized training sessions. The brain-based NIBS and behavior-based VST approach was combined with function-based and clinically relevant outcome measures, assessed both in the short term and the long term, to provide a comprehensive evaluation of the intervention. EEG data was also collected to allow us to test whether tACS successfully modulated alpha power lateralization and whether this led to changes in visuospatial attention performance. Since the EEG analyses are still ongoing, these results have not been included in this thesis. In these same chapters, we used linear mixed model regression analysis to address the complexities inherent in stroke rehabilitation studies (Goedert et al., 2013). These complexities include unbalanced longitudinal data, missing data, small sample sizes, and significant between-subject variability, common due to the diverse impairments and recovery trajectories in neglect. Unlike traditional methods such as repeated measures analysis of variance (ANOVA), linear mixed models are more robust and provide a more powerful analysis of rehabilitation outcomes (Goedert et al., 2013).

While the patient studies in **chapters 4 and 6** demonstrated effectiveness at a group level, analyzing the data from an individual perspective – such as by assessing whether patients surpassed thresholds for minimal clinically significant change – could provide additional relevant insights. Furthermore, the data collected in the studies were entirely quantitative. Incorporating a qualitative perspective, including the experiences of patients, caregivers, and therapists, could offer valuable insights and add greater depth to the findings.

Besides the strengths of RCTs, as discussed above, they can be resource-intensive and may have limitations related to external validity. **Chapter 6** indeed reported a low response rate of 17.6%, which may raise concerns about the generalizability of the findings to the broader neglect population. This low response rate may be due to the strict inclusion criteria used for research purposes, which may not fully represent the diversity within the clinical stroke population. Additionally, some patients were deceased or unreachable after discharge from rehabilitation, further affecting the response rate.

In terms of generalizability of the studies in healthy participants, the studies in **chapters 2 and 3** highlighted potential causes of inter-individual variability, particularly of theta burst stimulation (TBS)-induced neuromodulation, and pointed out the brain-state dependency of tACS. Such variability may have limited the generalizability of the results.

To improve the generalizability of NIBS, it is crucial to employ strategies that reduce inter- and intra-individual variability. This issue is further discussed in the following paragraph, which focuses on reducing variability in tACS response.

TACS in future research and clinical practice

Reducing inter- and intra-individual variability in tACS response

Alongside its role in exploring the interplay between attention processes, as discussed above in **part I**, a holistic or integrated approach in (any field of) research encompasses a broader perspective. It means considering various factors that could impact research outcomes, including those that cause inter- and intra-individual variability. Overlooking or neglecting factors that can influence research outcomes may lead to biased results, incomplete conclusions, and an inaccurate understanding of the subject matter, ultimately leading to inconsistent findings across studies (inter-study variability). To illustrate, the inclusion of flankers in the LANT (**chapters 2 and 3**), clearly distinguished our study's task from those used in previous TMS-PPC studies (methodological variability) and led to orienting effects that are in contrast to those in previous studies.

Besides the large inter- and intra-individual variability that has been found in TMS response (see **part I**), variability in tACS outcome has also been shown, especially over the past few years, bringing into question the reliability of tACS effects. For example, investigations into the effects of alpha-tACS on behavior have produced mixed outcomes: some studies observed significant effects on spatial attention (e.g., Deng et al., 2019; Kasten et al., 2020; Kemmerer, De Graaf, et al., 2022; Kemmerer, Sack, et al., 2022; Radecke et al., 2023; Schuhmann et al., 2019; Wöstmann et al., 2018), while others found none or reported inconsistent results (e.g., Coldea et al., 2021; Hopfinger et al., 2017; Van Schouwenburg et al., 2018; Veniero et al., 2017). Similarly, concerns regarding the replicability of tACS effects on oscillatory alpha power have emerged, as some studies (e.g., Clayton et al., 2018; Coldea et al., 2021; Fekete et al., 2018; Kemmerer, De Graaf, et al., 2022; Stecher & Herrmann, 2018) using similar protocols have failed to replicate the enhancements observed in initial (or later) alpha-tACS research (e.g., Kasten et al., 2016; Kemmerer, Sack, et al., 2022; Neuling et al., 2013; Stecher et al., 2021; Vossen et al., 2015; Zaehle et al., 2010).

Inconsistent tACS outcomes across conditions were also found in our study involving healthy individuals (see **part I**, **chapter 3**). Specifically, effects of alpha-tACS on alpha power lateralization were influenced by TMS preconditioning; sham TMS prior to left tACS led to the expected leftward shift of alpha power lateralization, but active TMS prior to left tACS oddly reversed this tACS effect, leading to a significant rightward shift of alpha power lateralization. These findings closely align with the important concept of state-dependence of brain stimulation effects, indicating that the impact of NIBS on brain physiology and behavior varies, at least in part, based on different brain states (Bradley et al., 2022; Feurra et al., 2019; Hartwigsen & Silvanto, 2023; Sack et al., 2023). TACS effects have indeed shown to depend on different brain states (Kasten & Herrmann, 2022). These include experimentally induced, relatively long-lasting brain states, such as when alpha-tACS shows differing responses on endogenous alpha oscillations when eyes are open versus closed (Neuling et al., 2013; Ruhnau et al., 2016), as well as rapidly and spontaneously fluctuating neural states that occur within seconds (Kasten & Herrmann, 2022). Additionally, psychological states, such as an individual's emotional or affective state prior to or during stimulation, can substantially influence outcomes (Schutter et al., 2023). Besides brain state, a large number of other factors might contribute to the inter-individual variability in transcranial electric stimulation (tES) studies, including individual natural frequency, brain anatomy (e.g., individual skull thickness and gyri configuration), age, gender, and hormonal levels (e.g., Krause & Cohen Kadosh, 2014; Veniero et al., 2017).

The numerous factors influencing tES outcome, which lead to variability observed both within and between studies, underscore the need for a more systematic investigation of these factors (Coldea et al., 2021; Veniero et al., 2017). By identifying sources of inconsistencies, it becomes possible to reduce them, such as through the individualization of stimulation parameters. Given its extensive range of options in the selection of parameters, tES offers the potential for personalization. This can be achieved, for example, by tailoring current strength/density, electrode montage, and stimulation frequency, duration, and location for each individual (Krause & Cohen Kadosh, 2014; Stecher & Herrmann, 2018; Veniero et al., 2017). Since numerous other confounding variables that influence susceptibility to tACS cannot always be controlled, it might be beneficial for studies to statistically model these additional factors (Stecher & Herrmann, 2018), in addition to personalizing tES protocols.

From basic to applied use of tACS

In contrast to the variable tACS outcomes across conditions in healthy individuals (**chapter 3**), we found consistent effects of contralesional parietal alpha-tACS across our two patient studies (**chapters 4 and 6**). Despite differences in methodology between the two patient studies – single session versus multi-session – and differences in the populations tested – subacute versus chronic stroke patients – both studies demonstrated improvements specific to active 10-Hz tACS in a cancellation task and a visual detection task, but not in a line bisection task.

The significant effects on specifically *visual detection* in both patient studies raise important considerations. Contrary to our findings, in a prior study involving healthy participants, tACS at 10 Hz led to significant effects on an endogenous attention task but *not* on an exogenous attention task or a visual detection task (Schuhmann et al., 2019). These task-specific effects were later replicated with tACS at IAF, also in healthy individuals (Kemmerer, Sack, et al., 2022). The repeatedly divergent effects on visual detection between healthy and patient populations prompts a crucial question: how well do findings from basic research in healthy, fit individuals translate to applied clinical research? Are we potentially limiting ourselves by disregarding valuable interventions that did not show significant cognitive enhancement in healthy populations but may be effective in clinical contexts?

These questions also arise when considering the contrasting effects that we observed in the two parts of this thesis (**part I**: healthy participants vs. **part II**: stroke patients). In the case of virtual neglect patients, tACS was preceded by TMS in healthy participants and showed no effect on visuospatial attention bias (**chapter 3**). However, in actual stroke patients, tACS resulted in a significant reduction in neglect symptoms (**chapters 4 and 6**). Thus, the sequence of TMS before tACS yielded different behavioral outcomes compared to tACS alone in brain damaged patients without prior TMS. This difference was also reflected in the electrophysiological data in **chapter 3**, where TMS before tACS reversed the oscillatory aftereffects of tACS on offline rsEEG compared to tACS following sham TMS, indicating that tACS effects are dependent on prior brain stimulation protocols. TMS preconditioning clearly impacted the effects of tACS. Therefore, when evaluating the effects of alpha-tACS (or perhaps also of other NIBS interventions) in a TMS-induced lesion model in healthy participants, the results are not directly comparable to those in stroke patients with actual brain damage. This distinction does not diminish the significant value to brain research of studies investigating neglect-like effects induced by

TMS in healthy individuals, nor does it lessen the scientific relevance of studies documenting inconsistent and null findings of tACS in healthy individuals in recent years. Undoubtedly, the use of NIBS as a research tool has provided great insights and enhanced our pathophysiological understanding of neglect. The key point here is that for alpha-tACS to be effectively applied as a therapeutic intervention in stroke patients with neglect, it is crucial to explore what individual factors could influence the success of the treatment specifically in this population. Although various suggestions and hypotheses have been proposed for designing personalized tACS protocols (as discussed above), these have primarily been based on studies in healthy individuals. To date, no studies have tested these approaches in patients with neglect.

For instance, tailoring tACS frequencies to match individual brain rhythms has shown promise in enhancing the efficacy of tACS within healthy groups (Kemmerer, Sack, et al., 2022; Zaehle et al., 2010). This evidence supports the idea that aftereffects of tACS are driven by LTP/LTD processes due to entrainment of endogenous oscillations (Helfrich et al., 2014; Neuling et al., 2015; Stecher & Herrmann, 2018). While it is recommended to precisely match stimulation with natural frequencies to interact effectively with oscillatory activity (Stecher & Herrmann, 2018; Veniero et al., 2017), especially in heterogeneous groups with high variability in IAFs (Kemmerer, 2022), applying this approach to clinical populations, such as stroke patients where alpha rhythms are disrupted (Lasaponara et al., 2018, 2019), is more complex and requires further research. In our patient studies (**chapters 4, 5 and 6**), tACS frequency was not individually adjusted. This may have resulted in the stimulation being effective only in a subset of patients whose IAF was close to the predetermined, fixed stimulation frequency of 10 Hz, potentially leading to an underestimation of the effects. Future research should explore whether targeting the disrupted IAF in neglect patients yields better outcomes compared to using a single, prefixed alpha frequency.

Also, studies have demonstrated that alpha frequency shifts can occur over the course of a session, suggesting that IAF is not static but varies over time (Benwell et al., 2019). A potential next step in developing personalized tACS protocols for stroke patients could therefore be the use of closed-loop tACS (Bergmann et al., 2016; Thut et al., 2017), which adjusts to these frequency fluctuations in real-time. Although a recent study in healthy volunteers did not show beneficial effects of using adaptive tACS (closed-loop) over conventional tACS using a predetermined, fixed frequency (Stecher et al., 2021), this method may still provide valuable insights into effectively entraining IAF for therapeutic purposes.

Concluding remarks

In conclusion, future clinical studies should combine tACS with more ecologically valid scanning training to emphasize generalization to daily life functioning. While our findings across patient studies were consistent and robust, previous research indicates significant inter- and intra-individual variability in treatment responses in brain stimulation and neglect studies. This highlights the need for systematic investigation of factors influencing tES outcomes, including the individualization of stimulation parameters. Although personalized tACS protocols have been proposed based on studies in healthy individuals, they have not yet been tested in patients with neglect. This is crucial, as our findings suggest that the response of an injured brain to tACS may differ from that of a healthy brain. Future research should therefore focus on tailoring tACS protocols to enhance efficacy in neglect patients, ultimately translating into meaningful improvements in their daily lives.

References

Asanowicz, D., Marzecová, A., Jaśkowski, P., & Wolski, P. (2012). Hemispheric asymmetry in the efficiency of attentional networks. *Brain and Cognition*, *79*(2), 117–128. https://doi.org/10.1016/j.bandc.2012.02.014

Azouvi, P., Jacquin-Courtois, S., & Luauté, J. (2017). Rehabilitation of unilateral neglect: Evidence-based medicine. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 191–197. https://doi.org/10.1016/j.rehab.2016.10.006

Bakker, M. D. J., Boonstra, N., Nijboer, T. C. W., Holstege, M. S., Achterberg, W. P., & Chavannes, N. H. (2020). The design choices for the development of an augmented reality game for people with visuospatial neglect. *Clinical EHealth*, *3*, 82–88. https://doi.org/10.1016/j.ceh.2020.11.003

Bartolomeo, P., De Schotten, M. T., & Chica, A. B. (2012). Brain networks of visuospatial attention and their disruption in visual neglect. *Frontiers in Human Neuroscience*, *6*, 1–10. https://doi.org/10.3389/fnhum.2012.00110

Benwell, C. S. Y., London, R. E., Tagliabue, C. F., Veniero, D., Gross, J., Keitel, C., & Thut, G. (2019). Frequency and power of human alpha oscillations drift systematically with time-on-task. *NeuroImage*, *192*, 101–114. https://doi.org/10.1016/j.neuroimage.2019.02.067

Bergmann, T. O., Karabanov, A., Hartwigsen, G., Thielscher, A., & Siebner, H. R. (2016). Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives. *NeuroImage*, *140*, 4–19. https://doi.org/10.1016/j.neuroimage.2016.02.012

Bien, N., Goebel, R., & Sack, A. T. (2012). Extinguishing extinction: Hemispheric differences in the modulation of TMS-induced visual extinction by directing covert spatial attention. *Journal of Cognitive Neuroscience*, *24*(4), 809–818. https://doi.org/10.1162/jocn_a_00179

Boucher, P. O., Ozdemir, R. A., Momi, D., Burke, M. J., Jannati, A., Fried, P. J., Pascual-Leone, A., Shafi, M. M., & Santarnecchi, E. (2021). Sham-derived effects and the minimal reliability of theta burst stimulation. *Scientific Reports*, *11*(1), 21170. https://doi.org/10.1038/s41598-021-98751-w

Bouter, L. M., Van Dongen, M. C. J. M., & Zielhuis, G. A. (2006). *Epidemiologisch onderzoek*. Bohn Stafleu van Loghum. https://doi.org/10.1007/978-90-313-6527-2

Bradley, C., Nydam, A. S., Dux, P. E., & Mattingley, J. B. (2022). State-dependent effects of neural stimulation on brain function and cognition. *Nature Reviews Neuroscience*, *23*(8), 459–475. https://doi.org/10.1038/s41583-022-00598-1

Brighina, F., Bisiach, E., Piazza, A., Oliveri, M., La Bua, V., Daniele, O., & Fierro, B. (2002). Perceptual and response bias in visuospatial neglect due to frontal and parietal repetitive transcranial magnetic stimulation in normal subjects. *NeuroReport*, *13*(18), 2571–2575. https://doi.org/10.1097/00001756-200212200-00038

Callejas, A., Lupiàñez, J., Funes, M. J., & Tudela, P. (2005). Modulations among the alerting, orienting and executive control networks. *Experimental Brain Research*, *167*(1), 27–37. https://doi.org/10.1007/s00221-005-2365-z

Callejas, A., Lupiáñez, J., & Tudela, P. (2004). The three attentional networks: On their independence and interactions. *Brain and Cognition*, *54*(3), 225–227. https://doi.org/10.1016/j.bandc.2004.02.012

Cavedoni, S., Cipresso, P., Mancuso, V., Bruni, F., & Pedroli, E. (2022). Virtual reality for the assessment and rehabilitation of neglect: Where are we now? A 6-year review update. *Virtual Reality*, *26*(4), 1663–1704. https://doi.org/10.1007/s10055-022-00648-0

Cazzoli, D., Müri, R. M., Hess, C. W., & Nyffeler, T. (2009). Horizontal and vertical dimensions of visual extinction: A theta burst stimulation study. *Neuroscience*, *164*(4), 1609–1614. https://doi.org/10.1016/j.neuroscience.2009.09.044

Chica, A. B., Thiebaut de Schotten, M., Toba, M., Malhotra, P., Lupiáñez, J., & Bartolomeo, P. (2011). Attention networks and their interactions after right-hemisphere damage. *Cortex*, *48*(6), 654–663. https://doi.org/10.1016/j.cortex.2011.01.009

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2018). The effects of 10 Hz transcranial alternating current stimulation on audiovisual task switching. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00067

Coldea, A., Morand, S., Veniero, D., Harvey, M., & Thut, G. (2021). Parietal alpha tACS shows inconsistent effects on visuospatial attention. *PLOS ONE*, *16*(8), e0255424. https://doi.org/10.1371/journal.pone.0255424

Corbetta, M. (2014). Hemispatial neglect: Clinic, pathogenesis, and treatment. *Seminars in Neurology*, *34*(5), 514–523. https://doi.org/10.1055/s-0034-1396005

Corp, D. T., Bereznicki, H. G. K., Clark, G. M., Youssef, G. J., Fried, P. J., Jannati, A., Davies, C. B., Gomes-Osman, J., Stamm, J., Chung, S. W., Bowe, S. J., Rogasch, N. C., Fitzgerald, P. B., Koch, G., Di Lazzaro, V., Pascual-Leone, A., & Enticott, P. G. (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration.' *Brain Stimulation*, *13*(5), 1476–1488. https://doi.org/10.1016/j.brs.2020.07.018

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Topper, R., & Boroojerdi, B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, *1072*(1), 194–199. https://doi.org/10.1016/j.brainres.2005.05.075

Deng, Y., Reinhart, R. M., Choi, I., & Shinn-Cunningham, B. G. (2019). Causal links between parietal alpha activity and spatial auditory attention. *ELife*, *8*. https://doi.org/10.7554/eLife.51184

Duecker, F., & Sack, A. T. (2015). The hybrid model of attentional control: New insights into hemispheric asymmetries inferred from TMS research. *Neuropsychologia*, *74*, 21–29. https://doi.org/10.1016/j.neuropsychologia.2014.11.023

Fan, J., Gu, X., Guise, K. G., Liu, X., Fossella, J., Wang, H., & Posner, M. I. (2009). Testing the behavioral interaction and integration of attentional networks. *Brain and Cognition*, *70*(2), 209–220. https://doi.org/10.1016/j.bandc.2009.02.002

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*(3), 340–347. https://doi.org/10.1162/089892902317361886

Fan, J., Mccandliss, T. B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *NeuroImage*, *26*, 471–479. https://doi.org/10.1016/j.neuroimage.2005.02.004

Fekete, T., Nikolaev, A. R., De Knijf, F., Zharikova, A., & Van Leeuwen, C. (2018). Multi-electrode alpha tACS during varying background tasks fails to modulate subsequent alpha power. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00428

Ferber, S., & Karnath, H.-O. (2001). How to assess spatial neglect - Line bisection or cancellation tasks? *Journal of Clinical and Experimental Neuropsychology*, *23*(5), 599–607. https://doi.org/10.1076/jcen.23.5.599.1243

Fernandez-Duque, D., & Posner, M. I. (1997). Relating the mechanisms of orienting and alerting. *Neuropsychologia*, *35*(4), 477–486. https://doi.org/10.1016/S0028-3932(96)00103-0

Fernandez-Duque, D., & Posner, M. I. (2001). Brain imaging of attentional networks in normal and pathological states. *Journal of Clinical and Experimental Neuropsychology*, *23*(01), 74–93. https://doi.org/10.1076/jcen.23.1.74.1217

Feurra, M., Blagoveshchensky, E., Nikulin, V. V., Nazarova, M., Lebedeva, A., Pozdeeva, D., Yurevich, M., & Rossi, S. (2019). State-dependent effects of transcranial oscillatory currents on the motor system during action observation. *Scientific Reports*, *9*(1), 1–11. https://doi.org/10.1038/s41598-019-49166-1

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D., & Bisiach, E. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport*, *11*(7), 1519–1521.

Gallotto, S., Duecker, F., Ten Oever, S., Schuhmann, T., De Graaf, T. A., & Sack, A. T. (2020). Relating alpha power modulations to competing visuospatial attention theories. *NeuroImage*, *207*, 1–10. https://doi.org/10.1016/j.neuroimage.2019.116429

Goedert, K. M., Boston, R. C., & Barrett, A. M. (2013). Advancing the science of spatial neglect rehabilitation: An improved statistical approach with mixed linear modeling. *Frontiers in Human Neuroscience*, *7*(MAY). https://doi.org/10.3389/fnhum.2013.00211

Gould, I. C., Rushworth, M. F., & Nobre, A. C. (2011). Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *Journal of Neurophysiology*, *105*(3), 1318–1326. https://doi.org/10.1152/jn.00653.2010

Greene, D. J., Barnea, A., Herzberg, K., Rassis, A., Neta, M., Raz, A., & Zaidel, E. (2008). Measuring attention in the hemispheres: The lateralized attention network test (LANT). *Brain and Cognition*, *66*(1), 21–31. https://doi.org/10.1016/j.bandc.2007.05.003

Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha oscillations correlate with the successful inhibition of unattended stimuli. *Journal of Cognitive Neuroscience*, *23*(9), 2494–2502. https://doi.org/10.1162/jocn.2010.21557

Hartwigsen, G., & Silvanto, J. (2023). Noninvasive brain stimulation: Multiple effects on cognition. *The Neuroscientist*, *29*(5), 639–653. https://doi.org/10.1177/10738584221113806

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). Entrainment of brain oscillations by transcranial alternating current stimulation. *Current Biology*, *24*(3), 333–339. https://doi.org/10.1016/j.cub.2013.12.041

Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00279

Hilgetag, C. C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced “virtual lesions” of human parietal cortex. *Nature Neuroscience*, *4*(9), 953–957. https://doi.org/10.1038/nn0901-953

Hopfinger, J. B., Parsons, J., & Fröhlich, F. (2017). Differential effects of 10-Hz and 40-Hz transcranial alternating current stimulation (tACS) on endogenous versus exogenous attention. *Cognitive Neuroscience*, *8*(2), 102–111. https://doi.org/10.1080/17588928.2016.1194261

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*(2), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Huisman, K., Visser-Meily, A., Eijsackers, A., & Nijboer, T. (2013). Hoe kan de diagnostiek van visueel neglect verbeterd worden? *Tijdschrift Voor Neuropsychologie*, *8*(3), 134–140.

Husain, M., & Nachev, P. (2007). Space and the parietal cortex. *Trends in Cognitive Sciences*, *11*(1), 30–36. https://doi.org/10.1016/j.tics.2006.10.011

Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, *4*(1), 26–36. https://doi.org/10.1038/nrn1005

Jannati, A., Fried, P. J., Block, G., Oberman, L. M., Rotenberg, A., & Pascual-Leone, A. (2019). Test–retest reliability of the effects of continuous theta-burst stimulation. *Frontiers in Neuroscience*, *13*. https://doi.org/10.3389/fnins.2019.00447

Kasten, F. H., Dowsett, J., & Herrmann, C. S. (2016). Sustained aftereffect of α-tACS lasts up to 70 min after stimulation. *Frontiers in Human Neuroscience*, *10*. https://doi.org/10.3389/fnhum.2016.00245

Kasten, F. H., & Herrmann, C. S. (2022). The hidden brain-state dynamics of tACS aftereffects. *NeuroImage*, *264*, 119713. https://doi.org/10.1016/j.neuroimage.2022.119713

Kasten, F. H., Wendeln, T., Stecher, H. I., & Herrmann, C. S. (2020). Hemisphere-specific, differential effects of lateralized, occipital–parietal α- versus γ-tACS on endogenous but not exogenous visual-spatial attention. *Scientific Reports*, *10*. https://doi.org/10.1038/s41598-020-68992-2

Kemmerer, S. K. (2022). *Drawn to the rhythm: Measuring and modulating brain oscillations during visual attention and learning*. Gildeprint Drukkerijen. https://doi.org/10.26481/dis.20220131sk

Kemmerer, S. K., De Graaf, T. A., Ten Oever, S., Erkens, M., De Weerd, P., & Sack, A. T. (2022). Parietal but not temporoparietal alpha-tACS modulates endogenous visuospatial attention. *Cortex*, *154*, 149–166. https://doi.org/10.1016/j.cortex.2022.01.021

Kemmerer, S. K., Sack, A. T., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Schuhmann, T. (2022). Frequency-specific transcranial neuromodulation of alpha power alters visuospatial attention performance. *Brain Research*, *1782*, 147834. https://doi.org/10.1016/j.brainres.2022.147834

Koch, G., Oliveri, M., Torriero, S., & Caltagirone, C. (2005). Modulation of excitatory and inhibitory circuits for visual awareness in the human right parietal cortex. *Experimental Brain Research*, *160*(4), 510–516. https://doi.org/10.1007/s00221-004-2039-2

Krause, B., & Cohen Kadosh, R. (2014). Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience*, *8*. https://doi.org/10.3389/fnsys.2014.00025

Lasaponara, S., D'Onofrio, M., Pinto, M., Dragone, A., Menicagli, D., Bueti, D., De Lucia, M., Tomaiuolo, F., & Doricchi, F. (2018). EEG correlates of preparatory orienting, contextual updating, and inhibition of sensory processing in left spatial neglect. *Journal of Neuroscience, 38*(15), 3792–3808. https://doi.org/10.1523/JNEUROSCI.2817-17.2018

Lasaponara, S., Pinto, M., Aiello, M., Tomaiuolo, F., & Doricchi, F. (2019). The hemispheric distribution of a-band EEG activity during orienting of attention in patients with reduced awareness of the left side of space (spatial neglect). *Journal of Neuroscience*, *39*(22), 4332–4343. https://doi.org/10.1523/jneurosci.2206-18.2019

Lupiáñez, J., & Funes, M. J. (2005). Peripheral spatial cues modulate spatial congruency effects: Analysing the "locus" of the cueing modulation. *European Journal of Cognitive Psychology*, *17*(5), 727–752. https://doi.org/10.1080/09541440540000103

McCalley, D. M., Lench, D. H., Doolittle, J. D., Imperatore, J. P., Hoffman, M., & Hanlon, C. A. (2021). Determining the optimal pulse number for theta burst induced change in cortical excitability. *Scientific Reports*, *11*(1), 8726. https://doi.org/10.1038/s41598-021-87916-2

McIntosh, R. D., Ietswaart, M., & Milner, A. D. (2017). Weight and see: Line bisection in neglect reliably measures the allocation of attention, but not the perception of length. *Neuropsychologia*, *106*, 146–158. https://doi.org/10.1016/j.neuropsychologia.2017.09.014

Mohsen, S., Pourbakht, A., Farhadi, M., & Mahmoudian, S. (2019). The efficacy and safety of multiple sessions of multisite transcranial random noise stimulation in treating chronic tinnitus. *Brazilian Journal of Otorhinolaryngology*, *85*(5), 628–635. https://doi.org/10.1016/j.bjorl.2018.05.010

Neuling, T., Rach, S., & Herrmann, C. S. (2013). Orchestrating neuronal networks: Sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Frontiers in Human Neuroscience, 7*. https://doi.org/10.3389/fnhum.2013.00161

Neuling, T., Ruhnau, P., Fuscà, M., Demarchi, G., Herrmann, C. S., & Weisz, N. (2015). Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *NeuroImage*, *118*, 406–413. https://doi.org/10.1016/j.neuroimage.2015.06.026

Newman, D. P., O'Connell, R. G., & Bellgrove, M. A. (2013). Linking time-on-task, spatial bias and hemispheric activation asymmetry: A neural correlate of rightward attention drift. *Neuropsychologia*, *51*(7), 1215–1223. https://doi.org/10.1016/j.neuropsychologia.2013.03.027

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. (2016). The Clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimulation*, *9*(3), 336–346. https://doi.org/10.1016/j.brs.2016.03.010

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience*, *35*(1), 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Posner, M. I. (1994). Attention: The mechanisms of consciousness. *Proceedings of the National Academy of Sciences*, *91*(16), 7398–7403. https://doi.org/10.1073/pnas.91.16.7398

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*(1), 25–42. https://doi.org/10.1146/annurev.ne.13.030190.000325

Radecke, J.-O., Fiene, M., Misselhorn, J., Herrmann, C. S., Engel, A. K., Wolters, C. H., & Schneider, T. R. (2023). Personalized alpha-tACS targeting left posterior parietal cortex modulates visuo-spatial attention and posterior evoked EEG activity. *Brain Stimulation*, *16*(4), 1047–1061. https://doi.org/10.1016/j.brs.2023.06.013

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. https://doi.org/10.1038/25993

Robertson, I. H., Tegnér, R., Tham, K., Lo, A., & Nimmo-Smith, I. (1995). Sustained attention training for unilateral neglect: Theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology*, *17*(3), 416–430. https://doi.org/10.1080/01688639508405133

Rode, G., Pagliari, C., Huchon, L., Rossetti, Y., & Pisella, L. (2017). Semiology of neglect: An update. *Annals of Physical and Rehabilitation Medicine*, *60*(3), 177–185. https://doi.org/10.1016/j.rehab.2016.03.003

Ruhnau, P., Neuling, T., Fuscá, M., Herrmann, C. S., Demarchi, G., & Weisz, N. (2016). Eyes wide shut: Transcranial alternating current stimulation drives alpha rhythm in a state dependent manner. *Scientific Reports*, *6*(1), 27138. https://doi.org/10.1038/srep27138

Sack, A. T., Paneva, J., Küthe, T., Dijkstra, E., Zwienenberg, L., Arns, M., & Schuhmann, T. (2023). Target engagement and brain state dependence of transcranial magnetic stimulation: Implications for clinical practice. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2023.09.011

Salatino, A., Zavattaro, C., Gammeri, R., Cirillo, E., Piatti, M. L., Pyasik, M., Serra, H., Pia, L., Geminiani, G., & Ricci, R. (2023). Virtual reality rehabilitation for unilateral spatial neglect: A systematic review of immersive, semi-immersive and non-immersive techniques. *Neuroscience & Biobehavioral Reviews*, *152*, 105248. https://doi.org/10.1016/j.neubiorev.2023.105248

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W. R., & Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917–2926. https://doi.org/10.1111/j.1460-9568.2005.04482.x

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *PLoS ONE*, *14*(11), 1–25. https://doi.org/10.1371/journal.pone.0217729

Schultheis, M. T., & Rizzo, A. A. (2001). The application of virtual reality technology in rehabilitation. *Rehabilitation Psychology*, *46*(3), 296–311. https://doi.org/10.1037/0090-5550.46.3.296

Schutter, D. J. L. G., Smits, F., & Klaus, J. (2023). Mind matters: A narrative review on affective state-dependency in non-invasive brain stimulation. *International Journal of Clinical and Health Psychology*, *23*(3), 100378. https://doi.org/10.1016/j.ijchp.2023.100378

Spreij, L. A., Ten Brink, A. F., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2020). Increasing cognitive demand in assessments of visuo-spatial neglect: Testing the concepts of static and dynamic tests. *Journal of Clinical and Experimental Neuropsychology*, *42*(7), 675–689. https://doi.org/10.1080/13803395.2020.1798881

Stecher, H. I., & Herrmann, C. S. (2018). Absence of alpha-tACS aftereffects in darkness reveals importance of taking derivations of stimulation frequency and individual alpha variability into account. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.00984

Stecher, H. I., Notbohm, A., Kasten, F. H., & Herrmann, C. S. (2021). A comparison of closed loop vs. fixed frequency tACS on modulating brain oscillations and visual detection. *Frontiers in Human Neuroscience*, *15*. https://doi.org/10.3389/fnhum.2021.661432

Sturm, W., Schmenk, B., Fimm, B., Specht, K., Weis, S., Thron, A., & Willmes, K. (2006). Spatial attention : more than intrinsic alerting ? *Exp Brain Res*, *171*, 16–25. https://doi.org/10.1007/s00221-005-0253-1

Sturm, W., & Willmes, K. (2001). *On the Functional Neuroanatomy of Intrinsic and Phasic Alertness*. *84*, 76–84. https://doi.org/10.1006/nimg.2001.0839

Sturm, W., Willmes, K., Orgass, B., & Hartje, W. (1997). Do specific attention deficits need specific training? *Neuropsychological Rehabilitation*, *7*(2), 81–103. https://doi.org/10.1080/713755526

Suppa, A., Huang, Y.-Z., Funke, K., Ridding, M. C., Cheeran, B., Di Lazzaro, V., Ziemann, U., & Rothwell, J. C. (2016). Ten years of theta burst stimulation in humans: Established knowledge, unknowns and prospects. *Brain Stimulation*, *9*(3), 323–335. https://doi.org/10.1016/j.brs.2016.01.006

Szczepanski, S. M., & Kastner, S. (2013). Shifting attentional priorities: Control of spatial attention through hemispheric competition. *The Journal of Neuroscience*, *33*(12), 5411–5421. https://doi.org/10.1523/jneurosci.4089-12.2013

Thut, G., Bergmann, T. O., Fröhlich, F., Soekadar, S. R., Brittain, J.-S., Valero-Cabré, A., Sack, A. T., Miniussi, C., Antal, A., Siebner, H. R., Ziemann, U., & Herrmann, C. S. (2017). Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. *Clinical Neurophysiology*, *128*(5), 843–857. https://doi.org/10.1016/j.clinph.2017.01.003

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/jneurosci.0875-06.2006

Thut, G., Nietzel, A., & Pascual-Leone, A. (2005). Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. *Cerebral Cortex*, *15*(5), 628–638. https://doi.org/10.1093/cercor/bhh164

Van der Stigchel, S., & Nijboer, T. C. W. (2017). Temporal order judgements as a sensitive measure of the spatial bias in patients with visuospatial neglect. *Journal of Neuropsychology*, *12*(3), 427–441. https://doi.org/10.1111/jnp.12118

Van der Stoep, N., Visser-Meily, J. M. A., Kappelle, L. J., De Kort, P. L. M., Huisman, K. D., Eijsackers, A. L. H., Kouwenhoven, M., Van der Stigchel, S., & Nijboer, T. C. W. (2013). Exploring near and far regions of space: Distance-specific visuospatial neglect after stroke. *Journal of Clinical and Experimental Neuropsychology*, *35*(8), 799–811. https://doi.org/10.1080/13803395.2013.824555

Van Heugten, C. M. (2017). Novel forms of cognitive rehabilitation. In B. A. Wilson, J. Winegardner, C. M. Van Heugten, & T. Ownsworth (Eds.), *Neuropsychological rehabilitation: The international handbook.* (pp. 425–433). Routledge/Taylor & Francis Group.

Van Heugten, C. M., Bertens, D., & Spikman, J. (2017). Richtlijn neuropsychologische revalidatie. *Tijdschrift Voor Neuropsychologie*, *12*(3).

Van Heugten, C. M., Sillekens, N., Metsemakers, J., & Van den Akker, M. (2020). De onzichtbare gevolgen van hersenletsel. *Huisarts En Wetenschap*, *63*(2), 49–53. https://doi.org/10.1007/s12445-019-0415-1

Van Schouwenburg, M. R., Sörensen, L. K. A., De Klerk, R., Reteig, L. C., & Slagter, H. A. (2018). No differential effects of two different alpha-band electrical stimulation protocols over fronto-parietal regions on spatial attention. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00433

Veniero, D., Benwell, C. S. Y., Ahrens, M. M., & Thut, G. (2017). Inconsistent effects of parietal α-tACS on pseudoneglect across two experiments: A failed internal replication. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.00952

Vossen, A., Gross, J., & Thut, G. (2015). Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. *Brain Stimulation*, *8*(3), 499–508. https://doi.org/10.1016/j.brs.2014.12.004

Wang, T., De Graaf, T., Tanner, L., Schuhmann, T., Duecker, F., & Sack, A. T. (2023). Hemispheric asymmetry in TMS-induced effects on spatial attention: A meta-analysis. *Neuropsychology Review*. https://doi.org/10.1007/s11065-023-09614-2

Wang, T., De Graaf, T., Williams, J., Wang, Z., Schuhmann, T., Duecker, F., & Sack, A. T. (2023). The myth of TMS-induced ipsilateral enhancement in visual detection paradigms: A systematic review and meta-analysis of inhibitory parietal TMS studies in healthy participants. *Neuroscience & Biobehavioral Reviews*, *155*, 105437. https://doi.org/10.1016/j.neubiorev.2023.105437

Wischnewski, M., Alekseichuk, I., & Opitz, A. (2023). Neurocognitive, physiological, and biophysical effects of transcranial alternating current stimulation. *Trends in Cognitive Sciences*, *27*(2), 189–205. https://doi.org/10.1016/j.tics.2022.11.013

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience*, *20*(6), 1–6. https://doi.org/10.1523/jneurosci.20-06-j0002.2000

Wöstmann, M., Vosskuhl, J., Obleser, J., & Herrmann, C. S. (2018). Opposite effects of lateralised transcranial alpha versus gamma stimulation on auditory spatial attention. *Brain Stimulation*, *11*(4), 752–758. https://doi.org/10.1016/j.brs.2018.04.006

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE*, *5*(11), e13766. https://doi.org/10.1371/journal.pone.0013766

Zebhauser, P. T., Vernet, M., Unterburger, E., & Brem, A.-K. (2019). Visuospatial neglect - a theory-informed overview of current and emerging strategies and a systematic review on the therapeutic use of non-invasive brain stimulation. *Neuropsychology Review*, *29*(4), 397–420. https://doi.org/10.1007/s11065-019-09417-4

Impact paragraph

The objective of the research in this thesis was to enhance our understanding of visuospatial attention and treatment of neglect. Neglect, a frequent and disabling outcome after stroke, impairs a patient's ability to attend and respond to visual information in one side of space, leading to significant functional limitations. Despite its prevalence, treatment options for neglect remain limited, with visual scanning training (VST) as the recommended standard treatment, though not all patients benefit from this conventional approach. Additionally, VST and the assessment of neglect is typically conducted using paper-and-pencil tasks and tests, which, while useful, have limitations in capturing the full extent of a patient's deficits and in providing dynamic, real-time feedback. Our research represents a crucial step toward changing this, advancing both the treatment and assessment of neglect. Recognizing the need for more sophisticated tools, we developed a computerized battery designed for both training and testing visuospatial attention. This approach allows for the potential for more tailored and effective interventions, as well as more precise, objective measurements.

Especially in the chronic phase of brain injury, treatment traditionally emphasizes coping strategies to help patients adapt to their condition. However, there is a growing shift toward addressing the core deficits to achieve more substantial recovery. Institutions like the *Hersenstichting* (Dutch Brain Foundation), are increasingly emphasizing the importance of treatments that go beyond symptom management to target the root causes of impairments. Over the past fifty years, extensive fundamental research into the neural basis of brain deficits following injury, such as spatial attention deficits, has provided a robust scientific foundation. This substantial body of research, as well as the more recent technological advancements in neuromodulatory techniques, offers a credible rationale for considering non-invasive brain stimulation (NIBS) as a potential treatment that directly targets the biological basis for stroke-related impairments. Although investigations into the precise mechanisms underlying attention impairment after brain damage are still ongoing, stroke rehabilitation research has increasingly focused on exploring NIBS techniques in clinical studies.

In this thesis, NIBS techniques were employed across multiple studies, both as a research tool to modulate visuospatial attention in healthy individuals (**part I**) and as a therapeutic intervention for patients with neglect (**part II**). Over the years, most research in NIBS has focused on inhibiting the contralesional hemisphere to reduce neglect. However, this approach has yielded limited and inconsistent results, sometimes even causing undesired effects on the contralateral side. Our research introduced a new approach based on oscillatory entrainment using transcranial alternating current stimulation (tACS), which targets specific brain oscillations to modulate neural activity.

We firstly introduced a novel method for evaluating treatment options that could be applied in rehabilitation (**part I**). Transcranial magnetic stimulation (TMS) was used to induce neglect-like behavioral patterns in healthy volunteers, which were then 'virtually treated' using tACS at alpha frequency. The results from this part clarify the complex role of the posterior parietal cortex (PPC) in visuospatial attention. By demonstrating that disrupting the PPC through inhibitory brain stimulation (continuous theta burst stimulation; cTBS) causes behavioral impairments in alertness and executive control, this research highlights aspects of the PPC's role that previous TMS-attention studies may have missed, as they primarily focused on spatial orienting. This multifaceted contribution broadens our understanding of attention mechanisms and lays the groundwork for further exploration into how different components of attention interact. Although the subsequent application of alpha-tACS did not effectively reduce the neglect-like behavioral patterns in this experiment, the observed dependence of brain stimulation effects on the state of the brain – illustrated by the interaction between cTBS and tACS – provides critical insights for the development of more effective neurostimulation protocols.

Our research in **part I**, by showing the multifaceted contributions of the PPC to attention mechanisms, thus suggests that future TMS-attention studies could benefit from a more integrated or holistic approach and further advance clinical research and practice. For instance, the understanding gained from previous research on the interaction between the alerting and orienting networks has led to the development of alertness training programs, which have been shown to help neglect patients compensate for deficits in the orienting system and reduce neglect. Similarly, our studies uncovered significant interactions between the three components of attention (i.e., alerting, orienting, executive control) that could also contribute to clinical applications. For example, the observed inhibitory relationship between executive control and alerting suggests that alertness training might be more effective in reducing neglect when conducted in distraction-free, controlled environments.

In **part II** of this thesis, we investigated the effects of alpha-tACS in stroke patients. The results across our two patient studies are particularly compelling given the robust and reliable improvements observed. The proof-of-concept evidence presented here demonstrates that tACS can be an effective therapeutic intervention for patients with neglect following a stroke, particularly when combined with training (VST). In chronic neglect patients sustained improvements were observed up to three months post-treatment. These long-lasting effects highlight the potential for meaningful recovery, even in the chronic stages of stroke.

Our tACS approach aligns with the recent trend of directly tackling the underlying causes of impairments to facilitate improvement rather than solely managing its symptoms. At the same time, it is essential to complement this brain-targeted approach with a broader, holistic perspective that considers personal and contextual factors. This perspective aligns with the International Classification of Functioning (ICF) model, a biopsychosocial framework that views a person's level of functioning as a dynamic interaction between health conditions, environmental factors, and personal factors. The ICF model supports an integrated treatment approach, emphasizing that effective treatment should address not only the biological aspects of the impairment but also the limitations patients may experience in their daily lives (activities and participation), as well as other personal and environmental factors influencing overall functioning. Therefore, while targeting visuospatial attention bias, the core deficit of neglect, is crucial for advancing recovery, it must be balanced with an understanding of the individual's context to ensure comprehensive and effective care and treatment, with the ultimate goal to optimize quality of life.

This multidisciplinary approach highlights the importance of looking *beyond the brain* to consider the broader impact of interventions, a practice that will become increasingly common as NIBS is adopted in clinical settings. In this thesis, our research embraced such a holistic approach, examining not only the effects of NIBS on brain activity (electrophysiological effects) but also on clinically relevant functional outcomes, such as behavioral effects on neuropsychological tasks, and measures of daily life activities. While improvements were noted in functional measures of visuospatial attention bias, they did not extend to daily life activities. Future research should focus on enhancing the transfer of these effects to everyday tasks through more ecologically valid forms of VST.

The clinical and practical advantages of this new approach are significant. When combined with VST, tACS has the potential to be both safe and effective, with long-lasting effects. As stroke recovery moves beyond symptom management and given our promising results, it is time to advocate for the integration of tACS into standard rehabilitation programs, as part of a more holistic approach, offering a potentially stronger, faster, and more sustainable recovery path for patients with neglect. Also, the potential for personalizing the tACS-based VST approach could lead to more tailored rehabilitation strategies that address the individual variability in treatment responses, thereby enhancing the efficacy and meaningfulness of interventions. Collaborating with rehabilitation centers for future larger trials could validate these results, ensuring that our tACS-based combination therapy makes a lasting impact on clinical practice. Moreover, this method is adaptable; it could be implemented as part of a home-based rehabilitation program, making treatment more accessible to a wider range of patients and reducing the burden on healthcare facilities. Evaluating the cost-effectiveness of implementing the intervention in a home setting is crucial, as it may provide a more accessible and sustainable solution for ongoing rehabilitation.

The societal impact of this research is substantial. Stroke is a leading cause of disability worldwide, and neglect is a common and debilitating consequence. In The Netherlands, approximately 40,000 individuals suffer a stroke each year. Due to advancements in acute and subacute medical care, more individuals are surviving these events, leading to an increasing number of people living with the chronic effects of stroke. By introducing a novel and effective treatment option, this research offers hope for improving the quality of life for stroke survivors.

The research findings are especially relevant for neuroscientists, clinicians, neuropsychologists, and healthcare providers working in stroke rehabilitation. Scientific conferences and peer-reviewed publications have ensured – and will continue to ensure in the future – that the academic and medical communities are informed and able to build upon this research. Collaborations with rehabilitation centers and stroke support organizations can help bring these findings into clinical practice. Throughout this research journey, various Dutch rehabilitation centers and healthcare organizations that are specialized in supporting and treating stroke patients, have been involved to varying degrees (*InteraktContour*, *De Hoogstraat Revalidatie*, *Heliomare, Esdégé-Reigersdaal, De Noorderbrug/'s Heeren Loo*). Their contributions ranged from providing expertise in developing the study protocol and fully digitized training program to educating their organizations about neglect and the current evidence for its treatment, as well as recruiting patients. Furthermore, healthcare policymakers and administrators can benefit from understanding the implications of adopting innovative treatments like our tACS-based VST approach, which shows promise for home-based rehabilitation and could lead to better patient outcomes and more efficient use of healthcare resources.

In conclusion, the research presented in this thesis represents a significant advancement in the field of neurorehabilitation. By bridging scientific understanding and clinical application, this work lays the foundation for more effective, personalized, and accessible treatment options for stroke survivors affected by neglect. The continued exploration and application of these findings have the potential to make lasting contributions to both science and society. As we move forward, it is essential to maintain a holistic and interdisciplinary approach, integrating brain-based NIBS with behavior-based rehabilitation techniques and using function-based and clinically relevant outcome measures, both in the short term and the long term. By doing so, we can ensure that the benefits of these innovative treatments extend beyond functional improvements to enhance the quality of life for individuals living with stroke-related disabilities.

Samenvatting

Summary in Dutch

De genegeerde zijde aan het licht

Het beter begrijpen en behandelen van visueel-ruimtelijke aandachtstoornissen met niet-invasieve hersenstimulatie

Het onderzoek in dit proefschrift heeft tot doel ons inzicht in visueel-ruimtelijke aandacht te verdiepen en de behandeling van neglect te verbeteren. Neglect is een syndroom dat vaak voorkomt na een unilaterale beroerte en wordt gekenmerkt door verminderde aandacht voor één zijde van de ruimte. Het is een beperkende aandoening die dagelijkse activiteiten en zelfzorg aanzienlijk kan belemmeren. Er is een dringende behoefte aan behandelingen voor neglect die langdurige en klinisch-relevante verbeteringen kunnen bieden.

In de afgelopen twee decennia hebben studies bij gezonde proefpersonen, uitgevoerd met elektro-encefalografie (EEG), inzicht gegeven in hoe visueel-ruimtelijke aandacht wordt gereguleerd door elektrische activiteit in de hersenen (hersengolven). EEG-studies hebben specifiek aangetoond dat het verplaatsen van aandacht in de ruimte samenhangt met een asymmetrie in de sterkte van alfagolven tussen de hersenhelften, vooral in de posterieure (achterste) hersengebieden. Transcraniële wisselstroomstimulatie (*transcranial alternating current stimulation*, afgekort als tACS) is een vorm van niet-invasieve elektrische hersenstimulatie die ritmische hersenactiviteit kan beïnvloeden. TACS kan de natuurlijke ritmes van de hersenen versterken door sinusvormige stroompjes van lage intensiteit toe te dienen die op dezelfde frequentie trillen als de hersengolven. Omdat deze stroom in een ritmisch patroon wordt toegediend, kan deze synchroniseren met de natuurlijke ritmes van de hersengolven en zo de hersenactiviteit moduleren. TACS, toegediend op de alfafrequentie, is in verschillende recente studies gebruikt om de lateralisatie van alfasterkte en daarmee visueel-ruimtelijke aandacht te beïnvloeden. Opvallend is dat al deze eerdere studies uitsluitend bij gezonde individuen zijn uitgevoerd, terwijl er nog geen onderzoek is gedaan naar de effecten van alpha-tACS bij personen met asymmetrische aandachtstoornissen zoals neglect.

In dit proefschrift worden in meerdere studies niet-invasieve hersenstimulatietechnieken toegepast, hetzij als onderzoeksinstrument om visueel-ruimtelijke aandacht bij gezonde individuen te onderzoeken (**deel I; hoofdstukken 2 en 3**), hetzij als therapeutische interventie voor patiënten met neglect (**deel II; hoofdstukken 4, 5 en 6**).

Deel I

Het eerste deel van dit proefschrift (**hoofdstukken 2 en 3**) introduceert een vernieuwende aanpak voor het evalueren van behandelingsopties die toegepast zouden kunnen worden in de revalidatie. In de studies in deze hoofdstukken wordt transcraniële magnetische stimulatie (TMS) gebruikt om neglect-achtige gedragskenmerken op te wekken bij 32 gezonde proefpersonen. Vervolgens wordt alpha-tACS toegepast om deze gesimuleerde neglectpatiënten virtueel te behandelen. Voor de TMS maken we gebruik van een inhiberend protocol, namelijk het *continuous theta burst stimulation* (cTBS) protocol dat bekendstaat om zijn vermogen hersenactiviteit te onderdrukken. Dit protocol wordt toegepast om de activiteit in de rechter posterieure pariëtale cortex (PPC) te verstoren. Deze pariëtale structuren spelen een belangrijke rol in visueel-ruimtelijke aandachtsprocessen. Ondanks de korte duur van de stimulatie, slechts 40 seconden, kan cTBS langdurige effecten veroorzaken die tot een uur na de stimulatie kunnen aanhouden. We benutten deze periode om alpha-tACS toe te passen op de linker PPC. De effecten worden op gedragsniveau gemeten met een computertaak, de *lateralized-attention network test* (LANT) waarmee drie belangrijke componenten van aandacht (alertheid, oriëntatie en executieve controle) worden geëvalueerd. Alertheid verwijst naar het vermogen om in een staat van paraatheid en waakzaamheid te verkeren, zodat snel gereageerd kan worden op prikkels of veranderingen in de omgeving. Oriënterende aandacht verwijst naar het vermogen om de aandacht gericht te verplaatsen naar een bepaalde stimulus of plek in de omgeving. Oriëntatiebias verwijst naar de neiging om de aandacht consistent naar één kant van het visuele veld te verplaatsen, zoals bij neglect. Executieve controle helpt bij het selecteren van relevante informatie en het onderdrukken van irrelevante informatie wanneer er conflicterende of concurrerende informatie is die om verwerking vraagt. Daarnaast worden de effecten op neuronale niveau gemeten met behulp van EEG.

Door de effecten van TMS op alertheid en executieve controle bij gezonde individuen aan te tonen, benadrukt de studie in **hoofdstuk 2** de veelzijdige functionele bijdragen van de rechter PPC aan verschillende aandachtmechanismen. We vinden echter geen effect van TMS op oriënterende aandacht, hoewel de rol van de PPC in oriënterende aandacht regelmatig in de wetenschappelijke literatuur is aangetoond.

Zoals verwacht, resulteert TMS op de rechter PPC in een toegenomen sterkte van alfagolven in de rechterhersenhelft vergeleken met de linkerhersenhelft direct na de stimulatie, vergeleken met de placebo conditie. De mate van alpha-sterkte lateralisatie correleert bovendien met de veranderingen in alertheid en executieve control. Naast alfagolven onderzoeken we ook de effecten van TMS op theta-sterkte. Hoewel de groep als geheel geen duidelijke verandering in theta-sterkte lateralisatie laat zien na TMS, blijkt er wel een significant verband te zijn tussen de mate van theta-sterkte lateralisatie en de verandering in oriëntatiebias. Dit geeft aan dat er mogelijk individuele verschillen zijn die niet tot uiting komen in de gemiddelde groepsresultaten, maar wel belangrijke inzichten kunnen opleveren wanneer op individueel niveau wordt gekeken.

De studie levert ook interessante inzichten op in de interactie tussen de eerdergenoemde drie componenten van aandacht en bevestigt bevindingen uit eerder onderzoek. Het laat tevens zien hoe onze resultaten klinisch onderzoek en de toepassing in de klinische praktijk verder kunnen helpen. **Hoofdstuk 3** toont echter aan dat de daaropvolgende toepassing van alpha-tACS niet effectief is in het verminderen van neglect-achtige gedragskenmerken, waarschijnlijk omdat de kort daarvoor toegediende TMS de effecten van tACS op alfasterkte omkeerde. Dit wijst op het belangrijke concept *state-dependence* van hersenstimulatie-effecten, namelijk dat de effecten van stimulatie afhankelijk zijn van de toestand waarin de hersenen zich bevinden op het moment van stimulatie. De volgende stap die in de daaropvolgende hoofdstukken wordt beschreven, is het onderzoeken van de effecten van alpha-tACS bij patiënten met daadwerkelijk neglect. Dit is belangrijk, omdat de TMS bij gezonde proefpersonen de hersentoestand zodanig beïnvloedt dat de effecten van alpha-tACS mogelijk worden gemaskeerd of zelfs omgekeerd.

Deel II

Het tweede deel van dit proefschrift (**hoofdstukken 4, 5 en 6**) richt zich op de evaluatie van alpha-tACS als therapeutische interventie voor patiënten met neglect na een beroerte. In **hoofdstuk 4** wordt het eerste bewijs geleverd dat deze stimulatiemethode klinisch effectief zou kunnen zijn bij de behandeling van neglect bij patiënten in de subacute fase na een beroerte, zoals gedefinieerd in onze studie als binnen één tot vier maanden na de beroerte. In dit placebo-gecontroleerde onderzoek ondergaan zestien subacute beroertepatiënten met neglect zowel alpha-tACS als placebo stimulatie, gericht op de contralesionale PPC. Aandacht wordt gemeten met een gecomputeriseerd visueel detectieparadigma en twee veelgebruikte, standaard papier-en-potlood neglect tests (namelijk een cancellatie- en een lijnbisectietaak). We observeren een significante verschuiving van aandachtbias naar het ipsilaterale (contralesionale; verwaarloosde) gezichtsveld na alpha-tACS, maar niet na placebo-tACS. Dit resulteert in een vermindering van neglect symptomen, zoals gemeten met de visuele detectie- en cancellatietaak, maar niet op de lijnbisectietaak.

Op basis van de bevindingen uit deze eerste patiëntstudie ontwerpen we een grotere, dubbelblinde, gerandomiseerde gecontroleerde klinische studie om de effectiviteit van meerdere behandelsessies tijdens de revalidatie te onderzoeken, met als doel langdurige effecten te realiseren (**hoofdstuk 5**). Deze studie richt zich op de toegevoegde waarde van multi-sessie tACS als aanvulling op een zes weken durende periode van visuele scantraining (VST). Het doel is om te bepalen of de toevoeging van tACS sterkere effecten oplevert dan training alleen. We onderzoeken deze effecten bij 22 chronische beroertepatiënten met neglect, waarbij we gebruikmaken van gedigitaliseerde tests om de ernst van neglect op symptoomniveau nauwkeurig vast te leggen, naast metingen van neglect-achtig gedrag in dagelijkse activiteiten.

In **hoofdstuk 6** rapporteren we de resultaten van deze tweede patiëntstudie, die opnieuw taak-specifieke verbeteringen op de contralesionale (verwaarloosde) zijde toont, specifiek geassocieerd met actieve tACS. Verbeteringen hielden aan tot drie maanden na de behandeling. Dit wijst op het potentieel voor herstel door revalidatie, zelfs in de latere stadia na een beroerte. We vinden echter geen significante verbetering van tACS ten opzichte van placebo op lijnbisectietaken of op metingen van neglect-gedrag in dagelijkse activiteiten. Mogelijk zou een ecologisch meer valide vorm van scantraining die de nadruk legt op generalisatie naar het dagelijks functioneren, de impact van de gecombineerde tACS-VST-interventie op het dagelijks leven kunnen versterken.

Toekomstig onderzoek

In **hoofdstuk 7** worden alle bevindingen samengevat en wordt verder gereflecteerd op de implicaties van deze resultaten. Hoewel onze resultaten in beide patiëntstudies (**hoofdstukken 4 en 6**) consistent en robuust zijn, wijzen eerdere hersenstimulatie- en neglectstudies op aanzienlijke inter- en intra-individuele variabiliteit in behandelresponsen. Dit benadrukt de noodzaak van systematisch onderzoek naar factoren die de uitkomsten van onze interventie beïnvloeden en naar het personaliseren van zowel de tACS- als de VST-componenten. Suggesties zijn bijvoorbeeld: het inzetten van *augmented reality* (AR) voor VST, het afstemmen van analyses op basis van individuele patiëntprofielen en het personaliseren van stimulatieparameters. Hoewel gepersonaliseerde tACS-protocollen zijn voorgesteld op basis van eerdere studies bij gezonde individuen, zijn deze nog niet getest bij patiënten met neglect. Toekomstig onderzoek zou zich daarom moeten richten op het verder ontwikkelen van tACS-protocollen om de behandeling van neglectpatiënten te optimaliseren. Een gepersonaliseerde en gecombineerde tACS-VST-aanpak zou de effectiviteit kunnen verhogen en uiteindelijk kunnen leiden tot betekenisvolle verbeteringen in het dagelijks leven van mensen met neglect.

Acknowledgments

I know firsthand that it takes a village to raise a child. But it most certainly also takes a village to complete a PhD:

Teresa, ik had me geen betere begeleider kunnen wensen! Ik geloof dat een goede begeleider het verschil maakt tussen slagen en struikelen in een promotietraject. Ik bewonder hoe je precies wist wanneer je mij in de juiste richting moest sturen en wanneer je mij ruimte moest geven om mijn eigen weg te vinden. In de loop der jaren is er veel veranderd, zowel in jouw leven als in het mijne, en ik vond het fijn dat er altijd tijd en ruimte was om ook over persoonlijke dingen te praten. Ik weet dat je voor veel studenten een begeleider van goud bent, en dat ben je zeker ook voor mij geweest.

Caroline, ons eerste gesprek herinner ik me nog goed: op Utrecht Centraal. Wat was ik blij toen ik na onze kennismaking direct voor jou aan de slag mocht met de publicatie van het Hersenz onderzoek. Van jou heb ik zoveel geleerd; jouw scherpe inzichten en kennis over hersenletsel en wetenschappelijk onderzoek hebben mijn denken en werk echt verrijkt. Ik ben je dankbaar voor jouw begeleiding en vertrouwen.

Alex, your humor and ability to simplify complex topics were invaluable throughout this process. You had a way of making even the most intricate discussions accessible and engaging, and I truly appreciate that.

Alix, with you, I always had a place for meaningful conversations and shared moments. Throughout our PhD journeys, we could pour our hearts out, share laughs, and later exchange stories about the changing phases in our lives – especially about our little ones. Our baby showers truly stand out as unforgettable highlights! Not to mention all the sleepovers, which made this PhD journey not only more fun but also much more manageable for me, given the long travels. You've been there for me every step of the way, and it means so much that now you stand by my side as my paranymph.

Stefano, your programming skills were essential. Getting the LANT and eye-tracking experiments to run smoothly, analyzing the data, and discussing the results in depth. Your dedication and support made a significant difference.

Olof, al dat programmeerwerk… Wat een geluk dat jij dat als een hobby beschouwt! Dankzij jouw expertise en mijn neurotische controle kwamen we een heel eind. Ik heb onze samenwerking ontzettend gewaardeerd en ik vond het bovendien erg gezellig om samen de patiëntenstudies op te starten. Ik wens je veel succes met het afronden van jouw promotie!

Felix, your expertise in EEG analysis was indispensable. Your critical questions helped refine my interpretations, especially regarding the LANT studies, sharpening the story behind the data. I remember you telling me: “It’s the best part of science: where numbers turn into meaning.” It’s an honor to have you not only as a collaborator but also as my opponent. Your thought-provoking questions will undoubtedly contribute to a valuable discussion during my defense.

Inge, dank je wel voor je hulp bij het opzetten van de ingewikkelde mobiele EEG-set-up. Je input en ondersteuning waren ontzettend waardevol, en het is geweldig om nu de resultaten van de EEG te zien en die nu samen (met anderen) verder uit te werken.

Jelena, thank you for continuing with the EEG data analysis. It is so important to reap the rewards of years of hard work, not only from the researchers but also from the patients who endured the EEG sessions, thank you for your role in this.

Jeannette, altijd tijd voor een gezellige babbel en geïnteresseerd in hoe het met mij gaat. Je praktische hulp was van onschatbare waarde. Je zorgde ervoor dat de afstand tussen Maastricht en Amersfoort veel kleiner voelde. We stuurden pakketjes naar elkaar of spraken op slimme plekken af om spullen uit te wisselen. De gezellige lunches op de universiteit maakten Maastricht voor mij echt een stukje thuis.

Other colleagues and friends of the Brain Stimulation and Cognition group: Sanne, Qiannong, Ting, Jasmina, Tingting, Aline, Mathilde, Samantha, Selma, Tahnée, Lukas, Tom, Shanice, Geraldine, and Helen – what a vibrant and ever-changing group! I’m sure I’m forgetting some former BSC members, but I deeply appreciate the inspiring discussions and social moments we shared.

Tanja, wat hebben wij samen veel studenten begeleid! We raakten goed op elkaar ingespeeld en jouw expertise op het gebied van neglect was van onschatbare waarde. Bedankt voor al je waardevolle ideeën, feedback en het meeschrijven.

Jan, zonder jouw diepgaande statistische kennis zou de patiëntenstudie nooit zo grondig geanalyseerd en uitgewerkt zijn.

Een groot dankwoord aan alle studenten die betrokken waren bij de patiëntenstudie: Rika en Melissa, ik herinner me nog als de dag van gisteren hoe we de eerste sessies draaiden. Jullie hielpen bij het finetunen van de taken en werkten met zoveel enthousiasme. Manon en Marte, samen sterk! Marte, het was bijzonder om jouw laudatio te mogen uitspreken bij je afstuderen. Kobus, je was altijd trouw in je hulp bij de EEG-sessies. Soms moest je jezelf in allerlei bochten wringen om op tijd 'in het midden van het land' te zijn, maar je deed het altijd met inzet. Dimitry, jouw toewijding was bewonderenswaardig! Ik kon blind op jou vertrouwen en je nam me veel werk uit handen. Elisabeth, samenwerken met jou was ontzettend fijn. Je straalde rust uit, wat niet alleen je collega-onderzoekers maar ook de patiënten merkten. Kenneth, jouw programmeerwerk was van onschatbare waarde voor de analyses van de patiëntenstudie. Evenveel dank voor de gezellige (online) gesprekken die nooit saai waren maar om de één of andere reden ook grappig. Melissa and Julie, your programming work was also invaluable for the analyses. Eva, bedankt voor het 'op afstand' uitvoeren van de dataverzameling bij 'gezonden'. Ook Cécile, Kenny, Abdul, Nanda en Estelle, heel veel dank voor al jullie inzet. Rian en Kelsey, jullie waren de hekkensluiters!

Simone, Anna, and Paulina, thank you for helping me through the many, many (many!) sessions of the TMS-tACS study in Maastricht.

InteraktContour: Jan, Jaap, Mariska, jullie geloofden in mij vanaf het begin. Jullie gaven me de ruimte om mijn promotieonderwerp te kiezen en toonden altijd waardering voor mijn werk. Daarna Nicole en nu Gideon als mijn leidinggevende – jullie erkenning en steun betekenen veel voor me. Bovenal, Dianne, dank voor al die mailtjes en telefoontjes die je pleegde om me te helpen bij de werving van patiënten, zelfs tijdens mijn verlof. En aan alle begeleiders, trainers en behandelaars die ik 'gestalkt' heb – het was echt allemaal voor het goede doel!

Ook grote dank aan de wervende instellingen, in het bijzonder: Dianne (InteraktContour), Tanja (De Hoogstraat), Frank (De Noorderbrug/'s Heerenloo), Jeroen (Esdégé-Reigersdaal) en Marthe (Heliomare).

Aan alle mensen die deelnamen aan de onderzoeken – studenten en patiënten: wat een doorzettingsvermogen hebben jullie getoond. Jullie bijdrage was natuurlijk écht onmisbaar, want zonder deelnemers, geen data. Jullie geduld, medewerking en toewijding hebben ervoor gezorgd dat deze studie mogelijk werd en het resultaat nu realiteit is. Daar ben ik jullie allemaal enorm dankbaar voor.

Sylvia, Marjolein, Femke, Marije en Tom, het is bijna niet te geloven dat het inmiddels al zo'n dertien jaar geleden is dat we afstudeerden. Ik vind het geweldig en waardevol dat we nog steeds met ons 'VU groepje' afspreken, herinneringen delen en elkaar blijven volgen. Marije, in het bijzonder, bedankt voor je vriendschap, die sinds onze tijd op de VU en onze onderzoeksstage in Nepal, alleen maar hechter is geworden. Ik ben trots op jou, hoe je het moederschap omarmt, en op je prachtige zoon!

Lydia en Marjolijn, hoewel we ieder onze eigen weg zijn gegaan, is het altijd bijzonder hoe we, zodra we elkaar weer zien, met dezelfde humor en vertrouwdheid verdergaan alsof er sinds de PM geen tijd verstreken is. Bedankt voor jullie eerlijkheid en oprechte interesse (ook in mijn onderzoek), en bovenal voor al die jaren van trouwe vriendschap en voor alle die D.V. nog komen gaan.

Mr. King, you were the one who taught me my first English words, but what you gave me went far beyond language. You helped shape not just my ability to communicate internationally, but also my growth as a person, rooted in the values of faith and compassion. You showed me how to truly see and care for others. You even taught me how to smile more, reminding me that I didn’t always need to look so serious. And you once told me that the 'ij' in my name is like a smile itself. Your kindness, along with that of Rosslyn's other great teachers, has left a lasting impact in my life, and I’m forever grateful for that.

Wairimu, wewe ni rafiki yangu wa dhati! Asante kwa kunitania tulipokuwa katika darasa la tatu – hapo ndipo urafiki wetu ulipoanza. Nakupenda kama dada.

Joke, Wilco, Hinke, Mirthe, Ilse, Gerlinde, Henrike, Tom, Charlot en Floris, dank jullie wel voor jullie oprechte interesse in mijn onderzoek en promotie. Joke, in het bijzonder, soms voelde het bijna alsof ik een extra klankbord had! Het is fijn om te merken hoe betrokken jullie zijn, hoe jullie meeleven en altijd weer benieuwd zijn naar mijn werk. Ik ben blij dat ik dit met jullie mag delen.

Jonathan, gelukkig hoef je bij jouw werk geen Chinees te kunnen! Maar toch ben ik blij dat je altijd zo'n interesse hebt in mijn werk en alles wat ermee te maken heeft. Theo en Eveline, ook jullie wil ik bedanken voor jullie steun en belangstelling voor mijn promotie. Papa en mama, jullie hebben mij altijd gestimuleerd om mijn best te doen, niet alleen tijdens deze promotie, maar al vanaf jongs af aan. Jullie hebben mij niet alleen geleerd te streven naar kennis en groei, maar ook om vertrouwen te hebben in Hem. Jullie onvoorwaardelijke steun en liefde zijn de fundamenten geweest waarop ik heb kunnen bouwen. Pap, niet alleen als vader maar ook als doctor ben jij een rolmodel voor mij. Bedankt ook voor je hulp bij het uitgeven van mijn boek. En dan, als klap op de vuurpijl, ben jij mijn trotse paranymf.

Martijn, samen kunnen wij filosoferen over het leven en wat er écht toe doet. Het is fijn dat we elkaar zo goed aanvoelen en begrijpen, ook in ons werk. Jij komt altijd met goede ideeën waar ik zelf niet aan gedacht had, en dat helpt me enorm. Ik wil je ook bedanken voor je eindeloze geduld met mij. Het was niet altijd makkelijk om met mijn gestress om te gaan. Ik moet bekennen, het kwam me goed uit dat je zoveel hobby's hebt – zo voelde ik me nooit schuldig als ik me weer tot laat op de avond terugtrok in mijn kamer… en kon jij ook met een gerust hart een extra lang rondje gaan wielrennen. Ten slotte, onze drie grote kleine jongens, mama houdt zielsveel van jullie.

"*When I, in awesome wonder, consider all the works Thy hands have made, I see the stars and hear the rolling thunder – Thy power throughout the universe displayed. Then my soul sings to Thee, my Savior God: How great Thou art, how great Thou art!*"

About the author

Marij Middag-van Spanje was born on August 19th, 1989 in Dirksland, The Netherlands, and grew up moving frequently due to her parents' work, living in seven towns across the country and abroad. Her education took her to CSG Prins Maurits in Middelharnis and later to Driestar College in Gouda, where she earned her VWO diploma with a dual profile in *Natuur & Gezondheid* (Nature & Health) and *Natuur & Techniek* (Nature & Technology).

In 2007, she embarked on a Bachelor's degree in Health Sciences at Vrije Universiteit in Amsterdam. During her studies, she completed a research internship at Athena Institute, where she conducted a scientific literature review on brucellosis in India. Graduating cum laude, she continued with a Master's in Health Sciences in 2010, also at Vrije Universiteit, specializing in International Public Health and Prevention and Public Health. She spent a term in Nepal to do research for the Leprosy Foundation and International Nepal Fellowship, where she validated a psychological measurement tool to assess stigma in leprosy-affected individuals and people with disabilities across different cultural contexts.

After completing her Master's in 2012 (also cum laude), she briefly worked as a research assistant at Vrije Universiteit and also taught biology at Van Lodenstein College in Amersfoort. At the same time, she took on a role as a project leader at Zorggroep Syntein in Boxmeer, where she worked to improve primary diabetes care.

Longing to return to scientific research, in 2017 she had the opportunity to start a PhD project in a unique collaboration between InteraktContour (Nunspeet) and the Brain Stimulation and Cognition group at the Department of Cognitive Neuroscience of the Faculty of Psychology and Neuroscience at Maastricht University, headed by Prof. Dr. Alexander Sack. During her PhD trajectory under the supervision of Prof. Dr. Teresa Schuhmann, Prof. Dr. Caroline van Heugten, and Prof. Dr. Alexander Sack, she focused on exploring the potential of non-invasive brain stimulation to treat visuospatial neglect in stroke patients.

Marij is married to Martijn, and they have three sons: David, Manuel, and Pablo.

List of publications

Gallotto S., Schuhmann T., Duecker F., **Middag-van Spanje M.**, De Graaf T., & Sack A. T. (2022). Concurrent frontal and parietal network TMS for modulating attention. *iScience, 25*(3), 103962. https://doi.org/10.1016/j.isci.2022.103962

Middag-van Spanje, M., Duecker, F., Gallotto, S., De Graaf, T. A., Van Heugten, C., Sack, A. T., & Schuhmann, T. (2022). Transcranial magnetic stimulation over posterior parietal cortex modulates alerting and executive control processes in attention. *European Journal of Neuroscience, 56*(10). https://doi.org/10.1111/ejn.15830

Middag-van Spanje, M., Duecker, F., Sack, A. T., & Schuhmann, T. *(in preparation)*. State-dependence of therapeutic tACS: Preconditioning the brain with TMS reverses the oscillatory after effects of tACS on resting-state EEG.

Middag-van Spanje, M., Nijboer, T. C. W., Schepers, J., Van Heugten, C., Sack, A. T., & Schuhmann, T. (2024). Alpha transcranial alternating current stimulation as add-on to neglect training: A randomized trial. *Brain Communications, 6*(5). https://doi.org/10.1093/braincomms/fcae287

Middag-van Spanje, M., Schuhmann, T., Nijboer, T. C. W., Van der Werf, O., Sack, A. T., & Van Heugten, C. (2022). Study protocol of transcranial electrical stimulation at alpha frequency applied during rehabilitation: A randomized controlled trial in chronic stroke patients with visuospatial neglect. *BMC Neurology, 22*(1). https://doi.org/10.1186/s12883-022-02932-7

Middag-van Spanje, M., Smeets, S., Van Haastregt, J., & Van Heugten, C. (2019). Outcomes of a community-based treatment programme for people with acquired brain injury in the chronic phase: a pilot study. *Neuropsychological Rehabilitation*, 29(2). https://doi.org/10.1080/09602011.2017.1298527

Schuhmann, T., Duecker, F., **Middag-van Spanje, M.**, Gallotto, S., Van Heugten, C., Schrijnemaekers, A. C., Van Oostenbrugge, R., & Sack, A. T. (2022). Transcranial alternating brain stimulation at alpha frequency reduces hemispatial neglect symptoms in stroke patients. *International Journal of Clinical and Health Psychology, 22*(3). https://doi.org/10.1016/j.ijchp.2022.100326

Middag-van Spanje, M., & Schuhmann, T. *(submitted)*. Transcraniële wisselstroomstimulatie als aanvullende therapie bij visuospatieel neglect: Eerste evidentie voor werkzaamheid. *Tijdschrift voor Neuropsychologie*.

Trajkovic, J., **Middag-van Spanje, M.**, Leunissen, I., & Schuhmann, T. *(in preparation)*. Resting-state oscillatory markers of visuospatial neglect.