The potential of transcranial alternating current stimulation in application-oriented contexts

Von der Fakultät für Medizin und Gesundheitswissenschaften der Carl von Ossietzky Universität Oldenburg

zur Erlangung des Grades und Titels eines

Doktor rerum naturalium, Dr. rer. nat.

angenommene Dissertation

von Frau Birte Sofie Löffler

geboren am 04.02.1981 in Bremen

Gutachter: Prof. Dr.-Ing. Andreas Hein

Weitere Gutachter:

Prof. Dr. Christoph Siegfried Herrmann

Prof. Dr. Daniel Strüber

Tag der Disputation: 23.05.2024

Summary

Transcranial alternating current stimulation (tACS) is a non-invasive method of modulating brain activity in a frequency-specific manner. Through stimulation, the intrinsic oscillations are entrained by the external one, which leads not only to changes that can be measured in the EEG, but also in behavior. The latter indicates that tACs has the potential - with appropriate adaptations - to specifically improve performance. So far, tACS is used in basic research to investigate the functional role of brain oscillations in cognitive processes or in a therapeutic or clinical context to treat diseases with altered oscillation patterns. Since tACS is inexpensive, mobile, and relatively easy to apply, this method has great potential for application in complex tasks or in realistic context, which was investigated in this thesis. Two contexts were selected that are related to each other: older adults, whose proportion of the total population is increasing due to demographic change, and driving, which as complex task involves many cognitive functions. For older adults, driving represents quality of life, but represents risks due to cognitive decline with increasing age.

The aim of this thesis was – in a first step - to define a scenario and stimulation protocol in which tACS improves behavior, and – in two further steps - to transfer this protocol to the application context.

To develop the tACS protocol, findings from research were initially combined: In their 2014 study, Helfrich et al. showed that 40 Hz gamma tACS on posterior parietal brain areas decreases alpha amplitude. The alpha amplitude is known to increase over time under mental load or when sustained attention is required. The ability to remain alert for long periods of time and to react to a small number of stimuli is also known as vigilance. If the vigilance decreases, not only does the alpha amplitude increase, but the performance also decreases, which has been proven in experiments by longer reaction times and a lower detection rate. The correlation between the increasing alpha amplitude with decreasing vigilance and the possibility of reducing the alpha amplitude with 40 Hz tACS gave rise to the research question of Study I: Can stimulation with 40 Hz tACS at posterior brain regions counteract vigilance decrement and the increase of reaction times in a visual experiment in the laboratory with young participants? Since this question could be answered positively (the increase in reaction times over time was significantly lower in the intervention group compared to a placebo-stimulated group), the tACS protocol was repeated with the same task but with older adults (Study II) and with a task adapted to the application in a driving simulator (Study III). Although vigilance decrement was recorded in both Study II and Study III (Study II: increased reaction times with increasing time and a higher alpha amplitude after the test compared to before; Study III: slowing of brake reaction times with increasing time), no influence of the stimulation could be demonstrated. Due to the high variability of the older participants' characteristics (Study II) and behavior (Study III), it is unclear whether the stimulation had no effect or whether it is too small to be detected with the selected sample. Possible causes of the variability and its consequences for the experimental data are discussed. For future

studies, it is recommended to record and include as many factors as possible (age, medication, anatomy, behavioral types, anatomical traits and so on). Personalized stimulation protocols (e.g. adjusted to individual models of the electric field, frequencies adapted to physiological parameters or in a close-loop application) also appear to be preferable to a "one dose fits all" approach.

Zusammenfassung

Transkranieller Wechselstromstimulation (tACS) ist eine nicht invasive Methode Hirnaktivität frequenz-spezifisch zu modulieren. Durch die Stimulation werden die intrinsischen Oszillationen durch die äußeren „mitgenommen“, was nicht nur zu Veränderungen führt, die im EEG gemessen werden können, sondern auch im Verhalten. Letzteres indiziert, dass tACS das Potential hat - bei entsprechenden Anpassungen - gezielt die Leistung zu verbessern. tACS wird in der Grundlagenforschung eingesetzt, um die funktionelle Rolle von Hirnoszillationen bei kognitiven Prozessen zu untersuchen oder im therapeutischen oder klinischen Kontext, um Krankheiten mit veränderten Oszillationsmustern zu behandeln. Da tACS kostengünstig, mobil und relativ leicht anzuwenden ist, hat diese Methode großes Potential für die Anwendung bei komplexen Aufgaben bzw. in realitäts-nahen Kontexten, was in dieser Doktor-Arbeit untersucht wurde. Ausgewählt wurden zwei Kontexte, die miteinander verbunden sind: Ältere Menschen, deren Anteil aufgrund des demografischen Wandels zunimmt und Autofahren, das als komplexe Aufgabe viele kognitive Funktionen betrifft. Für ältere Menschen stellt Autofahren Lebensqualität dar, ist aber aufgrund kognitiver Abbauprozesse mit zunehmendem Alter riskant.

Ziel dieser Doktor-Arbeit war es im ersten Schritt ein Szenario und Stimulations-Protokoll zu definieren, in dem tACS Verhalten verbessert, sowie in weiteren Schritten dieses Protokoll in den Anwendungskontext zu übertragen.

Für die Entwicklung des tACS-Protokolls wurden zunächst Erkenntnisse aus der Forschung zusammengeführt: In ihrer 2014 erschienenen Studie zeigten Helfrich et al., dass 40 Hz gamma tACS an posterioren parietalen Gehirnbereichen die Alpha-Amplitude senkt. Die Alpha-Amplitude ist bekannt dafür, dass sie mit zunehmender Zeit unter Beanspruchung oder bei anhaltender Wachsamkeit zunimmt. Die Fähigkeit über lange Zeit aufmerksam zu bleiben und auch auf wenige Reize reagieren zu können wird auch als Vigilanz bezeichnet. Nimmt die Vigilanz ab, steigt nicht nur die Alpha-Amplitude, sondern auch die Performance nimmt ab, was in Versuchen anhand verlängerter Reaktionszeiten und einer geringeren Detektionsrate nachgewiesen werden. Aus dem Zusammenhang von steigender Alpha-Amplitude bei abnehmender Vigilanz und der Möglichkeit die Alpha-Amplitude mit 40 Hz tACS zu senken, ergab sich die Forschungsfrage von Studie I (Study I): Wirkt eine Stimulation mit 40 Hz tACS – gemessen anhand von weniger langsamen Reaktionszeiten – am Hinterkopf dem erwarteten Abfall der Vigilanz in einem visuellen Versuch im Labor mit jungen Probanden entgegen? Da diese Frage positiv beantwortet werden konnte (der Anstieg der Reaktionszeiten über die Zeit war signifikant geringer in der Interventionsgruppe im Vergleich zu einer Placebo-stimulierten Gruppe), wurde das tACS-Protokoll mit derselben Aufgabe, aber mit älteren Probanden (Study II) und mit einer an den Anwendungsfall angepassten Aufgabe im Fahrsimulator (Study III) wiederholt. Zwar wurden sowohl in Studie II als auch Studie III ein Abfall der Vigilanz erfasst (Study II:

erhöhte Reaktionszeiten mit zunehmender Zeit und eine höhere Alpha-Amplitude, nachdem Versuch im Vergleich zu vorher; Study III: Verlangsamung der Bremsreaktionszeiten mit zunehmender Zeit), es konnte aber kein Einfluss der Stimulation nachgewiesen werden. Aufgrund der hohen Variabilität der älteren Probanden (Study II) und des Verhaltens der Probanden (Study III), ist es unklar, ob die Stimulation keinen Effekt hatte oder ob dieser zu gering war, um ihn anhand der ausgewählten Stichprobe nachweisen zu können. Mögliche Ursachen der Variabilität und ihre Konsequenzen werden diskutiert. Für zukünftige Studien wird empfohlen weitere und möglichst viele Faktoren (Alter, Medikamenteneinnahme, Anatomie, Verhaltenstypen usw.) zu erfassen und mit einzubeziehen. Personalisierte Stimulations-Protokolle (z.B. anhand von individuellen Modellen des elektrischen Feldes, an physiologische Parameter angepasste Frequenzen oder eine Close-Loop-Anwendung) scheinen außerdem einem „one dose fits all“-Ansatz vorzuziehen zu sein.

Table of Contents

List of Abbreviations

AD	Alzheimer disease
CFC	Cross-frequency-coupling
DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalogram
IAF	Individual alpha frequency
MCI	mild cognitive impairment
NIBS	Non-invasive brain stimulation
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
tES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation

1. General Introduction

Transcranial alternating current stimulation (tACS) is a relatively recent non-invasive neuromodulation technique interfering with ongoing brain oscillations used for neurocognitive research. tACS technology has proven safe, with no adverse effects reported so far (Matsumoto & Ugawa, 2017; Sheffield et al., 2022). TACS devices are low-cost, easy to apply, and allow mobile use (Henao et al., 2018). TACS contributes to the understanding how the brain works and has been shown to improve cognitive performance and influences behavioral parameters, making it a potential tool to enhance performance in applied contexts (Klink et al., 2020). In the last decade, a growing amount of research has addressed the therapeutic application of tACS to treat neurological diseases in clinical settings (Strüber & Herrmann, 2020) and at home (Jones et al., 2022). Although there are comparable studies for stimulation techniques with direct current for applied contexts (e.g., Nelson et al., 2014; Sakai et al., 2014), there is a lack of practical research for tACS in this area so far. The much-studied ergonomic problem of declining attention in a monotonous scenario, associated with decreased behavioral performance over time (Oken et al., 2006; Pattyn et al., 2008), was chosen as context. At first, a promising stimulation setup based on recent tACS findings and well-known effects was defined and tested in a pilot study (Study I). In the two successive steps, the proven concept was transferred to older adults (Study II) and into the context of car driving (Study III).

Below detailed motivational reasons are given why older adults and car drivers were chosen (1.1), followed by a short description of brain oscillations, the working principle of tACS, the concept of vigilance (1.2)and the resulting research assumption (1.3). Further, the state of the art of relevant tACS research and drivers´ monitoring and interventional systems are described (1.4). The section closes with the aim and outline of this thesis (1.5) and an introduction to the three studies, which were conceptualized accordingly (1.6).

1.1 Motivation

For Western countries, one of the greatest challenges is dealing with the consequences of demographic change. By 2070, 30 % of the population will be 65 years and older (European Commission, 2020). Higher life expectancy and burdens on the retirement system require older adults to work longer, making them a considerable part of the active workforce. Furthermore, by 2030, 25 % of car drivers will be older than 65 years (Schlag et al., 2014). Getting old does not come without costs: Increasing restraints in mobility, the sensory system, and cognitive functions are inevitable. While restraints in mobility and the sensory system can be compensated reasonably well by assistive systems like elevators and hearing aids or substituting defective components (e.g., artificial hips, eye lenses) there is still a kind of helplessness regarding cognitive decline (Ganesan et al., 2019). Cognitive functions known to decrease with increasing age are speech

perception, working memory, processing speed, executive functions, reasoning, and spatial orientation (Hedden & Gabrieli, 2004; Salthouse, 2004) – all of which are also relevant for car driving, which is considered a complex task (Groeger, 2000, Chapter 10). As cognitive functions have been related to specific brain oscillations, tACS has great potential in older adults (e.g., Antonenko et al., 2016) and in the context of car driving (Groeger, 2000, Chapter 10).

However, car driving is not only relevant for older adults, but also essential for numerous jobs, commuting, or considered a pleasure. Car driving is a complex task, and individual failures harbor a high accident risk (Summala, 1996). In ergonomics, monotonous driving scenarios are a classical research theme as they resemble a prominent situation: Monotony leads to drowsiness, fatigue, or boredom, making it challenging for the driver to stay alerted and be able to react fast in the situation of a hazardous event – an effect called vigilance decrement (van Veen et al., 2020). Especially in the past years - due to increasing automation with partly automated driving systems that take the driver outside the loop but still leave her or him in charge and responsible, e.g., counteracting hazardous events (Greenlee et al., 2024; Körber et al., 2015) - systems to counteract vigilance decrement become essential. As car driving involves many cognitive processes that can be linked to specific brain oscillations and performance degeneration (Wascher et al., 2016), neurotechnology offers great potential for monitoring driver state and interventions (see 1.4.3) including tACS to enhance the driver`s state and behavior - at least for a limited time.

This thesis wants to investigate the application-oriented use of tACS to enhance cognitive (executive) functions expected to decline in age or while driving a car in vigilant situations: Can tACS be utilized to counterbalance vigilance decrement, especially addressing an older aged target group and in the context of car driving?

1.2 Background knowledge

The following knowledge is important for conceptualizing a study paradigm to answer the above question.

1.2.1 Brain oscillations and tACS

The brain consists of nerve cells that communicate with each other and are organized hierarchically. The electric activity of bunches of nerve cells can be measured via potential differences between scalp electrodes with an **electroencephalogram (EEG)** (Fröhlich, 2014). Rhythmic activity in distinct frequency bands is referred to as oscillations that are linked to specific cognitive functions. Roughly, delta (0 – 4 Hz) e.g., has been associated with deep sleep and memory consolidation, theta (4 – 7 Hz) with working and episodic memory, alpha (8 – 13 Hz) with executive functions, visual attention and memory processes, beta (13 – 30 Hz) with motor functions and attention, working memory and executive control, gamma (30 – 80 Hz) with the processing of incoming information, working and episodic memory (Klink et al., 2020). Alpha

oscillations are also supposed to have an inhibitory function and be closely linked to two fundamental functions of attention (suppression and selection) (Klimesch et al., 1996). Gamma oscillations emerge e.g., when a cat is observing prey (Bouyer et al., 1981) and have been linked to "Eureka!" moments when humans experience a burst of unexpected clarity (Santarnecchi et al., 2019).

Recent research has shown that fast and slow brain oscillations can be nested in and modify each other, an effect called **cross-frequency-coupling (CFC)**. CFC is believed to be a mechanism for information transfer and may provide information integration across several spatiotemporal scales (Canolty & Knight, 2010). CFC CFC can occur between distinct subharmonic frequency bands, e.g., gamma and alpha frequencies. Research has shown that interaction occurs during cognitive processes with the strongest coupling over occipital areas (Osipova et al., 2008; Palva et al., 2005). Gamma-alpha CFC is supposed to have a functional role in visual processing (Helfrich et al., 2016).

While scalp electrodes of an EEG are passive and only measure activity, electrodes for **transcranial electrical stimulation (tES)** are used to apply current through the scalp to influence brain activity. The intensity of the current is selected not to harm the patient or cause unpleasant feelings but still be able to induce an electrical field strong enough to potentially reach and influence the membrane potential of pyramid cells (and change the probability of the nerve cell generating an action potential) despite the resistance of hair, skin, and head bone (Antal & Herrmann, 2016; Fertonani & Miniussi, 2017). In tACS, an alternating current is used between two or more electrodes. Applied in the EEG frequency range, tACS is believed to work as an external oscillator or driving force on endogenous oscillations (Vosskuhl et al., 2018). The physiological principle is not entirely understood, but tACS is believed to modify intrinsic oscillations via entrainment (online) and be able to change spike-time-dependent plasticity, which explains aftereffects (offline). For example, tACS applied in the alpha range has been shown to enhance alpha power directly after stimulation for up to 70 minutes (Kasten et al., 2016). Because of interfering artifacts, it is not easily possible to apply tACS and measure EEG and tACS simultaneously (see Vosskuhl et al., 2018). Therefore, changes in behavioral parameters are often used as an indicator of stimulation success (e.g. see Lee et al., 2023). Stimulation with tACS does not always show effects, and the number of null results papers is increasing (Brignani et al., 2013; Lafleur et al., 2021; Lafon et al., 2017; van Schouwenburg et al., 2021). The success of tACS depends on carefully selecting stimulation parameters like electrode montage (size, shape, number, and stimulation site), stimulation frequency, intensity, and duration. Furthermore, tACS effects have been shown to vary by individual (trait differences), be task-specific, and strongly dependent on brain state (see Wischnewski et al., 2023, for a review and guideline).

Due to its nature to be able to modify intrinsic oscillations, tACS has been mainly applied in basic research to study cognitive functions (e.g. Cabral-Calderin & Wilke, 2020; Fröhlich et al., 2015) and in clinical and

therapeutical settings to treat diseases related to abnormal brain oscillations (Alexander et al., 2019; Elyamany et al., 2021; Moussavi et al., 2021; Strüber & Herrmann, 2020).

tACS is one procedure of tES and belongs with **transcranial magnetic stimulation (TMS)** to the **non-invasive brain stimulation (NIBS)** methods group. While TMS elicits nerve cells to fire, has safety issues, and has higher technical demands, tES has been referred to as easy to apply (Antal et al., 2022). Next to tACS, tES includes – among others - stimulation with direct current (**transcranial direct current stimulation – tDCS**) and random noise stimulation (Antal & Herrmann, 2016). Especially in the applied contexts tDCS has shown promising results (Nelson et al., 2014), and research in the driving field has been conducted (see section 1.4.3c). In tDCS a constant low-intensity (comparable to tACS) current between two (or more) electrodes is administered to the scalp. tDCS relies on modulating membrane polarization, with the brain tissue exposed to the anode becoming depolarized (excitatory effect) and the tissue underneath the cathode becoming hyperpolarized (inhibitory effect). Studies have shown that enhancing one brain region and introducing one desired behavior can have severe undesired effects on other functions (Iuculano & Cohen Kadosh, 2013). This "one wins, one loses"-effect could be explained by looking at the brain as a finite system with a limited processing capacity, also called a zero-sum model (Antal et al., 2022). This thesis concentrates on the potential of tACS, which interacts with intrinsic brain oscillations and works as an amplifier of what is already there and – is known to have less severe adverse until now (Matsumoto & Ugawa, 2017).

1.2.2 Vigilance

Vigilance is the capability to stay alerted and ready to react over prolonged tasks, e.g. required to detect rare and unpredictable stimuli (Pattyn et al., 2008; Warm et al., 2008). Vigilance is also referred to as sustained attention during intellectually unchallenging and monotonous tasks (Oken et al., 2006). Vigilance is important to maintain task performance against fatigue, distractions, and boredom. As Warm et al. (2008) postulate, “Vigilance requires hard mental work and is stressful.” Vigilance is accompanied by a performance decrement over prolonged tasks. On a behavioral level, vigilance decrement is reliably related to rising reaction times and reduced detection rates with time on task, as many studies have shown (Buck, 1966; Mackworth, 1948; Pattyn et al., 2008). For example, Pattyn et al. (2008) showed that the target detection capability decreases by 15% within 30 minutes of beginning a monotonous task. On a neuronal level vigilance decrement has been shown to correspond to rising posterior parietal alpha power (Clayton et al., 2015; Craig et al., 2012; Klimesch et al., 1996). Vigilance decrement is thought to be responsible for numerous accidents and other safety-critical events. It is therefore a much-studied research theme in ergonomics, e.g. in the context of work (operator, surveillance tasks) (Nelson et al., 2014) or considering vehicle control (pilots, car drivers) (Borghini et al., 2014). The connection between posterior parietal alpha power, more driving errors, and higher lane variability has also been observed with time on task in monotonous car driving (Wascher et al., 2016).

1.3 Conceptualization of research question

As mentioned before (1.2.2), one prominent neurophysiological marker of vigilance decrement over time is rising posterior parietal alpha power (Clayton et al., 2015; Craig et al., 2012; Klimesch et al., 1996). Neural brain oscillations in the alpha frequency range (8 -13 Hz) are the most dominant oscillations in healthy, awake, and resting humans (Klimesch, 2012). They are prepotent in the posterior parietal cortical region that involves the visual cortex (Klimesch, 2012; Palva et al., 2005) and have been under investigation in much tACS research (Koninck et al., 2023). Vigilance tasks are often used to compare the effects of stimulation with alpha tACS on alpha power at posterior parietal regions (Kasten et al., 2016; Stecher & Herrmann, 2018; Stecher et al., 2017). Under specific conditions stimulation with 10 Hz or **individual alpha frequency (IAF)** has been shown to enhance alpha power at posterior parietal regions (Helfrich et al., 2014a, 2014b; Kasten et al., 2016).

As already mentioned in section 1.2.1, it has been recently shown that tACS not only works when applied in the same frequency spectrum as the addressed oscillation but that stimulation can also affect the slow or fast partner in the before-mentioned nested oscillations (Helfrich et al. 2014b). Helfrich et al. (2014b) found that gamma tACS on posterior brain regions successfully down-regulated alpha power. Alpha and gamma oscillations are known to exhibit an antagonistic relationship. They stimulated both hemispheres but found the effect mentioned above despite stimulating in phase or with a 180° phase difference. In this thesis central regions were stimulated with a small stimulation and a bigger reference electrode to exclude hemispheric effects as has been proven beneficial (Kasten et al., 2016; Stecher & Herrmann, 2018).

From the background knowledge described in 1.2 and the experience mentioned above with tACS, two effects were combined:

1. **Vigilance decrement leads to an increase in reaction times and alpha power at posterior parietal brain regions.**
2. **Alpha power has been shown to be downregulated by gamma tACS at posterior parietal brain regions.**

The following research question was formulated:

Does the stimulation with gamma tACS on the posterior parietal regions counteract vigilance decrement by downregulating the rise in reaction times and alpha power?

1.4 State of the Art

In this section, we will summarize the current research and developments concerning tACS (its usage for general performance enhancement, addressing older adults, its application in the context of vigilance and driving-like contexts), followed by a summary of cognitive decline in older adults and its treatment options and an overview of systems and approaches available for car driving (monitoring and interventional systems with focus on vigilance).

1.4.1 tACS

TACS has gained increased attention in recent years, as the growing number of publications indicates (Figure 1).

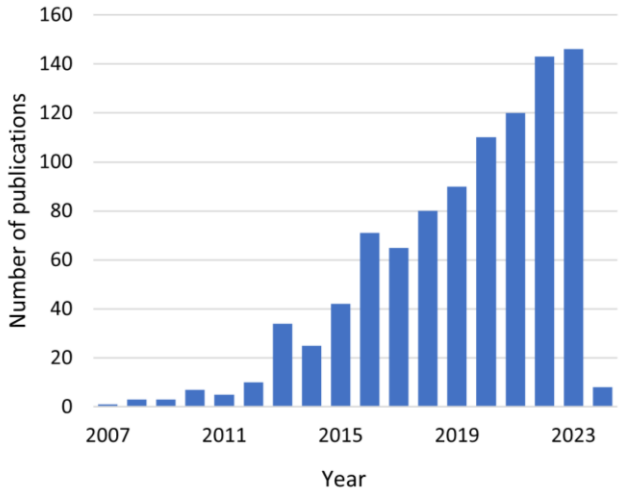

Figure 1.

A search on PubMed with the term "transcranial alternating current stimulation" shows the occurrence of 838 publications referring to this keyword from 1st January 2007 to 20th January 2024 (PubMed, 2024).

The publications include reviews, statements, and for the most part research papers. With intensifying research, the number of null-result papers has grown (Brignani et al., 2013; Lafleur et al., 2021; Lafon et al., 2017; van Schouwenburg et al., 2021) as papers where replication of stimulation success failed (Veniero et al., 2017) and leaving a debate on the effectiveness of tACS interventions and limiting factors (Wischnewski et al., 2023; Wu et al., 2021).

a. Effects in healthy young adults

A recent review summarizing 56 studies points out a small positive effect size of tACS protocols on cognitive performance in healthy young adults (Lee et al., 2023). Stimulation in the theta range seems beneficial for several cognitive functions, including working memory, executive functions, and declarative memory (Klink et al., 2020). Also, gamma-tACS has been successfully applied: Offline 40 Hz gamma-tACS over the right occipital cortex improved the accuracy of face and object perception compared to 5 Hz or sham stimulation (Gonzalez-Perez et al., 2019). Findings by Hoy et al. (2015) indicate that gamma-tACS over the left **dorsolateral prefrontal cortex (DLPFC)** may improve working memory performance and parietal

gamma-tACS significantly increased working memory recall precision (Thompson et al., 2021). Online gamma-tACS on the left middle frontal gyrus reduced the time needed to solve complex tasks related to fluid intelligence compared to theta and sham stimulation (Santarnecchi et al., 2016).

Considering motor learning, a couple of studies report positive effects, e.g., beta-tACS has been shown to improve the consolidation process after skill acquisition (Yamaguchi et al., 2020), while others, e.g., gamma-tACS on the left cerebellum (Wessel et al., 2020), showed no effect. Takeuchi & Izumi (2021) give a good summary of the application of tACS for motor learning. A recent review by Rostami et al. (2024) concludes that online and offline applications of alpha, beta, and gamma tACS over motor cortex improves motor function and tACS enhances motor function and cortical excitability but is dependent upon the stimulating parameters (i.e., frequency, electrode montage, electrode size, and timing). Takeuchi & Izumi (2021) argument that next to different stimulation parameters, task designs, and the great variability among tACS responders and non-responders may lead to the heterogeneous effect of uniform tACS over the primary motor cortex.

b. addressing older adults

In 2016, the first study successfully targeting healthy older adults aged 60 years and above with tACS was published (Antonenko et al., 2016). Here, theta-tACS over the temporal parietal cortex improved implicit language learning skills. Since then, quite some studies have been published, e.g., showing success in improving working memory performance (Reinhart & Nguyen, 2019), multi-tasking (Zanto et al., 2021), motor functions (Guerra et al., 2021) and motion learning (Fresnoza et al., 2020). A recent review also points out the benefits of tACS for an older target group (Grover et al., 2023).

Gamma-tACS has been applied to older adults suffering from mild cognitive impairment and dementia with promising results (Nissim et al., 2023). Ten minutes of gamma-tACS on frontal or parietal areas seem to be sufficient to improve cognitive functioning and modulate brain oscillations for at least 60 minutes after stimulation, and 60 minutes of 40 Hz-tACS over the precuneus can improve episodic memory (Manippa et al., 2023).

Some studies compared the same tACS protocol between young and older age groups. Rufener et al. (2016) found that 40 Hz tACS on the bilateral auditory cortex diminished task accuracy in young adults, but older adults benefitted from this stimulation, resulting in a more precise phonetic categorization. Fresnoza et al. (2020) found an age-dependent effect of tACS on motor skill consolidation. A group of young and old healthy adults performed a serial reaction time task before and after a tACS session with their individual or 2 Hz higher than their individual alpha frequency to the left motor cortex. While alpha stimulation at individual alpha frequency or plus 2 Hz improved skill consolidation in older adults, the same stimulation showed only minimal improvement in younger adults for IAF stimulation and a detrimental effect on

consolidation for IAF plus 2 Hz. Guerra et al. (2021) found out, that gamma tACS on the primary motor cortex has a greater effect in young that older adults. Zanto et al. (2021) transferred a tACS protocol improving multitasking ability in young adults to older adults where they applied theta tACS on the prefrontal cortex. They could not repeat stimulation success but found a correlation between an individualized tACS-induced electric field that was modeled according to previously obtained magnetic resonance imaging data and individual peak theta frequency.

c. Vigilance decrement

A few tACS studies try to modify vigilance decrement or investigate its effect on sustained attention (see Annarumma et al., 2018; for a review). Clayton et al. (2019) found out that alpha tACS on the occipitoparietal cortex prevented deterioration, but only in two of four different sustained attention tasks. Martínez-Pérez et al. (2022) stimulated the right dorsolateral prefrontal cortex with theta and alpha tACS during two different tasks. The typical vigilance decrement could only be prevented when the arousal level was low. For simple button press responses to red stimuli both theta and alpha-tACS succeeded, whereas only alpha was successful when digits were presented and the three had to be ignored. Rostami et al. (2021) stimulated the medial prefrontal cortex with theta tACS and found a significant impact on task and physiological measures. Wei et al. (2021) investigated the effect of theta-tACS over the lateral and medial frontal cortices and found a marginal trend that sustained attention was downregulated by tACS. While the researchers named so far were more or less interested in understanding brain functions, van Schouwenburg et al. (2021) set out to enhance sustained attention on the dorsomedial prefrontal cortex. Contrary to their expectations, they were not able to reduce the vigilant decrement using theta tACS.

d. Car driving

To the best knowledge, no tACS study explicitly addresses car driving related skills or is performed in a driving context (natural or simulated driving).

What has been used in tACS studies is the video game called “NeuroRacer” that consists of a driving task, i.e. control of a virtual car and keeping it in a specific area, combined with a reaction task to signs at the top of the screen, both to be handled via a gamepad controller. The game has been originally developed to enhance cognitive control in older adults (Anguera et al., 2013). Hsu et al. (2017, 2019) used “NeuroRacer” to test tACS effects on multitasking performance. In a first study, they found out that bilateral prefrontal cortex theta-tACS shows a significant enhancement of multitasking performance after a 90-minute session (Hsu et al., 2017). In a second study, they re-tested this paradigm and found out that manipulating the phase of current polarity does not, but that changing the inter-session interval of the stimulation protocol eliminated the previous observed performance improvements (Hsu et al., 2019).

1.4.2 Older adults

As already mentioned in section 1.1, aging is accompanied by cognitive decline. While long-term memory and crystalline intelligence stay intact, and this experience even be adventurous compared to younger people, there are strong indicators that fluid intelligence (Bugg et al. 2006) and short-term memory are going to deteriorate with age (Salthouse, 2004). The likelihood of developing neurodegenerative diseases like **mild cognitive impairment (MCI)** and **Alzheimer disease (AD)** increases with only rare treatment options. As it lacks effective pharmacological interventions for cognitive enhancement in the older population, countermeasures to prevent decline are physical exercise, cognitive training, functional nutrition and NIBS (Chu et al., 2021; Peters, 2006; Prehn & Flöel, 2015), e.g., anodal tDCS on the left DLPFC in combination with cognitive training may be beneficial for several subdomains of cognitive dysfunction in patients with MCI or AD (Chu et al., 2021).

1.4.3 Car driving

For many people driving constitutes an everyday task and cars and traffic are omnipresent in areas populated by humans. As driving is considered a complex task and errors can have severe consequences, much research is prompted on this topic (Groeger, 2000, Chapter 9). The phenomenon of driver fatigue or drowsiness - which is related to vigilance decrement - has been under investigation, especially (Albadawi et al., 2022; van Veen et al., 2020). This section will summarize how driver states related to vigilance decrement can be monitored, what vigilance enhancement systems exist so far and how tES has been applied in the driving context so far.

a. Driver drowsiness detection and monitoring systems

Driver drowsiness detection systems in general use following measures based on (Abbas & Alsheddy, 2020; Albadawi et al., 2022; Khan & Lee, 2019; Nasri et al., 2022):

- Facial Features Analysis / images (eye, mouth, head, face, yawning and so on)
- Physiological signals analysis (EEG, ECG, EOG, EMG, respiration rate, heart rate variability, skin temperature, electro dermal activity and so on)
- Driving pattern analysis / in-vehicle data (steering wheel, lane deviation, GPS, ultrasonic sensors and so on)

These measures are obtained with cameras and mobile and vehicle in-built sensors (Abbas & Alsheddy, 2020). Monitoring systems can be distinguished between their focus on the driver, the vehicle, or the environment. Assistive systems available in modern cars include in-vehicle sensors and cameras for eye tracking and to record head motion (see Khan & Lee, 2019, for an overview).

Smart cameras and deep learning techniques are used for image processing and feature extraction to estimate the amount of the driver´s tiredness (Kalisetti et al., 2023).

Neurophysiological measures have been proven to be effective in determining drowsiness while driving but are problematic in natural driving: Most studies using EEG recorded signals from occipital regions that are hairy and require dry electrodes, movement of drivers shows as artifacts in the EEG record requiring a motion sensor (Li & Chung, 2022).

A recent study used a wearable EEG headset and proposed the frontal theta / parietal alpha ratio as an alert-state objective measure for vigilance decrement as it was found to be associated with the magnitude of driver´s behavioral changes – namely cumulative slowing and erraticity of the braking reaction times - over the course of a 1,5-hour long car-following paradigm. The task was performed during assisted driving with adaptive cruise control, and drivers had to perform emergency braking when the leading car braked suddenly (Seet et al., 2023).

Other promising options to detect levels of vigilance are hybrid systems, that integrate driver´s EEG signals with driving context data. In a simulated driving task, Guo et al. (2018) showed that the combination of a support vector machine with particle swarm optimization methods improved classification accuracy. In their experiment participants were as well asked to react to the brake events of a leading car.

b. Vigilance enhancement systems for monotonous driving scenarios

The standard vigilance systems in the cars today usually monitor driving performance over time on task and alert and encourage the driver to take a brake if performance deteriorates (van Veen et al., 2020) or give other signals, e.g. vibrations (Khan & Lee, 2019) to alert the driver for a short time. But suffering from vigilance is not only a safety threat but has also a negative effect on well-being. Therefore, it is also of great interest for car manufacturers to find intervention systems and create a more pleasurable driving experience (van Veen et al., 2020). Conventional vigilance enhancement strategies contain caffeine , chewing-gum or fragrance exposure (Al-Shargie et al., 2019). In the context of car driving also talking to a passenger, opening a window, or listening to radio are common strategies (Gershon et al., 2011). More recent approaches in the context of car driving have shown that micro- or macro-movements (active or passive) or thermal stimuli like cooling maybe beneficial (van Veen et al., 2020), e.g. recent research has shown that passive fatigue in monotonous driving scenarios can be prevented by a seat-integrated mobilization system: Schneider et al. (2021) found a significant impact of the mobilization seat on alpha spindle rate after a two-hour ride. Tactile and rhythmic haptics (Bodala et al., 2020) or auditory stimulation (Al-Shargie et al., 2021; Al-Shargie et al., 2019) may also be promising vigilance enhancement tools. Also integrating challenges have been shown to counteract performance decline e.g. noisy visual stimuli like

artificially stimulated rain (Bodala et al., 2016) or integrating secondary, alertness maintaining tasks, while driving (Oron-Gilad et al., 2008).

c. Enhancing of driving with tES

As of January 2024, only in a couple of papers the effect of tES in a driving context was investigated with mixed results. All used tDCS as a stimulation method and applied it to more frontal parts of the head. Two papers conducted in a driving simulator found a positive effect of tACS on behavior: Beeli et al. (2008) found out that anodal tDCS on the dorsolateral prefrontal cortex evoked less risky driving behavior. Sakai et al. (2014) showed that in participants with an upregulation of the right DLPFC both car-following and lane-keeping performance were improved. Li & Chung (2018) developed a wearable and wireless EEG-Gyroscope-tDCS brain machine interface system consisting of a headset and smartwatch. They recorded EEG and head moving data and applied tDCS in a closed-loop manner. In a simple driving simulator, they measured in ten participants with slight drowsiness a prolonged period of wakefulness after 10 minutes of tDCS on the forehead, but they could not enhance driver´s alertness in every single tDCS session. No positive effects of tDCS on the DLPFC on driving skills were found out by Brunnauer et al. (2018) who used a standardized computerized psychomotor test and by Ward et al. (2017) who tested in a simulator behavior during distracted scenarios. A recent study successfully applied focal high-definition tDCS on the right frontal eye field and found behavioral improvement in brake reaction times and less distractive behavior in a secondary task. Interestingly, the enhancing effect was only found between focal high-definition and conventional tDCS or sham stimulation, not between conventional tDCS and sham stimulation (Facchin et al., 2023).

1.5 Aim and outline

This thesis wants to investigate the potential of tACS in applied contexts concerning older adults and in the context of car driving. Healthy older adults have been the target of some tACS studies showing promising results concerning the enhancement of cognitive performance (e.g., Antonenko et al., 2016; Kraft & Hampstead, 2023), but most tACS research focuses on young participants. tES was applied to investigate its potential in modifying driving behavior in some studies, but only with direct current (see section Enhancing of driving with tES). This thesis is – to the best knowledge - the first approach to utilize stimulation with alternating current. Vigilance was selected as an appropriate scenario relevant to older adults and in car driving. Recent research hinted a promising stimulation paradigm: Gamma tACS has been shown to down-regulate alpha power at the visual cortex, while rising alpha power links to vigilance decrement and rising reaction times: This thesis wants to investigate if gamma tACS on the visual cortex can counteract vigilance decrement and the increment of reaction times in general, in older adults, and in the context of car driving. In three successive studies, this question is going to be answered: Stimulation setup and effect of the

stimulation were first tested in a pilot study in a laboratory setting with young participants (Study I), repeated with older adults (Study II) and tested in a driving simulator with young participants (Study III). For the laboratory settings (Study I and Study II), a visual two-alternative-forced-choice reaction time task was developed; in the driving simulator, participants (Study III) were asked to follow a lead car in a fixed distance and react to spontaneous deceleration of the lead car via braking. Reaction times (Study I and Study II) and brake reaction times (Study III) were used to evaluate the occurrence of vigilance decrement and stimulation success. It was hypothesized that vigilance decrement occurs with time on task as shown in rising reaction or brake reaction times, error rates and alpha power (only Study II) and that this decrement is significantly less present in the group that received 40 Hz tACS compared to the SHAM- and control condition (only Study II and Study III).

In all three studies, the same stimulation parameters (electrode size, placement, and stimulation intensity) chosen according to successful tACS studies were applied (Kasten et al., 2016; Stecher et al., 2017). The duration was selected as the longest possible according to ethical standards to ensure enough time for vigilance decrement. The studies used a two-block design, with each 30-minute-long block containing 100 trials and a self-paced approximately 2-minute-long break in between. The first block served as the baseline. The second block served as an intervention, and participants were stimulated according to their addressed condition. Although following an in-between design, this study concept allowed the comparison of performance on an individual level (baseline vs. intervention) and ensured that the participants were already vigilant at the start of the intervention block. In principle, all three studies were accompanied by the same procedure: At the beginning of the experiment, exclusion criteria were checked, and participants were informed about the experimental procedure. After the experiment, participants were debriefed and asked to fill out questionnaires on adverse effects and the course of the experiment.

The following section will introduce the studies, how they differentiate, and their outcomes in more detail.

1.6 Introduction to studies I, II and III

Following three studies are presented in this thesis:

- Study I: Löffler et al. 2018
- Study II: Löffler et al. 2023
- Study III: Löffler et al., in review

Study I (Löffler et al., 2018) constituted the pilot study to ensure the effectiveness of the stimulation setup. 23 participants (11 SHAM, 12 stimulated with 40 Hz tACS) conducted a visual two-alternative-forced-choice reaction time task in a laboratory setting. This study showed that the 40 Hz tACS stimulated group has a significantly less steep increase in reaction time over time compared to baseline or sham stimulation.

1 General Introduction

Study II was a repetition of Study I, except that older adults (aged 65 or above) participated; a resting EEG was recorded before and after the experiment, and a control frequency of 5 Hz was added. The EEG record was used to evaluate the individual alpha frequency and investigate the effect of time, task, and stimulation on alpha power. 48 participants (15 sham, 15 5 Hz, 18 40 Hz) were analyzed. A vigilance decrement (rising reaction times, rising alpha power post the experiment) could be detected, but no positive effect of the stimulation could be found.

Study III was conducted in a driving simulator with a car-following and braking task and was different from the visual two-alternative-forced-choice reaction time tasks used in Study I and Study II. The 49 participants were at a comparable age to the ones in Study I but were asked to have at least two years of driving experience. Study III also applied a control frequency of 5 Hz, and participants were divided into three groups (17 sham, 16 5 Hz, 16 40 Hz). Due to complexity, no EEG was recorded. Like in Study II, brake reaction times significantly increased with time on task, suggesting that vigilance decreased. However, no significant effect of the intervention with 40 Hz tACS could be detected.

Following sections 2, 3, and 4 present the studies in detail. In section 5, general findings will be summarized and discussed, and an outlook for future research will be given.

2. Study I

Counteracting the Slowdown of Reaction Times in a Vigilance Experiment With 40-Hz Transcranial Alternating Current Stimulation

Publication bibliography:

Löffler, Birte S.; Stecher, Heiko I.; Fudickar, Sebastian; de Sordi, Dominik; Otto-Sobotka, Fabian; Hein, Andreas; Herrmann, Christoph S. (2018): Counteracting the Slowdown of Reaction Times in a Vigilance Experiment With 40-Hz Transcranial Alternating Current Stimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 26(10), 2053–2061*. doi.org/10.1109/TNSRE.2018.2869471

The following author-edited version of the above-mentioned study is identical in content to the published article.

Author contributions:

Birte S. Löffler (BL), Heiko I. Stecher (HS), Sebastian Fudickar (SF), Andreas Hein (AH) and Christoph S. Herrmann (CH) conceptualized the study. BL and HS acquired participants and performed measurements. BL analyzed the data and wrote the manuscript. Dominik de Sordi and Fabian Otto-Sobottka consulted the statistical analysis. All authors contributed to the article and approved the submitted version.

I hereby confirm that Birte Sofie Löffler contributed to this study as mentioned above:

_____

Signature of primary supervisor - Prof. Dr.-Ing. Andreas Hein, Oldenburg, 25 January 2024

2 Study I

Counteracting the Slowdown of Reaction Times in a Vigilance Experiment With 40-Hz Transcranial Alternating Current Stimulation

Abstract:

Indicators for a decrement in vigilance are a slowdown in reaction times and an increase in alpha power in the electroencephalogram in posterior regions of the brain. Transcranial alternating current stimulation (tACS) is a neuropsychological technique that has been found to interact with intrinsic brain oscillations and is able to enhance cognitive and behavioral performance. Recent studies show that tACS in the gamma frequency range (30-80 Hz) is able to downregulate amplitudes in the alpha frequency range (8-12 Hz), in accordance to the effect referred to as cross-frequency coupling, where intrinsic alpha and gamma waves modulate each other. We applied 40 Hz gamma-tACS to the visual cortex during a vigilance experiment and investigated if stimulation improves reaction times and error rates with time-on-task. In our sham controlled experiment, participants completed two blocks of 30 minutes duration while performing the same visual two-choice task. The first block was used as BASELINE. A statistical analysis with a linear mixed model revealed a significantly lower increase of modeled reaction times over time in the INTERVENTION-block of the tACS-group as compared with their BASELINE-block whereas there was no significant change between the BASELINE- and INTERVENTION-block for the SHAM-group. Error rates did not differ between groups. This paper indicates that gamma-tACS can enhance performance in vigilance tasks as it significantly decreased the slowdown of reaction times in our study.

Index Terms:

Alpha power, brain stimulation, enhancement, gamma-tACS, reaction times, vigilance

I. INTRODUCTION

In order to investigate functional principles of the brain, non-invasive brain stimulation (NIBS) is a widely used technique [1], [2]. Researchers over the world try to foster these techniques for applications, especially in therapeutic and clinical contexts like e.g. cognitive impairment [2], the treatment of neurological diseases [3] or eating disorders [4]. Transcranial electrical stimulation (TES) is a comparatively cheap and easy to apply technique working with low electrical fields – making it ideal for private and mobile applications [5]. A lot of research focused on the TES-technique called transcranial direct current stimulation (tDCS). In tDCS two electrodes are placed on the scalp with a steady current flowing from anode to cathode. The exposed tissue is polarized and tDCS modifies spontaneous neuronal excitability and activity by a tonic de- or hyperpolarization of resting membrane potential [6]. Potential tDCS applicability has been shown in many domains e.g. in the treatment of depression [7], for cognitive training [8] and in

driving scenarios [9]. Although researchers reported the successful use of tDCS to modify behavioral and cognitive parameters, it has lately been critiqued because cognitive enhancement occurred at the expense of other cognitive functions [10] or had opposite effects depending on individual state [11]. A promising alternative to tDCS is transcranial alternating brain stimulation (tACS) that is believed to interact with ongoing oscillatory cortical activities.

In tACS an alternating current with a specific frequency is applied to the scalp. There is evidence that tACS interferes with ongoing oscillations, although the underlying mechanism has not been solved yet. tACS applied in the EEG range is believed to modulate brain oscillations by entrainment, resonance or the synchronization of neuronal networks [12]. As brain oscillations can be linked to particular ongoing cognitive or sensory-motor processes, it is possible to interfere with tACS and induce a behavioral change and to investigate causal associations between brain oscillations and cognitive processes [1], [13].

Enhancing effects in behavior have been found by a number of tACS studies in various domains, e.g. perception, attention, decision making, motor control, memory/cognition (see [2] or [14] for a review). Some researchers proclaim a potential use of tACS for therapeutic implementation e.g. for the treatment of cognitive deficits [2]. One research field is the combination of video games and tACS for neuro-cognitive optimization [15].

Our vision is the application of tACS for enhancing performance while driving a car as an extension of cars' assistive and monitoring facilities. Staying alerted and concentrated is one essential aspect of driving, especially in monotonous, non-demanding situations on motorways or when adaptive cruise control systems are used. This property is referred to as sustained attention or vigilance, meaning the action or state of keeping careful attention for possible danger or difficulties over a prolonged period of time [16]. Nine tDCS-studies addressed this effect with mixed results [6]. On a neuronal level electrophysiological brain research showed that increasing fatigue or reduced attention corresponds to rising alpha power especially in occipital posterior regions and simultaneously increasing reaction times [17]–[20]. Buck [21] confirmed in 1966 a positive correlation between rising reaction times and worse detection rates with increased time-on-task. This concept has been widely used in vigilance research [22]–[24]. Increase in posterior alpha power, more driving errors and higher lane variability have also been observed with timeon-task in a monotonous car driving scenario in a simulator study [25].

Thus, we conclude: Vigilance decrement leads to rising reaction time and alpha power. Therefore, downregulating alpha power might lead to stable reaction times. Recently, two studies demonstrated that gamma-tACS downmodulates amplitudes in the alpha range [26], [27] - notably, Helfrich et al. [26] observed this effect independently of stimulating the two hemispheres in phase or with 180° phase difference. A possible reason for the down-modulating effect is the antagonistic relationship between alpha and gamma oscillations referred to as cross-frequency coupling (also known for other frequencies) [28]: Brain

oscillations of specific different frequencies modulate each other [29]. Neuropsychological brain research showed that gamma and alpha frequencies interact with each other during cognitive processes with the coupling being strongest over occipital areas [30], [31].

Concerning tACS-research, quite some studies report on reaction times, but only a few mention a positive influence on reaction times (see [2] and [32] for a review): 10 Hz tACS on the motor cortex, e.g., significantly decreased reaction times compared to sham and with time-on-task in a serial reaction time task [33]. Polanía et al. [34] considered reaction times in their experiment and found out, that 6 Hz stimulation in-phase (0°) between two parietal and one central electrode on the left hemisphere elicited faster reaction times during a delayed letter discrimination task (and even deteriorated reaction times when stimulating out-of-phase (180°) compared to sham) – showing an influence on performance in both directions.

Influence of tACS on motor control have been shown by Wach et al. [35] that found out that 20 Hz tACS on the primary motor cortex resulted in movement slowing of the right hand. In an additional study investigating the underlying neurophysiological mechanisms they found out that 10 Hz tACS significantly reduced low gamma band corticomuscular coherence [36], suggesting cross-frequency interplay between alpha and low gamma band modulating functional interaction between motor cortex and muscle.

40 Hz tACS is an often used stimulation frequency and was found to enhance cognitive skills by two studies [37], [38]. Stimulation sites were frontal parts of the left hemisphere relevant for cognitive processes. Interestingly, both studies found enhancing effects only in more complex trials: When addressing working memory, tACS induced significant improvement in accuracy during 3-back tasks, but did not affect reaction times [37]. In respect to fluid intelligence, 40 Hz tACS accelerated the time needed to solve logical reasoning tasks by 15 % to approx. 20 s [38].

Two studies showed that gamma-oscillations influence the amplitude of alpha waves [26], [39]. Helfrich et al. [39] stimulated the visual cortex with an electrode on Pz and the reference on Cz. Both electrodes were of the same size. Recent research has shown modulation effects of alpha amplitudes on stimulation area when current intensity per area is enhanced by downsizing the stimulation electrode [40]–[43]. To exclude hemispheric effects we decided to stimulate central regions with a small stimulation and a bigger reference electrode.

We set out to investigate the applicability of gamma-tACS to enhance performance in a vigilance experiment. To our knowledge, tACS was not applied in this context so far. Our hypothesis is that the reaction times increment over time can be reduced by gamma-tACS on the visual cortex.

II. MATERIAL AND METHODS

a. Participants

Twenty-four healthy subjects between 20 and 30 years old (mean age 25.71, SD 2.73, 50 % were female) participated in the experiment after giving written informed consent. Before the start of the experiment, participants filled out a questionnaire covering e.g. medication, experiences with TES, coffee and alcohol consumption on the day preceding the experiment and hours of sleep during the night before. All subjects reported to be right-handed, free of neurological diseases, had no known deficits in color vision and no history of drug abuse. One subject reported having had less sleep than normal. Five subjects had already participated in one tACS-experiment at least two weeks ago.

The study was conceptualized in an in-between-subjects design and participants were equally assigned either to the tACS-group that received stimulation or to the SHAM-group that received placebo stimulation only (see section on tACS for more details). Females and males were balanced between the groups (six in each) to avoid gender effects. Despite the aspect of gender, subjects were addressed randomly to each group. Participants were not informed about the study design and expected an experimental session of 1 hour.

One male participant of the SHAM-group (age 28) had to be excluded from further analysis because more than 40 % of his data was not valid (the most prominent error that was not obvious in any other participant: Reaction times longer than 1 second and therefore nearly doubled averaged reaction time of the remaining group).

All participants believed to receive tACS-stimulation and were debriefed after the experiment. The experimental protocol was approved by “Kommission für Forschungsfolgenabschätzung und Ethik” of the University of Oldenburg and was in accordance with the Declaration of Helsinki.

b. Study Design

The study was conducted in a laboratory room, where participants were seated on a comfortable office chair in front of a 24” computer screen (60 Hz, 1920 × 1800 px resolution, 16 ms flipping rate) in a distance of approx. 90 cm (eyes to the middle of the screen) and connected to the tACS-device (see section tACS for details). Participants were asked to put their left and right forefingers on the respective buttons of a custom-made, software-debounced button box placed on the table before them. For the experiment, participants and examiner were separated via a gray screen.

The study consisted of two 30 minutes long blocks with a baseline block (referred to as BASELINE-block) performed by all participants and a stimulation block (referred to as INTERVENTION-block) where participants were stimulated according to their addressed group (tACS or SHAM). See Fig. 1a for an

overview of the procedure. The order of blocks did not change, INTERVENTION always followed BASELINE. The BASELINE-block was needed to analyze individual development of reaction times and was needed to set participants into a state of vigilance due to the monotonous task.

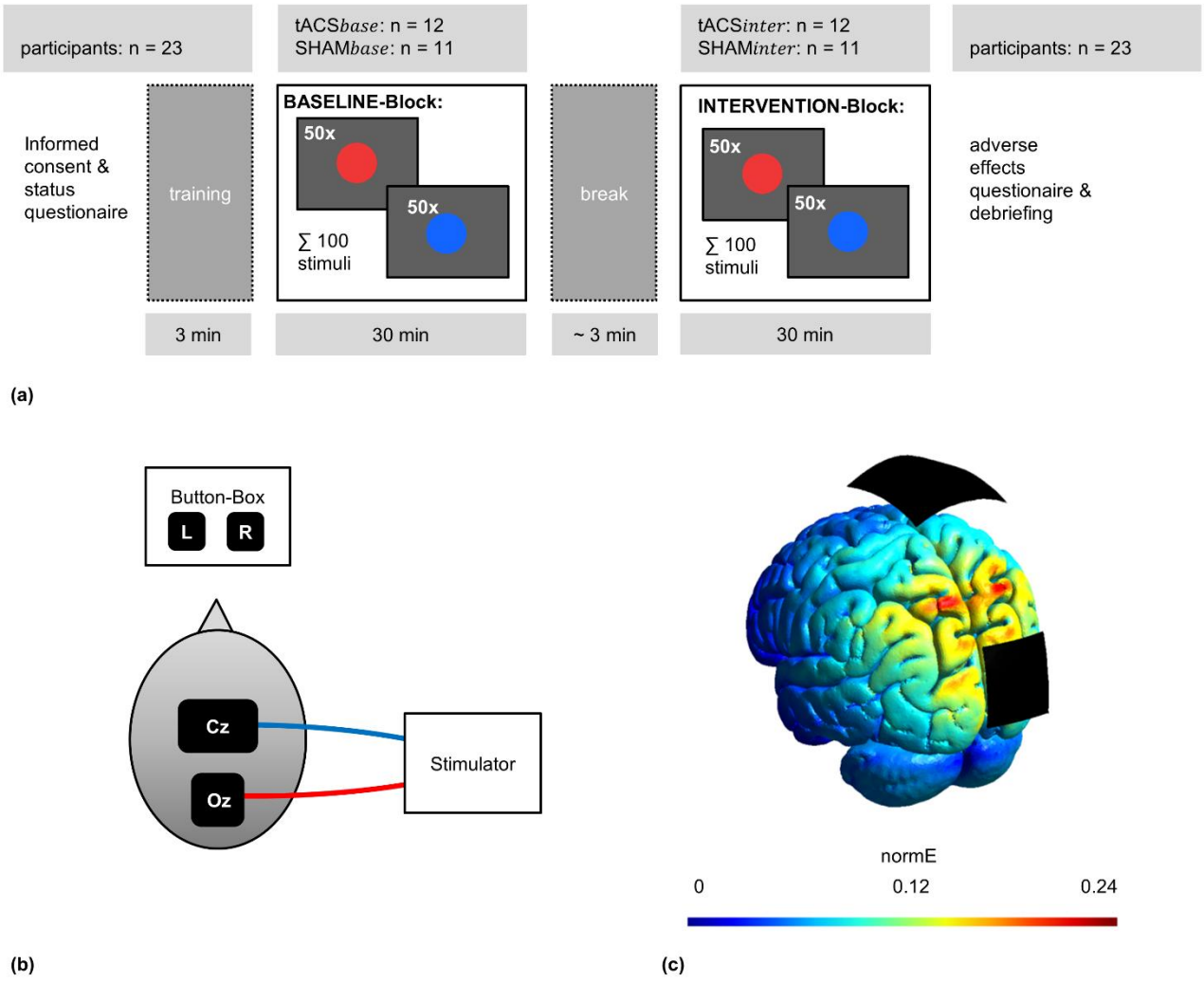

Fig. 1. *Experimental procedure and electrode setup. (a) After 3 minutes of training all participants performed the 30 minutes long BASELINE-block without stimulation. The INTERVENTION-block started after an approx. 3 minutes long, self-paced break. 12 of the analyzed participants received tACS-, 11 SHAM-stimulation. (b) A 5 cm × 7 cm electrode was placed on the vertex and a smaller 4.5 cm × 4.5 cm electrode on the visual cortex (Cz and Oz according to the international EEG 10/10 system). (c) Current simulation using SIMNIBS: simulation of the stimulation's electric field strength, covering the posterior brain areas (reproduced with permission of the authors from Stecher & Herrmann 2018 [43]).*

To assure participants understood the task, they performed a 3 minutes long training session prior to the experiment. The light was then switched off and communication stopped. During the BASELINE-block no participant received stimulation. The BASELINE-block stopped after 30 minutes. During an approx. 3 minutes (mean 163 s, SD 24 s) long break the participants were allowed to drink and rest while the examiner activated the stimulation device. In the following 30 minutes long INTERVENTION-block the participants were stimulated according to their group.

During the blocks, the participants were asked to fixate a white cross (10 × 10 px) displayed on a gray (RGB = 95 95 95) background. Every 6 – 56 s (median: 17 s) an either red (RGB = 240 55 55) or blue (RGB = 20 100 255) centered stimulus in the shape of a circle (400 px diameter) appeared for 500 ms. Half of the participants of each group were instructed to press the left, when the red stimulus and the right button when the blue stimulus appeared (the other half vice versa) as fast and correct as possible. The direction of button presses was balanced among genders. All colors (background, red and blue) were selected to be isoluminant. For each block, a specific set of 100 stimuli was used (50 red, 50 blue) in pseudo-randomized order.

Stimulus presentation and recording of button presses were handled with the Psychophysics Toolbox extension (version 3.0.12) [44]–[46] in Matlab (Release 2012a, The MathWorks Inc., Natick, MA, United States).

After the experiment, participants were asked to fill out a standardized questionnaire on adverse effects according to Brunoni et al. [47]. They were asked if they believed to be stimulated or not and if they experienced any of the common ten side effects such as a headache, neck pain, itching, tiredness etc. and whether they linked it to stimulation or not on a scale of 1 (none) to 4 (severe or definitely, respectively).

c. tACS

Two rubber electrodes were positioned with their center at Cz (size: 7 cm × 5 cm) and Oz (size: 4.5 cm × 4.5 cm) according to the 10-10 EEG-system (Fig. 1b) and fixated with adhesive electrode paste (ten20®conductive, Weaver and Company, Aurora, CO, USA). Electrode sizes and positions were in line with the effective montage from previous studies, where stimulation was applied to investigate effects on alpha bands in the visual cortex [40]–[43]. A battery-driven stimulator was used (neuroConn DC Stimulator with Remote-In function, Neuroconn GmbH, Ilmenau, Germany). The examiner ensured that impedance was at least below 8 kOhm and that subjects experienced no unpleasant sensations. The stimulation device remained turned off while subjects performed the training session and the BASELINE-block and turned on again during the break between the BASELINE- and INTERVENTION-block. For the INTERVENTION-block the tACS-device was remotely accessed via a Matlab controlled DAQ-module (Ni USB 6229, National Instruments, Austin, Texas, USA). Stimulation intensity was set to 1 mA. For the tACS-group current was linearly faded in and out for 30 s at the beginning and end of the 30 minutes long stimulation. For the SHAM-group current was faded in for 30 s, kept constant at 1 mA for 30 s and faded out for 30 s at the beginning (0 to 1.5 min) and end (28.5 to 30 min) of the INTERVENTION-block.

d. Data Analysis

Initial pre-processing of the performance data was done in Matlab: Invalid trials (trials when no reaction until the next stimuli was recorded), wrong button presses (participant pressing the left instead of the right

button or vice versa) and physiologically unreasonable reaction times below 200 or above 1000 ms were excluded from reaction time analysis and saved as “errors”.

Invalid trials (i.e. errors) and valid trials were analyzed separately.

For data analysis, four groups were used with the SHAM- (n = 11) and tACS-groups (n = 12) consisting of the same participants and the indexes base and inter indicating the block (BASELINE or INTERVENTION): $SHAM_{base}$, $tACS_{base}$, $SHAM_{inter}$, $tACS_{inter}$.

We chose LMM for data analysis for three reasons. First of all, they predict reaction times or the occurrence of errors as a consequence of a (generalized) linear regression, in our case of the covariates *time*, *group* and their combination and allow us to see whether these factors make a significant contribution to the model or not [50]. Second, *time* is not seen as a categorical factor like in an ANOVA, but as a metric covariate and therefore LMMs are ideal for the interpretation of time series data with time as a continuous variable [51], [52]. Variances - due to different individual specific characteristics and conditions - are taken into account by the model as random effects, which make LMM perfect for study designs not only with clustered but also with repeated-measurement concepts [53].

Group (indicating the four groups as mentioned before), *time* and *group* $*$ *time* (interaction term) were considered as fixed factors. The $SHAM_{base}$-group was used as base group to which the other three groups ($tACS_{base}$, $SHAM_{inter}$, $tACS_{inter}$) were compared to. The continuous variable *time* represents the pseudo-randomized stimuli onset time point (100 per block) starting from zero in each block. As random components, individuals and their individual variation of reaction times over time were used. We also tried to include more factors, such as gender or categorization of “slow” or “fast” participants by calculating a mean base reaction time of each individual as differentiation point, but these factors showed no effect.

A stepwise increase of the complexity (simple LMM with random intercepts to broken stick models with 8 degrees of freedom) and check for improvement testing the difference in the −2 log likelihood, revealed that a simple linear model with a continuous autoregressive covariance structure (corCAR 1) and differentiating between both blocks served best to describe the observed effects. A two-sided significance level of $\alpha = 0.05$ was used.

Invalid trials were summarized in total and according to error type. For error analysis, we tried to apply a generalized additive mixed model (GAMM) of the add-on-package “mgcv” [54]–[57] with the same covariates as for the LMM. We varied complexity and used the Akaike information criterion (AIC) to compare models. Random effects improved the fit, but introducing covariates did not. We could not find a suitable model (conditional $R2 < 0.3$) and any linear effect of time. Therefore only a descriptive error analysis is presented in the Results section: Error rates of each participant, group- and block-wise means and standard deviations (SD) were calculated.

III. RESULTS

Regarding the questionnaires concerning adverse effects, every side effect was at least mentioned by one participant (Table I). Adverse effects mentioned most often were sleepiness (tACS and SHAM: 10) and trouble concentrating (tACS 11, SHAM: 10), but in approx. 80 % of the cases not related to stimulation. Adverse effects were more or less equally often mentioned by both groups with a slightly higher rate in the tACS-group that also had one more member. Due to small numbers, no statistical test was applied.

Nearly all participants reported that the task was extremely boring and tiring and that they had difficulty to concentrate. Five participants reported the application of motivation strategies like counting; two of them were tACS-treated. Being asked whether they believed to being stimulated, eleven members of the tACS-group (91.7 %) and five of the SHAM-group (41.7%) answered with “yes”.

TABLE I

EXPERIENCED ADVERSE EFFECTS AS MENTIONED BY PARTICIPANTS ACCORDING TO THE INTERVENTION-GROUP THEY BELONGED TO AND WHETHER THEY RELATE THE EXPERIENCE TO BEING STIMULATED OR NOT. NUMBERS ARE THE FREQUENCY WITH WHICH PARTICIPANTS ANSWERED WITH 2 (MILD OR REMOTE), 3 (MODERATE OR PROBABLE) OR 4 (SEVERE OR DEFINITE) ON THE RELEVANT QUESTIONNAIRE

	tACS (n = 12)	Related to being stimulated?	SHAM (n = 11)	Related to being stimulated?
Headache	3	2	2	2
Neck pain	4	2	2	1
Scalp pain	3	1	2	2
Tingling	8	8	7	6
Itching	5	4	2	2
Burning sensation	3	3	2	2
Skin redness	5	3	1	0
Sleepiness	10	2	10	1
Trouble concentrating	11	2	10	2
Acute mood change	1	0	1	0

2 Study I

a. Error Analysis

All 23 participants performed quite well during the experiment and at least 89% valid trials were recorded for each participant per block. As it was not possible to fit any GAMM to the error data, no change in the probability of error occurrence could be detected over time.

Table II summarizes the most relevant data concerning errors and error types. Standard deviations (SD) represent the variation among participants and are - for all aspects - quite high; therefore final conclusions have to be taken with care. No participant showed reaction times faster than 200 ms. On average participants made 4.1 (SD 2.4) errors in the BASELINE-block. Overall more errors were made with the right- compared to the left-hand. A comparable amount of errors was made for both stimuli color.

TABLE II

MEAN ERRORS ACCORDING TO TYPE AND TOTAL AMOUNT OF ERRORS OF THE FOUR GROUPS ACCORDING TO BLOCK (BASELINE: $SHAM_{BASE}$, $TACS_{BASE}$; INTERVENTION: $SHAM_{INTER}$, $TACS_{INTER}$). THE TWO SHAM- AND TACS-GROUPS CONSISTED OF THE SAME PARTICIPANTS (SHAM: n = 11, TACS: n = 12 PARTICIPANTS). LEFT AND RIGHT HAND INDICATES WHICH HAND PRESSED THE WRONG BUTTON OR REACTED TOO SLOW. RED AND BLUE INDICATE WHICH COLOR THE STIMULI HAD WHEN THE ERROR (WRONG BUTTON PRESS, TOO SLOW OR MISSED STIMULI) WAS MADE. STANDARD DEVIATIONS (SD) ARE QUITE HIGH, REPRESENTING THE VARIATION AMONG PARTICIPANTS

	Errors	SD	Wrong button	SD	rt > 1 s	SD	Missed stimuli	SD
BASELINE:								
$SHAM_{base}$	4.3	2.6	3.7	2.2	0.4	0.7	0	0
$tACS_{base}$	4.0	2.3	2.9	1.8	1.1	2.1	0.2	0.4
INTERVENTION:								
$SHAM_{inter}$	4.3	3.2	1.8	1.9	0.7	1.5	0.4	1.2
$tACS_{inter}$	3.7	3.0	3.3	3.0	1.5	2.0	0.3	0.6

	Left hand	SD	Right hand	SD	Red	SD	Blue	SD
BASELINE:								
$SHAM_{base}$	1.8	1.4	2.3	1.2	2.1	1.4	2.2	1.5
$tACS_{base}$	1.8	1.1	2.3	1.8	2.1	1.6	1.9	1.4
INTERVENTION:								
$SHAM_{inter}$	1.6	1.6	2.4	1.7	2.0	1.4	2.3	2.4
$tACS_{inter}$	1.3	1.3	1.9	1.7	1.9	1.4	1.8	1.9

b. Reaction Time Analysis

The final model predicts reaction times from the covariates *group* ($SHAM_{base}$, $tACS_{base}$, $SHAM_{inter}$ or $tACS_{inter}$), *time* and *group* $*$ *time* (interaction term) according to the following equation:

$$\begin{aligned} rt = {} & \beta_0 * SHAM_{base} + \beta_1 * tACS_{base} + \beta_2 * SHAM_{inter} + \beta_3 * tACS_{inter} + \beta_4 * SHAM_{base} * time + \beta_5 \\ & * tACS_{base} * time + \beta_6 * SHAM_{inter} * time + \beta_7 * tACS_{inter} \\ & * time \end{aligned} \quad (1)$$

β-coefficients represent fixed effects and are listed in Table III. β_0 describes the intercept (i.e. baseline reaction time) of the $SHAM_{base}$-group with the p-value indicating the difference in comparison to zero. The coefficients β_1, β_2 and β_3 describe the group specific difference of the intercept compared to the one of the $SHAM_{base}$-group (β_0). Here, p-values indicate the significance of difference not compared to zero, but to the intercept of the $SHAM_{base}$-group (β_0). ($\beta_0 + \beta_1$) add up to the intercept of the $tACS_{base}$-group, ($\beta_0+\beta_2$) to the intercept of the $SHAM_{inter}$-group and ($\beta_0+\beta_3$) to the intercept of the $tACS_{inter}$-group. β_4 describes the slope (i.e. the increase of reaction time over time) of the $SHAM_{base}$-group with the p-value indicating the difference in comparison to zero. The coefficients β_5, β_6 and β_7 describe the group specific difference of the slope compared to the slope of the $SHAM_{base}$-group (β_4). Like with the intercepts, ($\beta_4 +\beta_5$) add up to the slope of the tACSbase-, ($\beta_3 + \beta_6$) to the slope of the $SHAM_{inter}$- and ($\beta_3 + \beta_7$) to the slope of the $tACS_{inter}$-group. Here, p-values indicate the significance of difference compared to the slope of the $SHAM_{base}$-group (β_4). Fig. 2 visualizes the resulting regression functions.

Random effects significantly contributed to the model: Individuals had significantly different initial reaction times (SD 54.6 ms, 95 % CI: 39.4 – 75.5) as well as different dynamics over time (SD 1.110 ms/min, 95 % CI: 0.692 - 1.781) and block (SD 26.1 ms, 95 % CI: 18.1 – 39.6). The coefficients of determination indicate that the final model explains approx. 30 % of the variance (fixed and random effects: R^2 conditional = 0.301).

At the beginning of the experiment, initial reaction times were approx. 470 ms (β_0) in the $SHAM_{base}$- and 499 ms ($\beta_0 + \beta_1$) in the $tACS_{base}$-group. In the BASELINE-block of the experiment, reaction times increased significantly with 2.4 ms/min (β_4, $p < 0.001$) as compared to zero for the $SHAM_{base}$-group and with 2.7 ms/min ($\beta_4 + \beta_5$) for the $tACS_{base}$-group. Statistical analysis showed no significant difference in intercepts and slopes between both BASELINE-groups.

After the break, i.e. at the beginning of block 2 (INTERVENTION), initial reaction times were significantly higher (approx. 504 ms in the $SHAM_{inter}$- and 534 ms in the $tACS_{inter}$-group) as compared to the $SHAM_{base}$-group. During block 2 (INTERVENTION), reaction times of non-stimulated participants ($SHAM_{inter}$-group) were modeled to increase by approx. 1.6 ms/min which is not significantly different from $SHAM_{base}$-group (i.e. data obtained by the same participants, but in BASELINE-block, $p = 0.130$). In contrast to this, for stimulated participants ($tACS_{inter}$-group) the model yielded a reduced increase in reaction times of only 1.0

ms/min. This is significantly less as compared to the $SHAM_{base}$-group ($p < 0.05$). Over 30 minutes, the LMM revealed that reaction times of the $tACS_{inter}$-group increase only by 28 ms (increase of 5.3 %), whereas the ones of the $SHAM_{inter}$-group increase by 47 ms 9.4 %). Thus, the increase in reaction times is approx. 19 ms larger for subjects who did not receive tACS. To make sure the effect also holds true in comparison to the $tACS_{base}$-group as base, we calculated a second model. In this model, the slope of $tACS_{inter}$ was significantly different from $tACS_{base}$, whereas the one of $SHAM_{inter}$ did not differ.

TABLE III

LMM RESULTS FOR REACTION TIMES: βS REPRESENT THE REGRESSION COEFFICIENTS, SE β THE STANDARD ERRORS OF β. β_0 REPRESENTS THE INITIAL REACTION TIME AND β_4 THE INCREASE IN REACTION TIME OVER TIME OF THE $SHAM_{BASE}$-GROUP, THEIR P-VALUES ARE MARKED WITH A ◦ AND SHOW A SIGNIFICANT DIFFERENCE COMPARED TO ZERO. ALL OTHER COEFFICIENTS ARE TESTED AGAINST β_0 AND β_4. β_1 AND β_5 DESCRIBE THE DIFFERENCE BETWEEN $SHAM_{BASE}$- AND $TACS_{BASE}$-GROUP, β_2 AND β_6 THE DIFFERENCE BETWEEN $SHAM_{BASE}$- AND $SHAM_{INTER}$-, β_3 AND β_7 THE DIFFERENCE BETWEEN $SHAM_{BASE}$- AND $TACS_{INTER}$-GROUP. HERE, P-VALUES BELOW 0.05 (MARKED WITH A STAR) INDICATE A SIGNIFICANT DIFFERENCE AS COMPARED TO THE COEFFICIENTS OF THE $SHAM_{BASE}$-GROUP. REGRESSION COEFFICIENTS REPRESENTING INTERCEPTS OR DIFFERENCE IN INTERCEPTS ARE GIVEN IN MILLISECONDS; REGRESSION COEFFICIENTS REPRESENTING SLOPES OR DIFFERENCES IN SLOPES IN MILLISECOND PER MINUTE. THE TWO SHAM- AND TACS-GROUPS CONSISTED OF THE SAME PARTICIPANTS (SHAM: n = 11, TACS: n = 12 PARTICIPANTS)

	β	SE β	t-value	p-value
Intercepts:				
β_0 $SHAM_{base}$	469.8	17.6	26.71	< 0.001°*
β_1 $tACS_{base}$	29.0	24.4	1.19	> 0.05
β_2 $SHAM_{inter}$	33.9	11.9	2.86	< 0.05*
β_3 $tACS_{inter}$	64.1	24.7	2.59	< 0.05*
Slopes:				
β_4 time x $SHAM_{base}$	2.364	0.499	2.66	< 0.001°*
β_5 time x $tACS_{base}$	0.270	0.692	0.39	> 0.05
β_6 time x $SHAM_{inter}$	-0.786	0.530	-1.48	> 0.05
β_7 time x $tACS_{inter}$	-1.428	0.688	-2.07	< 0.05*

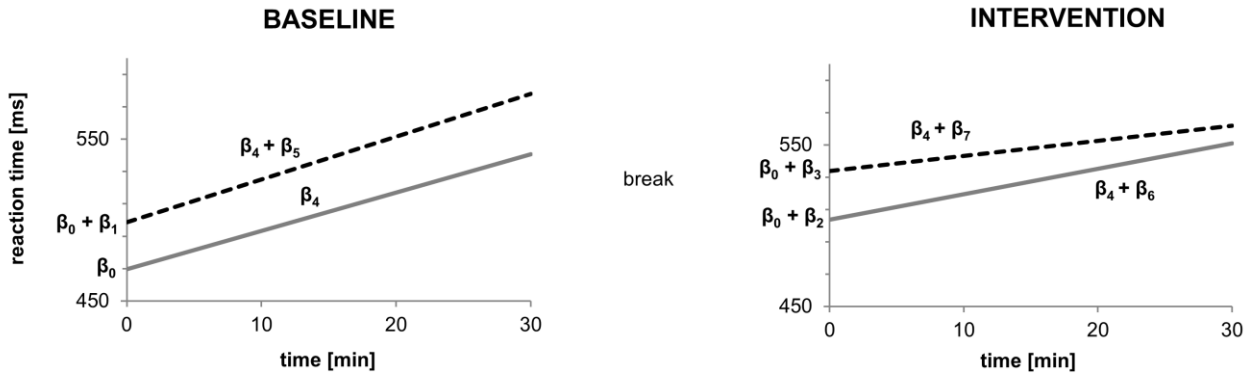

Fig. 2. *Results of the linear mixed model (LMM): Visualization of the regression functions representing reaction time (in milliseconds) against time (in minutes) for the tACS- (black dashed line) and SHAM-group (gray solid line) according to block (BASELINE or INTERVENTION). Regression lines represent the four groups (BASELINE: $SHAM_{base}$, $tACS_{base}$; INTERVENTION: $SHAM_{inter}$, $tACS_{inter}$) used for statistical analysis. The two SHAM- and tACS-groups consisted of the same participants (SHAM: n = 11, tACS: n = 12 participants). β-coefficients next to the lines indicate how intercepts (β_0, β_1, β_2, β_3) and slopes (β_4, β_5, β_6, β_7) were calculated*

IV. DISCUSSION

Due to its influence on reaction times and error rates, vigilance decrement is a well-known problem in monitoring and driving tasks and can be associated with rising alpha power [23]. For counteracting vigilance decrement, tACS shows potential due to its interaction with intrinsic oscillations and its modulation of behavior [1]. We applied gamma-tACS over the visual cortex and recorded reaction times and errors following visual stimuli in a SHAM-controlled experiment. Our results show that reaction times in the stimulated group ($tACS_{inter}$) rose significantly less compared to both BASELINE-groups ($SHAM_{base}$, tACSbase), whereas $SHAM_{inter}$ did not. With our model we can explain 30 % of variance. As the participants formed a very heterogeneous group which can be seen in the random effects, a higher R^2-value seems to be very unlikely, especially considering the small sample size due to and typical for this kind of experimental setup.

Overall, mean reaction times of all participants were in a similar range as typical for people between 20 - 30 years in a visual two-choice task [58]. In respect to vigilance experiments, the reaction time increment and a higher level of reaction times at the beginning of the INTERVENTION-block were also as expected [21], [59]. Breaks help participants to recover [60] -an effect that explains the predicted slower initial reaction times of all participants in the INTERVENTION-block.

The order between BASELINE- and INTERVENTION-block was not changed; INTERVENTION-blocks always followed BASELINE which was necessary for our study design. We therefore cannot exclude the possibility of training effects. We asked participants to fill out a questionnaire after the experiment. Next to critics or improvement wishes, participants were asked to report on strategies they used. Only six participants reported on strategies like counting or moving their limbs to stay focused. Only one participant reported on counting stimuli during INTERVENTION-block. This participant was in the SHAM-group.

2 Study I

Rising reaction times are thought to correlate with an increasing error rate [21], but we could not find a significant effect of any covariates. Errors seemed to have occurred randomly and individually specific with participants showing lower or higher rates independent of block or group. The performance was overall quite good (min. 89 % valid trials per block) with an average performance of 96 %. This is in line with other studies that have shown, that in experiments in which participants exhibit high levels of valid trials (90 – 100 %) and low levels of errors, reaction times may become the critical measure [59]. Still, there is a tendency, that participants of the tACS-group made fewer errors, especially concerning button presses.

As standardized protocols and guidelines do not exist, it is hard to compare tACS-studies [1]. Precisely 40 Hz tACS was found to enhance accuracy but not reaction times in 3-back tasks [37] and fastened the response time for logical reasoning tasks by 15 % [38]. In our study, 40 Hz tACS showed an effect on performance by decreasing the slope of reaction times by approx. 4 % as compared to a control group ($tACS_{inter}$ vs. $SHAM_{inter}$) and had no effect on error rates, but it is important to consider the differences in paradigms and stimulation sites.

Recent studies have shown, that tACS especially proves to be beneficial for “slow” or less accurate participants [61], [62]. We categorized participants as well but could not find any relationship between high or low individual level of base reaction time and improved reaction times due to stimulation. What we observed was a large variability among individuals: Reasons for that could be differences due to anatomic variance [63] or larger mismatches between intrinsic gamma oscillations and the 40 Hz stimulation frequency [26].

We focused solely on the behavioral outcome and did not record EEG, but it has been shown in other studies, that gamma-tACS on the visual cortex down-regulates alpha power [26] and that tACS at alpha frequency does not impact reaction times [39]. Our results are in line with their findings and the concept of a gamma-alpha antagonism. However – lacking a control group stimulated with a control frequency - we cannot make assumptions about our effects being frequency specific. Further, we cannot exclude the possibility that effects shown are due to perceiving the sensation of stimulation. A successive study would be needed to clarify this aspect.

On a neurophysiological level, intra-individual faster reaction times have been linked to a specific phase of either intrinsic alpha [64] or gamma [65] oscillations during stimulus onset. Concerning alpha oscillations, stimuli presented nearest to the amplitude elicited slowest reaction times [64]. In respect to gamma, EEG measurements revealed that only in trials in which participants performed a fast reaction, a pronounced slow negative potential over central electrodes starting approx. 800 ms before the response and highly phase-locked gamma oscillations over central and posterior electrodes shortly after the stimulus occurred [65]. We did not consider phase differences of intrinsic oscillations and their relation to stimuli

presentation. We conclude, as stimuli were presented randomly and in different intervals, any phase effects will be balanced out in the course of the experiment.

a. Outlook

Besides deeper investigation of the electrophysiological effects, another interesting question seems the application of tACS in a more sophisticated way, e.g. at specific points when individual alpha power increases above a certain threshold. Furthermore, the task could outlast the stimulation period to investigate if enhancing effects appear only online or if they can be maintained post stimulation. Helfrich et al. [26] could only observe a gamma-tACS online-effect on alpha power, but recently Kasten and Herrmann [40] demonstrated that the effect of alpha-stimulation on mental rotation persisted at least 50 minutes after stimulation.

There are only a few recent studies investigating tACS effects on elderly [32], [66]. Antonenko et al. [32] showed a tACS-induced learning effect especially in elderly – raising hope for the potential use of tACS in this age group: Especially in respect to addressing their well-known cognitive deficits, e.g. in car-driving [67]. Reaction times could also be a relevant performance parameter, as the slowing of performance is one essential aspect of aging [52]. Differences between younger and older participants concerning reaction times, but not errors, were observed in complex situations in a driving simulator study [68].

V. CONCLUSIONS

In our study, 40 Hz gamma-tACS over the visual cortex showed an improving effect on reactions times as compared to a BASELINE-block in a sham-controlled two-alternative-forced-choice experiment. Our results are in support of the concept of antagonistic alpha-gamma relationship. Although effects of tACS on time-on-task are rather weak, we see potential of this technique for application, especially in the context of car driving where 19 ms more reaction time is crucial.

REFERENCES

[1] C. S. Herrmann, S. Rach, T. Neuling, and D. Strüber, “Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes,” *Frontiers Hum. Neurosci.*, vol. 7, p. 279, May 2013.

[2] F. Fröhlich, K. K. Sellers, and A. L. Cordle, “Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation,” *Expert Rev. Neurother*., vol. 15, no. 2, pp. 145–167, 2015.

[3] R. Schulz, C. Gerloff, and F. C. Hummel, “Non-invasive brain stimulation in neurological diseases,” *Neuropharmacology*, vol. 64, pp. 579–587, Jan. 2013.

[4] P. A. Hall, C. M. Vincent, and A. M. Burhan, “Non-invasive brain stimulation for food cravings, consumption, and disorders of eating: A review of methods, findings and controversies,” *Appetite,* vol. 124, pp. 78–88, May 2017.

[5] A. Antal and W. Paulus, “Transcranial alternating current stimulation (tACS),” *Frontiers Hum. Neurosci*., vol. 7, p. 317, Jun. 2013.

[6] L. C. Reteig, L. J. Talsma, M. R. van Schouwenburg, and H. A. Slagter, "Transcranial electrical stimulation as a tool to enhance attention," *J. Cogn. Enhancement*, vol. 1, no. 11, pp. 10–25, 2017.

[7] D. Meron, N. Hedger, M. Garner, and D. S. Baldwin, "Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability," *Neurosci. Biobehav. Rev*., vol. 57, pp. 46–62, Oct. 2015.

[8] V. Fiori, M. Nitsche, L. Iasevoli, G. Cucuzza, C. Caltagirone, and P. Marangolo, "Differential effects of bihemispheric and unihemispheric transcranial direct current stimulation in young and elderly adults in verbal learning," *Behav. Brain Res*., vol. 321, pp. 170–175, Mar. 2017.

[9] H. Sakai, Y. Uchiyama, S. Tanaka, S. K. Sugawara, and N. Sadato, "Prefrontal transcranial direct current stimulation improves fundamental vehicle control abilities," *Behav. Brain Res.,* vol. 273, pp. 57–62, Oct. 2014.

[10] T. Iuculano and R. C. Kadosh, "The mental cost of cognitive enhancement," J. Neurosci., vol. 33, no. 10, pp. 4482–4486, 2013.

[11] A. Sarkar, A. Dowker, and R. C. Kadosh, "Cognitive enhancement or cognitive cost: Trait-specific outcomes of brain stimulation in the case of mathematics anxiety," *J. Neurosci*., vol. 34, no. 50, pp. 16605–16610, 2014.

[12] R. M. Battleday, T. Muller, M. S. Clayton, and R. C. Kadosh, "Mapping the mechanisms of transcranial alternating current stimulation: A pathway from network effects to cognition," *Frontiers Psychiatry*, vol. 5, p. 162, Nov. 2014.

[13] C. S. Herrmann, D. Strüber, R. F. Helfrich, and A. K. Engel, "EEG oscillations: From correlation to causality," Int. J. Psychophysiol., vol. 103, pp. 12–21, May 2016.

[14] D. Veniero, A. Vossen, J. Gross, and G. Thut, "Lasting EEG/MEG aftereffects of rhythmic transcranial brain stimulation: Level of control over oscillatory network activity," *Frontiers Cell. Neurosci*., vol. 9, p. 477, Dec. 2015.

[15] J. Mishra, J. A. Anguera, and A. Gazzaley, "Video games for neurocognitive optimization," *Neuron*, vol. 90, no. 2, pp. 214–218, 2016.

[16] J. S. Warm, R. Parasuraman, and G. Matthews, "Vigilance requires hard mental work and is stressful," *Hum. Factors, J. Hum. Factors Ergonom. So*c., vol. 50, no. 3, pp. 433–441, 2008.

[17] A. Craig, Y. Tran, N. Wijesuriya, and H. Nguyen, "Regional brain wave activity changes associated with fatigue," *Psychophysiology,* vol. 49, no. 4, pp. 574–582, 2012.

[18] M. S. Clayton, N. Yeung, and R. C. Kadosh, "The roles of cortical oscillations in sustained attention," *Trends Cogn. Sci.,* vol. 19, no. 4, pp. 188–195, 2015.

[19] W. Klimesch, M. Doppelmayr, H. Schimke, and T. Pachinger, "Alpha frequency, reaction time, and the speed of processing information," *J. Clin. Neurophysiol*., vol. 13, no. 6, pp. 511–518, 1996.

[20] E. Molina, A. Correa, D. Sanabria, and T.-P. Jung, "Tonic EEG dynamics during psychomotor vigilance task," in *Proc. 6th Int. IEEE/EMBS Conf. Neural Eng. (NER)*, Nov. 2013, pp. 1382–1385.

[21] L. Buck, "Reaction time as a measure of perceptual vigilance," *Psychol. Bull.*, vol. 65, no. 5, pp. 291–304, 1966.

[22] N. Pattyn, X. Neyt, D. Henderickx, and E. Soetens, "Psychophysiological investigation of vigilance decrement: Boredom or cognitive fatigue?" *Physiol. Behav.,* vol. 93, nos. 1–2, pp. 369–378, 2008.

[23] B. S. Oken, M. C. Salinsky, and S. Elsas, "Vigilance, alertness, or sustained attention: Physiological basis and measurement*," Clin. Neurophysiol*., vol. 117, no. 9, pp. 1885–1901, Sep. 2006.

[24] C.-T. Lin et al., "Wireless and wearable EEG system for evaluating driver vigilance," *IEEE Trans. Biomed. Circuits Syst.*, vol. 8, no. 2, pp. 165–176, Apr. 2014.

[25] E. Wascher, S. Getzmann, and M. Karthaus, "Driver state examination— Treading new paths," *Accident Anal. Prevention*, vol. 91, pp. 157–165, Jun. 2016.

[26] R. F. Helfrich et al., "Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception," *PLoS Biol.*, vol. 12, no. 12, p. e1002031, 2014.

[27] M. R. Boyle and F. Fröhlich, "EEG feedback-controlled transcranial alternating current stimulation," in *Proc. 6th Int. IEEE/EMBS Conf. Neural Eng. (NER),* Nov. 2013, pp. 140–143.

[28] A. Antal and C. S. Herrmann, "Transcranial alternating current and random noise stimulation: Possible mechanisms," *Neural Plasticity*, vol. 2016, Apr. 2016, Art. no. 3616807.

[29] O. Jensen and L. L. Colgin, "Cross-frequency coupling between neuronal oscillations," *Trends Cogn. Sci.,* vol. 11, no. 7, pp. 267–269, 2007.

[30] D. Osipova, D. Hermes, and O. Jensen, "Gamma power is phase-locked to posterior alpha activity," *PLoS ONE*, vol. 3, no. 12, p. e3990, 2008.

[31] J. M. Palva, S. Palva, and K. Kaila, "Phase synchrony among neuronal oscillations in the human cortex," *J. Neurosci.,* vol. 25, no. 15, pp. 3962–3972, 2005.

[32] D. Antonenko, M. Faxel, U. Grittner, M. Lavidor, and A. Floel, "Effects of transcranial alternating current stimulation on cognitive functions in healthy young and older adults," *Neural Plasticity*, vol. 2016, Apr. 2016, Art. no. 4274127.

[33] A. Antal, K. Boros, C. Poreisz, L. Chaieb, D. Terney, and W. Paulus, "Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans," *Brain Stimulation*, vol. 1, no. 2, pp. 97–105, 2008.

[34] R. Polanía, M. A. Nitsche, C. Korman, G. Batsikadze, and W. Paulus, "The importance of timing in segregated theta phase-coupling for cognitive performance," *Current Biol*., vol. 22, no. 14, pp. 1314–1318, 2012.

[35] C. Wach, V. Krause, V. Moliadze, W. Paulus, A. Schnitzler, and B. Pollok, "Effects of 10 Hz and 20 Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability," *Behav. Brain Res*., vol. 241, pp. 1–6, Mar. 2013.

[36] C. Wach, V. Krause, V. Moliadze, W. Paulus, A. Schnitzler, and B. Pollok, "The effect of 10 Hz transcranial alternating current stimulation (tACS) on corticomuscular coherence," *Frontiers Hum. Neurosci*., vol. 7, p. 511, Aug. 2013.

[37] K. E. Hoy et al., "The effect of γ -tACS on working memory performance in healthy controls," *Brain Cogn.,* vol. 101, pp. 51–56, Dec. 2015.

[38] E. Santarnecchi et al., "Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials," *Current Biol.*, vol. 23, no. 15, pp. 1449–1453, 2013.

[39] R. F. Helfrich, T. R. Schneider, S. Rach, S. A. Trautmann-Lengsfeld, A. K. Engel, and C. S. Herrmann, "Entrainment of brain oscillations by transcranial alternating current stimulation," *Current Biol.*, vol. 24, no. 3, pp. 333–339, Feb. 2014.

[40] F. H. Kasten and C. S. Herrmann, "Transcranial alternating current stimulation (tACS) enhances mental rotation performance during and after stimulation," *Frontiers Hum. Neurosci.*, vol. 11, no. 2, pp. 1–16, 2017.

[41] F. H. Kasten, J. Dowsett, and C. S. Herrmann, "Sustained aftereffect of α-tACS lasts up to 70 min after stimulation," *Frontiers Hum. Neurosci*., vol. 10, p. 245, May 2016.

[42] H. I. Stecher, T. M. Pollok, D. Strüber, F. Sobotka, and C. S. Herrmann, "Ten minutes of α-tACS and ambient illumination independently modulate EEG alpha-power," *Frontiers Hum. Neurosci*., vol. 11, p. 11262, May 2017.

[43] H. I. Stecher and C. S. Herrmann, "Absence of α-tACS aftereffects in darkness reveals importance of taking derivations of stimulation frequency and individual alpha variability into account," *Frontiers Psychol*., vol. 9, p. 984, Jun. 2018. [44] D. H. Brainard, "The psychophysics toolbox," Spatial Vis., vol. 10, no. 4, pp. 433–436, 1997.

[45] M. Kleiner, D. Brainard, D. Pelli, A. Ingling, R. Murray, and C. Broussard, "What's new in psychtoolbox-3?" Perception, vol. 36, no. 14, pp. 1–16, 2007.

[46] D. G. Pelli, "The VideoToolbox software for visual psychophysics: Transforming numbers into movies," *Spatial Vis.,* vol. 10, no. 4, pp. 437–442, 1997.

[47] A. R. Brunoni, J. Amadera, B. Berbel, M. S. Volz, B. G. Rizzerio, and F. Fregni, "A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation," *Int. J. Neuropsychopharmacol*., vol. 14, no. 8, pp. 1133–1145, 2011.

[48] R Core Team, "R: A language and environment for statistical computing," in R Foundation for Statistical Computing. Vienna, Austria, 2016. [Online]. Available: http://www.R-project.org/

[49] J. Pinheiro, D. Bates, S. DebRoy, D. Sarkar, and R. C. Team. (Feb. 6, 2017). Nlme: Linear and Nonlinear Mixed Effects Models. R Package Version 3.1-131. [Online]. Available: https://cran.r-project.org/package=nlme

[50] A. P. Field, J. Miles, and Z. Field, Discovering Statistics Using R. Thousand Oaks, CA, USA: Sage, 2012.

[51] C. Krueger and L. Tian, "A comparison of the general linear mixed model and repeated measures ANOVA using a dataset with multiple missing data points," *Biol. Res. Nursing*, vol. 6, no. 2, pp. 151–157, 2004.

[52] F. Fregni et al., "A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients," *Stroke*, vol. 37, no. 8, pp. 2115–2122, 2006.

[53] T. A. B. Snijders, "Multilevel analysis," in *International Encyclopedia of Statistical Science*, M. Lovric, Ed. Berlin, Germany: Springer, 2011, pp. 879–882.

[54] S. N. Wood, "Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models," *J. Roy. Stat. Soc. B, Stat. Methodol*., vol. 73, no. 1, pp. 3–36, 2011.

[55] S. N. Wood, Generalized Additive Models: An Introduction With R. Hoboken, NJ, USA: Wiley, 2006.

[56] S. N. Wood, "Stable and efficient multiple smoothing parameter estimation for generalized additive models," *J. Amer. Stat. Assoc.*, vol. 99, no. 467, pp. 673–686, 2004.

[57] S. N. Wood, "Thin plate regression splines," *J. Roy. Stat. Soc. B, Stat. Methodol*., vol. 65, no. 1, pp. 95–114, 2003.

[58] A. T. Welford, "Reaction time, speed of performance, and age," *Ann. New York Acad. Sci*., vol. 515, no. 1, pp. 1–17, 1988.

[59] M. Sarter, B. Givens, and J. P. Bruno, "The cognitive neuroscience of sustained attention: Where top-down meets bottom-up," *Brain Res. Rev*., vol. 35, no. 2, pp. 146–160, 2001.

[60] H. A. Ross, P. N. Russell, and W. S. Helton, "Effects of breaks and goal switches on the vigilance decrement," *Exp. Brain Res*., vol. 232, no. 6, pp. 1729–1737, 2014.

[61] E. Santarnecchi et al., "Individual differences and specificity of pre-frontal gamma frequency-tACS on fluid intelligence capabilities," *Cortex*, vol. 75, pp. 33–43, Feb. 2016.

[62] K. Kar and B. Krekelberg, "Transcranial alternating current stimulation attenuates visual motion adaptation," *J. Neurosci.,* vol. 34, no. 21, pp. 7334–7340, 2014.

[63] B. Krause and R. C. Kadosh, "Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation," *Frontiers Syst. Neurosci*., vol. 8, p. 25, Feb. 2014.

[64] E. Callaway and C. L. Yeager, "Relationship between reaction time and electroencephalographic alpha phase," *Science*, vol. 132, no. 3441, pp. 1765–1766, 1960.

[65] I. Fründ, N. A. Busch, J. Schadow, U. Körner, and C. S. Herrmann, "From perception to action: Phase-locked gamma oscillations correlate with reaction times in a speeded response task," *BMC Neurosci*., vol. 8, p. 27, Apr. 2007.

[66] K. S. Rufener, M. S. Oechslin, T. Zaehle, and M. Meyer, "Transcranial alternating current stimulation (tACS) differentially modulates speech perception in young and older adults," *Brain Stimulation,* vol. 9, no. 4, pp. 560–565, 2016.

[67] M. Falkenstein, S. Poschadel, N. Wild-Wall, and M. Hahn, "Kognitive Veraenderungen im Alter und ihr Einfluss auf die Verkehrssicherheit aelterer Verkehrsteilnehmer: Defizite, Kompensationsmechanismen und Praeventionsmoeglichkeiten," in Aeltere Verkehrsteilnehmer—Gefæhrdet Oder Gefæhrlich? vol. 5, K. Kocherscheid and G. Rudinger, Eds. Göttingen, Germany: V & R unipress, 2011, pp. 43–49.

[68] J. S. R. Leversen, B. Hopkins, and H. Sigmundsson, "Ageing and driving: Examining the effects of visual processing demands," *Transp. Res., F, Traffic Psychol. Behav.,* vol. 17, pp. 1–4, Feb. 2013.

3. Study II

Attempting to counteract vigilance decrement in older adults with brain stimulation

Publication bibliography:

Löffler, Birte S.; Stecher, Heiko I.; Meiser, Arnd; Fudickar, Sebastian; Hein, Andreas; Herrmann, Christoph S. (2023): Attempting to counteract vigilance decrement in older adults with brain stimulation. In *Front. Neuroergonomics* 4, Article 1201702. DOI: 10.3389/fnrgo.2023.1201702.

The following author-edited version of the above-mentioned study is identical in content to the published article.

Author contributions:

BL, HS, SF, AH, and CH conceptualized the study. BL and Arnd Meiser (AM) acquired participants. BL, HS, and AM performed measurements and analyzed the data. BL wrote the manuscript. CH and HS commented and gave practical hints throughout the study. All authors contributed to the article and approved the submitted version.

I hereby confirm that Birte Sofie Löffler contributed to this study as mentioned above:

_____

Signature of primary supervisor - Prof. Dr.-Ing. Andreas Hein, Oldenburg, 25 January 2024

Following mistake is in the manuscript:

- p. 41 the reference “(Klink et al, 2020a)” after “Matlab” should be replaced with “(Release 2023a)

3 Study II

Attempting to counteract vigilance decrement in older adults with brain stimulation

Abstract

Introduction: Against the background of demographic change and the need for enhancement techniques for an aging society, we set out to repeat a study that utilized 40-Hz transcranial alternating current stimulation (tACS) to counteract the slowdown of reaction times in a vigilance experiment but with participants aged 65 years and older. On an oscillatory level, vigilance decrement is linked to rising occipital alpha power, which has been shown to be downregulated using gamma-tACS.

Method: We applied tACS on the visual cortex and compared reaction times, error rates, and alpha power of a group stimulated with 40 Hz to a sham and a 5-Hz-stimulated control group. All groups executed two 30-min-long blocks of a visual task and were stimulated according to group in the second block. We hypothesized that the expected increase in reaction times and alpha power would be reduced in the 40-Hz group compared to the control groups in the second block (INTERVENTION).

Results: Statistical analysis with linear mixed models showed that reaction times increased significantly over time in the first block (BASELINE) with approximately 3 ms/min for the SHAM and 2 ms/min for the 5-Hz and 40-Hz groups, with no difference between the groups. The increase was less pronounced in the INTERVENTION block (1 ms/min for SHAM and 5-Hz groups, 3 ms/min for the 40-Hz group). Differences among groups in the INTERVENTION block were not significant if the 5-Hz or the 40-Hz group was used as the base group for the linear mixed model. Statistical analysis with a generalized linear mixed model showed that alpha power was significantly higher after the experiment (1.37 µV2) compared to before (1 µV2). No influence of stimulation (40 Hz, 5 Hz, or sham) could be detected.

Discussion: Although the literature has shown that tACS offers potential for older adults, our results indicate that findings from general studies cannot simply be transferred to an old-aged group. We suggest adjusting stimulation parameters to the neurophysiological features expected in this group. Next to heterogeneity and cognitive fitness, the influence of motivation and medication should be considered.

3 Study II

1 Introduction

In 2018, we found that the application of transcranial alternating current stimulation (tACS) on the visual cortex significantly reduced the slowdown of reaction times in a vigilance experiment in a group of young adults (Löffler et al., 2018). We set out to repeat the study but with older adults.

In Europe, as well as other industrialized countries, the demography is changing toward an older society: By 2070, the number of people aged 65 years and older will mount up to 30% of the total population in Europe (European Commission, 2020). Due to the population aging, more people will likely be required to work longer before retirement and therefore make up a huge portion of not only car and bicycle drivers but also the active workforce. Getting old does not come without costs: In aging, neurobiological, cognitive, and behavioral changes are seen (Hedden and Gabrieli, 2004; Grady, 2012). Aging may have severe effects on the brain and often leads to a continuous and reliable decline in numerous perceptual and cognitive functions (Hedden and Gabrieli, 2004; Salthouse, 2010) with only rare treatment options (Abbott, 2012). These effects can be mainly observed not only in behavioral and neuropsychological tasks assessing speech perception, working memory, processing speed, executive functions, reasoning, and spatial orientation (Hedden and Gabrieli, 2004; Salthouse, 2010) but also in rapid mental fatigue when performing a long-lasting task (Wascher and Getzmann, 2014)—important functions for activities mentioned by older adults as relevant for a good, participative lifestyle (Owsley, 2002).

Vigilance is the capability to stay alert and ready to react to prolonged tasks (Warm et al., 2008) and represents an executive function (Cristofori et al., 2019). Vigilance decrement is the decline in performance with time on task, for example, expressed by rising reaction times and reduced detection rates (Buck, 1966; Pattyn et al., 2008). Vigilance decrement is thought to be responsible for numerous accidents and other safety-critical events. It is becoming more relevant lately due to the propagation of automatization and the increasing number of monitoring tasks (Dinges, 1995). Therefore, much research focuses on investigating vigilance-decrement detecting systems (McWilliams and Ward, 2021; Tamanani et al., 2021) and vigilance-enhancing strategies (see Al-Shargie et al., 2019, for a review).

Conventional vigilance-enhancing strategies include caffeine or chewing gum (Al-Shargie et al., 2019). Recent research has shown that an increase in cognitive load works beneficial: Vigilance is enhanced by integrating challenges to monitoring tasks like artificial rain (Bodala et al., 2016), adding visual and haptic stimuli (Abbasi et al., 2017) or a pure audio tone at 250 Hz (Al-Shargie et

al., 2021). Another promising enhancing strategy is transcranial electrical stimulation (TES), which is an easy-to-apply and relatively low-cost technique ideal for private and mobile applications (Antal and Paulus, 2013). In TES, two (or more) electrodes are placed on the scalp that are used to induce low electrical fields. Successful vigilance enhancement has been shown for transcranial direct current stimulation (tDCS; McIntire et al., 2014; Nelson et al., 2014) and tACS (Löffler et al., 2018; Rostami et al., 2021). In tDCS, stimulation electrodes are used as an anode and a cathode, leading to a de- or hyperpolarization of the exposed brain tissue. Negative aspects of this method are the enhancement of cognitive functions at the expense of other cognitive functions (Iuculano and Cohen Kadosh, 2013) or opposing effects depending on the individual's state (Sarkar et al., 2014). tACS uses alternating current and allows direct interference with the ongoing oscillatory brain activity with no serious adverse events reported as of 2017 (Matsumoto and Ugawa, 2017). Applied in the conventional electroencephalogram (EEG) frequency range, tACS is believed to modulate brain oscillations by the synchronization of neuronal networks and has been shown to induce behavioral and neurophysiological effects that occur immediately (on-line) but have also been shown to outlast stimulation (off-line or so-called aftereffects; Kasten et al., 2016). Lately, tACS has gained broad interest as a possible therapeutic method in treating neuropsychological disorders linked to abnormal brain oscillations, such as Parkinson's disease (Guerra et al., 2020) or dementia (Moussavi et al., 2021) and Alzheimer's disease (Sprugnoli et al., 2021). Several studies showed that the application of tACS can induce a behavioral change and increase performance (for a review, see Klink et al., 2020a), making it a promising tool for neuro-enhancement. In the context of vigilance, it has been applied with mixed results. While stimulating the medial prefrontal cortex with 6-Hz tACS improved performance in a visual sustained attention task (Rostami et al., 2021), stimulating with 4 Hz and 10 Hz did not reduce vigilance decrement (van Schouwenburg et al., 2021).

In our study (Löffler et al., 2018), we reduced vigilance decrement by stimulating the visual cortex with 40 Hz. We combined two insights to conceptualize the study. First, we combined neurophysiological knowledge and then, second, looked for the appropriate stimulation setup.

First, rising reaction times and worsening detection rates show a positive correlation with time on task (Buck, 1966)—a concept widely used in vigilance research (for review, see, e.g., Oken et al., 2006; Pattyn et al., 2008). Furthermore, on a neurophysiological scale, reaction time slowing and vigilance decrement have been linked to rising posterior alpha power with time on task (Klimesch, 1999; Schmidt et al., 2009; Molina et al., 2013; Clayton et al., 2015). The rise in posterior alpha

power is associated with experienced mental fatigue (Craig et al., 2012) and relates to reaction time slowing (Klimesch et al., 1996). These relationships led us to the conclusion that reaction time slowing can be prevented if alpha power is downregulated. The latter has successfully been demonstrated by Helfrich et al. (2014a, 2016) who down-modulated alpha amplitudes with gamma tACS. They stimulated the visual cortex with 40 Hz and a high-definition tACS electrode montage, where five electrodes were positioned on each hemisphere, allowing stimulation in or with 180° phase difference between them. Notably, downregulation of alpha amplitudes was observed independently of in- or antiphase stimulation.

A possible reason for the down-modulating effect derives from a phenomenon called cross-frequency coupling (CFC), also known for other frequencies: Brain oscillations of specific frequencies interact with each other (Jensen and Colgin, 2007). In general, during CFC, specific subharmonic sets of faster and slower oscillations are nested in each other and modify each other. CFC is believed to be a mechanism for information transfer in nested or coupled neuronal networks and may provide information integration across several spatiotemporal scales (Canolty and Knight, 2010). CFC can occur in different ways, depending on its function and whether the slow or fast oscillation is master or slave (Helfrich et al., 2016). Coupling can occur between amplitudes, power, phase, or frequency (Abubaker et al., 2021). It is believed that amplitude coupling regulates the activation of distributed neuronal populations, while phase coupling mediates specific inter-areal cortical information flow (Engel et al., 2013). In their study, Helfrich et al. (2016) showed that gamma-alpha CFC gamma-band entrainment enhanced amplitude–envelope correlations and reduced alpha power, indicating an antagonistic relationship between them. They concluded that coupled alpha and gamma oscillations have a functional role in visual processing. Also, other studies showed that gamma and alpha frequencies interact during cognitive processes, with the strongest coupling over occipital areas (Palva et al., 2005; Osipova et al., 2008). Therefore, we decided to investigate the possibility of gamma tACS to downregulate the expected rise in occipital alpha power on the visual cortex, this time addressing older adults.

In 2016, the first successful tACS study targeting healthy older adults aged 60 years and older improving implicit language learning skills was published (Antonenko et al., 2016). Since then, most studies have investigated the impact of tACS on the prefrontal cortex (PFC), addressing higher cognitive functions like working memory (Reinhart and Nguyen, 2019; Draaisma et al., 2022), associative memory encoding (Klink et al., 2020b) and multitasking (Zanto et al., 2021). Furthermore, tACS stimulation of the PFC has been shown to support cognitive training in cases of

dementia (Moussavi et al., 2021). Other successful tACS studies enhanced motor functions (Guerra et al., 2021) and motion learning (Rumpf et al., 2019; Fresnoza et al., 2020) or addressed auditory functions (Rufener et al., 2016; Baltus et al., 2020). One study found that alpha tACS (but not theta or gamma) at parietal regions improved performance in a working memory paradigm (Borghini et al., 2018). Only a few studies have compared young and old target groups using the same protocol and stimulation setup (Rufener et al., 2016; Reinhart and Nguyen, 2019; Fresnoza et al., 2020; Guerra et al., 2021; Zanto et al., 2021).

We repeated our study (Löffler et al., 2018) but with older adults to analyze the impact of identical tACS setup on different age groups and test if the setup is beneficial for older adults as well. In order to validate our hypothesis of a vigilance-induced rise of alpha power and its downregulation by gamma tACS, we extended the study by recording EEG and an additional 5-Hz control group to ensure that any enhancing effects are frequency-specific (Davis et al., 2013). We used the same study design consisting of two blocks—a baseline and an intervention—and recorded the EEG before and after both blocks. We expected that our experiment would lead to a vigilance decrement expressed by rising reaction times over time on task in the baseline block and higher alpha power post the experiment for the sham and control group. We hypothesized that our intervention with 40-Hz tACS would lead to a significantly flatter slope of increased reaction times in the intervention block and a significantly lower level of alpha power after the experiment as compared to the sham and 5-Hz control groups.

To the best of our knowledge, no study has previously applied 40-Hz gamma tACS on the visual cortex to address vigilance decrement in older adults. We believe that this research has high technical relevance given the changing demographics and increasing number of monitoring tasks such as automated driving (Gartenberg et al., 2018), which older adults cite as important for participating in society and as part of a good quality of life (Owsley, 2002). As there are few options for treating cognitive deficits—inevitable in age—we think investigating performance-enhancing techniques, especially for an older age group, is of great practical relevance.

2 Material and methods

For comparability, the experimental procedures and behavioral data analysis followed the approach of Löffler et al. (2018) except for the extension of EEG and a 5-Hz-stimulation control group. The experimental protocol was approved by Medizinische Ethikkommission of the

University of Oldenburg. Written informed consent was acquired from all participants prior to the experiment in line with the Declaration of Helsinki.

2.1 Participants

Forty-nine independent-living people aged 65 or older (mean age 72.4 years, SD 5.5, range 65–89) participated in the study. Participants received monetary compensation and were recruited from previous studies (not related to stimulation) and via a newspaper advertisement. Due to recording problems, one subject had to be excluded entirely from the analysis. Furthermore, reaction time recording failed in three subjects and the EEG recording failed in one subject, and they were excluded from the respective analysis. Therefore, only 45 (SHAM = 14, 5 Hz = 15, 40 Hz = 16) participants could be used for behavioral and 47 (SHAM = 15, 5 Hz = 14, 40 Hz = 18) for EEG analysis. Table 1 summarizes the group sizes and the characteristics of the remaining 48 participants. None of them reported the presence or history of neurological or psychiatric disorders. Twenty-eight subjects needed regular cardiovascular medication. Three subjects had vision impairment in one eye. Forty-five subjects were right-handed and three both-handed according to the Edinburgh handedness scale (Oldfield, 1971). One subject had experience with brain stimulation 4 years ago. One subject was remeasured after 18 months because sleep deprivation led to exorbitant reaction times (>2 s). Only the remeasurement was entered into the analysis.

Table 1. *Group-wise sample size (total n = 48), mean age, and the number of female participants in total and according to the data analysis method*

Group	**SHAM**	**5 Hz**	**40 Hz**
TOTAL			
n	15	15	18
Age	71.7, SD 5.5	70.3, SD 3.6	74.3, SD 6.3
female	8 (53%)	6 (40%)	9 (50%)
Behavioral data analysis			
n	14	15	16
Age	71.7, SD 5.7	70.3, SD 3.6	73.2, SD 5.3
female	7 (50 %)	6 (40%)	8 (50%)
EEG analysis			
n	15	14	18
Age	71.7, SD 5.5	70.6, SD 3.4	74.3, SD 6.3
female	8 (53%)	5 (36 %)	9 (50%)

EEG, electroencephalogram

3 Study II

Participants were randomly assigned to one of the three experimental groups receiving 40-Hz, 5-Hz, or SHAM stimulation in a single-blind design. The groups were counterbalanced for participants' sex, age, and button press conditions. All participants believed they were receiving tACS stimulation and were debriefed after the experiment.

To select an appropriate sample size, we performed an a priori power analysis based on the findings of our study (Löffler et al., 2018), which suggested a sufficient power ($1 – \beta = 0.85$) at a total sample size of 42 (14 participants per group).

2.2 Procedure

The experiment took place in a laboratory room, where participants were seated on an office chair at a distance of approximately 90 cm in front of a 24-in. computer screen (60 Hz, 1,920 × 1,800 px resolution) and connected to the EEG and stimulation device. Before the experiment, participants were given an introduction and a small training session to avoid confusion. During the experiment, participants and examiner were separated via a gray screen, communication stopped, and the light was switched off. Participants were not informed about the time of tACS onset. After the experiment, participants were asked if they believed to be stimulated or not and were informed about the actual stimulation settings applied to them. Furthermore, they were asked to fill out a standardized questionnaire on adverse effects according to Brunoni et al. (2011). Questions contained the common 10 side effects as *headache, neck pain, itching, tiredness*, and others and the link to being stimulated or not. Items were on a scale of 1 (*none*) to 4 (*severe* or *definitely*, respectively). See Figure 1A for the course of the experiment.

2.3 Study design

The experiment consisted of two 30-min-long blocks with a baseline block (referred to as the BASELINE block) and a stimulation block (referred to as the INTERVENTION block) in which participants were stimulated according to their group (SHAM, 5-Hz, or 40-Hz tACS). To ensure the presence of a vigilance decrement, the block order was not randomized, and no participant received stimulation during the BASELINE block. Therefore, all participants irrespective of group affiliation should show similar behavioral outcomes during the BASELINE block, while differentiation into the stimulation groups should only be relevant in the INTERVENTION block. Before the BASELINE and after the INTERVENTION block, a 5-min-long resting EEG was recorded, and participants were asked to sit still, relax, and keep their eyes open. This time span has been used in similar studies by other researchers investigating EEG in older adults (Babiloni et al., 2015; Scally et al., 2018; Rumpf et al., 2019; Varastegan et al., 2023). During an approximately 2–3-min-long self-paced break (mean 148 s, SD 66 s) between the blocks, the participants were allowed to drink and rest.

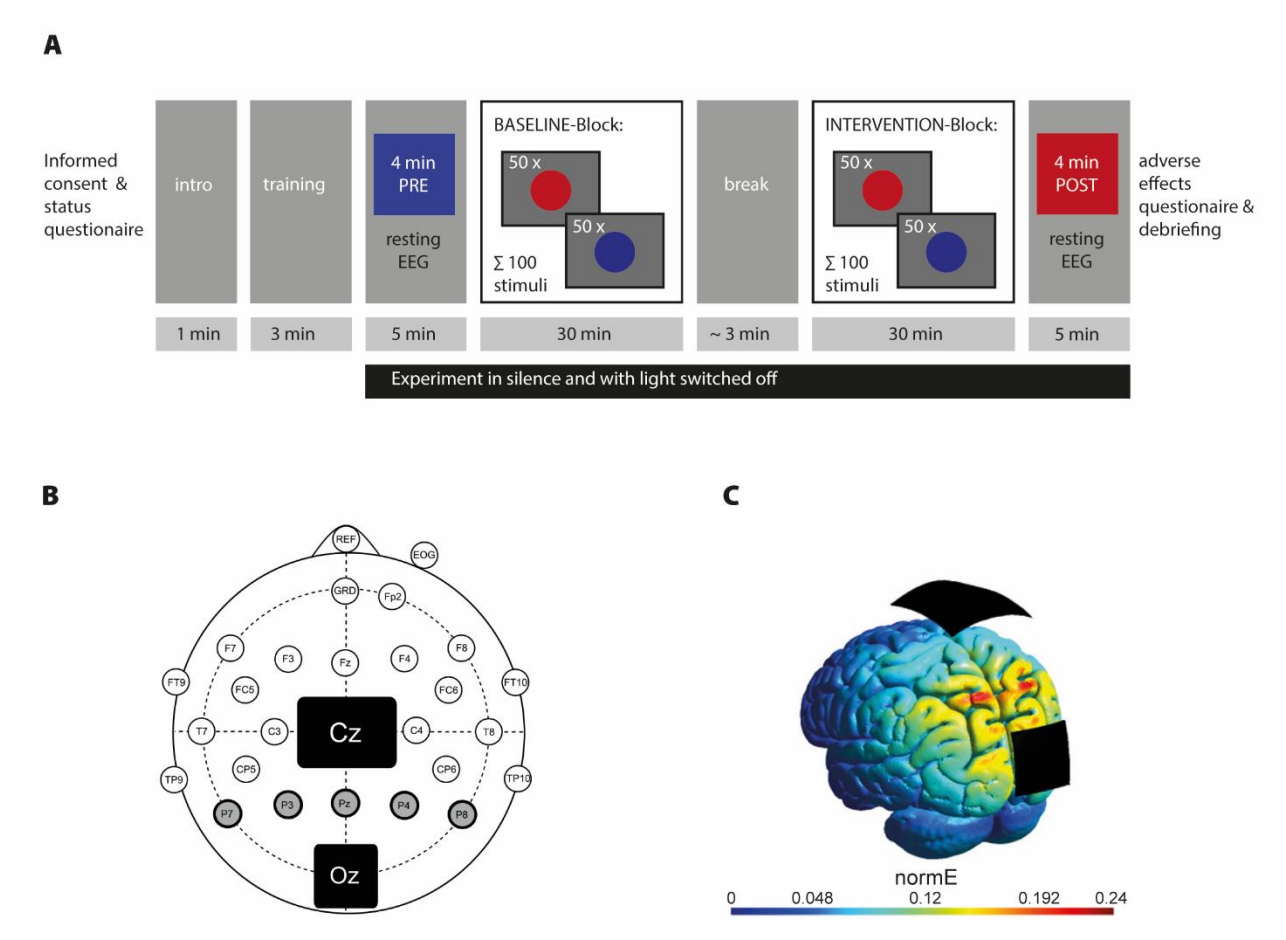

Figure 1. *Design of the experiment: (A) Course of the experiment showing the timing of resting EEG-recording and behavioral records. (B) Electrode setup with a 5-cm × 7-cm stimulation electrode placed on the vertex (Cz) and a smaller 4.5-cm × 4.5-cm one on the visual cortex (Oz) according to the 10-10 system. Circles represent active electrodes used for EEG recording according to the modified 10-10 system. Posterior alpha power was calculated from five EEG electrodes (P7, P3, Pz, P4, P8) highlighted in gray with a bold line. (C) Current simulation using SIMNIBS showing the stimulation's electric field strength addressing the visual cortex (reproduced with permission of the authors from Stecher and Herrmann, 2018). The color bar represents the normal vector of the electric field in V/m.*

2.4 Task

Participants were asked to put their left and right index fingers on the respective buttons of a custom-made, software-debounced button box placed on the table before them and asked to fixate a white cross (10 × 10 px) displayed on a gray (RGB = 95 95 95) background. Every 6–56 s (median: 17 s), either a red (RGB = 240 55 55), or a blue (RGB = 20 100 255) stimulus in the shape of a circle (400-px diameter) appeared for 500 ms at the center of the screen. Half of the participants of each group were instructed to press the left button when the red stimulus and the right button when the blue stimulus appeared (the other half vice versa) as fast and correctly as possible. A specific set of 100 stimuli was used (50 red, 50 blue) in a pseudo-randomized order for each block. Stimulus presentation was handled with the Psychophysics Toolbox extension (version 3.0.12) and button presses recorded in MATLAB (Release 2012a, The MathWorks Inc., Natick, MA, United States).

2.5 EEGs

EEGs were acquired with a rate of 10 kHz from 23 active electrodes using an actiCHamp amplifier (Brain Products GmbH, Gilching, Germany) and recorded via Pycorder software (Brain Products GmbH, Gilching, Germany). The 10-10 system was used to place the electrodes (see Figure 1B for an overview of recording channels), omitting the sites of the stimulation electrodes. The ground electrode was positioned at FPz. An electrode attached to the nose was chosen as a reference since it is widely used in neural research addressing visual cognition as the electrodes of interest at the visual cortex are far away from the nose (e.g., Helfrich et al., 2014a,b; Kasten et al., 2016). A vertical electrooculogram was recorded underneath the right eye to monitor eye movements. All impedances were kept below 20 kOhm.

2.6 tACS

Two rubber electrodes were positioned with their center at Cz (7 × 5 cm^2) and Oz (4.5 × 4.5 cm^2) according to the 10-10 EEG system and fixated with adhesive electrode paste (ten20®conductive, Weaver and Company, Aurora, CO, USA). A battery-driven stimulator was used (neuroConn DC Stimulator with Remote-In function, Neuroconn GmbH, Ilmenau, Germany), and impedance was kept below 10 kOhm. For the STIMULATION block, the tACS device was remotely accessed via a MATLAB-controlled DAQ module (Ni USB 6229, National Instruments, Austin, Texas, USA). Stimulation intensity was set to 1 mA. For the 5-Hz and 40-Hz group, the current was linearly faded in and out for 30 s at the beginning and end of the INTERVENTION block. Current in the SHAM group was faded in for 30 s, kept constant at 1 mA (at either 40 or 5 Hz) for 30 s, and faded out for 30 s at the beginning and end of the INTERVENTION block. Electrode sizes, positions, and stimulation intensity were in line with the effective montage used in our study (Löffler et al., 2018) and by other studies, in which stimulation affected alpha bands in the visual cortex (Kasten et al., 2016; Stecher et al., 2017). The intensity of 1 mA has been proven to induce neurophysiological and behavioral effects without causing unpleasant feelings by the same studies and is a widely used stimulation intensity (e.g., Klink et al., 2020b). Figure 1C shows a computer simulation of the tACS setup and its induced electric field addressing the visual cortex. tACS at 40 Hz has been shown to successfully downregulate alpha power at the visual cortex (Helfrich et al., 2014a, 2016).

2.7 Data processing

Data processing and analysis were performed using MATLAB (Klink et al., 2020a) and the Fieldtrip toolbox (Oostenveld et al., 2011).

Initial preprocessing of the behavioral data was done in MATLAB. Missed stimuli, wrong button presses, and reaction times below 200 or above 2,000 ms were excluded from reaction time analysis and considered “errors.”

The EEG data was down-sampled to 500 Hz and high-pass filtered at 1 Hz. We used a 48-Hz low-pass filter to remove line noise and high frequency (e.g., muscle artifacts). Two 4-min chunks of resting EEG (PRE: before and POST: after the experiment) starting 30 s after the beginning of the respective resting EEG measurement were cut into trials of 1 s to easily help identify and reject artifactual segments. These trials were then used in an independent component analysis approach. The identification of ocular components was based on topography (frontal and fronto-lateral bipolar) and time course (strong sigmoid shapes and boxcar shapes). Components containing vertical or horizontal eye movements were manually removed. Furthermore, we removed trials containing voltage differences >200 μV in the Pz electrode signal. On average, 230.23 out of 240 s were left after threshold-based rejection (STD: 16.18, min: 154).

As occipital electrode positions were covered by the stimulation electrodes, posterior alpha power was estimated using all parietal electrodes from both hemispheres (Pz, P3, P4, P7, P8) except for one participant, for whom P4 and P7 were excluded due to excessive noise. A fast Fourier transform using a Hanning window with 5-s zero padding was computed on the data. The results were 1–48-Hz-long bands of 236 data points with a resolution of 0.2 Hz. We calculated the mean value of all P-electrodes. We used the MATLAB function findpeaks to find the maximum power value between 6.8 and 13 Hz and its respective peak frequency, the individual alpha frequency (IAF). We defined alpha power as the mean power value +/– 1 Hz around peak frequency.

2.8 Statistical analysis

The software R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

For statistical analysis of the behavioral data, a linear mixed model (LMM) with the add-on-package “nlme” (Pinheiro et al., 2022) for reaction time and a generalized additive mixed model (GAMM) of the add-on package “mgcv” (Wood, 2017) for error analysis were used. In line with the statistical analysis used in our previous study (Löffler et al., 2018), data were separated into six groups, with the indexes base and inter indicating the block (BASELINE or INTERVENTION): $SHAM_{base}$, 5 Hz_{base}, 40 Hz_{base}, $SHAM_{inter}$, 5 Hz_{inter}, 40 Hz_{inter}. $SHAM_{base}$ and $SHAM_{inter}$, 5 Hz_{base} and 5 Hz_{inter}, and 40 Hz_{base} and 40 Hz_{inter} consisted of the same participants, respectively. We expected the three base groups ($SHAM_{base}$, 5 Hz_{base}, and 40 Hz_{base}) to show similar outcomes as no participant was stimulated during BASELINE block. Fixed factors were *group* (indicating the six groups as mentioned earlier), *time*, and the interaction term of both *group * time*. The $SHAM_{base}$ group served as the base group to which the other five were compared. The continuous variable time represented the pseudo-randomized stimuli onset time point (100 per block) starting from zero in each block. As random effects, individuals and their variation of reaction times or error probability over time were used. We increased complexity stepwise (intercept to broken-stick models with 8 degrees of freedom). We checked for models' improvement using likelihood ratio tests of the R package “performance” (Lüdecke et al., 2021)

for the LMM and Akaike information criterion (AIC) for the GAMM. A two-sided significance level of $\alpha = 0.05$ was used.

For the LMM, a simple linear model with a continuous autoregressive covariance structure best described the observed effects. We also checked the influence of other factors, such as *gender* as fixed or *age* and *IAF* as random factors, but these did not improve the model's fit. The literature shows that tACS is often more beneficial for a specific subgroup of participants, for example, the influence of baseline performance (Santarnecchi et al., 2016; Thompson et al., 2021) or in participants showing a low level of arousal (Martínez-Pérez et al., 2022). Therefore, we defined a subset of subgroups (classifying participants into two groups by using the median) that we integrated as fixed effects. While *slow performance*, *IAF level*, and *alpha power difference* showed no effect, we found a significant contribution to the model for *ageclass* (younger than the median age of all participants of 72 years or equal and older) and *medication* (yes/no) over time and group. While *ageclass* seemed only to show variation and was not interpretable, *medication* attributed to our model. But, as *medication* was not part of our hypothesis and not balanced over groups, we feared overfitting. A more extensive data set is needed to make reliable statements about this factor. In tDCS studies, *medication* has significantly influenced the stimulation effect (McLaren et al., 2018).

Concerning errors, we were not able to fit a satisfying mixed model. Random effects improved the fit of the GAMM, but introducing covariates did not. We could not find a suitable model (conditional $R^2 < 0.3$) and any linear effect of time.

The EEG data's mean power values PRE and POST were not normally distributed according to Shapiro–Wilk test. QQ and density plots of the data showed the uneven distribution of the data, with a concentration of small power values at approximately 1 μV^2, while some participants showed high power values of 10 μV^2 and more. Due to this huge inter-individual variance but intra-individual-specific voltage level, we decided on a statistical analysis with a generalized linear mixed model (GLMM) using the gamma-distribution family to describe the data. We used the R package “lme4” (Bates et al., 2015). We applied *treatment* (SHAM, 5 Hz, and 40 Hz) and *timepoint* (PRE and POST) as fixed factors. Increasing the models' complexity stepwise, introducing different link functions, and comparing AIC values showed a GLMM with individual random effects and a log-link function, but excluding the factor *treatment* served best to describe the data.

As not only the absolute power values of each participant but also the difference between POST and PRE alpha power were relevant for this study, we calculated a Wilcoxon rank-sum test to show the effect size of the differences between POST and PRE alpha power.

We calculated linear regression models testing different correlations during the BASELINE block to support theories about our cohort's behavior and neurophysiological nature. We tested *age, mean reaction time, mean-variance of reaction times, amount of errors, alpha power differences, IAF*, and *alpha PRE power*

(block-wise and in total, where appropriate) against each other. Shapiro–Wilk tests were used for assessing normal distributions of the data sets. Kendall *r* was used as the correlation coefficient for non-normally distributed data sets; for normally distributed ones, Pearson's *r* was used.

3 Results

3.1 Debriefing

One participant (SHAM group) did not answer the questionnaire about side effects and stimulation. The side effects mentioned most frequently by the remaining 47 participants (intensities rated higher than 1) were *tiredness* (47%) and *trouble concentrating* (66%), but only 15% (*tiredness*) or 13% (*concentration*) of the participants attributed it to being stimulated. Other side effects mentioned by more than three participants were *tingling* and *itching* both mentioned by 7 out of 47 of the participants (15%). Of the subjects, 35% (33% of the SHAM, 21% of the 5-Hz, and 44% of the 40-Hz group) thought they were stimulated (n = 46, one participant of the 5-Hz group did not answer this question).

3.2 Behavioral analysis

3.2.1 Reaction times analysis

The LMM predicting reaction times shows a slight increase over time, higher in the BASELINE block. In the INTERVENTION block, initial reaction times (intercepts) are higher than in BASELINE, and the slopes for the $SHAM_{inter}$ and 5-Hz_{inter} groups show a less steep increase, while the one for the 40-Hz group shows a steady one (see Figure 2).

Reaction times are predicted according to the following Equation 1 from the covariates *group* ($SHAM_{base}$, 5 Hz_{base}, 40 Hz_{base}, $SHAM_{inter}$, 5 Hz_{inter}, 40 Hz_{inter}), *time*, and *group* * *time* (interaction term):

$$\begin{aligned} \mathrm{rt} = \ & \boldsymbol{\beta_0} * \boldsymbol{SHAM_{base}} + \beta_1 * 5Hz_{base} + \beta_2 * 40Hz_{base} + \beta_3 * SHAM_{inter} + \beta_4 * 5Hz_{inter} + \beta_3 \\ & * 40Hz_{inter} + \boldsymbol{\beta_6} * \boldsymbol{SHAM_{base}} * \mathbf{time} + \beta_7 * 5Hz_{base} * time + \beta_8 * 40Hz_{base} * time \\ & + \beta_9 * SHAM_{inter} * time + \beta_{10} * 5Hz_{inter} * time + \beta_{11} * 40Hz_{inter} \\ & * time \end{aligned} \quad (1)$$

β coefficients represent fixed effects and are listed in Table 2. β_0 describes the intercept of the $SHAM_{base}$ group and β_6 its slope (i.e., increase of reaction time over time). *p*-values for the $SHAM_{base}$ group indicate the difference between zero (bold font). The coefficients β_1-β_5 describe the group-specific difference of intercepts compared to $SHAM_{base}$ group (β_0), and β_7-β_{11} are their slopes. For other groups,

respective coefficients need to be added to the ones of the $SHAM_{base}$ group. For example, ($\beta_0 + \beta_1$) add up to the intercept of the 5-Hz_{base} group, ($\beta_0 + \beta_2$) to the intercept of the 40-Hz_{base}, and so on. For coefficients, β_1-β_5 and β_7-β_{11}, *p*-values indicate the significance of the difference compared to the $SHAM_{base}$ group (β_0 und β_6). Figure 2 visualizes the resulting regression functions. The final model, including fixed and random effects, explains approximately 47% of the observed variance (R^2 conditional = 0.470).

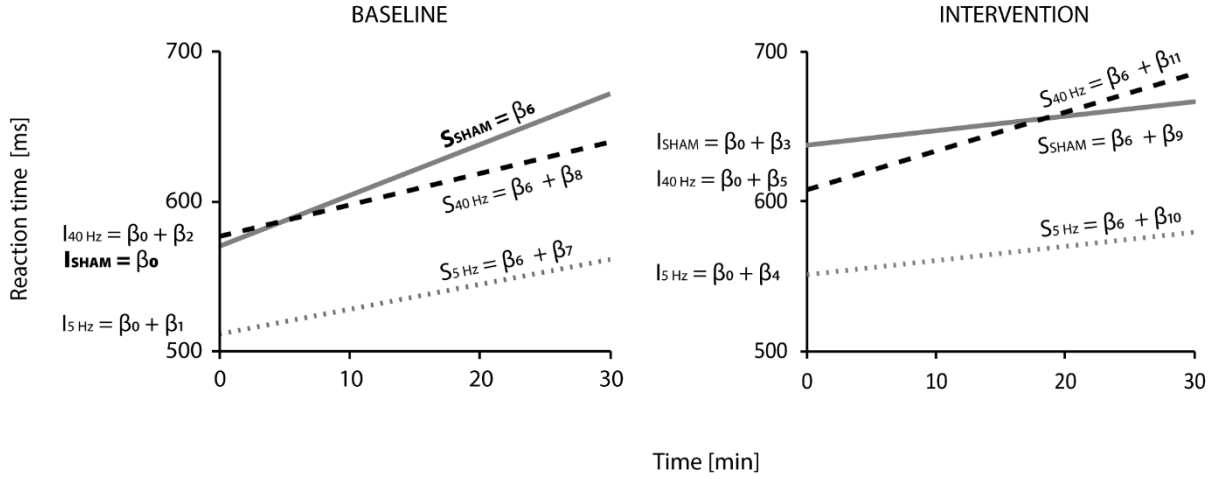

***Figure 2**. Linear mixed model results for reaction times (n = 45, observations = 8,413): Visualization of the regression functions representing reaction time (in ms) against time (in min) for the SHAM (gray solid line), 5-Hz (gray pointed line), and 40-Hz (black dashed line) according to block (BASELINE or INTERVENTION). Regression lines represent the six groups (BASELINE: $SHAM_{base}$, $5Hz_{base}$, $40Hz_{base}$; INTERVENTION: $SHAM_{inter}$, 5-Hz_{inter}, 40-Hz_{inter}). The two SHAM, 5-Hz, and 40-Hz-groups consisted of the same participants. β-coefficients (from Table 2) indicate how intercepts—indicated by I (β_0-β_5) and slopes—indicated by s – (β_6-β_{11}) were calculated. β_0 is the intercept of the $SHAM_{base}$ group, and β_6 is its increase over time—their significance is compared to zero and shows a highly significant difference ($p < 0.001$). All other intercepts and slopes are compared to $SHAM_{base}$: Significant differences according to the model can be found for the intercept of the $SHAM_{inter}$ group ($I_{SHAM} = \beta_0 + \beta_3$; $p < 0.001$) and the slopes of the $SHAM_{inter}$ ($S_{SHAM} = \beta_6 + \beta_9$) and 5-$Hz_{inter}$ ($S_{5Hz} = \beta_6 + \beta_{10}$; $p < 0.05$) groups. Model parameters are R^2 marginal = 0.056, R^2 conditional = 0.470, and Akaike information criterion = −9,055.448.*

According to the LMM, initial reaction times were approximately 570 ms (β_0) in the $SHAM_{base}$, 512 ms in the 5-Hz_{base} ($\beta_0 + \beta_1$), and 577 ms ($\beta_0 + \beta_2$) in the 40-Hz_{base} groups at the beginning of the experiment. In the BASELINE block, reaction times of the $SHAM_{base}$ group increased significantly with 3.4 ms/min (β_6, $p < 0.001$) compared to zero. The expected reaction time at the end of the BASELINE block and after 30 min added up to 672 ms (which results in a difference of Δ102 ms—the Δ symbol marks the value as a difference) for the SHAM, 562 ms (Δ50 ms) for the 5-Hz, and 640 ms (Δ63 ms) for the 40-Hz groups. This equalizes to a rise of 18, 10, and 11%, respectively. There was no statistical difference among the BASE groups (although the slope of the 5-Hz_{base} group nearly touched significance with a *p*-value of 0.073).

All participants started the INTERVENTION block higher than their group-specific initial reaction time but lower than they finished the BASELINE. Participants of the SHAM group started Δ 68 ms; of the 5-Hz group, Δ40 ms; and of the 40-Hz group, Δ31 ms slower than they began in BASELINE. The difference between the expected reaction time at the end of BASELINE compared to the start in INTERVENTION was Δ-34 ms for the SHAM group, Δ-10 ms for the 5-Hz group, and Δ-32 ms for the 40-Hz group. In comparison to $SHAM_{base}$, the

intercept of the $SHAM_{inter}$ group showed a significant difference ($p < 0.001$). During block 2 (INTERVENTION), the increase of reaction times slowed down for the $SHAM_{inter}$ group (by Δ2.42 ms/min) and the 5-Hz_{inter} group (by Δ0.70 ms/min) to approximately 1 ms/min. The 40-Hz_{inter} group showed a slight increase of Δ 0.51 ms/min to 2.5 ms/min. Compared to $SHAM_{base}$, the change was significant for the $SHAM_{inter}$ and 5-Hz_{inter} groups ($p < 0.05$) but not for the 40-Hz_{inter} group. The rise during the INTERVENTION block equalizes to 5% for the SHAM and 5-Hz groups (~Δ30 ms) and 13% (Δ78 ms) for the 40-Hz group. At the end of the INTERVENTION block, the expected reaction times are 667 ms for the SHAM group, 580 ms for the 5-Hz group, and 685 ms for the 40-Hz group.

***Table 2**. Linear mixed model results for reaction times (n = 45, observations = 8,413): β presents the regression coefficients; SE β, the standard error of β.*

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 $SHAM_{base}$	**569.9**	**28.9**	**19.70**	**0.000**	**< 0.001°*** **
β_1 $5Hz_{base}$	-58.2	40.3	-1.45	0.149	> 0.05
β_2 $40Hz_{base}$	7.3	39.6	0.18	0.855	> 0.05
β_3 $SHAM_{inter}$	67.6	11.9	5.67	0.000	< 0.001***
β_4 $5Hz_{inter}$	-18.7	40.2	-0.47	0.642	> 0.05
β_5 $40Hz_{inter}$	37.6	39.6	0.95	0.342	> 0.05
Slopes:					
β_6 time x $SHAM_{base}$	**3.403**	**0.698**	**4.88**	**0.000**	**< 0.001°*** **
β_7 time x $5Hz_{base}$	-1.746	0.974	-1.79	0.073	> 0.05
β_8 time x $40Hz_{base}$	-1.320	0.955	-1.38	0.166	> 0.05
β_9 time x $SHAM_{inter}$	-2.424	0.700	-3.46	0.001	< 0.01**
β_{10} time x $5Hz_{inter}$	-2.448	0.965	-2.54	0.011	< 0.05*
β_{11} time x $40Hz_{inter}$	-0.810	0.959	-0.85	0.395	> 0.05

*β presents the regression coefficients, SE β the standard error of β. β_0 represents the initial reaction time and β_6 the increase in reaction time over time of the $SHAM_{base}$-group (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β_0 and β_6. Intercepts are given in ms, slopes in ms/min. *** p-value >0.001, ** p-value > 0.01 and * p-value > 0.05.*

We also calculated models with 5 Hz and 40 Hz as the base group to test the difference between base and inter-conditions. See the Supplementary Material for more details. We confirmed that 5-Hz_{base} and 5-Hz_{inter} intercepts and the 40-Hz_{base} and 40-Hz_{inter} intercepts differ significantly from each other: All groups started the INTERVENTION block significantly slower compared to their initial reaction times (5-Hz_{base} intercept vs. 5 Hz_{inter}: $p < 0.001$, 40-Hz_{base} intercept vs. 40 Hz_{inter}: $p < 0.01$). No significant difference in slopes could be detected for both models.

3.2.2 Error analysis

It was impossible to fit a GAMM explaining a substantial amount of variance (R^2 = 0.000898) to the error data, so no change in the error occurrence probability could be detected over time. Mean performance was 93% (*SD* 5%, range 78–99%).

3.3 EEG

Mean IAF was 8.9 Hz (*SD* 1 Hz). Comparing PRE and POST alpha power, 78% of the participants showed an increase in alpha power after the experiment (Figure 3)—irrespective of group (SHAM = 80%, 5 Hz = 71%, 40 Hz = 82%). The best-fitting GLMM (gamma distribution with log link) predicts alpha power with participant ID as a random effect (intercept) and *timepoint* as the only covariate according to Equation 2:

$$\text{alpha power} = \exp(\boldsymbol{\beta_0} + \boldsymbol{\beta_1} * \boldsymbol{timepoint}) \quad (2)$$

Coefficients are log-scaled (β_0 = −0.00113, β_1 = 0.313). Back transferred, alpha power PRE is predicted to be 1 μV^2 and POST to be 1.37 μV^2. According to the model, the increase in POST was significantly different from zero ($p < 0.001$). The model's AIC is 166.2, with R^2 marginal = 0.021 for the fixed and R^2 conditional = 0.838 for the random and fixed effects.

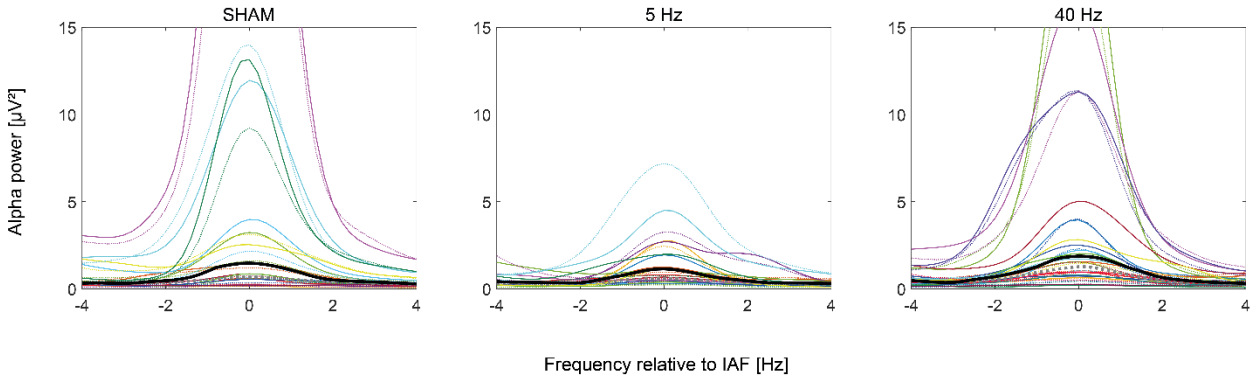

***Figure 3**. Plots of the alpha power (n = 47) spectrum in μV^2 normalized to individual alpha frequency in Hertz according to group (SHAM, 5 Hz, and 40 Hz). The dotted curves show PRE, solid POST alpha power. Bold curves show the median alpha power of all participants per group (PRE: gray, POST: black). Individual participants' curves are represented by individual colors.*

We also looked at the absolute differences in alpha power (POST–PRE): A one-sided Wilcoxon rank-sum test showed a significant difference ($p < 0.001$) with an effect size of 0.55 (strong; see Figure 4). A Kruskal–Wallis Test testing differences in alpha power between the three treatment groups revealed no significance (p = 0.3).

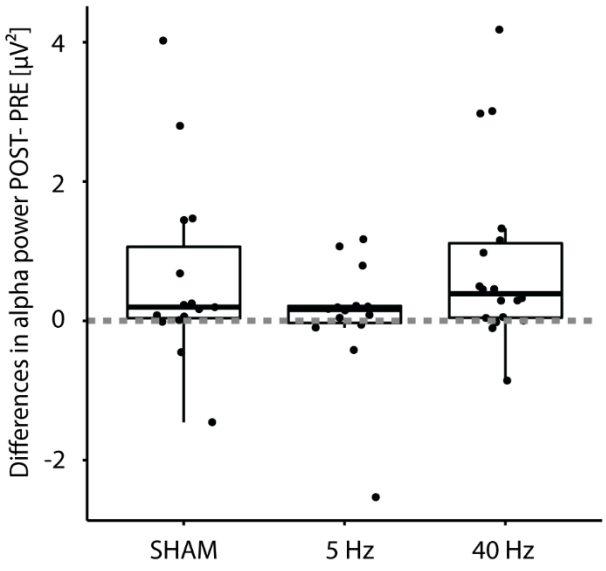

Figure 4*. Boxplot of differences (POST – PRE) in alpha power (n = 47) according to Treatment group (SHAM, 5 Hz, and 40 Hz). Filled dots indicate individual measurements; the dashed line indicates the zero crossing.*

3.4 Regression analysis

A modest significant linear correlation could be obtained for *IAF* vs. *errors* (Kendall $r = -0.22$, $p = 0.046$) and *IAF* vs. *mean variance of reaction times* (Kendall $r = -0.23$, $p = 0.034$) and a strong one for *mean reaction time* vs. *mean variance of reaction times* (Kendall $r = 0.74$, $p < 0.001$). A positive linear tendency ($r > 0.2$) was detected for *mean reaction time* vs. *age*, the *mean variance of reaction time* vs. *age*, and the *mean variance of reaction time* vs. *errors* and a negative tendency ($r > -0.2$) for *alpha power* vs. *age* and *IAF* vs. *mean reaction times*, but these correlations were not significant.

4 Discussion

Aging is accompanied by growing cognitive deficits (Grady, 2012). In the eye of demographic change, enhancing the cognitive performance of older adults becomes essential. One aspect of cognitive performance is vigilance, which plays a critical role in professional and private settings where tasks can be safety-relevant but tiring (Warm et al., 2008). We, therefore, repeated our study (Löffler et al., 2018) in which we applied gamma tACS to counteract vigilance decrement but with older adults. We hypothesized that participants treated with 40-Hz tACS would exhibit less increase in reaction time increment and have a lower alpha power level after the experiment compared to SHAM and 5-Hz control groups. Results of reaction time slowing and higher POST alpha power indicate that we succeeded in inducing vigilance decrement (Buck, 1966; Molina et al., 2013) but failed to show an effect of our intervention—and if then only a trend in reaction time increment but in the opposite direction as expected. In the following, we discuss our results and give possible explanations.

3 Study II

4.1 Anatomical and functional differences of the aging brain

There is some debate about the nature of brain aging, it is generally agreed that aging leads to a loss of brain volume and further physiological changes especially considering alpha and slow rhythms (Hedden and Gabrieli, 2004; Ishii et al., 2017). These changes could be critical for the success of tACS, which strongly depends—among others—on internal frequencies and the electrical field strength of the addressed tissue. In line with this, one recent tACS study addressing older adults used magnetic resonance imaging (MRI) scans to model individual electric fields and correlate them to the success of tACS together with EEG measuring the closeness of stimulation frequency (6 Hz) to internal brain waves (theta peak; Zanto et al., 2021). The researchers found that performance change correlates to the modeled electric fields and frequency mismatch. This explained 54–65% of the variance in tACS-related performance improvements. Important: On a group level, it was not possible for them to find any significant stimulation effect.

We did not measure the electrical field strength in our participants and can only speculate. Research has shown that brain volume seems to greatly decrease within the anterior regions while neural loss is rarely observed in occipital regions (Raz et al., 2005). So we still addressed—on the tissue level—a probable intact region. However, in aging, activation seems to shift from posterior to anterior areas (Dennis and Cabeza, 2011). Regarding alpha oscillations, many studies observed a significant alpha increase in frontal regions (Ishii et al., 2017). This activation shift has been associated with a compensatory mechanism (Mattay et al., 2002) and hyperactivation (Berchicci et al., 2012). Thus, it is conceivable that the visual cortex is not the relevant stimulation site for aged brains, as has been shown for stimulus processing and formulated in the posterior–anterior shift in aging hypothesis (Dennis and Cabeza, 2011).

Considering posterior alpha oscillations, it is generally agreed that older adults show a lower IAF, a marked reduction in amplitude, and declined reactivity (Babiloni et al., 2006; Ishii et al., 2017; Knyazeva et al., 2018). Although the general working principle of tACS is not completely understood, it is generally believed that tACS works as an external oscillator entraining internal brain oscillations (Vosskuhl et al., 2018). Therefore, stimulation success is dependent on selecting the correct stimulation site, electrode size, duration, frequency, and intensity according to the intrinsic properties of the addressed brain (Herrmann et al., 2013).

The mean IAF of the older subjects in our study was 8.9 Hz (*SD* 1 Hz), which is slightly less but still comparable to values from the literature (Klimesch, 1999; Barry and de Blasio, 2017). The average IAF obtained for a younger target group with the same equipment and measurement in our laboratory group at electrode Pz was 10 Hz (*SD* 0.3 Hz; Stecher et al., 2021). The variance was smaller, and the IAF was closer to the optimal 10 Hz, a subharmonic of the 40 Hz stimulation frequency and probably needed to induce CFC. We assume that our 40-Hz stimulation frequency was too far a mismatch from the lower IAF in older adults to induce any behavioral or physiological effect.

In physiological aging, alpha sources in posterior regions seem to have significantly less magnitude compared to young ones (Babiloni et al., 2006; Ishii et al., 2017). As the power level of the addressed intrinsic frequency is important for successful stimulation, lower power could have influenced the stimulation outcome. It has been shown that alpha tACS can only enhance IAF amplitude if the initial power level is low (Neuling et al., 2013). We observed alpha power of more than 15 μV^2 in seven participants; others showed only marginal power values of approximately 0.2 μV^2. This is in line with the literature because alpha power can show a high inter-individual variability due to anatomic and genetic differences among people (Bazanova and Vernon, 2014; Haegens et al., 2014). Comparable studies measured 0.8–1 μV^2 for participants with an average age of 69 years (Vaden et al., 2012; Barry and de Blasio, 2017).

We integrated IAF and power level in our LMM and performed further linear correlation analyses but could not detect any effect.

4.2 Motivation and difference in mindsets

We did not document the motivation or arousal level in our study, but higher motivation—as compared to younger participants—is a well-documented phenomenon in studies with older adults (Tomporowski and Tinsley, 1996). We can only speculate, but it may have been possible that at least part of the tested group of older adults experienced mental depletion instead of boredom. As mental depletion is associated with frontal brain regions in older adults (Arnau et al., 2017), the visual cortex might again not have been the correct stimulation area for inducing a performance change. Other tACS studies also show that mindsets are critical for stimulation success (Mierau et al., 2017).

4.3 Heterogeneity

Due to differences in scalp and skull thickness, hairs, and IAF, it is hard to repeat the effects of stimulation in a younger group, which, in general, consists of 20–30-year-old students (Kasten et al., 2019). With growing age, heterogeneity increases due to different life experiences and styles, nutrition, education, cognitive fitness, agility, medication and illnesses, and probably even more aspects (Light et al., 1996)—digital media use to name one more (Taipale et al., 2021). Compared to the repeated study (Löffler et al., 2018), the age range of the target group was higher (65–89 years compared to 20–30 years), as well as the educational background.

Next, to the already mentioned IAF and alpha power, this is reflected by reaction times and power differences: Fast-performing participants showed mean reaction times of 450 ms and small variance; others needed approximately 1 s to make a choice: Reaction times become more variable with age (Hultsch et al., 2002; Gorus et al., 2008). While alpha power decreased in roughly one-third of the participants (three in the SHAM group, four in the 5-Hz group, and three in the 40-Hz group; see Figure 4), seven participants showed a substantial increase of 200% and more (two in the SHAM group, three in the 5-Hz group, and two

in the 40-Hz group). These inter-individual differences were irrespective of group. Linear regression analysis showed a significant interaction between mean reaction time and reaction time variance, as known from the literature (Welford, 1971). Inter-individual differences seem consistent: The groups' mean reaction times differed, with the 5-Hz group showing the fastest. We nearly observed a significant difference between the 5-Hz group and the other groups in the BASELINE block for intercept and slope, which we did not expect, because participants were selected to be out of the same basic population. This performance gap continues in the INTERVENTION block, with a lower mean reaction time but not in the slope compared to the SHAM group. Group differences are also reflected in alpha power, with candidates of the 5-Hz group showed no power values of 10 μV^2 and more.

Still, our data show that we were able to induce vigilance decrement as expected by a constant reaction time slowing with time on task and a higher alpha power level post the experiment: Reaction times of approximately 545 ms are in close range of similar experiments with older adults (Welford, 1988) but slower than in the previous study (Löffler et al., 2018), with an average initial reaction time of approximately 485 ms. The reason for slower reaction times can be not only physiological (Welford, 1988) but also because of a different mindset: Older adults tend to be more careful and do not like to make mistakes (Botwinick, 1966). As expected, participants started the INTERVENTION block with a significantly higher initial reaction time compared to their initial BASELINE time. The break between blocks led to a slight recovery—a well-known effect (Ross et al., 2014) that has been also observed with young participants (Löffler et al., 2018). The less steep slope in the INTERVENTION block might be due to a ceiling (Neuling et al., 2013) or learning effect (Arnau et al., 2017; Getzmann et al., 2018).

No pattern of error-making could be detected nor any difference between the blocks: This is consistent with previous findings (Löffler et al., 2018), confirming that making mistakes is not critical to good performance (Sarter et al., 2001) and fits with the idea mentioned earlier that older adults are slower but also more careful.

Despite not being part of our hypothesis, we want to quickly discuss the factor *medication*. Of our 48 participants, 28 needed regular cardiovascular medication known to influence stimulation effects (McLaren et al., 2018). In the LMM not considering the factor *group*, people on *medication* suffered significantly less from reaction time increment. In the LMM with the factor *group*, people on *medicatio*n suffered significantly less from reaction time increment as well, but this effect was significantly strengthened only in the INTERVENTION block for the 40-Hz group. This indicates that 40-Hz tACS was especially beneficial for people on cardiovascular treatment (see the Supplementary Material). Due to the small sample size, we can only speculate but still want to emphasize the influence of medication on tACS findings.

The model presented in our Results section shows a significant difference between groups. Although alternative versions of the model (see the Supplementary Material) indicate that this significance is only due

to the high interindividual variance, we still want to discuss this point as other tACS studies comparing young and old participants also found opposing effects of stimulation between age groups. In one study (Rufener et al., 2016), stimulating the auditory cortex with 40-Hz tACS to improve performance-diminished task accuracy in young adults, whereas older adults benefited from the stimulation. No behavioral differences were found in the 6-Hz condition between both age groups. Here, 40-Hz tACS was applied to the bilateral auditory cortex to counteract age-dependent changes of gamma oscillations relevant for processing temporal features of spoken language. They argue that in young adults, gamma oscillations are optimal and that introducing more energy via tACS perturbs the balance, leading to the observed inaccuracy. Another study reports a positive effect of IAF tACS on general motor skills and sequence-specific skill consolidation in an old target group, while the same stimulation parameters were detrimental for the young group (Fresnoza et al., 2020). The researchers argue that this opposing effect might be due to the age-related difference in the electrical field of older adults' brains which is in general not as conductive as a younger brain. As a consequence, only a comparably low stimulation intensity reaches the relevant brain tissue that—as known from studies stimulating with direct current—shows inhibitory effects while high intensities act excitatory (Moliadze et al., 2012; Batsikadze et al., 2013). We observed a similar behavior in our control groups (SHAM and 5 Hz), which supports the notion that stimulation with 5 Hz on the visual cortex shows no effect and works as a control frequency. The opposing behavior of the 40-Hz-stimulated group might be due to age-dependent changes in the brain, possibly due to inhibitory effects of the stimulation like Fresnoza and colleagues (2020) argue or because of changes or disturbances of internal gamma (or other) oscillations like in Rufener et al. (2016)—preventing CFC and the down-modulation of the alpha amplitude via 40-Hz tACS and distracting behavioral optimization processes otherwise observed in the control groups.

In general, most studies stimulating older adults with a visible effect of stimulation-applied intensities of 1.5 mA or higher (Rufener et al., 2016; Borghini et al., 2018; Reinhart and Nguyen, 2019; Fresnoza et al., 2020; Benussi et al., 2021; Kim et al., 2021; Draaisma et al., 2022). Therefore, we conclude that, next to the heterogeneity of our target group and high variance of our data, low intensity and frequency mismatch might be possible reasons for our stimulation to show no effect on the level of alpha power, which increased from PRE to POST but irrespective of group.

Our tACS montage has been shown to successfully modify alpha power (Kasten et al., 2016; Stecher et al., 2017) or behavior (Löffler et al., 2018) at the visual cortex. The conventional tACS electrodes used in these studies covered the areas targeted by the stimulation and do not allow EEG recordings; therefore, parietal EEG electrodes were used to estimate occipital alpha power. These were positioned on the spots where the simulation shows maximal field strength. A more focal stimulation with high-definition tACS may be more beneficial for entraining alpha through gamma stimulation—as shown by Helfrich et al. (2014a).

Due to the high technical and organizational expenditure source localization and individual MRI scans were not included in this study. These methods allow the stimulation setup to be adapted to the individual characteristics of each participant. Due to the heterogeneity of the older population, we strongly encourage further tACS research addressing older adults to use individual stimulation setups.

Finally, we can also not exclude the possibility that our EEG analysis masked potential findings. We instructed participants to keep their eyes open during the recordings of the rest EEG but had no possibility of visually checking if participants followed this instruction. Because alpha power changes fundamentally in an eyes-closed or eyes-open condition (Barry and de Blasio, 2017), this is a limitation of the study. Due to eye blinks and other muscular artifacts, data chunks needed to be removed that might have contained relevant information.

Due to difficulties in recruiting participants, we included (as already discussed) participants on medication (which is, in general, also an exclusion criterion in tACS studies) as well as three participants with visual impairment in one eye. Reaction times, amount of errors, and alpha power values were in line with the non-impaired participants. Still, visual impairment (especially monocular vision) may affect vigilance. Monocular vision leads to reduced sensory input, which may lead to increased cognitive load (Casson and Racette, 2000). Furthermore, the field of view is limited, and binocular summation for stereoscopic vision is not possible (Cattaneo et al., 2008). Research has shown that people with visual impairment use compensatory strategies on a behavioral and a neural level (Steeves et al., 2008; Polat et al., 2012). As we used a stimulus positioned centrally in the visual field and tested change of performances on an individual basis, we justified integrating these participants into the overall analysis. Nevertheless, one has to keep in mind that visual impairment might be another influential factor.

4.4 Outlook

Recent research has reported on the success of tACS being a promising tool in therapeutic and neuro-enhancement contexts with great potential, especially for older adults (Reinhart and Nguyen, 2019).

Our study suggests that in tACS experiments addressing older adults more factors need to be controlled or participants be measured. It also indicates that many factors, for example, medication, cognitive fitness, education, and digital media, use should be kept in mind. The combination of medication and tACS for treatment success could be beneficial and should be further researched. Paradigms working in young adults should be adjusted and tested in multiple configurations. Higher intensities might be especially profitable. Where possible, individual anatomical and neurophysiological properties should be considered and stimulation frequency mismatch reduced. The altered mechanisms of CFC in aging should be investigated as well.

In general, we recommend considering a*ge* as an important factor and investigating middle-aged cohorts: More studies comparing different age groups are needed to utilize this promising technique for everyday use.

5 Conclusion

In this study, we tried to repeat a successful paradigm and tACS setup with a target group aged 65 years and older. We succeeded in inducing a vigilance decrement (rising reaction times with time on task and higher POST alpha power) but could not detect any effect of the intervention with 40-Hz tACS. We conclude that it is not appropriate to simply transfer a successful tACS protocol to an older target group without adjusting stimulation parameters. We observed high variations in all data obtained (reaction times, IAF, and alpha power) that could have masked any effect of intervention. Therefore, we recommend reducing the heterogeneity of the target group for future studies. Next to this, we cannot not exclude the possibility, that older adults differ in their neuro-anatomical characteristics and functioning from a young target group and that our protocol might not be useful for them. Reasons could be the different anatomical and neurophysiological properties of an aged brain, cognitive compensatory mechanisms and the usage of anterior and frontal brain regions or different mindsets and motivations. Therefore, it is necessary to continue research—in the hope that, in the future, not only our bodies will stay healthy and live long but also our minds.

Data availability statement

The datasets presented in this article are not readily available because datasets are protected by the data privacy concept of the study. They are available by request to the corresponding or BL. Requests to access the datasets should be directed to birte.loeffler@uni-oldenburg.de.

Ethics statement

The studies involving humans were approved by Medizinische Ethikkommission of the University of Oldenburg. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BL, HS, SF, AH, and CH conceptualized the study. BL and AM acquired participants. BL, HS, and AM performed measurements and analyzed the data. BL wrote the manuscript. CH and HS commented and gave practical hints throughout the study. All authors contributed to the article and approved the submitted version.

Funding

This research has been funded by the Volkswagen Foundation, Ministry of Science and Culture of Lower Saxony as a part of the Interdisciplinary Research Centre on Critical Systems Engineering for Socio-Technical Systems (Grant No.: VWZN2861 VWZN2998) and by own resources of the OFFIS e.V., Institute for Information Technology, Oldenburg, Germany.

Acknowledgments

The authors thank the laboratory staff and work group of the Department of Psychology for helping accomplish this study.

Conflict of interest

CH holds a patent on brain stimulation.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnrgo.2023.1201702/full#supplementary-material

References

Abbasi, N. I., Bodala, I. P., Bezerianos, A., Yu, S., Al-Nashash, H., and Thakor, N. V. (2017). Role of multisensory stimuli in vigilance enhancement- a single trial event related potential study. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference* 2017, 2446–2449. doi: 10.1109/EMBC.2017.8037351.

Abbott, A. (2012). Cognition: The brain's decline. *Nature* 492, S4-5. doi: 10.1038/492S4a.

Abubaker, M., Al Qasem, W., and Kvašňák, E. (2021). Working Memory and Cross-Frequency Coupling of Neuronal Oscillations. *Frontiers in psychology* 12, 756661. doi: 10.3389/fpsyg.2021.756661.

Al-Shargie, F., Tariq, U., Babiloni, F., and Al-Nashash, H. (2021). Cognitive Vigilance Enhancement Using Audio Stimulation of Pure Tone at 250 Hz. *IEEE Access* 9, 22955–22970. doi: 10.1109/ACCESS.2021.3054785.

Al-Shargie, F., Tariq, U., Mir, H., Alawar, H., Babiloni, F., and Al-Nashash, H. (2019). Vigilance Decrement and Enhancement Techniques: A Review. *Brain sciences* 9. doi: 10.3390/brainsci9080178.

3 Study II

Antal, A., and Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in human neuroscience* 7, 317. doi: 10.3389/fnhum.2013.00317.

Antonenko, D., Faxel, M., Grittner, U., Lavidor, M., and Flöel, A. (2016). Effects of Transcranial Alternating Current Stimulation on Cognitive Functions in Healthy Young and Older Adults. *Neural plasticity* 2016, 4274127. doi: 10.1155/2016/4274127.

Arnau, S., Möckel, T., Rinkenauer, G., and Wascher, E. (2017). The interconnection of mental fatigue and aging. An EEG study. *International Journal of Psychophysiology* 117, 17–25. doi: 10.1016/j.ijpsycho.2017.04.003.

Babiloni, C., Binetti, G., Cassarino, A., Dal Forno, G., Del Percio, C., Ferreri, F., Ferri, R. et al. (2006). Sources of cortical rhythms in adults during physiological aging: a multicentric EEG study. *Human brain mapping* 27, 162–172. doi: 10.1002/hbm.20175.

Baltus, A., Vosskuhl, J., Boetzel, C., and Herrmann, C. S. (2020). Transcranial alternating current stimulation modulates auditory temporal resolution in elderly people. *The European journal of neuroscience* 51, 1328–1338. doi: 10.1111/ejn.13940.

Barry, R. J., and Blasio, F. M. de (2017). EEG differences between eyes-closed and eyes-open resting remain in healthy ageing. *Biological psychology* 129, 293–304. doi: 10.1016/j.biopsycho.2017.09.010.

Bates, D., Mächler, M., Bolker, B., and Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software* 67, 1–48. doi: 10.18637/jss.v067.i01.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.-F., and Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of physiology* 591, 1987–2000. doi: 10.1113/jphysiol.2012.249730

Bazanova, O. M., and Vernon, D. (2014). Interpreting EEG alpha activity. *Neuroscience and biobehavioral reviews* 44, 94–110. doi: 10.1016/j.neubiorev.2013.05.007.

Benussi, A., Cantoni, V., Cotelli, M. S., Cotelli, M., Brattini, C., Datta, A., Thomas, C., Santarnecchi, E., Pascual-Leone, A., and Borroni, B. (2021). Exposure to gamma tACS in Alzheimer's disease: A randomized, double-blind, sham-controlled, crossover, pilot study. *Brain stimulation* 14, 531–540. doi: 10.1016/j.brs.2021.03.007.

Berchicci, M., Lucci, G., Pesce, C., Spinelli, D., and Di Russo, F. (2012). Prefrontal hyperactivity in older people during motor planning. *NeuroImage* 62, 1750–1760. doi: 10.1016/j.neuroimage.2012.06.031.

Bodala, I. P., Li, J., Thakor, N. V., and Al-Nashash, H. (2016). EEG and Eye Tracking Demonstrate Vigilance Enhancement with Challenge Integration. *Frontiers in human neuroscience* 10, 273. doi: 10.3389/fnhum.2016.00273.

Borghini, G., Candini, M., Filannino, C., Hussain, M., Walsh, V., Romei, V., Zokaei, N., and Cappelletti, M. (2018). Alpha Oscillations Are Causally Linked to Inhibitory Abilities in Ageing. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 38, 4418–4429. doi: 10.1523/JNEUROSCI.1285-17.2018.

Botwinick, J. (1966). Cautiousness in advanced age. *Journal of gerontology* 21, 347–353. doi: 10.1093/geronj/21.3.347.

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., and Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology* 14, 1133–1145. doi: 10.1017/S1461145710001690.

Buck, L. (1966). Reaction time as a measure of perceptual vigilance. *Psychological Bulletin* 65, 291–304. doi: 10.1037/h0023207.

Canolty, R. T., and Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in cognitive sciences* 14, 506–515. doi: 10.1016/j.tics.2010.09.001.

Casson, E. J., and Racette, L. (2000). Vision standards for driving in Canada and the United States. A review for the Canadian Ophthalmological Society. *Canadian Journal of Ophthalmology* 35, 192–203.

Cattaneo, Z., Vecchi, T., Cornoldi, C., Mammarella, I., Bonino, D., Ricciardi, E., and Pietrini, P. (2008). Imagery and spatial processes in blindness and visual impairment. *Neuroscience and biobehavioral reviews* 32, 1346–1360. doi: 10.1016/j.neubiorev.2008.05.002.

Clayton, M. S., Yeung, N., and Cohen Kadosh, R. (2015). The roles of cortical oscillations in sustained attention. *Trends in cognitive sciences* 19, 188–195. doi: 10.1016/j.tics.2015.02.004.

Craig, A., Tran, Y., Wijesuriya, N., and Nguyen, H. (2012). Regional brain wave activity changes associated with fatigue. *Psychophysiology* 49, 574–582. doi: 10.1111/j.1469-8986.2011.01329.x.

Cristofori, I., Cohen-Zimerman, S., and Grafman, J. (2019). Executive functions. *Handbook of clinical neurology* 163, 197–219. doi: 10.1016/B978-0-12-804281-6.00011-2.

Davis, N. J., Gold, E., Pascual-Leone, A., and Bracewell, R. M. (2013). Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. *The European journal of neuroscience* 38, 2973–2977. doi: 10.1111/ejn.12307.

Dennis, N. A., and Cabeza, R. (2011). "Neuroimaging of Healthy Cognitive Aging," in *The Handbook of Aging and Cognition* (Psychology Press), 10–63.

Dinges (1995). An overview of sleepiness and accidents. *Journal of sleep research* 4, 4–14. doi: 10.1111/j.1365-2869.1995.tb00220.x.

Draaisma, L. R., Wessel, M. J., Moyne, M., Morishita, T., and Hummel, F. C. (2022). Targeting the frontoparietal network using bifocal transcranial alternating current stimulation during a motor sequence learning task in healthy older adults. *Brain stimulation* 15, 968–979. doi: 10.1016/j.brs.2022.06.012.

Engel, A. K., Gerloff, C., Hilgetag, C. C., and Nolte, G. (2013). Intrinsic coupling modes: multiscale interactions in ongoing brain activity. *Neuron* 80, 867–886. doi: 10.1016/j.neuron.2013.09.038.

Essl, M., and Rappelsberger, P. (1998). EEG coherence and reference signals: experimental results and mathematical explanations. *Medical & biological engineering & computing* 36, 399–406. doi: 10.1007/BF02523206.

European Commission (2020). "European Commission Report on the Impact of Demographic Change,". Accessed August 24, 2023. https://commission.europa.eu/system/files/2020-06/demography_report_2020_n.pdf.

Fresnoza, S., Christova, M., Bieler, L., Körner, C., Zimmer, U., Gallasch, E., and Ischebeck, A. (2020). Age-Dependent Effect of Transcranial Alternating Current Stimulation on Motor Skill Consolidation. *Frontiers in aging neuroscience* 12, 25. doi: 10.3389/fnagi.2020.00025.

Gartenberg, D., Gunzelmann, G., Hassanzadeh-Behbaha, S., and Trafton, J. G. (2018). Examining the Role of Task Requirements in the Magnitude of the Vigilance Decrement. *Frontiers in psychology* 9, 1504. doi: 10.3389/fpsyg.2018.01504

Getzmann, S., Arnau, S., Karthaus, M., Reiser, J. E., and Wascher, E. (2018). Age-Related Differences in Pro-active Driving Behavior Revealed by EEG Measures. *Frontiers in human neuroscience* 12, 321. doi: 10.3389/fnhum.2018.00321.

Gorus, E., Raedt, R. de, Lambert, M., Lemper, J.-C., and Mets, T. (2008). Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. *Journal of geriatric psychiatry and neurology* 21, 204–218. doi: 10.1177/0891988708320973.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature reviews. Neuroscience* 13, 491–505. doi: 10.1038/nrn3256.

Guerra, A., Asci, F., D'Onofrio, V., Sveva, V., Bologna, M., Fabbrini, G., Berardelli, A., and Suppa, A. (2020). Enhancing Gamma Oscillations Restores Primary Motor Cortex Plasticity in Parkinson's Disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 40, 4788–4796. doi: 10.1523/JNEUROSCI.0357-20.2020.

Guerra, A., Asci, F., Zampogna, A., D'Onofrio, V., Berardelli, A., and Suppa, A. (2021). The effect of gamma oscillations in boosting primary motor cortex plasticity is greater in young than older adults. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 132, 1358–1366. doi: 10.1016/j.clinph.2021.01.032.

Haegens, S., Cousijn, H., Wallis, G., Harrison, P. J., and Nobre, A. C. (2014). Inter- and intra-individual variability in alpha peak frequency. *NeuroImage* 92, 46–55. doi: 10.1016/j.neuroimage.2014.01.049.

Hedden, T., and Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature reviews. Neuroscience* 5, 87–96. doi: 10.1038/nrn1323.

Helfrich, R. F., Herrmann, C. S., Engel, A. K., and Schneider, T. R. (2016). Different coupling modes mediate cortical cross-frequency interactions. *NeuroImage* 140, 76–82. doi: 10.1016/j.neuroimage.2015.11.035.

Helfrich, R. F., Knepper, H., Nolte, G., Strüber, D., Rach, S., Herrmann, C. S., Schneider, T. R., and Engel, A. K. (2014a). Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. *PLoS biology* 12, e1002031. doi: 10.1371/journal.pbio.1002031.

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., and Herrmann, C. S. (2014b). Entrainment of brain oscillations by transcranial alternating current stimulation. *Current biology*: CB 24, 333–339. doi: 10.1016/j.cub.2013.12.041.

Herrmann, C. S., Rach, S., Neuling, T., and Strüber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in human neuroscience* 7, 279. doi: 10.3389/fnhum.2013.00279.

Hultsch, D. F., MacDonald, S. W. S., and Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *The journals of gerontology. Series B, Psychological sciences and social sciences* 57, P101-15. doi: 10.1093/geronb/57.2.p101.

Ishii, R., Canuet, L., Aoki, Y., Hata, M., Iwase, M., Ikeda, S., Nishida, K., and Ikeda, M. (2017). Healthy and Pathological Brain Aging: From the Perspective of Oscillations, Functional Connectivity, and Signal Complexity. *Neuropsychobiology* 75, 151–161. doi: 10.1159/000486870.

Iuculano, T., and Cohen Kadosh, R. (2013). The mental cost of cognitive enhancement. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 33, 4482–4486. doi: 10.1523/JNEUROSCI.4927-12.2013.

Jensen, O., and Colgin, L. L. (2007). Cross-frequency coupling between neuronal oscillations. *Trends in cognitive sciences* 11, 267–269. doi: 10.1016/j.tics.2007.05.003.

3 Study II

Kasten, F. H., Dowsett, J., and Herrmann, C. S. (2016). Sustained Aftereffect of α-tACS Lasts Up to 70 min after Stimulation. *Frontiers in human neuroscience* 10, 245. doi: 10.3389/fnhum.2016.00245.

Kasten, F. H., Duecker, K., Maack, M. C., Meiser, A., and Herrmann, C. S. (2019). Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. *Nature communications* 10, 5427. doi: 10.1038/s41467-019-13417-6.

Kim, J., Kim, H., Jeong, H., Roh, D., and Kim, D. H. (2021). tACS as a promising therapeutic option for improving cognitive function in mild cognitive impairment: A direct comparison between tACS and tDCS. *Journal of psychiatric research* 141, 248–256. doi: 10.1016/j.jpsychires.2021.07.012.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain research reviews* 29, 169–195. doi: 10.1016/S0165-0173(98)00056-3.

Klimesch, W., Doppelmayr, M., Schimke, H., and Pachinger, T. (1996). Alpha Frequency, Reaction Time, and the Speed of Processing Information. *Journal of Clinical Neurophysiology* 13, 511. doi: aspx.

Klink, K., Paßmann, S., Kasten, F. H., and Peter, J. (2020a). The Modulation of Cognitive Performance with Transcranial Alternating Current Stimulation: A Systematic Review of Frequency-Specific Effects. *Brain sciences* 10. doi: 10.3390/brainsci10120932.

Klink, K., Peter, J., Wyss, P., and Klöppel, S. (2020b). Transcranial Electric Current Stimulation During Associative Memory Encoding: Comparing tACS and tDCS Effects in Healthy Aging. *Frontiers in aging neuroscience* 12, 66. doi: 10.3389/fnagi.2020.00066.

Knyazeva, M. G., Barzegaran, E., Vildavski, V. Y., and Demonet, J.-F. (2018). Aging of human alpha rhythm. *Neurobiology of aging* 69, 261–273. doi: 10.1016/j.neurobiolaging.2018.05.018.

Light, J. M., Grigsby, J. S., and Bligh, M. C. (1996). Aging and heterogeneity: genetics, social structure, and personality. *The Gerontologist* 36, 165–173. doi: 10.1093/geront/36.2.165.

Löffler, B. S., Stecher, H. I., Fudickar, S., de Sordi, D., Otto-Sobotka, F., Hein, A., and Herrmann, C. S. (2018). Counteracting the Slowdown of Reaction Times in a Vigilance Experiment With 40-Hz Transcranial Alternating Current Stimulation. *IEEE transactions on neural systems and rehabilitation engineering* 26, 2053–2061. doi: 10.1109/TNSRE.2018.2869471.

Lüdecke, D., Ben-Shachar, M. S., Patil, I., Waggoner, P., and Makowski, D. (2021). performance: An R Package for Assessment, Comparison and Testing of Statistical Models. *Journal of Open Source Software* 6, 3139. doi: 10.21105/joss.03139.

Martínez-Pérez, V., Tortajada, M., Palmero, L. B., Campoy, G., and Fuentes, L. J. (2022). Effects of transcranial alternating current stimulation over right-DLPFC on vigilance tasks depend on the arousal level. *Scientific reports* 12, 547. doi: 10.1038/s41598-021-04607-8.

Matsumoto, H., and Ugawa, Y. (2017). Adverse events of tDCS and tACS: A review. *Clinical neurophysiology practice* 2, 19–25. doi: 10.1016/j.cnp.2016.12.003.

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Das, S., Callicott, J. H., and Weinberger, D. R. (2002). Neurophysiological correlates of age-related changes in human motor function. *Neurology* 58, 630–635. doi: 10.1212/wnl.58.4.630.

McIntire, L. K., McKinley, R. A., Goodyear, C., and McIntire, J. P. (2014). Detection of vigilance performance using eye blinks. *Applied ergonomics* 45, 354–362. doi: 10.1016/j.apergo.2013.04.020.

McLaren, M. E., Nissim, N. R., and Woods, A. J. (2018). The effects of medication use in transcranial direct current stimulation: A brief review. *Brain stimulation* 11, 52–58. doi: 10.1016/j.brs.2017.10.006.

McWilliams, T., and Ward, N. (2021). Underload on the Road: Measuring Vigilance Decrements During Partially Automated Driving. *Frontiers in psychology* 12, 631364. doi: 10.3389/fpsyg.2021.631364.

Mierau, A., Klimesch, W., and Lefebvre, J. (2017). State-dependent alpha peak frequency shifts: Experimental evidence, potential mechanisms and functional implications. *Neuroscience* 360, 146–154. doi: 10.1016/j.neuroscience.2017.07.037.

Moliadze, V., Atalay, D., Antal, A., and Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain stimulation* 5, 505–511. doi: 10.1016/j.brs.2011.11.004.

Molina, E., Correa, A., Sanabria, D., and Jung, T.-P. (2013). "Tonic EEG dynamics during psychomotor vigilance task," in *2013 6th International IEEE/EMBS Conference on Neural Engineering (NER) (*IEEE), 1382–1385.

Moussavi, Z., Kimura, K., Kehler, L., Oliveira Francisco, C. de, and Lithgow, B. (2021). A Novel Program to Improve Cognitive Function in Individuals With Dementia Using Transcranial Alternating Current Stimulation (tACS) and Tutored Cognitive Exercises. *Front. Aging* 2. doi: 10.3389/fragi.2021.632545.

Nelson, J. T., McKinley, R. A., Golob, E. J., Warm, J. S., and Parasuraman, R. (2014). Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *NeuroImage* 85 Pt 3, 909–917. doi: 10.1016/j.neuroimage.2012.11.061.

Neuling, T., Rach, S., and Herrmann, C. S. (2013). Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Frontiers in human neuroscience* 7, 161. doi: 10.3389/fnhum.2013.00161.

3 Study II

Oken, B. S., Salinsky, M. C., and Elsas, S. M. (2006). Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 117, 1885–1901. doi: 10.1016/j.clinph.2006.01.017.

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

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational intelligence and neuroscience* 2011, 156869. doi: 10.1155/2011/156869.

Osipova, D., Hermes, D., and Jensen, O. (2008). Gamma power is phase-locked to posterior alpha activity. *PloS one* 3, e3990. doi: 10.1371/journal.pone.0003990.

Owsley, C. (2002). Driving Mobility, Older Adults, and Quality of Life. *Gerontechnology* 2, 220–230.

Palva, J. M., Palva, S., and Kaila, K. (2005). Phase synchrony among neuronal oscillations in the human cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 25, 3962–3972. doi: 10.1523/JNEUROSCI.4250-04.2005.

Pattyn, N., Neyt, X., Henderickx, D., and Soetens, E. (2008). Psychophysiological investigation of vigilance decrement: boredom or cognitive fatigue? *Physiology & behavior* 93, 369–378. doi: 10.1016/j.physbeh.2007.09.016.

Pinheiro, J., Bates, D., DebRoy, S., and Sarkar, D. (2022). nlme: Linear and Nonlinear Mixed Effects Models. *R package version* 3.1-96. http://cran. r-project. org/web/packages/nlme/.

Polat, U., Schor, C., Tong, J.-L., Zomet, A., Lev, M., Yehezkel, O., Sterkin, A., and Levi, D. M. (2012). Training the brain to overcome the effect of aging on the human eye. *Sci Rep* 2, 278. doi: 10.1038/srep00278.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., and Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral cortex (New York, N.Y. : 1991)* 15, 1676–1689. doi: 10.1093/cercor/bhi044.

Reinhart, R. M. G., and Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature neuroscience* 22, 820–827. doi: 10.1038/s41593-019-0371-x.

Ross, H. A., Russell, P. N., and Helton, W. S. (2014). Effects of breaks and goal switches on the vigilance decrement. *Exp Brain Res* 232, 1729–1737. doi: 10.1007/s00221-014-3865-5.

Rostami, R., Kazemi, R., Mozaffarinejad, F., Nasiri, Z., Rostami, M., L Hadipour, A., and Sadeghihassanabadi, F. (2021). 6 Hz transcranial alternating current stimulation of mPFC improves sustained attention and modulates alpha phase synchronization and power in dorsal attention network. *Cognitive Neuroscience* 12, 1–13. doi: 10.1080/17588928.2020.1817881.

Rufener, K. S., Oechslin, M. S., Zaehle, T., and Meyer, M. (2016). Transcranial Alternating Current Stimulation (tACS) differentially modulates speech perception in young and older adults. *Brain stimulation* 9, 560–565. doi: 10.1016/j.brs.2016.04.002.

Rumpf, J.-J., Barbu, A., Fricke, C., Wegscheider, M., and Classen, J. (2019). Posttraining Alpha Transcranial Alternating Current Stimulation Impairs Motor Consolidation in Elderly People. *Neural plasticity* 2019, 2689790. doi: 10.1155/2019/2689790.

Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society : JINS* 16, 754–760. doi: 10.1017/S1355617710000706.

Santarnecchi, E., Muller, T., Rossi, S., Sarkar, A., Polizzotto, N. R., Rossi, A., and Cohen Kadosh, R. (2016). Individual differences and specificity of prefrontal gamma frequency-tACS on fluid intelligence capabilities. *Cortex; a journal devoted to the study of the nervous system and behavior* 75, 33–43. doi: 10.1016/j.cortex.2015.11.003.

Sarkar, A., Dowker, A., and Cohen Kadosh, R. (2014). Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 34, 16605–16610. doi: 10.1523/JNEUROSCI.3129-14.2014.

Sarter, M., Givens, B., and Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain research reviews* 35, 146–160. doi: 10.1016/S0165-0173(01)00044-3.

Scally, B., Burke, M. R., Bunce, D., and Delvenne, J.-F. (2018). Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging. *Neurobiology of aging* 71, 149–155. doi: 10.1016/j.neurobiolaging.2018.07.004.

Schmidt, E. A., Schrauf, M., Simon, M., Fritzsche, M., Buchner, A., and Kincses, W. E. (2009). Drivers' misjudgement of vigilance state during prolonged monotonous daytime driving. *Accident; analysis and prevention* 41, 1087–1093. doi: 10.1016/j.aap.2009.06.007.

Sprugnoli, G., Munsch, F., Cappon, D., Paciorek, R., Macone, J., Connor, A., El Fakhri, G. et al. (2021). Impact of multisession 40Hz tACS on hippocampal perfusion in patients with Alzheimer's disease. *Alzheimer's research & therapy* 13, 203. doi: 10.1186/s13195-021-00922-4.

3 Study II

Stecher, H. I., Notbohm, A., Kasten, F. H., and 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, 661432. doi: 10.3389/fnhum.2021.661432.

Stecher, H. I., Pollok, T. M., Strüber, D., Sobotka, F., and Herrmann, C. S. (2017). Ten Minutes of α-tACS and Ambient Illumination Independently Modulate EEG α-Power. *Frontiers in human neuroscience* 11, 257. doi: 10.3389/fnhum.2017.00257.

Steeves, J. K. E., González, E. G., and Steinbach, M. J. (2008). Vision with one eye: a review of visual function following unilateral enucleation. *Spatial Vis* 21, 509–529. doi: 10.1163/156856808786451426.

Taipale, S., Oinas, T., and Karhinen, J. (2021). Heterogeneity of traditional and digital media use among older adults: A six-country comparison. *Technology in Society* 66, 101642. doi: 10.1016/j.techsoc.2021.101642.

Tamanani, R., Muresan, R., and Al-Dweik, A. (2021). Estimation of Driver Vigilance Status Using Real-Time Facial Expression and Deep Learning. *IEEE Sens. Lett.* 5, 1–4. doi: 10.1109/LSENS.2021.3070419.

Thompson, L., Khuc, J., Saccani, M. S., Zokaei, N., and Cappelletti, M. (2021). Gamma oscillations modulate working memory recall precision. *Experimental brain research* 239, 2711–2724. doi: 10.1007/s00221-021-06051-6.

Tomporowski, P. D., and Tinsley, V. F. (1996). Effects of Memory Demand and Motivation on Sustained Attention in Young and Older Adults. *The American Journal of Psychology* 109, 187. doi: 10.2307/1423272.

Vaden, R. J., Hutcheson, N. L., McCollum, L. A., Kentros, J., and Visscher, K. M. (2012). Older adults, unlike younger adults, do not modulate alpha power to suppress irrelevant information. *NeuroImage* 63, 1127–1133. doi: 10.1016/j.neuroimage.2012.07.050.

van Schouwenburg, M. R., Sligte, I. G., Giffin, M. R., Günther, F., Koster, D., Spronkers, F. S., Vos, A., and Slagter, H. A. (2021). Effects of Midfrontal Brain Stimulation on Sustained Attention. *J Cogn Enhanc* 5, 62–72. doi: 10.1007/s41465-020-00179-z.

Varastegan, S., Kazemi, R., Rostami, R., Khomami, S., Zandbagleh, A., and Hadipour, A. L. (2023). Remember NIBS? tACS improves memory performance in elders with subjective memory complaints. GeroScience 45, 851–869. doi: 10.1007/s11357-022-00677-2.

Vosskuhl, J., Strüber, D., and Herrmann, C. S. (2018). Non-invasive Brain Stimulation: A Paradigm Shift in Understanding Brain Oscillations. *Frontiers in human neuroscience* 12, 211. doi: 10.3389/fnhum.2018.00211.

Warm, J. S., Parasuraman, R., and Matthews, G. (2008). Vigilance requires hard mental work and is stressful. *Human factors* 50, 433–441. doi: 10.1518/001872008X312152.

Wascher, E., and Getzmann, S. (2014). Rapid Mental Fatigue Amplifies Age-Related Attentional Deficits. *Journal of Psychophysiology* 28, 215–224. doi: 10.1027/0269-8803/a000127.

Welford, A. T. (1971). What is the basis of choice reaction-time? *ERGONOMICS* 14, 679–693. doi: 10.1080/00140137108931291.

Welford, A. T. (1988). Reaction time, speed of performance, and age. *Annals of the New York Academy of Sciences* 515, 1–17. doi: 10.1111/j.1749-6632.1988.tb32958.x.

Widmann, A., and Schröger, E. (2012). Filter effects and filter artifacts in the analysis of electrophysiological data. *Frontiers in psychology* 3, 233. doi: 10.3389/fpsyg.2012.00233.

Wood, S. N. (2017). *Generalized additive models: An introduction with R.* 2nd ed. Chapman and Hall / CRC.

Zanto, T. P., Jones, K. T., Ostrand, A. E., Hsu, W.-Y., Campusano, R., and Gazzaley, A. (2021). Individual differences in neuroanatomy and neurophysiology predict effects of transcranial alternating current stimulation. *Brain stimulation* 14, 1317–1329. doi: 10.1016/j.brs.2021.08.017.

Supplementary Material

1. Supplementary Tables

1.1 Reaction times analysis:

1.1.1 LMM: 5 Hz Base

Supplementary Table 1. *5 Hz as base-group. LMM results for reaction times (n = 45, observations = 8413): β presents the regression coefficients, SE β the standard error of β. β0 represents the initial reaction time and β6 the increase in reaction time over time of the 5 Hzbase-group (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β0 and β6. Intercepts are given in ms, slopes in ms/min. Model parameters are: R^2 marginal = 0.056, R^2 conditional = 0.470 and AIC -9055.448*

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 5 Hz_{base}	**511.7**	**28.0**	**18.29**	**0.000**	**< 0.001°**
β_1 $SHAM_{base}$	58.2	40.3	1.45	0.149	> 0.05
β_2 $40Hz_{base}$	65.4	38.9	1.68	0.093	> 0.05
β_3 5 Hz_{inter}	39.5	11.6	3.40	0.001	< 0.01
β_4 $SHAM_{inter}$	125.8	40.2	3.13	0.002	< 0.01
β_5 $40Hz_{inter}$	95.8	38.9	2.46	0.014	< 0.05
Slopes:					
β_6 time x 5 Hz_{base}	**1.662**	**0.679**	**2.44**	**0.015**	**< 0.05°**
β_7 time x $SHAM_{base}$	1.746	0.974	1.79	0.073	> 0.05
β_8 time x $40Hz_{base}$	0.420	0.941	0.45	0.654	> 0.05
β_9 time x 5 Hz_{inter}	-0.702	0.683	-1.03	0.303	> 0.05
β_{10} time x $SHAM_{inter}$	-0.678	0.968	-0.70	0.483	> 0.05
β_{11} time x $40Hz_{inter}$	0.936	0.937	1.00	0.317	> 0.05

1.1.2 LMM: 40 Hz Base

***Supplementary Table 2**. 40 Hz as base-group. LMM results for reaction times (n = 45, observations = 8413): β presents the regression coefficients, SE β the standard error of β. β0 represents the initial reaction time and β6 the increase in reaction time over time of the 40 Hzbase-group (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β0 and β6. Intercepts are given in ms, slopes in ms/min. Model parameters are: R^2 marginal = 0.056, R^2 conditional = 0.470 and AIC -9055.448*

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 40 Hz_{base}	**577.1**	**27.0**	**21.34**	**0.000**	**< 0.001°**
β_1 5 Hz_{base}	-65.4	38.9	-1.68	0.093	> 0.05
β_2 $SHAM_{base}$	-7.3	39.6	-0.18	0.855	> 0.05
β_3 40 Hz_{inter}	30.4	11.1	2.73	0.006	< 0.01
β_4 5 Hz_{inter}	-26.0	38.8	-0.67	0.504	> 0.05
β_5 $SHAM_{inter}$	60.4	39.5	1.53	0.127	> 0.05
Slopes:					
β_6 time x 40 Hz_{base}	**2.082**	**0.652**	**3.19**	**0.001**	**< 0.01°**
β_7 time x 5 Hz_{base}	-0.420	0.941	-0.45	0.654	> 0.05
β_8 time x $SHAM_{base}$	1.320	0.955	1.38	0.166	> 0.05
β_9 time x 40 Hz_{inter}	0.516	0.655	0.79	0.432	> 0.05
β_{10} time x 5 Hz_{inter}	-1.128	0.932	-1.21	0.227	> 0.05
β_{11} time x $SHAM_{inter}$	-1.104	0.949	-1.16	0.246	> 0.05

1.1.3 LMM: Factor *medication*

***Supplementary Table 3**. LMM results for reaction times (n = 45, observations = 8413) with cardiovascular medication (yes/no) as the only factor: β presents the regression coefficients, SE β the standard error of β. β0 represents the initial reaction time and β2 the increase in reaction time over time for the healthy, i.e. participants without medication (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. The other coefficients are tested against β0 and β2. Intercepts are given in ms, slopes in ms/min. Model parameters are: R^2 marginal = 0.021, R^2 conditional = 0.467 and AIC -9076.73*

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 healthy	**586.4**	**24.4**	**24.04**	**0.000°**	**< 0.001°**
β_1 medication	-18.4	32.7	-0.56	0.576	> 0.05
Slopes:					
β_2 time x healthy	**2.796**	**0.476**	**5.87**	**0.000°**	**< 0.001°**
β_3 time x medication	-1.584	0.638	-2.48	0.013	< 0.05

3 Study II

***Supplementary Table 4**. LMM results for reaction times (n = 45, observations = 8413) with cardiovascular medication (yes/no), group, and their interaction over time as factors: β presents the regression coefficients, SE β the standard error of β. β0 represents the initial reaction time and β6 the increase in reaction time over time of the SHAMbase-group without medication (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β0 and β6. Intercepts are given in ms, slopes in ms/min. Model parameters are: R^2 marginal = 0.152, R^2 conditional = 0.462 and AIC -8959.546*

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 $SHAM_{base}$	**495.0**	**41.7**	**11.86**	**0.000**	**< 0.001°**
β_1 $5Hz_{base}$	41.6	55.2	0.75	0.451	> 0.05
β_2 $40Hz_{base}$	122.8	589.8	2.08	0.037	< 0.05
β_3 $SHAM_{inter}$	103.3	18.1	5.72	0.000	< 0.001
β_4 $5Hz_{inter}$	103.2	55.1	1.87	0.612	> 0.05
β_5 $40Hz_{inter}$	181.4	58.9	3.08	0.002	< 0.01
β_6 $SHAM_{base}$ + medication	130.2	55.1	2.36	0.229	> 0.05
β_7 $5Hz_{base}$ + medication	-183.5	76.5	-2.40	0.016	< 0.05
β_8 $40Hz_{base}$ + medication	-195.4	76.3	-2.56	0.011	< 0.05
β_9 $SHAM_{inter}$ + medication	-61.7	23.8	-2.59	0.010	< 0.05
β_{10} $5Hz_{inter}$ + medication	-230.9	76.3	-3.03	0.003	< 0.01
β_{11} $40Hz_{inter}$ + medication	-240.5	76.2	-3.16	0.002	< 0.01
Slopes:					
β_{12} time x $SHAM_{base}$	**3.624**	**0.993**	**3.65**	**0.000**	**< 0.001°**
β_{13} time x $5Hz_{base}$	-1.05	1.315	-0.80	0.425	> 0.05
β_{14} time x $40Hz_{base}$	0.264	1.400	0.19	0.850	> 0.05
β_{15} time x $SHAM_{inter}$	-2.376	1.059	-2.24	0.025	< 0.05
β_{16} time x $5Hz_{inter}$	-2.28	1.305	-1.75	0.081	> 0.05
β_{17} time x $40Hz_{inter}$	1.404	1.389	1.01	0.313	> 0.05
β_{18} time x $SHAM_{base}$ x medication	-0.354	1.308	-0.27	0.788	> 0.05
β_{19} time x $5Hz_{base}$ x medication	-1.62	1.819	-0.89	0.374	> 0.05
β_{20} time x $40Hz_{base}$ x medication	-2.538	1.808	-1.40	0.161	> 0.05
β_{21} time x $SHAM_{inter}$ x medication	-0.132	1.399	-0.09	0.926	> 0.05
β_{22} time x $5Hz_{inter}$ x medication	-0.486	1.800	-0.27	0.788	> 0.05
β_{23} time x $40Hz_{inter}$ x medication	-3.552	1.796	-1.98	0.048	< 0.05

4. Study III

Transcranial alternating current stimulation to reduce the increase in braking reaction time in a monotonous simulated driving task

Unpublished manuscript:

Löffler, Birte S.; Stecher, Heiko I.; Weber, Lars; Fudickar, Sebastian; Herrmann, Christoph S.; Hein, Andreas: Transcranial alternating current stimulation to reduce the increase in braking reaction time in a monotonous simulated driving task. Submitted in *IET Intelligent Transport Systems* on 25 January 2024

The following author-edited version of the above-mentioned study is identical in content to the submitted article.

Author contributions:

BL, HS, SF, AH, and CH conceptualized the study. LW programmed the driving simulator task. BL acquired participants, performed measurements, and analyzed the data. BL wrote the manuscript. AH, CH, SF and HS commented and gave practical hints throughout the study. All authors contributed to the article and approved the submitted version.

I hereby confirm that Birte Sofie Löffler contributed this study as mentioned above:

_____

Signature of primary supervisor - Prof. Dr.-Ing. Andreas Hein, Oldenburg, 25 January 2024

Following mistake is in the Supplementary material:

- p. 100 the last sentence of the caption of Table A7 (“Model 2 is presented in Table A8, model 7 in Table A9 and model 8 in Table A10.”) needs to be replaced with: “Model 2 is presented in Table A8 and model 8 in Table A9.”

Transcranial alternating current stimulation to reduce the increase in brake reaction time in a monotonous simulated driving task

ABSTRACT

Non-invasive brain stimulation with 40 Hz alternating current has recently been shown to reduce vigilance decrement in a visual task in the laboratory, showing its potential for application in driving contexts to enhance driver vigilance states. Electrical brain stimulation is inexpensive, portable, and easy to apply. While some studies have investigated stimulation with direct current in driving contexts, this is the first study applying stimulation with alternating current. We used the stimulation setup from the laboratory study in a monotonous driving task and analyzed the behavior of 49 participants in a car-following task in a two-block design. Participants were asked to keep a distance from the leading car at about 20 m and brake as fast as possible when the leading car unintentionally reduced speed. We hypothesized that brake reaction times and trials with inappropriate behavior (i.e., invalid trials) would increase during the first block where no participants were stimulated and that stimulation with 40 Hz in the second block would downregulate these increases compared to two control conditions (5 Hz- and sham-stimulation). Analysis with linear and generalized additive showed that brake reaction times and the probability of invalid trials increased significantly over time but did not show any significant effect of stimulation. Possible reasons like too small effect sizes, task difference, and individual brain states are discussed. Although our study could not unmask the effect of stimulation, recent technological developments have been reported to increase the stimulation effect, which may be needed to apply tACS in closer to real-world contexts.

KEYWORDS: transcranial alternating current stimulation, monotonous driving task, brain, vigilance, brake reaction times, car, driving simulator

I. INTRODUCTION

This study aimed to investigate the potential of transcranial alternating current stimulation (tACS) for application in the context of car driving, here as an intervention in case of vigilance decrement during monotonous car rides.

In a previous study, we demonstrated that transcranial alternating current stimulation at 40 Hz (gamma tACS) reduces reaction time increase in a monotonous visual two-alternative-forced-choice task (Löffler et al., 2018). Now, we set out to investigate the effect of the same stimulation parameters in an applied context: Driving a car. We analyzed brake reaction times in a driving simulator during a monotonous car-

following scenario. To the best of our knowledge, this is the first study applying tACS to modify behavior in an explicit driving context.

Already for the past two decades, non-invasive transcranial electrical stimulation techniques (tES) have been used by neuropsychologists to investigate the functioning of the brain (Beliaeva et al., 2021). Two main modalities are distinguished depending on the type of current used for stimulation: Transcranial direct current stimulation (tDCS) works by de- or hyperpolarization of cortical brain areas, while tACS is believed to entrain brain oscillations. There is strong evidence, that tES leads to a change in cognitive and/or behavioral performance (Brunyé et al., 2019; Santarnecchi et al., 2015). Because the equipment needed is low cost and mobile, tES is of great interest for practical applications like neuro-enhancement (Antal et al., 2022) or therapy (Cho et al., 2022; Ganguly et al., 2020; Solomons & Shanmugasundaram, 2019; Strüber & Herrmann, 2020).

Due to an increasing number of computers and automation systems in our daily and work life, several tasks that were previously done manually by humans now require the human to monitor or supervise the automation systems. Performance of monitoring and supervision tasks can be negatively impacted by a lack of active involvement in the task itself. Different effects have been observed, e.g. boredom, fatigue, or mind-wandering (Körber et al., 2015; McWilliams & Ward, 2021). Experiments conducted in the 1950s showed that time on task vigilance decrements lead to prolonged reaction times and worse signal detection rates (Buck, 1966; Mackworth, 1948) and correlate with brain functioning (Oken et al., 2006; Pattyn et al., 2008). Therefore, it is an important factor in the design of such automation systems to increase the human's ability to stay engaged and increase the vigilance or sustained attention (Oken et al., 2006). As vigilance plays a viable role in everyday life and work contexts, a lot of research focuses on enhancement strategies (Al-Shargie et al., 2019), including tES techniques.

Vigilance decrement is a key safety concern when driving. Prolonged monotonous driving elevates the risk of driving errors and accidents (Klauer et al., 2006). Although partially automated vehicle technology provides safety benefits to the driver, recent research shows that it introduces new concerns about driver attention with vigilance decrement being more severe (Greenlee et al., 2018; Körber et al., 2015; McWilliams & Ward, 2021). Therefore, maintaining vigilance is important for accident prevention and a lot of effort has been made to monitor drivers' states (Albadawi et al., 2022; Tamanani et al., 2021). Prolonged brake reaction times (BRT) are a consequence of vigilance decrement and a critical component in safe driving (Greenlee et al., 2018). As Warshawsky-Livne & Shinar (2002) state: "Impact on Industry: At 90 km/h, a car travels 0.25 m in 0.01 s. Consequently, even such small effects multiplied by millions of vehicle kilometers can significantly contribute to save lives and damages."

The effect of tDCS on driving performance has been investigated in a few studies with contrary results. Beeli et al. (2008) tested the influence of tDCS over the left or right dorsolateral prefrontal cortex (DLPFC) and

found that excitation of the DLPFC by anodal tDCS evoked less risky driving behavior as compared to cathodal stimulation. Sakai et al. (2014) demonstrated that up-regulation of the right DLPFC improved both car-following and lane-keeping performance when participants were asked to maintain an inter-vehicle distance from a leading car traveling a winding road at a constant speed. In 2018, Li & Chung (2018) presented an EEG-Gyroscope-tDCS Brain Machine Interface System for early management of driver drowsiness. The wearable and wireless system measures EEG and gyroscope-based head movement simultaneously allows to detect early signs of driver drowsiness. tDCS applied on the non-hairy forehead and simultaneous EEG are used in a closed-loop system to enhance the driver's state. In their pilot study, they showed that 10 minutes of closed-loop tDCS helped to prolong the period of wakefulness in ten participants under the condition of slight drowsiness, however, it was not possible to effectively enhance the driver´s alertness in every single tDCS session. Brunnauer et al. (2018) investigated the effect of tDCS on driving skills via standardized computerized psychomotor tests and stimulated the DLPFC as well. They did not find significant improvements and concluded, that left prefrontal tDCS may not alter driving skills affording more automated action patterns but -as shown in previous studies- may have an influence on driving behavior requiring executive control processes. The same holds true for a study by Ward et al. (2017) who also stimulated the left DLPFC and found no evidence that stimulation changed driving behavior during distracting scenarios. Facchin et al. (2023) report on successful focal high-definition tDCS on the right frontal eye field to improve reaction time to the braking lights of a preceding car and performance in a second distracting task. Their focus was driver distraction, not vigilance, and they collected 216 trials in the 25 minutes long experimental procedure. They found a significant difference between sham and focal high-definition tDCS and between conventional and focal high-definition tDCS, but not between sham and conventional tDCS.

Despite successful improvements in performance or behavior, tDCS has been under critique because the enhancement of cognitive functions comes at the expense of other cognitive functions being impaired (Colzato et al., 2017; Iuculano & Cohen Kadosh, 2013) or showing opposing effects depending on the individual state (Sarkar et al., 2014). An alternative method to tDCS is tACS. During tACS alternating current is used which allows direct and subtle interference with the ongoing oscillatory brain activity. Through alternation of the direction of the current, the membrane potential is not affected and therefore tACS is probably not so well suited to de- or hyperpolarize the cortex over a long period as tDCS (Antal & Herrmann, 2016). Applied in the conventional EEG frequency range, tACS is believed to target and entrain specific frequencies thereby modulating brain oscillations (Tavakoli & Yun, 2017) with no serious adverse events and can be applied safely for duration up to 30 minutes in healthy adults (Matsumoto & Ugawa, 2017). Although this might be a shorter duration than many car rides, it should provide sufficient time to get to a resting place. tACS has been shown to induce behavioral and neurophysiological effects during (online) and outlasting stimulation (offline) (Kasten et al., 2016). tACS has been widely used to enhance

cognitive performance (for a review, see Klink et al., 2020). Considering its effect on vigilance, results are mixed: While Rostami et al. (2021) successfully improved sustained attention by 6 Hz tACS on the mPFC, van Schouwenburg et al. (2021) found no effect of stimulation when stimulating the same brain region with 4 Hz. Currently, a lot of applied tACS research concentrates on its application in treating psychological diseases, especially relating to aging (Kim et al., 2021; Strüber & Herrmann, 2020). Hsu et al. (2019, 2017) applied theta-tACS on the bilateral PFC to enhance multitasking performance in a simulated environment driving game.

In this study, we want to investigate if the stimulation setup from our previous study (Löffler et al., 2018) works beneficial also in an applied context. In 2018, we were able to reduce the vigilance decrement during a monotonous reaction time task in the laboratory setup by tACS. After 30 minutes of stimulation - participants of the stimulation group showed significantly reduced reaction time increment than a sham control group. After 1-hour experimental session, their reaction time was 19 ms faster on average. This would equal to a travelled distance of 0.5 m at a speed of 90 km/h. We combined two insights when we conceptualized our study: 1. Vigilance decrement and rising reaction times have been associated with a rise in posterior alpha power (Clayton et al., 2015; Klimesch, 1999; Klimesch et al., 1996; Molina et al., 2013). 2. Recent research has shown that gamma stimulation with 40 Hz can down-regulate alpha power (Helfrich et al., 2016; Helfrich et al., 2014). A possible explanation for this effect comes from a mechanism called cross-frequency coupling (CFC). During CFC brain oscillations of specific slower and faster frequencies are nested in and modify each other (Jensen & Colgin, 2007).

In the context of car driving, rising alpha power with time on task has also been linked to vigilance decrement. In monotonous scenarios, this is explained by passive fatigue and the decrease in the level of alertness and attention (Gahragozlou et al., 2015; Schier, 2000) and mind-wandering (Körber et al., 2015). Rising posterior alpha power has been linked to increased driving errors and driving lane variability, but not crosswind compensation, stressing that alpha power reflects boredom or attentional withdrawal rather than the decline of processing abilities (Wascher et al., 2016). During a monotonous 3-hour long drive, a linear degradation of drivers´ subjective state, long average reaction times, and parietal alpha with increasing time on task was observed (Schmidt et al., 2007).

Our vision is the use of tACS as a car assistive system that helps to maintain the vigilance level of drivers or make them more alert, especially for user groups like older adults and drivers with limitations due to neurological diseases, e.g. Parkinson’s disease. Due to the increase in car automatization, we see a large potential for tACS applications in the context of car driving. Therefore, we transferred the setup and experimental design of the study by Löffler et al. (2018) to the context of car-driving extending it with an additional 5 Hz control group to ensure that any enhancing effects are frequency-specific (Davis et al., 2013). We designed a scenario where participants are asked to keep a constant distance from a preceding

car on a rural road with no other distractions. Every 13 – 22 seconds the preceding car unexpectedly reduces its speed indicated by its flashing brake lights. Participants were asked to react as fast as possible by braking. The experiment consisted of two blocks of 30 minutes with 100 brake events in each block. The first block served as BASELINE and none of the participants were stimulated. In the second block, referred to as INTERVENTION, one-third of the participants were stimulated with 40 Hz, another third with 5 Hz control frequency and one-third received only sham stimulation. We hypothesized, that participants would slow down with time on task due to the monotonous nature of the task (vigilance decrement) and exhibit longer brake reaction times (BRT). The 40 Hz stimulation group was hypothesized to show a less steep increase in BRT than the two control groups (5 Hz stimulation and sham).

II. MATERIALS AND METHODS

The experimental protocol was approved by medical ethics board (Medizinische Ethikkommission) of the University of Oldenburg. Written informed consent was acquired from all participants before the experiment in line with the Declaration of Helsinki. Participants received monetary compensation for taking part in the study.

a. Participants

54 participants completed the experiment, of which 49 entered analysis (5 had to be deleted, reasons see below). All participants were university students aged between 20 and 30 years and were obliged to have at least 2 years of active driving experience. None of them reported the presence or history of neurological or psychiatric disorders.

In a single-blind design, participants were randomly assigned to one of the three experimental groups receiving 40 Hz-, 5 Hz- or SHAM-stimulation. Females and males were balanced between the groups to avoid gender effects. All participants were believed to receive tACS-stimulation and were debriefed after the experiment.

Due to battery issues with the stimulation device and an operator error, two participants had to be excluded from the data analysis. For statistical analysis, three more participants needed to be excluded because they did not follow experimental instructions. One participant pressed the gas and brake pedal simultaneously, one mainly used the brake pedal, and another regulated the distance with just the gas pedal, making computation of brake reaction time impossible. From the remaining 49 participants 17 belonged to the SHAM- (8 female, age = 23.3 years SD 2.22), 16 to the 5 Hz- (9 female, age = 22.8 years SD 2.33), and 16 to the 40 Hz-group (9 female, age = 23.9 years SD 3.15). 9 of these participants had previous experience with tACS, which was longer than 2 months ago (SHAM: 4, 5 Hz: 2, 40 Hz: 3).

An *a priori* power analysis based on the findings of Löffler et al. (2018) suggests a sufficient power (1- β = 0.85) at a total sample size of 42 (14 per group).

b. Driving simulator

The experiment took place in a full-scale fixed-based right-hand traffic driving simulator at OFFIS - Institute for Information Technology (Oldenburg, Germany). The driving simulator consisted of an original car cabin used as a mock-up with an automatic transmission. Three projectors offered a maximum field of view of 150 degrees. The participants controlled the mock-up car with pedals (gas and brake) and a steering wheel. The driving scenario was simulated using the driving simulator software SILAB (Version 5, Krueger et al., 2005). Behavioral data, such as velocity, steering wheel angle, relative lane position, and pressure on the gas or brake pedal were recorded in SILAB, as well as environmental data, which was measured by external sensors such as light onset time and distance to the leading car. Data was recorded at a rate of 120 Hz. The room was dimmed, and the instructor sat in the back of the driving simulator.

c. Study design

The experiment consisted of two days: A training and an experimental day (Fig. 1a). On the training day, participants were informed about the procedure, asked to fill out a questionnaire on medication and tACS experience, and completed one 30 minutes long experimental block in the driving simulator. The experimental day was at least one day after the training day. After a short status update on sleep quality and caffeine consumption, the tACS device was attached to the participants, and impedances and comfort with the stimulation were checked. Participants performed a test drive of approx. 3 minutes and were reminded of the task. During the experiment communication stopped. The experiment consisted of two blocks of 30 minutes. The first block served as a baseline block (referred to as BASELINE-block) in which none of the participants was stimulated. In the second block (referred to as INTERVENTION-block) participants were stimulated according to their assigned group (SHAM, 5 Hz- or 40 Hz-tACS). Block order was not randomized. During the approximately two minutes long break between the blocks, the stimulation device was switched on and impedance checked again. Participants were offered a glass of water but told not to leave the stimulator. After the experiment, participants were asked whether they believed to be stimulated or not and were informed about their actual stimulation condition. To evaluate the presence of adverse effects (e.g. *headache*, *neck pain*, *itching*, *tiredness*) and its linkage to stimulation, participants were asked to fill out a standardized questionnaire according to Brunoni et al. (2011) with items on a scale of 1 (none) to 4 (severe or definitely).

d. Task

In a monotonous rural landscape with a slightly winding road, participants were asked to keep a distance to a leading car moving at a varying speed between 65 and 90 km/h at an optimum of about 20 m. The

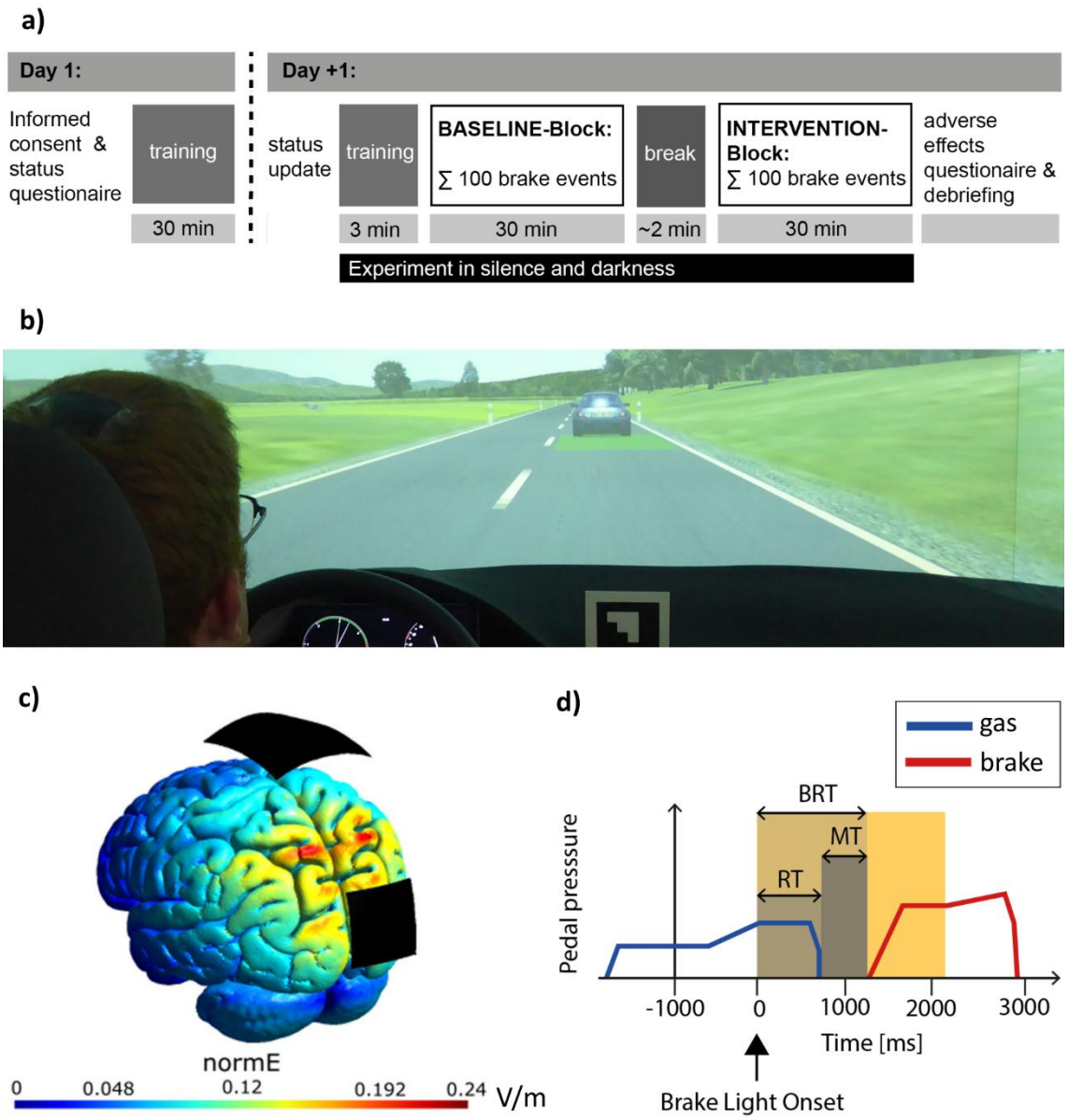

Fig. 1

Experimental Design: (a) Procedure of the experiment. At least one day prior to the actual experiment (Day +1), participants trained in the driving simulator (Day 1). The actual experiment consisted of two 30 minutes long blocks each containing 100 brake events. (b) Driving simulator and scenario. Participants were asked to follow a leading car and keep the distance at 20 m – indicated by a green moving bar projected on the road before them (black arrow). At brake events, the leading car spontaneously decelerated, and its brake lights turned red. (c) Electrode setup and current simulation using SIMNIBS. A 5 cm x 7 cm electrode was placed on the vertex and a smaller 4.5 cm x 4.5 cm electrode was on the visual cortex (Cz and Oz as corresponding positions of the 10-10 EEG system). The simulation shows the electric field strength, covering the posterior brain areas. The color bar represents the normal vector of the electric field in V/m (reproduced with permission of the authors from Stecher & Herrmann 2018). (d) Brake event. Timepoint 0 indicates the turning red of the brake lights of the leading car (brake light onset). The blue line corresponds to force on the gas, the red on the brake pedal. Reaction time (RT) indicates the time from brake light onset to release of the gas pedal. The brake-movement time (MT) is the time needed to switch from gas to brake pedal. The brake reaction time (BRT) constitutes the sum of RT + MT. The yellow window shows the time the brake lights of the leading car are lit.

optimum distance was marked on the street as a half transparent green moving bar. After specific driven meters, the leading car unexpectedly reduced speed and its brake lights turned red (see Fig. 1b). To avoid collision, the car reduced speed by approx. 10 km/h for the first 400 ms and then more abruptly by approx. 8 km/h in the next 100 ms. At such events – referred to as brake events - participants were asked to hit the brake pedal as fast as possible and to return to the optimum distance. Brake lights were lit for

approximately 2 s, before the leading car began to accelerate again. The gap between brake events varied between 13 – 22 s. Except for the leading car, no traffic occurred. To avoid distraction or entertainment, the rural scenery only showed small variations.

e. tACS

Adhesive electrode paste (ten20®conductive, Weaver and Company, Aurora, CO, USA) was used to fixate two rubber electrodes with their center at Cz (7 x 5 cm^2) and Oz (4,5 x 4,5 cm^2) according to the 10-10 EEG system. Stimulation was applied via a battery-driven stimulator (neuroConn DC Stimulator with Remote-In function, Neuroconn GmbH, Ilmenau, Germany). For the STIMULATION-block, the tACS-device was remotely accessed via a Matlab controlled digital-to-analog-converter (Ni USB 6229, National Instruments, Austin, Texas, USA). Stimulation intensity was set to 1 mA and impedance was kept below 10 kOhm. Fig. 1c shows a computer simulation of the proposed electric field. For both tACS-groups, the current linearly faded in and out for 30 s at the beginning and end of the INTERVENTION-block, respectively. Current in the SHAM-group was faded in for 30 s, kept constant at 1 mA (at either 40 or 5 Hz) for 30 s and faded out for 30 s at the beginning and end and end of the block. We chose electrode sizes, positions, and stimulation intensity in line with other studies that showed effective stimulation of posterior alpha bands (Kasten et al., 2016; Löffler et al., 2018; Stecher et al., 2017). The intensity of 1 mA is a widely used stimulation intensity that induces neurophysiological and behavioral effects without causing unpleasant sensations (e.g., Klink et al., 2020). Application of a frequency of 40 Hz with this setup has been shown to reduce reaction time increment in a laboratory setting (Löffler et al., 2018).

f. Data analysis & Statistics

Data analysis was performed using Matlab (Release 2023a, The MathWorks Inc., Natick, MA, United States). Driving behavior (pressure on gas or brake pedal, steering wheel angle, lane keeping variability, distance to leading car) was analyzed and visually inspected around brake events and across the experiment.

For analysis, we differentiated between valid and invalid trials. We considered trials as valid only, if the presses on the brake pedal occurred within reasonable reaction times (RT), which we defined as the time needed to release the foot from the gas pedal within 100 – 1500 ms. Additionally, we defined a brake-movement time (MT) – the time needed to switch the foot from gas to brake pedal – of at least 50 ms. The brake reaction time (BRT) constitutes the sum of RT + MT (see Fig. 1d). Trials where participants had no contact with the gas pedal at brake light onset, did not use the brake pedal, or showed MTs, RTs or BRTs longer than 2000 ms were saved as invalid trials. We analyzed RT and MT in separated LMMs but could not find any trend that could not be explained by BRT analysis. Same accounts for the classification of participants – analog to BRT (see next section g.) - with a MT or RT lower the median as *slow.* Therefore, we only describe mean values for MT and RT in the discussion section.

g. Statistics

For statistical analysis, we used the software R (Version 4.3.1, R Core Team, 2023) and the packages “nlme” (Pinheiro et al., 2023), “MuMin” (Bartoń, 2023), and “mgcv” (Wood, 2017).

In line with our previous study (Löffler et al. 2018) a linear mixed model (LMM) was used for BRT analysis and a generalized additive mixed model (GAMM) for analysis of invalid trials. Following our hypothesis, we tested the factor *group* with six levels ($SHAM_{base}$, $SHAM_{inter}$, 5 Hz_{base}, 5 Hz_{inter}, 40 Hz_{base}, 40 Hz_{inter}). We added participants' identity and their behavior over time as random effects to account for participants being part of the respected base and inter-group. To ensure the goodness-of-fit of our model we started with simple models without random effects and increased complexity stepwise. We added an auto-correlated covariance structure of order 1 per participant and block for the random effects. As further factors we tested *gender* and whether participants experienced the problem of *concentration or/and tiredness* (true, if participants answered on the adverse effects questionnaire with the respective questions with 3 or higher). As literature shows that tACS is often more beneficial for a specific subgroup of participants, e.g. high-baseline (Thompson et al., 2021) or slower performers at baseline receiving greater benefits (Santarnecchi et al., 2016), we classified participants with a BRT lower than the median as *slow.* The loglikelihood-ratio was used to compare LMMs, and the Akaike Information Criterion (AIC) to compare GAMMs. A two-sided significance level of $\alpha = 0.05$ was used.

To check the overall differences in errors between blocks and groups, we used Shapiro-Wilk-Tests and QQ-Plots to check for normality. We compared the number of errors between blocks with a paired t-test and differences between groups with Kruskal-Wallis-tests.

Further, we inspected general driving behavior along the track over time. We visualized the mean and median change in variability for distance to the leading car, steering wheel angle, and variance in lane position with sliding windows per participant and group. Through visual inspection around brake events and cluster analysis (K-means), we could classify *driver types* with either relaxed or strong braking actions (brake pedal value below or higher than 0.5 – with 1 being the maximum - after 1 s of light onset) and range of distance to the leading car (smaller and wider than 10 m). We added the factor *driver type* with four levels (a) 1: “low pressing” & “small range”, b) 2: “low pressing” & “wide range”, c) 3: “high pressing” & “small range” and d) 4: “high pressing” & “wide range”) to our mixed models as a further factor. These types are similar to the ones identified by Yang et al. (2019) (1: unaggressive – stable, 2: unaggressive – unstable, 3: aggressive – stable, 4: aggressive – unstable) except that we have no normal state. As we classified *driver types* post the experiment, the four identified types were not balanced between groups. See Fig. 2 for an abstracted overview or SUPPLEMENTARY MATERIAL Fig. 1A for plots including single trials.

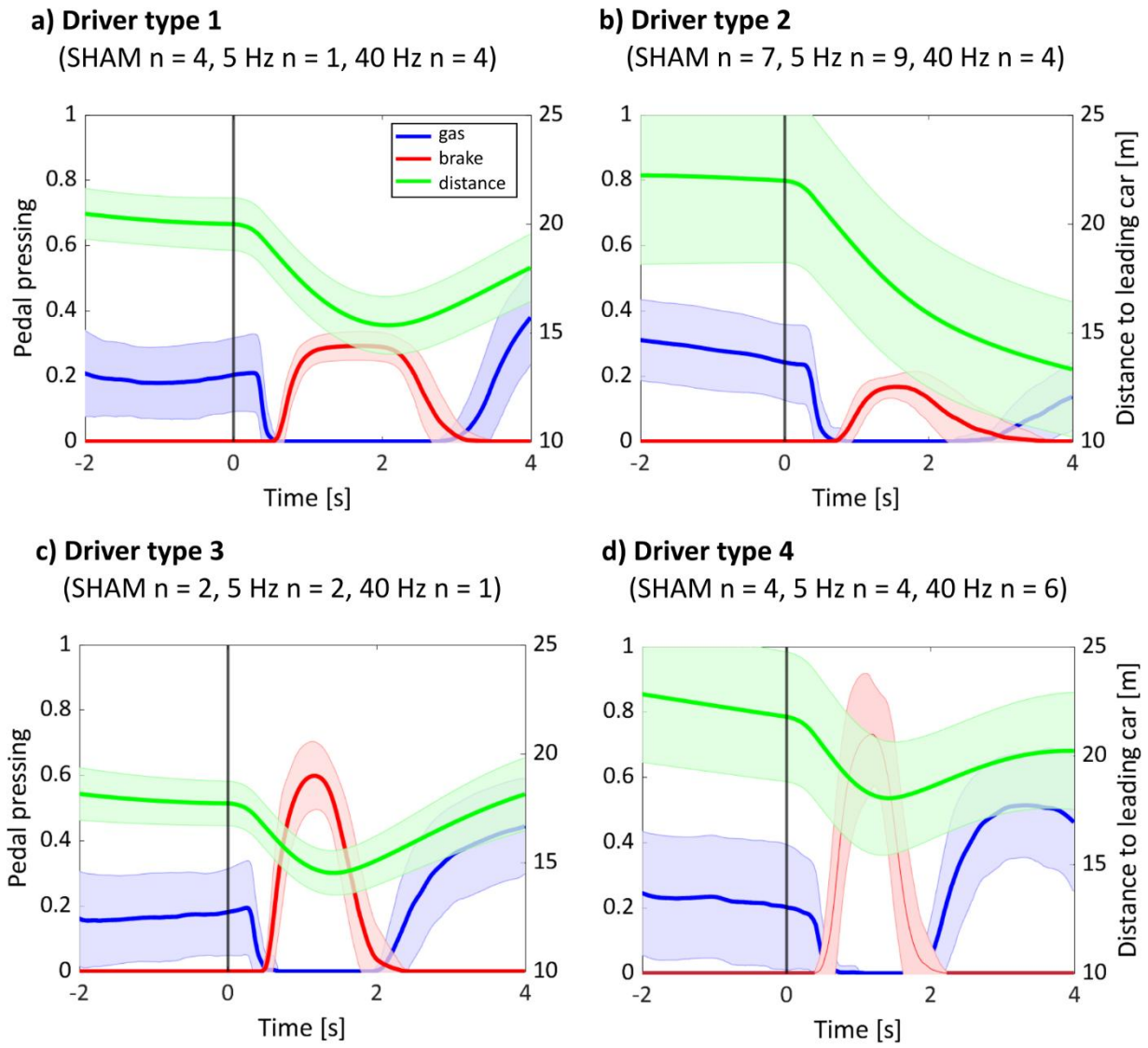

Fig. 2

Exemplary plots of behavioral data of valid trials (BASELINE-block) of four participants were used to illustrate the four different driver types. Origin of X-Axis (in seconds), marked by a black vertical line, indicates the brake light onset of the leading car. Blue marks the pressing of the gas, red the pressing of the brake pedal. Both measures represent the linear way and have a maximum of one and refer to the primary Y-axis. Green marks the distance to the leading car (secondary Y-Axis, in meter, with a cut off at 10 m). Bold lines indicate the average, shaded areas along the average line represent the corresponding standard deviation. a) Driver type 1: "unaggressive – stable", b) Driver type 2: "unaggressive – unstable", c) Driver type 3: "aggressive – stable"", d) Driver type 4: "aggressive - unstable".

III. RESULTS

a. Debriefing

63 % of the participants in total (n = 49) mentioned problems with *concentration or/and tiredness* along the experiment (n = 31, 59 % SHAM, 69 % 5 Hz, 63 % 40 Hz). 10 % of them link it to being stimulated (n = 5). 14 % of the participants experienced severe *tingling* or *itching* (n = 7, 6 % SHAM, 13 % 5 Hz, 25 % 40 Hz), 100 % of them linked it to stimulation. 67 % of participants (n = 33) believed to be stimulated (53 % SHAM, 75 % 5 Hz, 75 % 40 Hz).

4 Study III

b. General behavioral analysis

No rear-end collisions occurred. 61 % of the trials (n = 5956) were considered valid and entered the LMM. 5.7 % of trials (n = 219) counted as invalid due to the exclusion criteria for minimal and maximal durations of BRTs or RTs as defined in section II.f. In the remaining trials, mostly the brake (93.7 %, n = 3602) and only a few times the gas pedal (0.6 %, n = 23) was used to regulate distance. The number of invalid trials was approximately equivalent between both blocks (BASELINE: 38.7 % SD 17.57, INTERVENTION: 39.7 % SD 15.43) and showed no significant difference (t = -0.60175, df = 48, p-value = 0.5502). No significant difference in errors could be detected between groups (BASELINE: Kruskal-Wallis chi-squared = 2.4127, df = 2, p-value = 0.2993; INTERVENTION: Kruskal-Wallis chi-squared = 1.5926, df = 2, p-value = 0.451).

Average BRT overall participants was approx. 750.0 ms (SD 206.7), MT 280.4 ms (SD 123.6) and RT 469.6 ms (SD 139.6). The median BRT was 708.3 ms.

Block- and group wise moving medians of leading car distance, variance in lateral position or steering wheel angle showed no changes over time. Variance of lateral position showed a linear trend ($r > 0.3$) in 22.4 % of the participants, but only in either BASELINE- (SHAM: n = 3, 5 Hz: n = 2, 40 Hz: n = 2) or INTERVENTION-block (SHAM: n = 2, 5 Hz: n = 0, 40 Hz: n = 2).

57 % of the participants (n = 28, 29 % SHAM, 69 % 5 Hz, 75 % 40 Hz) mentioned the use of a *strategy* during the experiment. Common strategies were concentrating on a fixation-point (n =7), looking for a pattern (n = 5), counting (seconds ore brake events, n = 4) and conscious mind-wandering (n = 2).

c. Analysis of BRT and invalid trials with time on task (LMM and GAMM)

Stepwise increase in model complexity and valuation of models´ goodness-of-fit showed that the best model predicts BRT from *time + group* with *participant over time* as random effect and a continuous autoregressive covariance structure (corCAR 1) (see SUPPLEMENTARY MATERIAL Table A1 for a comparison of different model configurations and Table A2 for the best fitting model): Despite our hypothesis, the interaction of the factor *time * group* did not improve the model. The factors *gender, strategy*, *concentration or/and tiredness* did not contribute to the model. Adding a classifier characterizing participants as *slow* improves the model's fit more than adding the factor d*river type* or a combination of both but did not reveal any group effect and showed no effect over time (see SUPPLEMENTARY MATERIAL Table A3 for the LMM_{slow} and Table A4 for the $LMM_{drivertype}$). To still show the effect of the factor *group * time*, we decided to present the following model, that predicts BRT from the covariate *group* ($SHAM_{base}$, 5 Hz_{base}, 40 Hz_{base}, $SHAM_{inter}$, 5 Hz_{inter}, 40 Hz_{inter}) and its interaction over time according to the following equation 1:

$$\begin{aligned} rt = {} & \boldsymbol{\beta_0} * \boldsymbol{SHAM_{base}} + \beta_1 * 5Hz_{base} + \beta_2 * 40Hz_{base} + \beta_3 * SHAM_{inter} + \beta_4 * 5Hz_{inter} + \beta_3 \\ & * 40Hz_{inter} + \boldsymbol{\beta_6} * \boldsymbol{SHAM_{base}} * \mathbf{time} + \beta_7 * 5Hz_{base} * time + \beta_8 * 40Hz_{base} * time \\ & + \beta_9 * SHAM_{inter} * time + \beta_{10} * 5Hz_{inter} * time + \beta_{11} * 40Hz_{inter} \\ & * time \end{aligned} \quad (1)$$

β-coefficients represent fixed effects and are listed in Table 1. β_0 describes the intercept, β_6 describes the slope (i.e. increase of BRT over time) of the $SHAM_{base}$-group. The p-value of β_0 and β_6 indicate the difference in comparison to zero (bold font). The coefficients β_1 - β_5 describe the group-specific difference of intercepts compared to $SHAM_{base}$-group (β_0). To calculate the predictor for the specific group, coefficients need to be added up to the ones of the $SHAM_{base}$-group. For example (β_0 + β_1) add up to the intercept of the $5Hz_{base}$-group, (β_0 + β_2) to the intercept of the $40Hz_{base}$, and so on. The Same accounts for the coefficients of the slopes (β_6 - β_{11}). The final model including fixed and random effects explains approx. 60 % of the observed variance (R^2 conditional = 0.587).

Table 1

LMM results for BRT (n = 49, observations = 5956, R^2 marginal = 0.0380, R^2 conditional = 0.590): β presents the regression coefficients, SE β the standard error of β. β_0 represents the initial BRT and β_6 the increase in BRT of the $SHAM_{base}$-group over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients of intercepts are tested against β_0, slopes against β_6. Intercepts are given in ms, slope β_6 in ms/min.

	β	**SE beta**	**t-value**	**p-value**	
Intercepts:					
β_0 $SHAM_{base}$	**673.4**	**37.18**	**18.12**	**0.0000**	**< 0.001°***
β_1 $5Hz_{base}$	71.9	53.47	1.34	0.1790	> 0.05
β_2 $40Hz_{base}$	8.1	53.36	0.15	0.8792	> 0.05
β_3 $SHAM_{inter}$	59.7	12.50	4.78	0.0000	< 0.001*
β_4 $5Hz_{inter}$	100.2	53.50	1.87	0.0611	> 0.05
β_5 $40Hz_{inter}$	35.8	53.34	0.67	0.5022	> 0.05
Slopes:					
β_6 time * $SHAM_{base}$	**2.490**	**0.6504**	**3.83**	**0.0001**	**< 0.001°***
β_7 time * $5Hz_{base}$	0.738	0.9468	0.78	0.4366	> 0.05
β_8 time * $40Hz_{base}$	-0.756	0.9258	-0.81	0.4159	> 0.05
β_9 time * $SHAM_{inter}$	-1.152	0.7224	-1.60	0.1105	> 0.05
β_{10} time * $5Hz_{inter}$	-0.660	0.9522	-0.69	0.4879	> 0.05
β_{11} time * 40 Hz_{inter}	-1.296	0.9258	-1.40	0.1610	> 0.05

The model shows a significant effect of time for the $SHAM_{base}$-group (β_6 time $p < 0.001$): BRT are predicted to increase by 2.5 ms/min. The coefficient of the slope for the 5 Hz_{base}-group is predicted to be slightly higher (β_7), while the slopes for all other groups ($\beta_8 - \beta_{11}$) are predicted to be less, but none of these differences is significant. The only significant coefficient is the intercept of the $SHAM_{inter}$-group: Participants belonging to this group are predicted to start the INTERVENTION-time with a 59.7 ms (β_3) higher initial BRT ($\beta_0 + \beta_3 = 733.4$ ms). The 5 Hz_{base}-group has a higher ($\beta_0 + \beta_1 = 774.0$ ms) and 40 Hz_{base}-group a slightly higher ($\beta_0 + \beta_2 = 709.5$ ms) initial BRT, but they do not significantly differ from $SHAM_{base}$. Same accounts for the difference between the intercepts of the 5 Hz_{inter}- and 40 Hz_{inter}-group and the $SHAM_{base}$-group. As the model tests coefficients against $SHAM_{base}$, we also calculated version of the model with 5 Hz and 40 Hz base groups (see SUPPLEMENTARY MATERIAL Table A5 and Table A6). We can confirm that after the BASELINE-block all groups start with a significantly higher initial BRT into the INTERVENTION-Block compared to their respected base group: The 5 Hz base group model shows a significant difference in intercepts between 5 Hz_{base} and 5 Hz_{inter}, as well as the 40 Hz base model between 40 Hz_{base} and 40 Hz_{inter}. The break between the blocks leads to a recovery of BRT (SHAM: Δ 15.0 ms, 5 Hz: Δ 68.5 ms, 40 Hz: Δ 24.3 ms). The 5 Hz-group has the steepest slope in BASELINE and the best recovery time between the blocks. See Fig. 3 for an illustration.

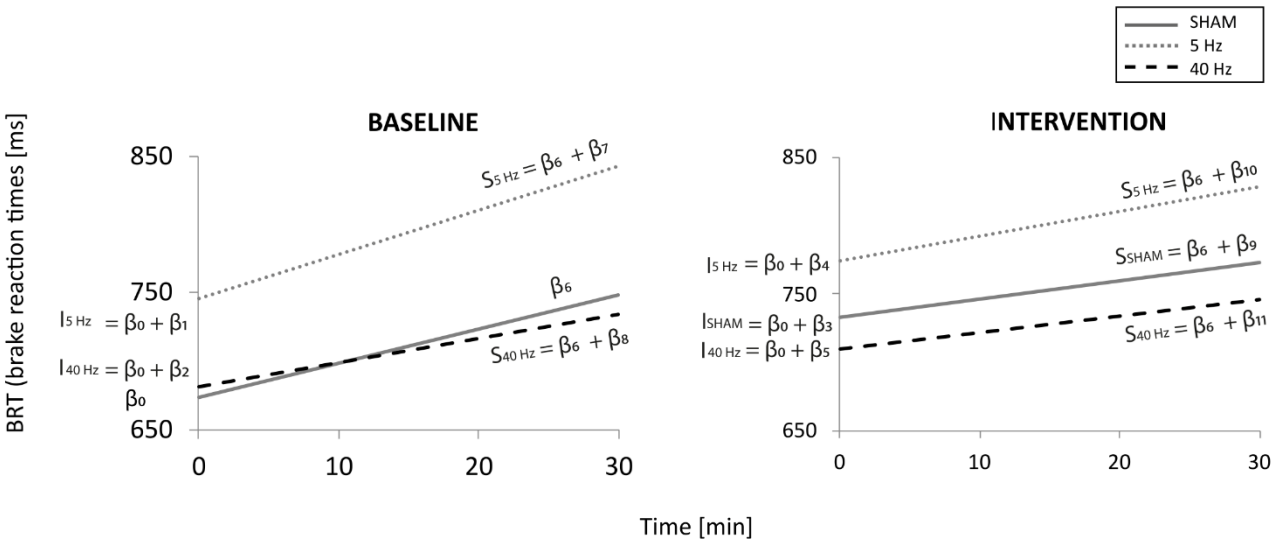

Fig. 3

LMM results for BRT (n = 49, observations = 5956, R^2 marginal = 0.040, R^2 conditional = 0.576): Visualization of the regression functions representing BRT (in ms) against time (in minutes) for the SHAM- (gray solid line), 5 Hz- (grey pointed line) and 40 Hz- (black dashed line) according to block (BASELINE or INTERVENTION). Regression lines represent the six groups (BASELINE: $SHAM_{base}$, $5Hz_{base}$, $40Hz_{base}$; INTERVENTION: $SHAM_{inter}$, $5Hz_{inter}$, $40Hz_{inter}$) used for statistical analysis. The two SHAM-, 5 Hz and 40 Hz-groups consisted of the same participants. β-coefficients (from Table 1) indicate how intercepts ($\beta_0 - \beta_5$) -marked with an I- and slopes ($\beta_6 - \beta_{11}$) were calculated. β_0 is the intercept and β_6 the increase over time of the SHAM-group. Their significance is compared to zero. β_0 and β_6 are significantly different from zero with $p < 0.001$. The intercept of the $SHAM_{inter}$-group ($I_{SHAM} = \beta_0 + \beta_3$) is significantly different from $SHAM_{base}$ ($I_{SHAM} = \beta_0$, $p < 0.001$).

The change of probability over time for invalid trials was tested with a GAMM (logit model). As with the LMM, the factors *gender, strategy*, *concentration or/and tiredness* did not contribute to the GAMM. The best-fitting model predicted the probability from *time* only and only participant ID was used as a random

effect (AIC = 43204.12, see SUPLLEMENTARY MATERIAL Table A7 for model comparison and Table A8 for best fitting model). To nevertheless show the influence of the factor *group*, we show the model following equation 2: For odd ratio (OR) and coefficients of the GAMM, see Table 2. When testing different model configuration, the factor *driver type* performed better than *group* (AIC = 43206.14). Here, *driver type* 2 and 4 are predicted to have a highly significant approx. 315 % higher probability for invalid trials compared to *driver type* 1 (see SUPPLEMENTARY MATERIAL Table A9).

$$\begin{aligned}&\text{probability for invalid trial}\\ &= \exp\left(\beta_0 * \boldsymbol{SHAM_{base}} + \beta_1 * 5Hz_{base} + \beta_2 * 40Hz_{base} + \beta_3 * SHAM_{inter} + \beta_4 * 5Hz_{inter} + \beta_5 * 40Hz_{inter} + \boldsymbol{\beta_6} * \mathbf{time}\right)\end{aligned} \quad (2)$$

Table 2

GAMM (AIC 43210.85) for the probability for invalid trials (n = 49, observations = 9800, R^2 marginal = 0.041, R^2 conditional = 0.372): OR represents the odd ratio calculated by exponentiating the regression coefficients β, SE β is the standard error of β. β_0 represents the initial probability for an invalid trial of the $SHAM_{base}$-group and β_6 the increase in probability for invalid trials over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β_0. Intercepts indicate the 6 groups, the slope β_6 represents the probability of an invalid trial/min. β coefficients and their standard error are on a logit scale.

	OR	β	SE beta	t-value	p-value	
Intercepts:						
β_0 $SHAM_{base}$	0.383	-0.960	0.1896	-5.1	0.000	< 0.001°*
β_1 $5Hz_{base}$	1.566	0.448	0.2651	1.69	0.091	> 0.05
β_2 $40Hz_{base}$	1.033	0.032	0.2655	0.12	0.903	> 0.05
β_3 $SHAM_{inter}$	1.033	0.032	0.0784	0.41	0.680	> 0.05
β_4 $5Hz_{inter}$	1.623	0.484	0.2650	1.83	0.068	> 0.05
β_5 $40Hz_{inter}$	1.107	0.101	0.2653	0.38	0.703	> 0.05
Slope:						
β_6 time	1.0181	0.0179	0.00253	7.08	0.000	< 0.001°*

The probability of invalid trials significantly rises by 1.81 % with time on task (OR = 1.0181, p < 0.001), but irrespective of BASELINE- or INTERVENTION-block. The initial probability for an invalid trial in the $SHAM_{base}$-group is 38 % (OR = 0.383), for the 5 Hz_{base}-group 60 % (OR = $\exp(\beta_0 + \beta_1)$ = 0.600) and for the 40 Hz_{base}-group 40 % (OR = $\exp(\beta_0 + \beta_2)$ = 0.400). At the beginning of the INTERVENTION-block the probability is predicted to be higher compared to the initial OR of the corresponding $_{base}$-group in the BASELINE-block for all groups, but none of these differences is significant (p > 0.05, SHAM:3.2, 5 Hz: 5.7 %, 40 Hz: 7.4 %). In general, there is only a slight difference between members of the SHAM- and 40 Hz-group, while members

of the 5 Hz-group show a tendency for more invalid trials in both BASELINE- (57 %, p = 0.091) and INTERVENTION-block (62 %, p = 0.068) compared to $SHAM_{base}$.

In summary, the LMM and GAMM show, that BRT and the probability of invalid trials rise with time on task, but despite our hypothesis, they show no difference between groups as expected for the INTERVENTION-block only.

For BRT-analysis (LMM), participants categorized as *slow* (i.e. on average slower than the median BRT) or having a calm driving style (*driver type 1* and *2*), for the invalid-trials (GAMM) a variable distance to the leading car (*driver type 2* and *4*), explained variance (higher R^2 marginal: LMM_{slow} = 0.396, $LMM_{driver\ type}$ = 0.209, $GAMM_{driver\ type}$ = 0.146) that otherwise would have been explained by the random effects. Neither the factor *slow* nor *driver type* showed any effect on time on task and did not unmask stimulation effects (see SUPPLEMENTARY MATERIAL Table A5 and Table A6).

IV. DISCUSSION

This study investigated the influence of 40 Hz tACS on brake reaction times (BRT) in a monotonous, rural car-following scenario. The hypothesis was, that BRT will increase significantly less with time on task in the gamma tACS stimulated group during the INTERVENTION-block compared to two control groups (5 Hz- and sham stimulated). Improving vigilance during monotonous rides is relevant to safety - especially nowadays, as the increasing automation of cars turns the human driver into a supervisor for a large part of the journey (Klauer et al., 2006; McWilliams & Ward, 2021). This study is -to the best of our knowledge- the first study to apply tACS in a driving simulator investigating behavioral improvements relevant to driving.

Analysis of BRT and invalid trials shows that BRT and the probability for invalid trials rise significantly over time on task, but that this rise is stable during the BASELINE and INTERVENTION-block irrespective of group. Therefore, this study is in line with studies showing vigilance decrement by prolonging BRT (Cisler et al., 2019; Schrauf et al., 2011; Seet et al., 2023) and increasing error rates over time (Greenlee et al., 2018, 2022), but fails in showing any effects of stimulation. In the next paragraphs, we will discuss potential reasons.

a. Difference between the laboratory and driving simulator task

Löffler et al. (2018) successfully downregulated the increase in reaction times with 40 Hz tACS on posterior brain regions, but in a laboratory where participants were only confronted with a grey screen and either a red or blue stimuli and asked to press a button, accordingly. We transferred their visual task and tACS setup to a similar scenario but in the applied context of driving a car. Although research has shown that increased posterior alpha power is an indicator of vigilance decrement while driving a car (Li & Chung, 2018; Wascher et al., 2016), its down-regulation may not be relevant for improving behavior and counteracting BRT

slowing. In fact, Li & Chung (2018) used posterior electrodes to detect an increase in alpha power but stimulated the frontal cortex to counteract driver drowsiness by tDCS. While Sakai et al. (2014) and Beeli et al. (2008) successfully enhanced behavior at the DLPFC with tDCS in a driving simulator scenario, Brunnauer et al. (2018) could not show positive effects of a similar stimulation during standardized computerized psychomotor tests. This might indicate that stimulation setups cannot be simply transferred from applied to laboratory setups because they are task sensitive. As also discussed by Brunnauer et al. (2018), driving processes can be grouped into three interacting hierarchical levels from 1: strategical, affording more executive control processes, to 2: operational, with predominantly automatic action patterns, and 3: perceptual processing (Michon, 1985). Each level is associated with activations in specific brain regions (Spiers & Maguire, 2007). Further, the experiment of Löffler et al. (2018) required the participants to distinguish between two colors, while participants in our driving scenario needed to react to the flashing light and reduced speed of the leading car without a choice – so although the environment in the driving simulator is more complex and requires more coordination, the task itself may involve fewer executive processes. This is supported by a recent study by Seet et al. (2023) who found out that the neurometric, frontal theta / parietal alpha ratio (and not alpha) was associated with the magnitude of drivers' behavioral changes (cumulative slowing and erraticity of their brake reaction times) throughout the assisted driving tour. Guo et al. (2018) recently developed a driver vigilance detection system that not only uses diver's EEG signals but also driving context inputs. They found out that introducing the driving context factor "road curves" improved the prediction accuracy by 2 – 5 % with 30 – 80 ms smaller errors – highlighting the relevance of context to the experience and neuro-correlates of vigilance decrement in monotonous scenarios.

This effect may be enhanced because the interval between brake events in this study has a smaller range than in Löffler et al. (2018), making brake events expectable and therefore promoting solving the braking task in a uniform operationalization pattern. On the other hand, winding roads require continuous correction of the lane-position which has been shown to reduce vigilance (Eoh et al., 2005). The review by Cabrall et al. (2016) summarizes the difference between classical vigilance tasks and their corresponding tasks in driving simulators and on road, stressing the little overlap between the vigilance decrement phenomenon and experimental tasks of driving vigilance.

Clayton et al. (2019) investigated the influence of alpha tACS on four visual attention tasks in a laboratory setup with a stimulation electrode configuration like ours. Despite his hypothesis that alpha tACS will additionally worsen performance, he found out that alpha tACS prevented deteriorations. The control frequency of 50 Hz showed no effect. This highlights the task-specificity of stimulation success in healthy populations.

b. State of mind difference

The state of mind is essential for stimulation success (Mierau et al., 2017). Other studies investigating the effects of monotony while driving found that participants developed different strategies to counteract boredom, e.g. mind-wandering or performing secondary tasks (Steinberger et al., 2016). Although the factor *strategy* showed no influence, mindsets may vary across participants according to their way of coping with their vigilance decrement and boredom. Internal processes may have led to the engagement of different brain regions not being addressed or influenced by our stimulation setup. Highly motivated or internally distracted participants might have experienced mental fatigue due to cognitive overload rather than underload or boredom (Pattyn et al., 2008).

We needed to exclude 3 participants due to mis- or changing behavior across the experiment. For the rest of the participants, we did not observe different behavior: Lane-Keeping, steering wheel angle, etc. stayed more or less constant across time, participant, and block. Still, analysis around brake events allowed the classification of 4 *driver types*. Differentiating drivers into behavioral classes is a widely used concept in driving research (Lin et al., 2014; Zheng et al., 2019). tACS research on the other hand has shown, that performance gains are often only established in a specific subset of participants, e.g. low-performing (Santarnecchi et al., 2016; Thompson et al., 2021) or low arousal (Martínez-Pérez et al., 2022). Although the integration of the factor *driver type* into our mixed models did not unmask any effects of intervention, it shows that the experimental setup allowed the expression of personality traits which increases variability. As *driver types* were not part of our hypothesis and not balanced over groups a bigger sample size might be needed to analyze the concrete influence of this factor.

c. Heterogeneity and small effect size

The investigated group exhibited heterogeneous behavior, and the effect sizes of tACS are known to be small (Salfi et al., 2020); therefore, it might not have been possible to measure an effect. The driving task had many degrees of freedom, which led to a variability in behavior and the possibility to apply strategies. Further factors we will discuss also below. Although we only included drivers with at least two years of experience, driving habits, practice and frequency are other qualities we did not assess. Experienced drivers tend to automatically steer a car, while novices need to put a lot of afford in controlling a car, e.g. in a secondary task inexperienced driver had an approximately 250 ms longer reaction time to a peripheral stimulus compared to experienced drivers (Patten et al., 2006). The study of (Löffler et al., 2018) showed that a 40 Hz stimulated group exhibited 19 ms faster reaction times after one hour experiment and 30 minutes of stimulation. The average reaction times in their experiment were around 500 ms long and as expected - due to missing MT – faster than the BRT observed here. Performance in their study was enhanced by approximately 4 %, but not for all, as their LMM shows a R^2 conditional of 0.3. In a recent review Lee et al. (2023) computed effect sizes for tACS studies and concluded that tACS has a positive, small

effect. As the effect was also small in Löffler et al. (2018), it might be possible that the effect of tACS is too small to show up in complex, real-world tasks.

d. Influence of further factors

As behavioral characteristics are known to have a substantial influence on success of tACS (Martínez-Pérez et al., 2022; Santarnecchi et al., 2016), we also tested other factors. While *gender*, the experience of *tiredness*, application of a *strategy* did not improve the model, *driver type* and *slow* performance did. Following the literature, aggressive driving behavior would have 2.5 times more driving errors than the behavior in a control group (Su et al., 2023). *Slow* performance could be characterized by adding a constant and improving the marginal R^2. Both factors showed no effect with time on task and did not mask any effect of the factor group.

Lane-keeping is another parameter used in driving research to evaluate performance (Larue et al., 2011). We could not identify any pattern of changes across groups or participants over both blocks over time. As we used a windy road and lane-keeping was not a special task the participants were asked for, it might not be a relevant parameter in our scenario.

e. Minor results

Overall, our results imply the task worked:

- We can confirm that after a 30-minute car ride in a monotonous environment, vigilance decrement occurs, as has been shown by Saxby et al. (2008).
- As BRT should have risen due to the vigilance decrement onset during the BASELINE-block, we expected a significantly higher initial BRT at the beginning of the INTERVENTION-block which we could confirm in the model presented in Table 2.
- As expected, the break between both blocks led to a recovery as shown by the lower initial BRT in the INTERVENTION-block compared to the end BRT of the BASELINE-block (Ross et al., 2014).
- Levels of BRT have been found to correlate the expectation of the brake event (Green, 2000). The average BRT of approx. 750 ms (SD 206.7) measured in our study is in line with the literature for expected events (Green, 2000) as well as the average RT and MT (Warshawsky-Livne & Shinar, 2002).
- In opposite to the laboratory study by Löffler et al. (2018), where participants showed a performance of 98 %, we had to exclude 40 % of the brake events as invalid trials. We analyzed the probability of invalid trials and found a significant increase over time, but irrespective of block (i.e. concerning the probability of invalid trials, the initial probability in the INTERVENTION-block was

not higher than in BASELINE). This fits well with Mackworth's investigations on vigilance, where both reaction times and errors rise with time on task (Mackworth, 1964).

Our classification of four different *driver types* differentiated behavior according to soft or hard presses on the brake pedal and keeping the range of distance to the leading car small or not: Participants pressing hard on the brake pedal showed faster reaction times, participants with a high range of distance exhibited more invalid trials. This fits well with other studies who classified drivers in four classes with attributed to aggressive, cautious, experienced, and professional behavior (Hassan et al., 2023; Zheng et al., 2019) or as cited above unaggressive-aggressive and stable-unstable (Yang et al., 2019). In our case *driver types* may reflect character traits of conscientiousness – risky behavior and mental state of motivation – boredom.

Participants were divided into three groups, but participants of the 5 Hz group exhibited different behaviors in BASELINE and INTERVENTION: The 5 Hz control group had, on average, higher BRTs than the SHAM- and 40 Hz-group. In the INTERVENTION-block, the slope of the 5 Hz group increases less steeply; a possible explanation might be the reaching of a ceiling effect from which reaction times stop worsening (Neuling et al., 2013). The trend of group difference is also present in the GAMM, where the 5-Hz group tends to exhibit more invalid trials. Both can be explained by the composition of the 5-Hz group, which had a high number of *driver type* 2 participants (n = 9).

f. Limitations

One major concern it that our analysis is based on behavioral data. As no EEG was recorded, we cannot access neuropsychological parameters and can only speculate about the neuronal effect of our 40 Hz stimulation.

Further, participants were instructed before the experiment to keep their foot on the gas pedal, brake as fast as possible if needed, and otherwise keep the distance constant. This is a forced and not natural behavior, and it was difficult to address participants to perform right. During the experiment, participants were not controlled, and communication stopped as any kind of interaction might have stopped the vigilance decrement. In the end, we needed to exclude participants who did not behave appropriately and therefore limited our sample size.

Other research concerning vigilance decrement and driving implement questionnaires on driving style, workload, stress or level of arousal and mind-wandering (e.g. NASA TLX, Dundee Stress State Questionnaire). Although this wouldn't have been too difficult to add, our study lacks this information that might have been useful to further explain behavior or variance or even unmask stimulation effects.

As the limit for tACS application is 30 minutes, our experiment is relatively short. A longer experiment with more variable time differences between brake events might be more beneficial to gain surprise moments and prevent operationalized behavior.

Last, we found out that participants could be classified into 4 classes of *driver types*. Although the factor did not unmask stimulation effects, it significantly improved our mixed models and explained the variability of our data. The presence of influential factors unbalanced among groups is a weakness of this study.

g. Outlook

Although we were not able to enhance behavior in our experimental setup, we see potential for the application of tACS in an applied context. A recent study by Facchin et al. (2023) showed that focal high-definition tDCS improved reaction time in a car-following task in a secondary distracting task. Therefore, it should be tested if the effect of tACS can also be enhanced by more sophisticated stimulation setups and if the performance gain shows in secondary tasks, that are less sensitive for individual behavior and driving styles and involve less motoric movement patterns.

In general, future tACS studies in driving simulators should consider character traits and level of arousal. Training drives and questionnaires could be analyzed before the experimental day and participants be balanced among groups accordingly. To ensure participants follow the task, test drives with tracking of driving performance and feedback could be beneficial. A bigger sample size and longer time on task might help to unmask stimulation effects and the use of EEG to understand the neuro-correlates of vigilance decrement and the effect of stimulation. Stimulating the frontal cortex might be beneficial for sustaining attention in car driving as well (Klink et al., 2020). Recent research has also shown that focal stimulation has a higher impact on behavioral outcomes (Vacchi et al., 2023) as well as closed-loop (Li & Chung, 2018) or individualized stimulation settings (Zanto et al., 2021) and should be considered in future study designs.

V. CONCLUSIONS

Although posterior alpha power seems to be an indicator for vigilance decrement while driving in a monotonous scenario (Li & Chung, 2018; Wascher et al., 2016), its down-regulation may not be relevant for improving performance because driving is a complex task involving different brain regions. Further, as the task did not involve a decision like in Löffler et al. (2018), participants might have applied strategies e.g. mind-wandering that changed their brain state in a way, that gamma tACS was not beneficial for counter-acting the slowdown of BRTs. Another reason might be that the effect of stimulation was masked by the heterogeneity of our driver population as variation in behavior and the classification of driver types showed.

4 Study III

Author contributions:

BL, HS, SF, AH, and CH conceptualized the study. LW programmed the driving simulator task. BL acquired participants, performed measurements, and analyzed the data. BL wrote the manuscript. AH, CH, SF and HS commented and gave practical hints throughout the study. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors would like to thank OFFIS for allowing us to use the driving simulator.

Funding

This research has been funded by the Volkswagen Foundation, Ministry of Science and Culture of Lower Saxony as a part of the Interdisciplinary Research Centre on Critical Systems Engineering for Socio-Technical Systems (Grant No.: VWZN2861 VWZN2998) and by own resources of the OFFIS e.V., Institute for Information Technology, Oldenburg, Germany.

Conflict of interest

CH holds a patent on brain stimulation.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement / Patient consent statement

The study involving humans was approved by the medical ethics board (Medizinische Ethikkommission) of the University of Oldenburg. The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Data availability statement

The datasets presented in this article are not readily available because datasets are protected by the data privacy concept of the study. They are available by request to the corresponding author or BL. Requests to access the datasets should be directed to birte.loeffler@uni-oldenburg.de.

REFERENCES

Albadawi, Y., Takruri, M., & Awad, M. (2022). A Review of Recent Developments in Driver Drowsiness Detection Systems. *Sensors*, 22(5), 2069. https://doi.org/10.3390/s22052069

Al-Shargie, F., Tariq, U., Mir, H., Alawar, H., Babiloni, F., & Al-Nashash, H. (2019). Vigilance Decrement and Enhancement Techniques: A Review. *Brain Sciences*, 9(8). https://doi.org/10.3390/brainsci9080178

Antal, A., & Herrmann, C. S. (2016). Transcranial Alternating Current and Random Noise Stimulation: Possible Mechanisms. *Neural Plasticity*, 2016, 3616807. https://doi.org/10.1155/2016/3616807

Antal, A., Luber, B., Brem, A.-K., Bikson, M., Brunoni, A. R., Cohen Kadosh, R., Dubljević, V., Fecteau, S., Ferreri, F., Flöel, A., Hallett, M., Hamilton, R. H., Herrmann, C. S., Lavidor, M., Loo, C., Lustenberger, C., Machado, S., Miniussi, C., Moliadze, V., . . . Paulus, W. (2022). Non-invasive brain stimulation and neuroenhancement. *Clinical Neurophysiology Practice*, 7, 146–165. https://doi.org/10.1016/j.cnp.2022.05.002

Bartoń, K. (2023). MuMIn: Multi-Model Inference [Computer software]. https://CRAN.R-project.org/package=MuMIn, last accessed 2024-01-10

Beeli, G., Koeneke, S., Gasser, K., & Jancke, L. (2008). Brain stimulation modulates driving behavior. *Behavioral and Brain Functions: BBF*, 4, 34. https://doi.org/10.1186/1744-9081-4-34

Beliaeva, V., Savvateev, I., Zerbi, V., & Polania, R. (2021). Toward integrative approaches to study the causal role of neural oscillations via transcranial electrical stimulation. *Nature Communications*, 12(1), 2243. https://doi.org/10.1038/s41467-021-22468-7

Brunnauer, A., Segmiller, F. M., Löschner, S., Grun, V., Padberg, F., & Palm, U. (2018). The Effects of Transcranial Direct Current Stimulation (tDCS) on Psychomotor and Visual Perception Functions Related to Driving Skills. *Frontiers in Behavioral Neuroscience*, 12, 16. https://doi.org/10.3389/fnbeh.2018.00016

Brunoni, A. R. , Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, 14(8), 1133–1145. https://doi.org/10.1017/S1461145710001690

Brunyé, T. T., Hussey, E. K., Fontes, E. B., & Ward, N. (2019). Modulating Applied Task Performance via Transcranial Electrical Stimulation. *Frontiers in Human Neuroscience*, 13, 140. https://doi.org/10.3389/fnhum.2019.00140

Buck, L. (1966). Reaction time as a measure of perceptual vigilance. *Psychological Bulletin*, 65(5), 291–304. https://doi.org/10.1037/h0023207

Cabrall, C., Happee, R., & Winter, J. de (2016). From Mackworth's clock to the open road: A literature review on driver vigilance task operationalization. *Transportation Research Part F: Traffic Psychology and Behaviour*, 40, 169–189. https://doi.org/10.1016/j.trf.2016.04.001

Cho, H., Razza, L. B., Borrione, L., Bikson, M., Charvet, L., Dennis-Tiwary, T. A., Brunoni, A. R, & Sudbrack-Oliveira, P. (2022). Transcranial Electrical Stimulation for Psychiatric Disorders in Adults: A Primer. *Focus (American Psychiatric Publishing)*, 20(1), 19–31. https://doi.org/10.1176/appi.focus.20210020

Cisler, D., Greenwood, P. M., Roberts, D. M., McKendrick, R., & Baldwin, C. L. (2019). Comparing the Relative Strengths of EEG and Low-Cost Physiological Devices in Modeling Attention Allocation in Semiautonomous Vehicles. *Frontiers in Human Neuroscience*, 13, 109. https://doi.org/10.3389/fnhum.2019.00109

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2015). The roles of cortical oscillations in sustained attention. *Trends in Cognitive Sciences*, 19(4), 188–195. https://doi.org/10.1016/j.tics.2015.02.004

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2019). Electrical stimulation of alpha oscillations stabilizes performance on visual attention tasks. *Journal of Experimental Psychology: General*, 148(2), 203–220. https://doi.org/10.1037/xge0000502

Colzato, L. S., Nitsche, M. A., & Kibele, A. (2017). Noninvasive Brain Stimulation and Neural Entrainment Enhance Athletic Performance—A Review. *Journal of Cognitive Enhancement*, 1(1), 73–79. https://doi.org/10.1007/s41465-016-0003-2

Davis, N. J., Gold, E., Pascual-Leone, A., & Bracewell, R. M. (2013). Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. *The European Journal of Neuroscience*, 38(7), 2973–2977. https://doi.org/10.1111/ejn.12307

Eoh, H. J., Chung, M. K., & Kim, S.-H. (2005). Electroencephalographic study of drowsiness in simulated driving with sleep deprivation. *International Journal of Industrial Ergonomics*, 35(4), 307–320. https://doi.org/10.1016/j.ergon.2004.09.006

Facchin, A., La Rocca, S., Vacchi, L., Daini, R., Gobbo, M., Fontana, S., & Lega, C. (2023). Effects of conventional and high-definition transcranial direct current stimulation (tDCS) on driving abilities: A tDCS-driving simulator study. *Journal of Environmental Psychology*, 90, 102111. https://doi.org/10.1016/j.jenvp.2023.102111

4 Study III

Gahragozlou, F., Nasl Sarajim Gebraeil, Mazloumi, A., Nahvi, A., Motie Nasrabadi, A., Rahimi Fororoushani, A., Arab Kheradman, A., Ashouri, M., & Samaavati, M. (2015). Detecting Driver Mental Fatigue Based on EEG Alpha Power Changes during Simulated Driving, *Iranian Journal of Public Health*, 44(12), 1693–1700.

Ganguly, J., Murgai, A., Sharma, S., Aur, D., & Jog, M. (2020). Non-invasive Transcranial Electrical Stimulation in Movement Disorders. *Frontiers in Neuroscience*, 14, 522. https://doi.org/10.3389/fnins.2020.00522

Green, M. (2000). "How Long Does It Take to Stop?" Methodological Analysis of Driver Perception-Brake Times. *Transportation Human Factors*, 2(3), 195–216. https://doi.org/10.1207/STHF0203_1

Greenlee, E. T., DeLucia, P. R., & Newton, D. C. (2018). Driver Vigilance in Automated Vehicles: Hazard Detection Failures Are a Matter of Time. *Human Factors*, 60(4), 465–476. https://doi.org/10.1177/0018720818761711

Greenlee, E. T., DeLucia, P. R., & Newton, D. C. (2022). Driver Vigilance Decrement is More Severe During Automated Driving than Manual Driving. *Human Factors*. https://journals.sagepub.com/doi/pdf/10.1177/00187208221103922

Guo, Z., Pan, Y., Zhao, G., Cao, S., & Zhan, J. (2018). Detection of Driver Vigilance Level Using EEG Signals and Driving Contexts. *IEEE Transactions on Reliability*, 67, 370–380. 10.1109/TR.2017.2778754

Hassan, A., Lee, C., Cramer, K., & Lafreniere, K. (2023). Analysis of driver characteristics, self-reported psychology measures and driving performance measures associated with aggressive driving. *Accident; Analysis and Prevention*, 188, 107097. https://doi.org/10.1016/j.aap.2023.107097

Helfrich, R. F., Herrmann, C. S., Engel, A. K., & Schneider, T. R. (2016). Different coupling modes mediate cortical cross-frequency interactions. *NeuroImage*, 140, 76–82. https://doi.org/10.1016/j.neuroimage.2015.11.035

Helfrich et al. (2014). Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. *PLoS Biology*, 12(12), e1002031. https://doi.org/10.1371/journal.pbio.1002031

Hsu, W.-Y., Zanto, T. P., & Gazzaley, A. (2019). Parametric effects of transcranial alternating current stimulation on multitasking performance. *Brain Stimulation*, 12(1), 73–83. https://doi.org/10.1016/j.brs.2018.10.010

Hsu, W.-Y., Zanto, T. P., van Schouwenburg, M. R., & Gazzaley, A. (2017). Enhancement of multitasking performance and neural oscillations by transcranial alternating current stimulation. *PloS One*, 12(5), e0178579. https://doi.org/10.1371/journal.pone.0178579

Iuculano, T., & Cohen Kadosh, R. (2013). The mental cost of cognitive enhancement. *The Journal of Neuroscience*, 33(10), 4482–4486. https://doi.org/10.1523/JNEUROSCI.4927-12.2013

Jensen, O., & Colgin, L. L. (2007). Cross-frequency coupling between neuronal oscillations. *Trends in Cognitive Sciences*, 11(7), 267–269. https://doi.org/10.1016/j.tics.2007.05.003

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, 245. https://doi.org/10.3389/fnhum.2016.00245

Kim, J., Kim, H., Jeong, H., Roh, D., & Kim, D. H. (2021). Tacs as a promising therapeutic option for improving cognitive function in mild cognitive impairment: A direct comparison between tACS and tDCS. *Journal of Psychiatric Research*, 141, 248–256. https://doi.org/10.1016/j.jpsychires.2021.07.012

Klauer, S. G., Dingus, T. A., Neale, V. L., Sudweeks, J. D., & Ramsey, D. J. (2006). The impact of driver inattention on near-crash/crash risk: An analysis using the 100-car naturalistic driving study data. (FHWA-HRT-04-138). Washington, DC: United States. *National Highway Traffic Safety Administration*. Retrieved from http://www.nhtsa.gov/DOT/NHTSA/NRD/Multimedia/PDFs/Crash%20Avoidance/2006/DriverInattention.pdf, last accessed 2024-01-22

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Research Reviews*, 29(2-3), 169–195. https://doi.org/10.1016/S0165-0173(98)00056-3

Klimesch, W., Doppelmayr, M., Schimke, H., & Pachinger, T. (1996). Alpha Frequency, Reaction Time, and the Speed of Processing Information. *Journal of Clinical Neurophysiology*, 13(6), 511. https://doi.org/aspx

Klink, K., Paßmann, S., Kasten, F. H., & Peter, J. (2020). The Modulation of Cognitive Performance with Transcranial Alternating Current Stimulation: A Systematic Review of Frequency-Specific Effects. *Brain Sciences*, 10(12). https://doi.org/10.3390/brainsci10120932

Körber, M., Cingel, A., Zimmermann, M., & Bengler, K. (2015). Vigilance Decrement and Passive Fatigue Caused by Monotony in Automated Driving. *Procedia Manufacturing*, 3, 2403–2409. https://doi.org/10.1016/j.promfg.2015.07.499

Krueger, H.-P., Grein, M., Kaußner, A., & Mark, C. (2005). SILAB—A Task Oriented Driving Simulation. In SILAB-A task-oriented driving simulation. In *Driving Simulator Conference - North America (DSC-NA.* Symposium conducted at the meeting of Iowa Driving Safety Research Institute, Orlando, FL, USA. https://api.semanticscholar.org/CorpusID:11019771

Larue, G. S., Rakotonirainy, A., & Pettitt, A. N. (2011). Driving performance impairments due to hypovigilance on monotonous roads. *Accident; Analysis and Prevention*, 43(6), 2037–2046. https://doi.org/10.1016/j.aap.2011.05.023

4 Study III

Lee, T. L., Lee, H., & Kang, N. (2023). A meta-analysis showing improved cognitive performance in healthy young adults with transcranial alternating current stimulation. *Npj Science of Learning*, 8(1), 1. https://doi.org/10.1038/s41539-022-00152-9

Li, G., & Chung, W.-Y. (2018). Combined EEG-Gyroscope-tDCS Brain Machine Interface System for Early Management of Driver Drowsiness. *IEEE Transactions on Human-Machine Systems*, 48(1), 50–62. https://doi.org/10.1109/THMS.2017.2759808

Lin, N., Zong, C., Tomizuka, M., Song, P., Zhang, Z., & Li, G. (2014). An Overview on Study of Identification of Driver Behavior Characteristics for Automotive Control. *Mathematical Problems in Engineering*, 2014, 1–15. https://doi.org/10.1155/2014/569109

Löffler, B. S., Stecher, H. I., Fudickar, S., Sordi, D. de, Otto-Sobotka, F., Hein, A., & Herrmann, C. S. (2018). Counteracting the Slowdown of Reaction Times in a Vigilance Experiment With 40-Hz Transcranial Alternating Current Stimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 26(10), 2053–2061. https://doi.org/10.1109/TNSRE.2018.2869471

Mackworth, J. F. (1964). Performance decrement in vigilance, threshold, and high-speed perceptual motor tasks. *Canadian Journal of Psychology*, 18, 209–223. https://doi.org/10.1037/h0083302

Mackworth, N. H. (1948). The Breakdown of Vigilance during Prolonged Visual Search. *Quarterly Journal of Experimental Psychology*, 1(1), 6–21. https://doi.org/17470214808416738

Martínez-Pérez, V., Tortajada, M., Palmero, L. B., Campoy, G., & Fuentes, L. J. (2022). Effects of transcranial alternating current stimulation over right-DLPFC on vigilance tasks depend on the arousal level. *Scientific Reports*, 12(1), 547. https://doi.org/10.1038/s41598-021-04607-8

Matsumoto, H., & Ugawa, Y. (2017). Adverse events of tDCS and tACS: A review. *Clinical Neurophysiology Practice*, 2, 19–25. https://doi.org/10.1016/j.cnp.2016.12.003

McWilliams, T., & Ward, N. (2021). Underload on the Road: Measuring Vigilance Decrements During Partially Automated Driving. *Frontiers in Psychology*, 12, 631364. https://doi.org/10.3389/fpsyg.2021.631364

Michon, J. A. (1985). A critical view of driver behavior models: what do we know, what should we do? *Human Behavior and Traffic Safety*, 485–524. https://www.jamichon.nl/jam_writings/1985_criticial_view.pdf

Mierau, A., Klimesch, W, & Lefebvre, J. (2017). State-dependent alpha peak frequency shifts: Experimental evidence, potential mechanisms and functional implications. *Neuroscience*, 360, 146–154. https://doi.org/10.1016/j.neuroscience.2017.07.037

Molina, E., Correa, A., Sanabria, D., & Jung, T.-P. (2013). Tonic EEG dynamics during psychomotor vigilance task. In 2013 *6th International IEEE/EMBS Conference on Neural Engineering (NER)* (pp. 1382–1385). IEEE. https://doi.org/10.1109/NER.2013.6696200

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, 161. https://doi.org/10.3389/fnhum.2013.00161

Oken, B. S., Salinsky, M. C., & Elsas, S. M. (2006). Vigilance, alertness, or sustained attention: Physiological basis and measurement. *Clinical Neurophysiology*, 117(9), 1885–1901. https://doi.org/10.1016/j.clinph.2006.01.017

Patten, C. J. D., Kircher, A., Ostlund, J., Nilsson, L., & Svenson, O. (2006). Driver experience and cognitive workload in different traffic environments. *Accident Analysis & Prevention*, 38(5), 887–894. https://doi.org/10.1016/j.aap.2006.02.014

Pattyn, N., Neyt, X., Henderickx, D., & Soetens, E. (2008). Psychophysiological investigation of vigilance decrement: Boredom or cognitive fatigue? *Physiology & Behavior*, 93(1-2), 369–378. https://doi.org/10.1016/j.physbeh.2007.09.016

Pinheiro, J., Bates, D., & R Core Team. (2023). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-162 [Computer software]. https://CRAN.R-project.org/package=nlme, last accessed on 2014-01-10

R Core Team. (2023). R: A Language and Environment for Statistical Computing [Computer software]. https://www.R-project.org/, last accessed on 2014-01-10

Ross, H. A., Russell, P. N., & Helton, W. S. (2014). Effects of breaks and goal switches on the vigilance decrement. *Experimental Brain Research*, 232(6), 1729–1737. https://doi.org/10.1007/s00221-014-3865-5

Sakai, H., Uchiyama, Y., Tanaka, S., Sugawara, S. K., & Sadato, N. (2014). Prefrontal transcranial direct current stimulation improves fundamental vehicle control abilities. *Behavioural Brain Research*, 273, 57–62. https://doi.org/10.1016/j.bbr.2014.07.036

Salfi, F., D'Atri, A., Tempesta, D., Gennaro, L. de, & Ferrara, M. (2020). Boosting Slow Oscillations during Sleep to Improve Memory Function in Elderly People: A Review of the Literature. *Brain Sciences*, 10(5). https://doi.org/10.3390/brainsci10050300

Santarnecchi, E., Muller, T., Rossi, S., Sarkar, A., Polizzotto, N. R., Rossi, A., & Cohen Kadosh, R. (2016). Individual differences and specificity of prefrontal gamma frequency-tACS on fluid intelligence capabilities. *Cortex,* 75, 33–43. https://doi.org/10.1016/j.cortex.2015.11.003

4 Study III

Santarnecchi, E, Brem, A.-K., Levenbaum, E., Thompson, T., Kadosh, R. C., & Pascual-Leone, A. (2015). Enhancing cognition using transcranial electrical stimulation. *Current Opinion in Behavioral Sciences*, 4, 171–178. https://doi.org/10.1016/j.cobeha.2015.06.003

Sarkar, A, Dowker, A., & Cohen Kadosh, R. (2014). Cognitive enhancement or cognitive cost: Trait-specific outcomes of brain stimulation in the case of mathematics anxiety. *The Journal of Neuroscience*, 34(50), 16605–16610. https://doi.org/10.1523/JNEUROSCI.3129-14.2014

Saxby, D. J., Matthews, G., Hitchcock, E. M., Warm, J. S., Funke, G. J., & Gantzer, T. (2008). Effect of Active and Passive Fatigue on Performance Using a Driving Simulator. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 52(21), 1751–1755. https://doi.org/10.1177/154193120805202113

Schier, M. A. (2000). Changes in EEG alpha power during simulated driving: a demonstration. *International Journal of Psychophysiology*, 37(2), 155–162. https://doi.org/10.1016/S0167-8760(00)00079-9

Schmidt, E. A., Kincses, W. E, Schrauf, M., Haufe, S., Schubert, R., & Curio, G. (2007). Assessing Drivers' Vigilance State During Monotonous Driving. *Driving Assessment Conference*, 4(2007), 138–145. https://doi.org/10.17077/drivingassessment.1228

Schrauf, M., Sonnleitner, A., Simon, M., & Kincses, W. E. (2011). EEG Alpha Spindles as Indicators for Prolonged Brake Reaction Time During Auditory Secondary Tasks in a Real Road Driving Study. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 55(1), 217–221. https://doi.org/10.1177/1071181311551045

Seet, M., Bezerianos, A., Panou, M., Bekiaris, E., & Thakor, N. & Dragomir, A. (2023). Individual Susceptibility to Vigilance Decrement in Prolonged Assisted Driving Revealed by Alert-State Wearable EEG Assessment. *IEEE Transactions on Cognitive and Developmental Systems*, 15(3), 1586–1594. doi: 10.1109/TCDS.2022.3231691

Solomons, C. D., & Shanmugasundaram, V. (2019). A review of transcranial electrical stimulation methods in stroke rehabilitation. *Neurology India*, 67(2), 417–423. https://doi.org/10.4103/0028-3886.258057

Spiers, H. J., & Maguire, E. A. (2007). Neural substrates of driving behaviour. *NeuroImage*, 36(1), 245–255. https://doi.org/10.1016/j.neuroimage.2007.02.032

Stecher, H. I., Pollok, T. M., Strüber, D., Sobotka, F., & Herrmann, C. S. (2017). Ten Minutes of α-tACS and Ambient Illumination Independently Modulate EEG α-Power. *Frontiers in Human Neuroscience*, 11, 257. https://doi.org/10.3389/fnhum.2017.00257

Steinberger, F., Moeller, A., & Schroeter, R. (2016). The antecedents, experience, and coping strategies of driver boredom in young adult males. *Journal of Safety Research*, 59, 69–82. https://doi.org/10.1016/j.jsr.2016.10.007

Strüber, D., & Herrmann, C. S. (2020). Modulation of gamma oscillations as a possible therapeutic tool for neuropsychiatric diseases: A review and perspective. *International Journal of Psychophysiology*, 152, 15–25. https://doi.org/10.1016/j.ijpsycho.2020.03.003

Su, Z., Woodman, R., Smyth, J., & Elliott, M. (2023). The relationship between aggressive driving and driver performance: A systematic review with meta-analysis. *Accident; Analysis and Prevention*, 183, 106972. https://doi.org/10.1016/j.aap.2023.106972

Tamanani, R., Muresan, R., & Al-Dweik, A. (2021). Estimation of Driver Vigilance Status Using Real-Time Facial Expression and Deep Learning. *IEEE Sensors Letters*, 5(5), 1–4. https://doi.org/10.1109/LSENS.2021.3070419

Tavakoli, A. V., & Yun, K. (2017). Transcranial Alternating Current Stimulation (tACS) Mechanisms and Protocols. Frontiers in *Cellular Neuroscience*, 11, 214. https://doi.org/10.3389/fncel.2017.00214

Thompson, L., Khuc, J., Saccani, M. S., Zokaei, N., & Cappelletti, M. (2021). Gamma oscillations modulate working memory recall precision. *Experimental Brain Research*, 239(9), 2711–2724. https://doi.org/10.1007/s00221-021-06051-6

Vacchi, L., La Rocca, S., Facchin, A., Schifano, A., Fontana, S., Gobbo, M., & Lega, C. (2023). The effect of focal HD-tDCS on right frontal eye fields in age-related differences to visual distractors during driving: a neuromodulation study. *Brain Stimulation*, 16(1), 273. https://doi.org/10.1016/j.brs.2023.01.462

Ward, N., Hussey, E., Gaspar, J., & Kramer, A. (2017). Distracted driving and high-definition tDCS. *Brain Stimulation*, 10(4), e27. https://doi.org/10.1016/j.brs.2017.04.027

Warshawsky-Livne, L., & Shinar, D. (2002). Effects of uncertainty, transmission type, driver age and gender on brake reaction and movement time. *Journal of Safety Research*, 33(1), 117–128. https://doi.org/10.1016/S0022-4375(02)00006-3

Wascher, E., Getzmann, S., & Karthaus, M. (2016). Driver state examination--Treading new paths. *Accident; Analysis and Prevention*, 91, 157–165. https://doi.org/10.1016/j.aap.2016.02.029

Wood, S. N. (2017). *Generalized additive models: An introduction with R* (2nd ed.). Chapman and Hall / CRC.

Yang, L., Guan, W., Ma, R., & Li, X. (2019). Comparison among driving state prediction models for car-following condition based on EEG and driving features. *Accident; Analysis and Prevention*, 133, 105296. https://doi.org/10.1016/j.aap.2019.105296

4 Study III

Zanto, T. P., Jones, K. T., Ostrand, A. E., Hsu, W.-Y., Campusano, R., & Gazzaley, A. (2021). Individual differences in neuroanatomy and neurophysiology predict effects of transcranial alternating current stimulation. *Brain Stimulation*, 14(5), 1317–1329. https://doi.org/10.1016/j.brs.2021.08.017

Zheng, F., Li, J., Zuylen, H. J., & Lu, C. (2019). Influence of driver characteristics on emissions and fuel consumption. *IET Intelligent Transport Systems*, 13(12), 1770–1779. https://doi.org/10.1049/iet-its.2018.5562

Supplementary Material

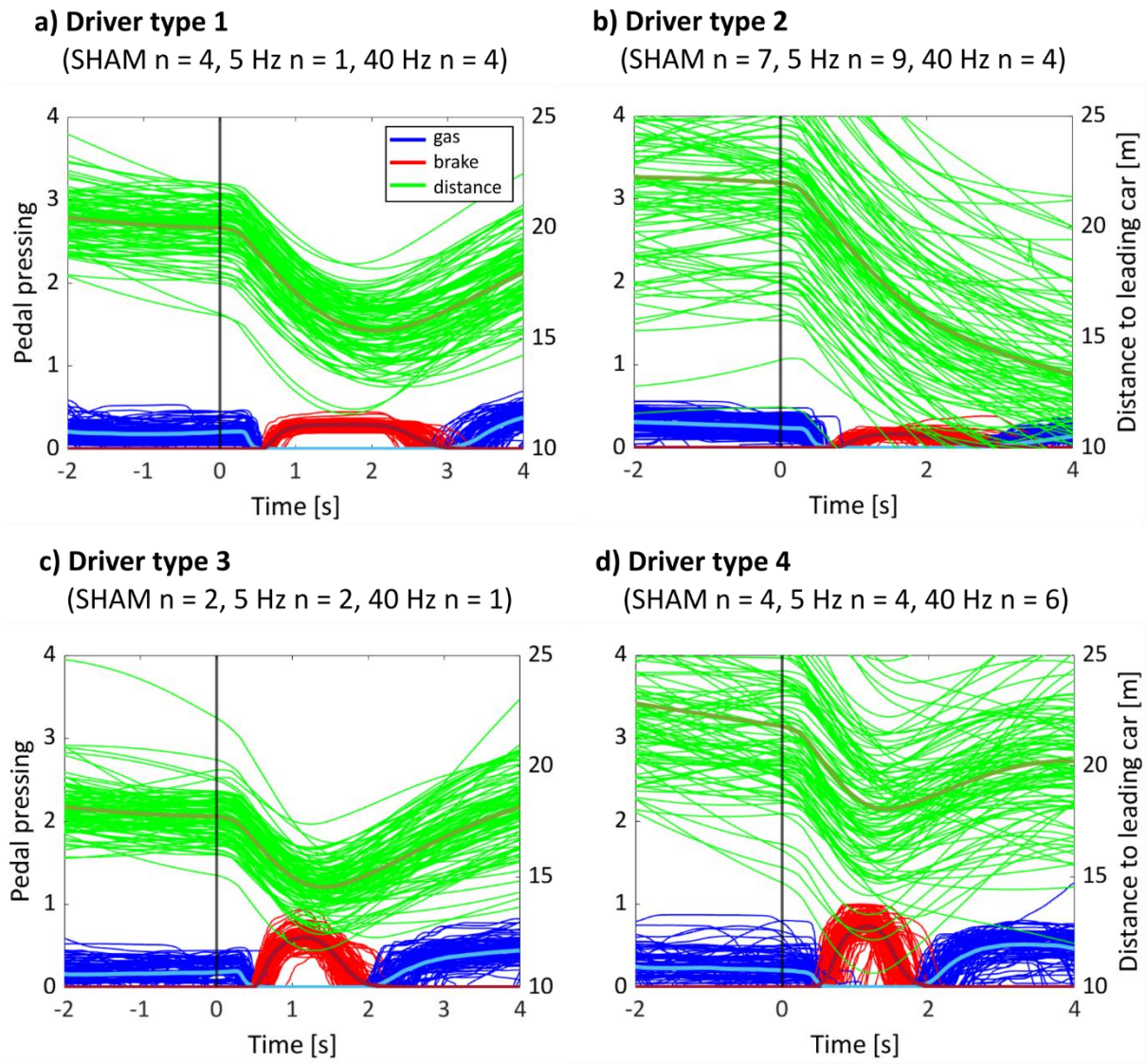

Fig. A1

Exemplary plots of behavioral data of valid trials (BASELINE-block) of four participants were used to illustrate the four different driver types. Origin of X-Axis (in seconds), marked by a black vertical line, indicates the brake light onset of the leading car. Blue traces mark the pressing of the gas, red ones on the brake pedal. Both measures represent the linear way and have a maximum of one and refer to the primary Y-axis. Green traces mark the distance to the leading car (secondary Y-Axis, in meter, with a cut off at 10 m). Bold lines indicate the average. a) Driver type 1: "unaggressive – stable", b) Driver type 2: "unaggressive – unstable", c) Driver type 3: "aggressive – stable"", d) Driver type 4: "aggressive - unstable".

4 Study III

Table A1

LMM selection: The table shows a selection of different linear mixed models predicting brake reaction times to find the best fitting one. First column represents the model number, followed by the formula for the fixed effects that show which further factors and interactions were tested. The third column shows the random effects structure, the fourth is the employed autocorrelation (if any). The fifth column shows the Akaike information criterion (AIC), followed by the marginal R^2 (R^2m) for the fixed and conditional R^2 (R^2c) also including the random effects. Models good-fit were tested and compared via the loglikelihood ratio whose test conditions (which model versus which) and resulting p-value are represented in the last column. Here, p-values < 0.05 indicate, that the second model is superior to the first one and a p-value > 0.05, that the extended (second) model does not improve the first model´s fit. Models in bold font are the best fitting models. Model 5 is presented in the manuscript expect that a Restricted Maximum Likelihood (REML) instead of maximum likelihood (ML) was used to fit the model. Model 4 is the best fitting model and presented in the SUPPLEMENTARY MATERIAL (Table A2), as well as Model 9 (Table A3) and model 11 (Table A4).

	Model	**Random**	**Correlation**	**AIC**	**R^2 m**	**R^2c**	**loglik**
1	~ time	= ~ 1 | ID	-	75594.5	0.007	0.569	
2	~ time	= time | ID	-	75563.8	0.007	0.575	1 vs 2: p < 0.001
3	~ time + group	= time | ID	-	75506.1	0.029	0.576	2 vs 3: p < 0.001
4	**~ time + group**	**= time | ID**	**corCAR1(form=~ 1|ID/Block))**	**75454.9**	**0.030**	**0.572**	**3 vs 4: P < 0.001**
5	~ time * group	= time | ID	corCAR1(form=~ 1|ID/Block))	75456.6	0.040	0.576	4 vs 5: P = 0.141
6	~ time + group + slow	= time | ID	corCAR1(form=~ 1|ID/Block))	75403.3	0.392	0.570	4 vs 6: P < 0.001
7	~ time * group + slow	= time | ID	corCAR1(form=~ 1|ID/Block))	75404.9	0.394	0.571	6 vs 7: P = 0.136
8	~ time * slow + group	= time | ID	corCAR1(form=~ 1|ID/Block))	75403.1	0.403	0.577	6 vs 8: P = 0.141
9	**~ time + group * slow**	**= time | ID**	**corCAR1(form=~ 1|ID/Block))**	**75382.4**	**0.396**	**0.573**	**6 vs 9: P < 0.001**
10	~ time * group * slow	= time | ID	corCAR1(form=~ 1|ID/Block))	75385.4	0.411	0.582	9 vs 10: P = 0.062
11	~ time + group + driver type	= time | ID	corCAR1(form=~ 1|ID/Block))	75440.9	0.209	0.568	4 vs 11: P < 0.001

4 Study III

Table A2

LM Model 4: Best fitting model

Coefficients of the linear mixed model 4 from table A1 (n = 49, observations = 5956, R^2 marginal = 0.029, R^2 conditional = 0.587) except that REML was used to fit the data: β presents the regression coefficients, SE β the standard error of β. β_0 represents the initial BRT of the $SHAM_{base}$-group and β_6 the increase in BRT over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β_0. Intercepts are given in ms, slope β_6 in ms/min.

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 $SHAM_{base}$	682.3	36.49	18.70	0.000	< 0.001°*
β_1 $5Hz_{base}$	73.7	52.46	1.40	0.160	> 0.05
β_2 $40Hz_{base}$	4.8	51.57	0.09	0.925	> 0.05
β_3 $SHAM_{inter}$	42.6	6.41	6.64	0.000	< 0.001*
β_4 $5Hz_{inter}$	81.3	52.47	1.55	0.121	> 0.05
β_5 $40Hz_{inter}$	26.0	51.56	0.50	0.614	> 0.05
Slope:					
β_6 time	1.974	0.3132	6.30	0.000	< 0.001°*

Table A3

LM Model 9: further factor class slow

Coefficients of the linear mixed model 9 from table A1 (n = 49, observations = 5956, R^2 marginal = 0.396, R^2 conditional = 0.573, fit by ML): β presents the regression coefficients, SE β the standard error of β. β_0 represents the initial BRT of the $SHAM_{base}$-group and β_{12} the increase in BRT over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β_0. $\beta_6 - \beta_{11}$ need to be added to participants being classified as slow according to their respective group. Intercepts $\beta_0 - \beta_{11}$ are given in ms, slope β_{12} in ms/min.

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 $SHAM_{base}$	**579.2**	**28.60**	**20.25**	**0.000**	**< 0.001°***
β_1 $5Hz_{base}$	15.3	47.85	0.32	0.749	> 0.05
β_2 $40Hz_{base}$	-8.9	40.33	-0.22	0.826	> 0.05
β_3 $SHAM_{inter}$	15.3	8.58	1.79	0.074	> 0.05
β_4 $5Hz_{inter}$	44.0	47.96	0.92	0.359	> 0.05
β_5 $40Hz_{inter}$	-1.7	40.31	-0.04	0.966	> 0.05
β_6 $SHAM_{base}$*slow	218.5	41.60	5.25	0.000	< 0.001*
β_7 $5Hz_{base}$ *slow	22.4	62.28	0.36	0.719	> 0.05
β_8 $40Hz_{base}$*slow	38.0	59.86	0.64	0.525	> 0.05
β_9 $SHAM_{inter}$*slow	60.3	12.76	4.73	0.000	< 0.001*
β_{10} $5Hz_{inter}$*slow	-7.4	62.36	-0.12	0.906	> 0.05
β_{11} $40Hz_{inter}$*slow	65.6	59.86	1.10	0.273	> 0.05
Slope:					
β_{12} time	**1.956**	**0.3120**	**6.27**	**0.000**	**< 0.001°***

4 Study III

Table A4

LM Model 9: further factor class driver type

Coefficients of the linear mixed model 11 from table A1 (n = 49, observations = 5956, R^2 marginal = 0.209, R^2 conditional = 0.568, fit by ML): β presents the regression coefficients, SE β the standard error of β. $β_0$ represents the initial BRT of the $SHAM_{base}$-group of driver type A and $β_{12}$ the increase in BRT over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against $β_0$. Intercepts $β_0 – β_8$ are given in ms, slope $β_9$ in ms/min.

	β	SE beta	t-value	p-value	
Intercepts:					
$β_0$ $SHAM_{base}$* Driver Type A	**727.8**	**45.24**	**16.09**	**0.000**	**< 0.001°***
$β_1$ $5Hz_{base}$ * Driver Type A	76.3	42.82	1.78	0.075	> 0.05
$β_2$ $40Hz_{base}$ * Driver Type A	11.2	42.37	0.26	0.791	> 0.05
$β_3$ $SHAM_{inter}$ * Driver Type A	42.5	6.40	6.64	0.000	< 0.001*
$β_4$ $5Hz_{inter}$ * Driver Type A	83.9	42.83	1.96	0.050	= 0.05
$β_5$ $40Hz_{inter}$ * Driver Type A	31.0	42.36	0.73	0.464	> 0.05
$β_6$ * Driver Type B	24.9	49.16	0.51	0.615	> 0.05
$β_7$ Driver Type C	-207.4	67.65	-3.07	0.004	< 0.01*
$β_8$ Driver Type D	-133.9	51.59	-2.60	0.013	< 0.05*
Slope:					
$β_9$ time	**1.956**	**0.3156**	**6.20**	**0.000**	**< 0.001°***

4 Study III

Table A5

LM Model 5: 5 Hz base-group.

LMM results for BRT (n = 49, observations = 5956, R^2 marginal = 0.0380, R^2 conditional = 0.590): β presents the regression coefficients, SE β the standard error of β. $β_0$ represents the initial BRT and $β_6$ the increase in BRT of the 5 Hz_{base}-group over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients of intercepts are tested against $β_0$, slopes against $β_6$. Intercepts ($β_0$ - $β_5$) are given in ms, slopes ($β_6$ – $β_{11}$) in ms/min.

	β	SE beta	t-value	p-value	
Intercepts:					
$β_0$ 5 Hz_{base}	745.5	37.32	19.98	0.0000	**< 0.001°***
$β_1$ $SHAM_{base}$	-71.7	51.91	-1.38	0.1675	> 0.05
$β_2$ $40Hz_{base}$	-63.6	52.66	-1.21	0.2270	> 0.05
$β_3$ 5 Hz_{inter}	28.5	13.58	2.10	0.0359	< 0.05*
$β_4$ $SHAM_{inter}$	-12.0	51.93	-0.23	0.8175	> 0.05
$β_5$ $40Hz_{inter}$	-36.0	52.64	-0.68	0.4944	> 0.05
Slopes:					
$β_6$ time * 5 Hz_{base}	3.234	0.6744	4.79	0.0000	**< 0.001°***
$β_7$ time * $SHAM_{base}$	-0.750	0.9270	-0.81	0.4194	> 0.05
$β_8$ time * $40Hz_{base}$	-1.494	0.9330	-1.60	0.1089	> 0.05
$β_9$ time * 5 Hz_{inter}	-1.404	0.7842	-1.79	0.0734	> 0.05
$β_{10}$ time * $SHAM_{inter}$	-1.902	0.9282	-2.05	0.0406	< 0.05*
$β_{11}$ time * 40 Hz_{inter}	-2.040	0.9324	-2.19	0.0289	< 0.05*

4 Study III

Table A6

LM Model 5: 40 Hz base-group.

LMM results for BRT (n = 49, observations = 5956, R^2 marginal = 0.0380, R^2 conditional = 0.590): β presents the regression coefficients, SE β the standard error of β. β_0 represents the initial BRT and β_6 the increase in BRT of the 40 Hz_{base}-group over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients of intercepts are tested against β_0, slopes against β_6. Intercepts (β_0 - β_5) are given in ms, slopes (β_6 – β_{11}) in ms/min.

	β	SE beta	t-value	p-value	
Intercepts:					
β_0 40 Hz_{base}	**681.9**	**37.16**	**18.35**	**0.0000**	**< 0.001°***
β_1 5Hz_{base}	63.6	52.66	1.21	0.2270	> 0.05
β_2 $SHAM_{base}$	-8.0	51.80	-0.15	0.8768	> 0.05
β_3 40 Hz_{inter}	27.7	12.54	2.21	0.0275	< 0.05*
β_4 5Hz_{inter}	92.1	52.69	1.75	0.0804	> 0.05
β_5 $SHAM_{inter}$	51.6	51.82	1.00	0.3190	> 0.05
Slopes:					
β_6 time * 40 Hz_{base}	**1.734**	**0.6450**	**2.69**	**0.0071**	**< 0.01°***
β_7 time * 5Hz_{base}	1.494	0.9330	1.60	0.1089	> 0.05
β_8 time * $SHAM_{base}$	0.750	0.9060	0.82	0.4096	> 0.05
β_9 time * 40 Hz_{inter}	-0.540	0.7284	-0.74	0.4563	> 0.05
β_{10} time * 5Hz_{inter}	0.090	0.9384	0.10	0.9219	> 0.05
β_{11} time * $SHAM_{inter}$	-0.402	0.9072	-0.45	0.6555	> 0.05

4 Study III

Table A7

GAMM selection: The table shows a selection of different generalized additive mixed models predicting predicting the probability for invalid trials to find the model with best-fit. The first column represents the model number, followed by the formula for the fixed effects including further factors and interactions were tested. The third column shows the random effects structure, the fourth the employed autocorrelation (if any). The fifth column shows the Akaike information criterion (AIC). The GAMM with lowest AIC has the best fit. Marginal R^2 (R^2m) for the fixed and conditional R^2 (R^2c) also including the random effects are only given for the best models. Models in bold font are the best fitting models. Model 6 is presented in the manuscript. Model 2 is presented in Table A8, model 7 in Table A9 and model 8 in Table A10.

	Model	Random	Correlation	AIC	R^2 m	R^2c
1	~ time	ID = ~ 1	-	43225.7		
2	**~ time**	**ID = ~ 1**	**corCAR1(form=~ 1|ID/Block)**	**43204.1**	**0.016**	**0.372**
	~ time	ID = ~ time	corCAR1(form=~ 1|ID/Block)	43208.11		
3	~ time + group	ID = ~ 1	-	43232.1		
4	~ time * group	ID = ~ 1	-	43245.9		
5	~ time + group	ID = ~ time	-	43236.1		
6	**~ time + group**	**ID = ~ 1**	**corCAR1(form=~ 1|ID/Block)**	**43210.9**	**0.041**	**0.372**
7	~ time * group	ID = ~ 1	corCAR1(form=~ 1|ID/Block)	43224.94	0.043	0.373
8	**~ time + Driver Type**	**ID = ~ 1**	**corCAR1(form=~ 1|ID/Block)**	**43206.14**	**0.146**	**0.373**
9	~ time +Driver Type + group	ID = ~ 1	corCAR1(form=~ 1|ID/Block)	43213.04		

Table A8

GAM Model 2: Best fitting model

GAMM (AIC 43204.1) for the probability for invalid trials with the best fit according to comparison via lowest AIC (n = 49, observations = 9800, R^2 marginal = 0.016, R^2 conditional = 0.372): OR represents the odd ratio calculated by exponentiating the regression coefficients β, SE β is the standard error of β. β_0 represents the initial probability for an invalid trial, β_1 the increase (slope) in probability for invalid trials per minute (time). Their p-values show a significant difference compared to zero. β coefficients and their standard error are on a logit scale.

	OR	β	SE beta	t-value	p-value	
β_0 intercept	0.458	-0.790	0.11686	-6.7	0.000	< 0.001°*
β_1 slope (time)	1.0180	0.0179	0.00253	7.08	0.000	< 0.001°*

4 Study III

Table A9

GAM Model 8: with further factor driver type

GAMM (AIC 43206.14) for the probability for invalid trials with factor driver type (n = 49, observations = 9800, R^2 marginal = 0.016, R^2 conditional = 0.372): OR represents the odd ratio calculated by exponentiating the regression coefficients β, SE β is the standard error of β. β_0 represents the initial probability for an invalid trial of the $SHAM_{base}$-group of driver type 1 and β_6 the increase in probability for invalid trials over time (bold font). Their p-values, indexed with a °, show a significant difference compared to zero. All other coefficients are tested against β_0. Intercepts β_0 - β_3 indicate the 4 driver type classes, the slope β_6 represents the probability of an invalid trial/min. β coefficients and their standard error are on a logit scale.

	OR	β	SE beta	t-value	p-value	
Intercepts:						
β_0 $SHAM_{base}$ + Driver Type 1	0.189	-1.670	0.2159	-7.74	0.0000	< 0.001°*
β_1 $5Hz_{base}$ + Driver Type 2	3.130	1.141	0.2517	4.53	0.0000	< 0.001*
β_2 $40Hz_{base}$ + Driver Type 3	1.797	0.586	0.3505	1.67	0.1015	> 0.05
β_3 $SHAM_{inter}$+ Driver Type 4	3.284	1.189	0.2694	4.41	0.0001	< 0.001*
Slope:						
β_6 time	1.018	0.0179	0.00253	7.08	0.000	< 0.001°*

5. General Discussion

This thesis investigated the potential of tACS to counteract vigilance decrement and to transfer possible findings to the applied contexts of addressing older adults and car driving. It was hypothesized that gamma tACS on posterior parietal regions reduces vigilance decrement represented by rising reaction times over time. Therefore, a stimulation setup was configured and tested in a pilot study, repeated with older adults, and – in a modified version – tested in a monotonous driving scenario. While gamma tACS successfully slowed down reaction time increment in a pilot study (Study I), the analyzed data failed to show a similar effect when repeating the study with older adults (Study II) or in a monotonous driving scenario in a simulator (Study III) although in both cases a significant vigilance decrement – expressed by an increase of reaction time with time on task - was observed which was substantial in the baseline block in both studies and for the driving simulator study also during the intervention block. Concerning the study addressing older adults, the reaction time increment significantly continued to increase – contrary to the hypothesis – in the intervention block for the 40 Hz stimulated group only. However, alpha power was significantly higher after the experiment, irrespective of group. Concerning Study III a significant increase in the probability of invalid trials was also observed, which is an indicator of vigilant decrement as well.

In conclusion, it can be said: It could be shown that gamma tACS can reduce reaction time increment in a relatively homogenous group of young participants (mostly students) in a laboratory setting, but no significant effect of this stimulation setup could be shown in the more complex group of older adults or during the complex task of car driving. The question remains whether the effect of stimulation is not there or is too small for practical application – at least in the generalized approach that has been applied in this thesis. In the following paragraphs, possible reasons will be discussed, this research related to other findings, the limitations discussed, and implications for future studies given.

Although the number of tACS research papers has substantially increased in recent years (see section 1.4.1), little is known about the working principles for successful stimulation protocols, and standards are missing (Wischnewski et al., 2023). The research of this thesis fits in there as it fills a gap: Up to 2023, tACS was not applied in a driving simulator task, and only a few studies compare the same tACS protocol in different age groups (Fresnoza et al., 2020; Guerra et al., 2021; Rufener et al., 2016; Zanto et al., 2021) or for different task demands (e.g., Clayton et al., 2019). Furthermore, it also fits in with other research that failed to show - despite careful planning – the proposed effect of stimulation (Brignani et al., 2013; Lafleur et al., 2021; Lafon et al., 2017; van Schouwenburg et al., 2021) or failed to replicate a successful study (Veniero et al., 2017).

5 General Discussion

The following subsections discuss possible reasons why the transfer of the successful tACS setup in the pilot study (Study I) to more complex tasks (Study II, Study III) was unsuccessful.

a. The influence of covariates

In the tACS community, much-discussed issues are further influencing factors that either prevent successful stimulation, increase the sample size variability, or make tACS exhibit only weak effect sizes.

Next to individual differences in traits (anatomic or genetic differences, hair), recent research has also shown that covariates significantly influence stimulation success, and that subgroup analysis is worth a try. Also, environmental factors - e.g., ambient illumination (Stecher et al., 2017) may impact stimulation success. Considering performance, two studies identified the influence of baseline performance on stimulation success: While Thompson et al. (2021) showed that parietal gamma tACS significantly modulated working memory recall precision with the effect being stronger in high-baseline performers, gamma tACS in a study by Santarnecchi et al. (2016) especially improved performance of slow baseline performers. Santarnecchi et al. (2016) stimulated prefrontal brain regions and tested improvements in fluid intelligence. Also, age has been shown to be an influential factor for stimulation success: In a study with participants aged between 18 and 65 years. Zhu et al. (2023) found an effect of age in a subgroup analysis with older participants experiencing significant benefits from tACS. They targeted the forehead and both mastoids for 40 minutes at 77.5 Hz with 15 mA in 20 sessions over four weeks to treat chronic insomnia. Krebs et al. (2023) investigated the moderating effects of sex, age, and education on the outcome of combined cognitive training and transcranial electrical stimulation in older adults (mean age 71.7 years, SD 6.1). They stimulated the left dorsolateral prefrontal cortex for 20 minutes with 5 Hz tACS at 1 mA during 10 sessions of computerized cognitive training and performed a neuropsychological assessment before and after the intervention. Their results indicate that the youngest participants with fewer years of education benefit more from the tACS stimulation compared to older and more educated participants. Also, circadian rhythm and chronotype seem to influence stimulation success: Martínez-Pérez et al. (2022) found a task-specific significant effect of alpha- or/and theta-tACS when applied to the right DLPFC on vigilance when arousal was low. They measured arousal according to participants ´chronotypes with low arousal, meaning that evening-types performed the task at their non-optimal time of day.

In the studies presented in this thesis, further factors were – where possible- included in the analysis. In all studies, no influence of the factors of gender or baseline performance on stimulation could be detected. Study III had a different task design and allowed individual behavior. Participants classified with the behavioral pattern “unstable” showed a higher probability for invalid trials, and “slow” or “passive” participants exhibited, on average, 200 ms longer brake reaction times. However, these classifications did not unmask any stimulation effect. However, in Study II – although not part of the initial hypothesis and

therefore unbalanced over groups - a significant effect of the factor medication could be found, giving another hint for an influential covariate worth investigating in further studies.

Further, it has been shown that stimulation works detrimental among different age groups: What works in an enhancing way in young participants inhibits or even deteriorates performance in older or vice versa (Fresnoza et al., 2020; Rufener et al., 2016). Although insignificant, the results in Study II point in this direction: While in the intervention block, the increase in reaction time gets less in the sham and 5 Hz stimulated group, reaction times continued to rise in a steep slope in the 40 Hz stimulated group.

b. Age- and task-specificity of stimulation

Oscillations are known to change with age (Ishii et al., 2017). Further, it has been shown that stimulation works detrimental among different age groups: What works in an enhancing way in young participants inhibits or even deteriorates performance in older or vice versa (Fresnoza et al., 2020; Rufener et al., 2016). Although insignificant, the results of Study II point in this direction: While in the intervention block, the increase in reaction time gets less in the sham and 5 Hz stimulated group, reaction times continued to rise in a steep slope in the 40 Hz stimulated group.

Online improvement in performance is not always reflected in changed endogenous oscillations recorded after the experiment: Clayton et al. (2019) investigated the influence of alpha tACS on the visual cortex in four visual tasks. They proposed that alpha tACS will enhance the alpha amplitude and thereby deteriorate the performance in sustained attention tasks – kind of the opposite to the approach in this thesis- but in two of four experiments, they observed a performance stabilizing effect of tACS: On a behavioral scale, the administration of alpha-tACS reduced the slope of deteriorations in reaction times from the start of the stimulation onwards, while in the other tasks – as expected – reaction times rose. They also recorded an EEG before and after the experiments: In all visual experiments, alpha power increased reliably from the start to the end of each task, regardless of stimulation condition.

Although vigilance decrement was measured by rising reaction times across all studies with time on task and rising alpha power (only Study II) after the experiment, these are mere behavioral or neurophysiological correlates. Speculation remains open over the exact cause of this decrement. In literature, vigilance decrement is often referred to as two kinds of fatigue: 1.) Active fatigue occurs due to the mental depletion of cognitive resources and is related to high arousal, workload, and task demands. 2.) Passive fatigue occurs in monotonous tasks due to low arousal, workload, and task demands and is related to boredom. Both have been postulated in the “overload vs. underload theory.” Recent research has shown that this theory only insufficiently explains vigilance decrement and that a combination of underload and overload probably results in vigilance decrement. Monotonous tasks invite participants to start mind-wandering, which consumes attentional resources. Depending on motivation, executive control is required to focus on the

task (attention resource theory) (Bodala et al., 2020). In all studies, passive fatigue was expected, but it remains unclear if this was the case. In Study II, the older participants were highly motivated and eager to compete with the younger group. Although they exhibited lower reaction times, performance was equal to the younger participants in Study I. Motivation may have led to the recruitment of frontal brain regions as a compensatory mechanism and, therefore, to active fatigue. Considering driving – although being a complex task – Wascher et al. (2016) found that vigilance decrement and rising alpha amplitude probably occurred due to boredom. To ensure boredom, driving behavior was not commented on during the experiment, or rewards for good behavior were promised (gamification element). Still, the possibility cannot be excluded that the predictable task led to an automatic behavioral pattern that invited participants to perform mind-wandering, thereby leading to cognitive depletions, i.e., inducing active fatigue. Further research is needed to clarify this question.

c. Variability and small effect size

In general, and across 56 studies, effect sizes for successful tACS studies on cognitive performance are positive but small (Lee et al., 2023). In Study I, the model had a conditional r^2 of 0.3 (i.e., it explains 30 % of the variance), which is relatively small. However, already back then, it was argued that it was hard to obtain higher effects due to anatomical differences. The a priori power analysis indicated that 42 participants (14 per group) were sufficient, and more participants were analyzed (Study II: 48, Study III: 49). Still, in Study II and Study III more variability was introduced: The older-aged participants of Study II were not as homogenous as the participants of Study I due to the selection process (all education levels, cardiovascular medication, visual impairment in one eye allowed), Study III had more degrees of freedom for individual behavior that is also reflected by the data.

d. Nonoptimal stimulation parameters

1 mA was used as stimulation intensity because it has been shown to influence behavioral parameters and endogenous brain oscillations by numerous studies (e.g., see for a review Lee et al., 2023). In contrast, stimulation intensities of higher than 2mA with a duration longer than 10 minutes have been shown to lead to blinding problems (Antal et al., 2022) and intensities higher than 1.5 mA at the visual cortex to promote phosphenes (Kanai et al., 2008). However, other recent studies applied tACS with intensities of 2 mA (Clayton et al., 2019), especially the ones addressing older adults (Zanto et al., 2021). Wischnewski et al. (2023) even recommend intensities of up to 4 mA in general. Zhu et al. (2023) used 15 mA to improve sleep quality and efficiency in older adults with diagnosed chronic insomnia. With higher intensities it is possible to entrain a broader range of frequencies – an effect referred to as Arnold tongue (Vosskuhl et al., 2018). Higher stimulation frequencies might be helpful, especially concerning older adults who generally have a lower electric field (Antonenko et al., 2016).

Next to intensity, recent research also highlights the importance of focality and stimulation frequency adjusted to the personal peak frequency of the addressed spectrum: Spooner & Wilson (2023) showed that individualized tACS to the peak movement-related gamma frequency over the primary motor cortex leads to enhanced motor performance/learning (i.e., the greatest reduction in time to complete motor sequences) compared to nonspecific gamma-tACS in humans. They used a 4x1 high-definition tES device and concluded that personalized neuromodulation may be advantageous to optimize behavioral outcomes.

Covariates and the variability of participants' characteristics might have masked an effect of the intervention in this thesis. Nonoptimal stimulation parameters and wrong task-specificity may have left the stimulation effectless. Hints for further research can be given, but the question of the effect being too small, and the stimulation effect being covered by variability OR if tACS has no effect remains for now.

In general, these aspects show why applying tACS in practical contexts is hard. In conclusion, it might be possible that the "one dose fits all" approach to simply transfer a tACS protocol among two different classes of participants (age groups) or tasks (choice reaction task vs. driving simulator) does not work. First, this thesis's limitations will be summarized before implications for further research and applications are given.

5.1 Limitations

As already mentioned in this thesis, a successful tACS protocol was transferred without adjustments to a different age group who are known to have different brain properties and to a different task that allowed individual behavior. Although more participants were measured, the increase in variability might have masked the effects of stimulation. The number of participants in Study II and Study III is comparable to other studies (Lee et al., 2023) but still a limitation as there are other studies with more participants and more exclusion criteria (e.g., no medication). Further, standardized questionnaires on cognitive impairment (e.g., Mini-mental State Examination, see Reinhart & Nguyen, 2019), workload (e.g., NASA TLX, see Dillard et al., 2019), that are used in comparable studies might have helped to reduce variability, give information on brain states, and helped to clarify influential factors and are missing in the studies.

It might have been helpful to adapt the frequency and intensity of the stimulation to the needs of an older age group and to gradually develop a task in Study III (e.g., via a secondary task) that shows clear reaction times and excludes individual behaviors. The preference for a realistic scenario probably came at the expense of certainty about the stimulation effect and the reason behind the prolonged brake reaction times. In Study II, he resting EEG recorded before the baseline block could have been used to estimate the individual alpha frequency of each participant, and gamma stimulation could have been adjusted as its appropriate harmonic partner oscillation (although one has to keep in mind that the individual alpha frequency may change during cognitive tasks with time on task as well, see Haegens et al., 2014). As the stimulation effect on behavior was more important for the investigation, no EEG was recorded during Study

III, which is a limitation. Therefore, it remains unknown if alpha amplitudes at posterior regions rose during the driving task - as known for Study II – and if 40 Hz as a harmonic partner mismatched the individual alpha frequency.

To establish a tACS protocol, a simulation of the electrical field of a standard computerized head model was used (Stecher & Herrmann, 2018). It is too cost-intensive and inappropriate for the studies here. fMRI scans allowing an individualized simulation of current flow for each participant´s head, as used by Zanto et al. (2021), might have highlighted stimulation effects but are cost-intensive. Antonenko et al. (2021) simulated electric fields across age groups for six conventional tACS montages, further highlighting age dependency and inter-individual variability.

All three studies of this thesis were conducted as single-blind experiments. Research has shown that operators might unintentionally give different instructions during the real than the sham session, leading to manipulation or influence of the participants (Antal et al., 2022).

Due to technical, operational, or other problems, participants needed to be excluded (Study I: 1; Study II: 4 for EEG, 2 for behavior; Study III: 5) which weakened the power of the studies.

5.2 Implications for future research

In general, the studies in this thesis highlight the importance of more precise and individualized tACS protocols, the importance of reducing internal and external factors, and careful task design. Although tACS is a promising and easy-to-apply tool to modify behavior, more needs to be understood, and more research is needed. Frequency, electrode size, number and position, stimulation duration, and stimulation are parameters that can be adjusted and need further investigation.

Increasing the focality of stimulation with high-definition tACS by using more than two electrodes and a ring—like montage seems promising (Spooner & Wilson, 2023), as well as personalization of stimulation protocols according to current flow modeling (Antonenko et al., 2021) or via adjusting stimulation parameters constantly according to actual brain state via a close-loop stimulation with EEG.

Active machine-learning techniques have also been shown to be good tools to personalize brain stimulation frequency and intensity based on cognitive ability (van Bueren et al., 2021). Vosskuhl et al. (2018) also point out the potential of stimulating with complex waveforms (e.g., sawtooth waves) and the importance of artifact reduction to measure and analyze EEG and stimulate simultaneously. Further tACS optimization approaches are also under investigation, like phase-shifted or amplitude-modulated stimulation (Wu et al., 2021) or cross-frequency coupled tACS (Kim et al., 2022).

Further, the control and reduction of further factors are recommended: Questionnaires before and after the experiment could help define the subjective brain state, EEG for the objective. Neuroimaging tools could be used to define brain traits. It might also be helpful to consider circadian rhythms (see Martínez-Pérez et al., 2022) and perform cognitive and driving tests before the experiment to further classify participants. Next to medication (Study II, or see McLaren et al., 2018, for a reference) and characteristics like slow and fast performance (Santarnecchi et al., 2016; Thompson et al., 2021), motivation could be an important factor to be considered, especially concerning research on vigilance decrement.

5.3 Outlook / Possible application

Although this thesis could not prove the potential of tACS for application in complex tasks, contexts could be identified, and recent research further highlights potential applicational scenarios. Especially concerning older adults with neurodegenerative diseases, e.g., the first in-home trials are under investigation, showing that theta tACS in combination with cognitive control training can improve attentional abilities and that tACS devices can be used by patients themselves at home without direct researcher assistance (Jones et al., 2023).

The personalization of stimulation features seems promising, although further investigation is needed. Technical devices (e.g., smartwatches, smartphones) that can be used as wearable sensors for tracking physiological parameters (e.g., heart rate) are widely in use; cars track all kinds of information on driver´s status and could be integrated into other required technology that is partially ready to be included (e.g., portable EEG headsets, stimulation headbands) for on-demand personal stimulation, e.g., enhancing vigilance esp. in safety-critical moments. Although acceptance of the use of headsets is questionable while car-driving by healthy populations and technology might need to advance first further here, it might be a help for pathological populations whose sickness affects driving abilities, e.g., people who have Parkinson´s disease (Buhmann & Gerloff, 2014). In an advanced stage of this disease, the implementation of deep brain tissue stimulation devices is a treatment option. Thereby, locally attached, and removable electrodes might be an acceptable option at the beginning of the disease and are already under investigation for therapy (Del Felice et al., 2019).

5.4 Conclusion

In this thesis, the potential of tACS to enhance vigilance was first tested in a pilot study. The successful tACS protocol was then tested with older adults and in the context of car driving. Although vigilance decrement could be shown in all three scenarios, 40 Hz tACS on the visual cortex only showed a counteracting effect in a pilot study with young participants in a laboratory setting. Following literature research and thorough discussion, the following conclusions can be made:

5 General Discussion

The positive effect of the tACS protocol on counteracting vigilance decrement could not be shown in complex contexts, i.e., when addressing older adults or in a driving scenario. Due to the higher variability of the older participants and their data, whether there is no effect, or the effect is too small remained unknown. More factors need to be controlled to reduce variability.

The potential of tACS in practical applications is there, but a "one-dose-fits-all" approach as investigated in this thesis is not recommended. Instead, the investigation of personalized stimulation protocols seems promising. In general, more research is needed, especially concerning different age groups.

References

Abbas, Q., & Alsheddy, A. (2020). Driver Fatigue Detection Systems Using Multi-Sensors, Smartphone, and Cloud-Based Computing Platforms: A Comparative Analysis. *Sensors*, *21*(1), Article Number: 56, pp. 1- 38. https://doi.org/10.3390/s21010056

Albadawi, Y., Takruri, M., & Awad, M. (2022). A Review of Recent Developments in Driver Drowsiness Detection Systems. *Sensors*, *22*(5), Article Number: 2069, pp. 1-41. https://doi.org/10.3390/s22052069

Alexander, M. L., Alagapan, S., Lugo, C. E., Mellin, J. M., Lustenberger, C., Rubinow, D. R., & Fröhlich, F. (2019). Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). *Translational Psychiatry*, *9*(1), Article Number: 106, pp.1-12. https://doi.org/10.1038/s41398-019-0439-0

Al-Shargie, F., Tariq, U., Babiloni, F., & Al-Nashash, H. (2021). Cognitive Vigilance Enhancement Using Audio Stimulation of Pure Tone at 250 Hz. *IEEE Access*, *9*, pp. 22955–22970. https://doi.org/10.1109/ACCESS.2021.3054785

Al-Shargie, F., Tariq, U., Mir, H., Alawar, H., Babiloni, F., & Al-Nashash, H. (2019). Vigilance Decrement and Enhancement Techniques: A Review. *Brain Sciences*, *9*(8), Article Number: 178, pp. 1-36. https://doi.org/10.3390/brainsci9080178

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., Kong, E., Larraburo, Y., Rolle, C., Johnston, E., & Gazzaley, A. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*(7465), pp. 97–101. https://doi.org/10.1038/nature12486

Annarumma, L., D'Atri, A., Alfonsi, V., & Gennaro, L. de (2018). The Efficacy of Transcranial Current Stimulation Techniques to Modulate Resting-State EEG, to Affect Vigilance and to Promote Sleepiness. *Brain Sciences*, *8*(7), Article Number: 137, pp. 1-14. https://doi.org/10.3390/brainsci8070137

Antal, A., & Herrmann, C. S. (2016). Transcranial Alternating Current and Random Noise Stimulation: Possible Mechanisms. *Neural Plasticity*, *2016*, Article ID: 3616807, pp. 1-12. https://doi.org/10.1155/2016/3616807

Antal, A., Luber, B., Brem, A.-K., Bikson, M., Brunoni, A. R., Cohen Kadosh, R., Dubljević, V., Fecteau, S., Ferreri, F., Flöel, A., Hallett, M., Hamilton, R. H., Herrmann, C. S., Lavidor, M., Loo, C., Lustenberger, C., Machado, S., Miniussi, C., Moliadze, V., . . . Paulus, W. (2022). Non-invasive brain stimulation and neuroenhancement. *Clinical Neurophysiology Practice*, *7*, pp. 146–165. https://doi.org/10.1016/j.cnp.2022.05.002

Antonenko, D., Faxel, M., Grittner, U., Lavidor, M., & Flöel, A. (2016). Effects of Transcranial Alternating Current Stimulation on Cognitive Functions in Healthy Young and Older Adults. *Neural Plasticity*, *2016*, Article ID: 4274127, pp. 1-14. https://doi.org/10.1155/2016/4274127

Antonenko, D., Grittner, U., Saturnino, G., Nierhaus, T., Thielscher, A., & Flöel, A. (2021). Inter-individual and age-dependent variability in simulated electric fields induced by conventional transcranial electrical stimulation. *NeuroImage*, *224*, Article ID: 117413, pages 9. https://doi.org/10.1016/j.neuroimage.2020.117413

Beeli, G., Koeneke, S., Gasser, K., & Jancke, L. (2008). Brain stimulation modulates driving behavior. *Behavioral and Brain Functions*, *4*, Article Number: 34, pages 7. https://doi.org/10.1186/1744-9081-4-34

References

Bodala, I. P., Ding, K., & Al-Nashash, H. (2020). Vigilance Assessment and Enhancement. In N. V. Thakor (Ed.), *Handbook of Neuroengineering* (pp. 1–24). Springer Singapore; Imprint Springer. https://doi.org/10.1007/978-981-15-2848-4_75-1

Bodala, I. P., Li, J., Thakor, N. V., & Al-Nashash, H. (2016). Eeg and Eye Tracking Demonstrate Vigilance Enhancement with Challenge Integration. *Frontiers in Human Neuroscience*, *10*, Article Number: 273, pp. 1-10. https://doi.org/10.3389/fnhum.2016.00273

Borghini, G., Astolfi, L., Vecchiato, G., Mattia, D., & Babiloni, F. (2014). Measuring neurophysiological signals in aircraft pilots and car drivers for the assessment of mental workload, fatigue and drowsiness. *Neuroscience and Biobehavioral Reviews*, *44*, pp. 58–75. https://doi.org/10.1016/j.neubiorev.2012.10.003

Bouyer, J. J., Montaron, M. F., & Rougeul, A. (1981). Fast fronto-parietal rhythms during combined focused attentive behaviour and immobility in cat: Cortical and thalamic localizations. *Electroencephalography and Clinical Neurophysiology*, *51*(3), pp. 244–252. https://doi.org/10.1016/0013-4694(81)90138-3

Bugg, J. M., Zook, N. A., DeLosh, E. L., Davalos, D. B., & Davis, H. P. (2006). Age differences in fluid intelligence: Contributions of general slowing and frontal decline. *Brain and cognition*, 62(1), pp. 9-16. https://doi.org/10.1016/j.bandc.2006.02.006

Brignani, D., Ruzzoli, M., Mauri, P., & Miniussi, C. (2013). Is transcranial alternating current stimulation effective in modulating brain oscillations? *PLOS ONE*, *8*(2), Article ID: e56589, pp. 1-8. https://doi.org/10.1371/journal.pone.0056589

Brunnauer, A., Segmiller, F. M., Löschner, S., Grun, V., Padberg, F., & Palm, U. (2018). The Effects of Transcranial Direct Current Stimulation (tDCS) on Psychomotor and Visual Perception Functions Related to Driving Skills. *Frontiers in Behavioral Neuroscience*, *12*, Article Number: 16, pp. 1-6. https://doi.org/10.3389/fnbeh.2018.00016

Buck, L. (1966). Reaction time as a measure of perceptual vigilance. *Psychological Bulletin*, *65*(5), pp. 291–304. https://doi.org/10.1037/h0023207

Buhmann, C., & Gerloff, C. (2014). Could deep brain stimulation help with driving for patients with Parkinson's? *Expert Review of Medical Devices*, *11*(5), pp. 427–429. https://doi.org/10.1586/17434440.2014.929495

Cabral-Calderin, Y., & Wilke, M. (2020). Probing the Link Between Perception and Oscillations: Lessons from Transcranial Alternating Current Stimulation. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *26*(1), pp. 57–73. https://doi.org/10.1177/1073858419828646

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, *14*(11), pp. 506–515. https://doi.org/10.1016/j.tics.2010.09.001

Chu, C.-S., Li, C.-T., Brunoni, A. R., Yang, F.-C., Tseng, P.-T., Tu, Y.-K., Stubbs, B., Carvalho, A. F., Thompson, T., Rajji, T. k., Yeh, T.-C., Tsai, C.-K., Chen, T.-Y., Li, D.-J., Hsu, C.-W., Wu, Y.-C., Yu, C.-L., & Liang, C.-S. (2021). Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild cognitive impairment: A component network meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *92*(2), pp. 195–203. https://doi.org/10.1136/jnnp-2020-323870

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2015). The roles of cortical oscillations in sustained attention. *Trends in Cognitive Sciences*, *19*(4), pp. 188–195. https://doi.org/10.1016/j.tics.2015.02.004

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2019). Electrical stimulation of alpha oscillations stabilizes performance on visual attention tasks. *Journal of Experimental Psychology: General*, *148*(2), pp. 203–220. https://doi.org/10.1037/xge0000502

Craig, A., Tran, Y., Wijesuriya, N., & Nguyen, H. (2012). Regional brain wave activity changes associated with fatigue. *Psychophysiology*, *49*(4), pp. 574–582. https://doi.org/10.1111/j.1469-8986.2011.01329.x

References

Del Felice, A., Castiglia, L., Formaggio, E., Cattelan, M., Scarpa, B., Manganotti, P., Tenconi, E., & Masiero, S. (2019). Personalized transcranial alternating current stimulation (tACS) and physical therapy to treat motor and cognitive symptoms in Parkinson's disease: A randomized cross-over trial. *NeuroImage. Clinical*, *22*, Article ID: 101768, pp. 1-9. https://doi.org/10.1016/j.nicl.2019.101768

Dillard, M. B., Warm, J. S., Funke, G. J., Nelson, W. T., Finomore, V. S., McClernon, C. K., Eggemeier, F. T., Tripp, L. D., & Funke, M. E. (2019). Vigilance Tasks: Unpleasant, Mentally Demanding, and Stressful Even When Time Flies. *Human Factors*, *61*(2), pp. 225–242. https://doi.org/10.1177/00187208.18796015

Elyamany, O., Leicht, G., Herrmann, C. S., & Mulert, C. (2021). Transcranial alternating current stimulation (tACS): From basic mechanisms towards first applications in psychiatry. *European Archives of Psychiatry and Clinical Neuroscience*, *271*(1), pp. 135–156. https://doi.org/10.1007/s00406-020-01209-9

European Commission. (2020). *European Commission Report on the Impact of Demographic Change*. https://ec.europa.eu/info/sites/default/files/demography_report_2020_n.pdf, last accessed on 2002-06-09

Facchin, A., La Rocca, S., Vacchi, L., Daini, R., Gobbo, M., Fontana, S., & Lega, C. (2023). Effects of conventional and high-definition transcranial direct current stimulation (tDCS) on driving abilities: A tDCS-driving simulator study. *Journal of Environmental Psychology*, *90*, Article Number: 102111, pp. 1-10. https://doi.org/10.1016/j.jenvp.2023.102111

Fertonani, A., & Miniussi, C. (2017). Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *23*(2), pp. 109–123. https://doi.org/10.1177/1073858416631966

Fresnoza, S., Christova, M., Bieler, L., Körner, C., Zimmer, U., Gallasch, E., & Ischebeck, A. (2020). Age-Dependent Effect of Transcranial Alternating Current Stimulation on Motor Skill Consolidation. *Frontiers in Aging Neuroscience*, *12*, Article Number: 25, pp. 1-15. https://doi.org/10.3389/fnagi.2020.00025

Fröhlich, F. (2014). Endogenous and exogenous electric fields as modifiers of brain activity: Rational design of noninvasive brain stimulation with transcranial alternating current stimulation. *Dialogues in Clinical Neuroscience*, *16*(1), pp. 93–102. https://doi.org/10.31887/DCNS.2014.16.1/ffroehlich

Fröhlich, F., Sellers, K. K., & Cordle, A. L. (2015). Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation. *Expert Review of Neurotherapeutics*, *15*(2), pp. 145–167. https://doi.org/10.1586/14737175.2015.992782

Ganesan, B., Gowda, T., Al-Jumaily, A., Fong, K. N., Meena, S. K., & Tong, R. K. (2019). Ambient assisted living technologies for older adults with cognitive and physical impairments: A review. *European review for medical and pharmacological sciences, 23 (23),* pp. 10470 – 10481. http://hdl.handle.net/10453/137559

Gershon, P., Shinar, D., Oron-Gilad, T., Parmet, Y., & Ronen, A. (2011). Usage and perceived effectiveness of fatigue countermeasures for professional and nonprofessional drivers. *Accident Analysis & Prevention*, *43*(3), pp. 797–803. https://doi.org/10.1016/j.aap.2010.10.027

Gonzalez-Perez, M., Wakui, E., Thoma, V., Nitsche, M. A., & Rivolta, D. (2019). Transcranial alternating current stimulation (tACS) at 40 Hz enhances face and object perception. *Neuropsychologia*, *135*, Article ID: 107237, pp. 1-6. https://doi.org/10.1016/j.neuropsychologia.2019.107237

Greenlee, E. T., DeLucia, P. R., & Newton, D. C. (2024). Driver Vigilance Decrement is More Severe During Automated Driving than Manual Driving. *Human Factors, 66(2),* pp. 574-588. https://doi.org/10.1177/00187208221103922

Groeger, J. A. (2000). *Understanding driving: Applying cognitive psychology to a complex everyday task*. (1st ed.). Routledge: London, GB. eBook ISBN 9780203769942. https://doi.org/10.4324/9780203769942

References

Grover, S., Fayzullina, R., Bullard, B. M., Levina, V., & Reinhart, R. M. G. (2023). A meta-analysis suggests that tACS improves cognition in healthy, aging, and psychiatric populations. *Science Translational Medicine*, *15*(697), Article ID: eabo2044, pp. 1-13. https://doi.org/10.1126/scitranslmed.abo2044

Guerra, A., Asci, F., Zampogna, A., D'Onofrio, V., Berardelli, A., & Suppa, A. (2021). The effect of gamma oscillations in boosting primary motor cortex plasticity is greater in young than older adults. *Clinical Neurophysiology*, *132*(6), pp. 1358–1366. https://doi.org/10.1016/j.clinph.2021.01.032

Guo, Z., Pan, Y., Zhao, G., Cao, S., & Zhan, J. (2018). Detection of Driver Vigilance Level Using EEG Signals and Driving Contexts. *IEEE Transactions on Reliability*, *67*, pp. 370–380. 10.1109/TR.2017.2778754

Haegens, S., Cousijn, H., Wallis, G., Harrison, P. J., & Nobre, A. C. (2014). Inter- and intra-individual variability in alpha peak frequency. *NeuroImage*, *92*, pp. 46–55. https://doi.org/10.1016/j.neuroimage.2014.01.049

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews. Neuroscience*, *5*(2), pp. 87–96. https://doi.org/10.1038/nrn1323

Helfrich, R. F., Herrmann, C. S., Engel, A. K., & Schneider, T. R. (2016). Different coupling modes mediate cortical cross-frequency interactions. *NeuroImage*, *140*, pp. 76–82. https://doi.org/10.1016/j.neuroimage.2015.11.035

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), pp. 333–339. https://doi.org/10.1016/j.cub.2013.12.041

Helfrich, R. F., Knepper, H., Nolte, G., Strüber, D., Rach, S., Herrmann, C. S., Schneider, T. R. & Engel, A. K. (2014). Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. *PLoS Biology*, *12*(12), Article ID: e1002031, pp. 1-15. https://doi.org/10.1371/journal.pbio.1002031

Henao, D., Zapata, V., Navarrete, M., Le Van Quyen, M., & Valderrama, M. (2018). In *IX International Seminar of Biomedical Engineering (SIB)*, Bogota, Colombia, 2018, pp. 1-4, IEEE. https://doi.org/10.1109/SIB.2018.8467724

Hoy, K. E., Bailey, N., Arnold, S., Windsor, K., John, J., Daskalakis, Z. J., & Fitzgerald, P. B. (2015). The effect of γ-tACS on working memory performance in healthy controls. *Brain and Cognition*, *101*, pp. 51–56. https://doi.org/10.1016/j.bandc.2015.11.002

Hsu, W.-Y., Zanto, T. P., & Gazzaley, A. (2019). Parametric effects of transcranial alternating current stimulation on multitasking performance. *Brain Stimulation*, *12*(1), pp. 73–83. https://doi.org/10.1016/j.brs.2018.10.010

Hsu, W.-Y., Zanto, T. P., van Schouwenburg, M. R., & Gazzaley, A. (2017). Enhancement of multitasking performance and neural oscillations by transcranial alternating current stimulation. *PloS One*, *12*(5), Article ID: e0178579, pp. 1-17. https://doi.org/10.1371/journal.pone.0178579

Ishii, R., Canuet, L., Aoki, Y., Hata, M., Iwase, M., Ikeda, S., Nishida, K., & Ikeda, M. (2017). Healthy and Pathological Brain Aging: From the Perspective of Oscillations, Functional Connectivity, and Signal Complexity. *Neuropsychobiology*, *75*(4), pp. 151–161. https://doi.org/10.1159/000486870

Iuculano, T., & Cohen Kadosh, R. (2013). The mental cost of cognitive enhancement. *The Journal of Neuroscience*, *33*(10), pp. 4482–4486. https://doi.org/10.1523/JNEUROSCI.4927-12.2013

Jones, K. T., Ostrand, A. E., Gazzaley, A., & Zanto, T. P. (2023). Enhancing cognitive control in amnestic mild cognitive impairment via at-home non-invasive neuromodulation in a randomized trial. *Scientific Reports*, *13*(1), Article Number: 7435, pp. 1-8. https://doi.org/10.1038/s41598-023-34582-1

Jones, K. T., Smith, C. C., Gazzaley, A., & Zanto, T. P. (2022). Research outside the laboratory: Longitudinal at-home neurostimulation. *Behavioural Brain Research*, *428*, Article ID: 113894, pp. 1-9. https://doi.org/10.1016/j.bbr.2022.113894

References

Kalisetti, V., Vasarla, V. S. C., Kolli, S. B., Varaparla, R., Enireddy, V., & Mohammed, M. (2023). Analysis of Driver Drowsiness Detection. In *2023 Second International Conference on Electronics and Renewable Systems (ICEARS), Tuticorin, India*, pp. 1481–1485. IEEE. https://doi.org/10.1109/ICEARS56392.2023.10084986

Kanai, R., Chaieb, L., Antal, A., Walsh, V., & Paulus, W. (2008). Frequency-dependent electrical stimulation of the visual cortex. *Current Biology*, *18*(23), pp. 1839–1843. https://doi.org/10.1016/j.cub.2008.10.027

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*, Article Number: 245, pp. 1-9. https://doi.org/10.3389/fnhum.2016.00245

Khan, M. Q., & Lee, S. (2019). A Comprehensive Survey of Driving Monitoring and Assistance Systems. *Sensors*, *19*(11), Article Number: 2574, pp. 1-32. https://doi.org/10.3390/s19112574

Kim, S.-E., Kim, H.-S., Kwak, Y., Ahn, M.-H., Choi, K. M., & Min, B.-K. (2022). Neurodynamic correlates for the cross-frequency coupled transcranial alternating current stimulation during working memory performance. *Frontiers in Neuroscience*, *16*, Article Number: 1013691, pp. 1-17. https://doi.org/10.3389/fnins.2022.1013691

Klimesch, W., Doppelmayr, M., Schimke, H., & Pachinger, T. (1996). Alpha Frequency, Reaction Time, and the Speed of Processing Information. *Journal of Clinical Neurophysiology*, *13*(6), pp. 511-518 https://doi.org/ 10.1097/00004691-199611000-00006

Klimesch, W. (2012). A-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*, *16*(12), pp. 606–617. https://doi.org/10.1016/j.tics.2012.10.007

Klink, K., Paßmann, S., Kasten, F. H., & Peter, J. (2020). The Modulation of Cognitive Performance with Transcranial Alternating Current Stimulation: A Systematic Review of Frequency-Specific Effects. *Brain Sciences*, *10*(12). Article Number: 932, pp. 1-33. https://doi.org/10.3390/brainsci10120932

Koninck, B. P. de, Brazeau, D., Guay, S., Herrero Babiloni, A., & Beaumont, L. de (2023). Transcranial Alternating Current Stimulation to Modulate Alpha Activity: A Systematic Review. *Neuromodulation*, *26*(8), pp. 1549–1584. https://doi.org/10.1016/j.neurom.2022.12.007

Körber, M., Cingel, A., Zimmermann, M., & Bengler, K. (2015). Vigilance Decrement and Passive Fatigue Caused by Monotony in Automated Driving. *Procedia Manufacturing*, *3*, pp. 2403–2409. https://doi.org/10.1016/j.promfg.2015.07.499

Kraft, J. D., & Hampstead, B. M. (2023). A Systematic Review of tACS Effects on Cognitive Functioning in Older Adults Across the Healthy to Dementia Spectrum. *Neuropsychology Review*, pp. 1–26. https://doi.org/10.1007/s11065-023-09621-3

Krebs, C., Peter, J., Brill, E., Klöppel, S., & Brem, A.-K. (2023). The moderating effects of sex, age, and education on the outcome of combined cognitive training and transcranial electrical stimulation in older adults. *Frontiers in Psychology*, *14*, Article Number: 1243099, pp. 1-9. https://doi.org/10.3389/fpsyg.2023.1243099

Lafleur, L.-P., Murray, A., Desforges, M., Pacheco-Barrios, K., Fregni, F., Tremblay, S., Saint-Amour, D., Lepage, J.-F., & Théoret, H. (2021). No aftereffects of high current density 10 Hz and 20 Hz tACS on sensorimotor alpha and beta oscillations. *Scientific Reports*, *11*(1), Article number: 21416, pp. 1-20. https://doi.org/10.1038/s41598-021-00850-1

Lafon, B., Henin, S., Huang, Y., Friedman, D., Melloni, L., Thesen, T., Doyle, W., Buzsáki, G., Devinsky, O., Parra, L. C., & A Liu, A. (2017). Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nature Communications*, *8*(1), Article number: 1199, pp. 1-14. https://doi.org/10.1038/s41467-017-01045-x

References

Lee, T. L., Lee, H., & Kang, N. (2023). A meta-analysis showing improved cognitive performance in healthy young adults with transcranial alternating current stimulation. *Npj Science of Learning*, *8*(1), Article Number: 1, pp. 1-20. https://doi.org/10.1038/s41539-022-00152-9

Li, G., & Chung, W.-Y. (2018). Combined EEG-Gyroscope-tDCS Brain Machine Interface System for Early Management of Driver Drowsiness. *IEEE Transactions on Human-Machine Systems*, *48*(1), pp. 50–62. https://doi.org/10.1109/THMS.2017.2759808

Li, G., & Chung, W.-Y. (2022). Electroencephalogram-Based Approaches for Driver Drowsiness Detection and Management: A Review. *Sensors*, *22*(3). Article Number: 1, pages 1-26. https://doi.org/10.3390/s22031100

Mackworth, N. H. (1948). The Breakdown of Vigilance during Prolonged Visual Search. *Quarterly Journal of Experimental Psychology*, *1*(1), pp. 6–21. https://doi.org/10.1080/17470214808416738

Manippa, V., Palmisano, A., Nitsche, M. A., Filardi, M., Vilella, D., Logroscino, G., & Rivolta, D. (2023). Cognitive and Neuropathophysiological Outcomes of Gamma-tACS in Dementia: A Systematic Review. *Neuropsychology Review*, pp. 1–24. https://doi.org/10.1007/s11065-023-09589-0

Martínez-Pérez, V., Tortajada, M., Palmero, L. B., Campoy, G., & Fuentes, L. J. (2022). Effects of transcranial alternating current stimulation over right-DLPFC on vigilance tasks depend on the arousal level. *Scientific Reports*, *12*(1), Article Number: 547, pages 10. https://doi.org/10.1038/s41598-021-04607-8

Matsumoto, H., & Ugawa, Y. (2017). Adverse events of tDCS and tACS: A review. *Clinical Neurophysiology Practice*, *2*, pp. 19–25. https://doi.org/10.1016/j.cnp.2016.12.003

McLaren, M. E., Nissim, N. R., & Woods, A. J. (2018). The effects of medication use in transcranial direct current stimulation: A brief review. *Brain Stimulation*, *11*(1), pp. 52–58. https://doi.org/10.1016/j.brs.2017.10.006

Moussavi, Z., Kimura, K., Kehler, L., Oliveira Francisco, C. de, & Lithgow, B. (2021). A Novel Program to Improve Cognitive Function in Individuals With Dementia Using Transcranial Alternating Current Stimulation (tACS) and Tutored Cognitive Exercises. *Frontiers in Aging*, *2(3)*, Article Number: 632545, pp. 1-11. https://doi.org/10.3389/fragi.2021.632545

Nasri, I., Karrouchi, M., Kassmi, K., & Messaoudi, A. (2022, May 22). *A Review of Driver Drowsiness Detection Systems: Techniques, Advantages and Limitations*. https://arxiv.org/pdf/2206.07489.pdf, 12 pages, last accessed 2024-01-20, https://doi.org/10.48550/arXiv.2206.07489

Nelson, J. T., McKinley, R. A., Golob, E. J., Warm, J. S., & Parasuraman, R. (2014). Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *NeuroImage*, *85*, pp. 909–917. https://doi.org/10.1016/j.neuroimage.2012.11.061

Nissim, N. R., Pham, D. V. H., Poddar, T., Blutt, E., & Hamilton, R. H. (2023). The impact of gamma transcranial alternating current stimulation (tACS) on cognitive and memory processes in patients with mild cognitive impairment or Alzheimer's disease: A literature review. *Brain Stimulation*, *16*(3), pp. 748–755. https://doi.org/10.1016/j.brs.2023.04.001

Oken, B. S., Salinsky, M. C., & Elsas, S. M. (2006). Vigilance, alertness, or sustained attention: Physiological basis and measurement. *Clinical Neurophysiology*, *117*(9), pp. 1885–1901. https://doi.org/10.1016/j.clinph.2006.01.017

Oron-Gilad, T., Ronen, A., & Shinar, D. (2008). Alertness maintaining tasks (AMTs) while driving. *Accident Analysis & Prevention*, *40*(3), pp. 851–860. https://doi.org/10.1016/j.aap.2007.09.026

Osipova, D., Hermes, D., & Jensen, O. (2008). Gamma power is phase-locked to posterior alpha activity. *PloS One*, *3*(12), Article ID: e3990, pp. 1-7. https://doi.org/10.1371/journal.pone.0003990

Palva, J. M., Palva, S., & Kaila, K. (2005). Phase synchrony among neuronal oscillations in the human cortex. *The Journal of Neuroscience*, *25*(15), pp. 3962–3972. https://doi.org/10.1523/JNEUROSCI.4250-04.2005

References

Pattyn, N., Neyt, X., Henderickx, D., & Soetens, E. (2008). Psychophysiological investigation of vigilance decrement: Boredom or cognitive fatigue? *Physiology & Behavior*, *93*(1-2), pp. 369–378. https://doi.org/10.1016/j.physbeh.2007.09.016

Peters, R. (2006). Ageing and the brain. *Postgraduate Medical Journal*, *82*(964), pp. 84–88. https://doi.org/10.1136/pgmj.2005.036665

Prehn, K., & Flöel, A. (2015). Potentials and limits to enhance cognitive functions in healthy and pathological aging by tDCS. *Frontiers in Cellular Neuroscience*, *9*, Article Number: 355, pp. 1-14. https://doi.org/10.3389/fncel.2015.00355

PubMed. (2024, January 20). *"transcranial alternating current stimulation" - Search Results - PubMed*. https://pubmed.ncbi.nlm.nih.gov/?term=%22transcranial%20alternating%20current%20stimulation%22

Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience*, *22*(5), pp. 820–827. https://doi.org/10.1038/s41593-019-0371-x

Rostami, M., Lee, A., Frazer, A. K., Akalu, Y., Siddique, U., Pearce, A. J., Tallent, J., & Kidgell, D. J. (2024). Determining the corticospinal, intracortical and motor function responses to transcranial alternating current stimulation of the motor cortex in healthy adults: A systematic review and meta-analysis. *Brain Research*, *1822*, Article ID: 148650, pp. 1-24. https://doi.org/10.1016/j.brainres.2023.148650

Rostami, R., Kazemi, R., Mozaffarinejad, F., Nasiri, Z., Rostami, M., L Hadipour, A., & Sadeghihassanabadi, F. (2021). 6 Hz transcranial alternating current stimulation of mPFC improves sustained attention and modulates alpha phase synchronization and power in dorsal attention network. *Cognitive Neuroscience*, *12*(1), pp. 1–13. https://doi.org/10.1080/17588928.2020.1817881

Rufener, K. S., Oechslin, M. S., Zaehle, T., & Meyer, M. (2016). Transcranial Alternating Current Stimulation (tACS) differentially modulates speech perception in young and older adults. *Brain Stimulation*, *9*(4), pp. 560–565. https://doi.org/10.1016/j.brs.2016.04.002

Sakai, H., Uchiyama, Y., Tanaka, S., Sugawara, S. K., & Sadato, N. (2014). Prefrontal transcranial direct current stimulation improves fundamental vehicle control abilities. *Behavioural Brain Research*, *273*, pp. 57–62. https://doi.org/10.1016/j.bbr.2014.07.036

Salthouse, T. A. (2004). What and when of cognitive aging. *Current directions in psychological science*, 13(4), pp. 140-144. https://doi.org/10.1111/j.0963-7214.2004.00293.x

Santarnecchi, E., Muller, T., Rossi, S., Sarkar, A., Polizzotto, N. R., Rossi, A., & Cohen Kadosh, R. (2016). Individual differences and specificity of prefrontal gamma frequency-tACS on fluid intelligence capabilities. *Cortex*, *75*, pp. 33–43. https://doi.org/10.1016/j.cortex.2015.11.003

Santarnecchi, E., Sprugnoli, G., Bricolo, E., Costantini, G., Liew, S.-L., Musaeus, C. S., Salvi, C., Pascual-Leone, A., Rossi, A., & Rossi, S. (2019). Gamma tACS over the temporal lobe increases the occurrence of Eureka! Moments. *Scientific Reports*, *9*(1), Article Number: 5778, pp. 1-12. https://doi.org/10.1038/s41598-019-42192-z

Schlag, B., Weller, G., & Strauzenberg Richter, H. (2014). *Accident patterns and prospects for maintaining the safety of older drivers*. (1st ed.). TÜV Media: Cologne, Germany. ISBN 978-3-8249-1831-7

Schneider, L., Frings, K., Rothe, S., Schrauf, M., & Jaitner, T. (2021). Effects of a seat-integrated mobilization system during passive driver fatigue. *Accident; Analysis and Prevention*, *150*, Article ID: 105883, pp. 1-9. https://doi.org/10.1016/j.aap.2020.105883

Seet, M., Bezerianos, A., Panou, M., Bekiaris, E., & Thakor, N. & Dragomir, A. (2023). Individual Susceptibility to Vigilance Decrement in Prolonged Assisted Driving Revealed by Alert-State Wearable EEG Assessment. *IEEE Transactions on Cognitive and Developmental Systems*, *15*(3), pp. 1586–1594. doi: 10.1109/TCDS.2022.3231691

References

Sheffield, J. G., Ramerpresad, S., Brem, A.-K., Mansfield, K., Orhan, U., Dillard, M., McKanna, J., Plessow, F., Thompson, T., Santarnecchi, E., Pascual-Leone, A., Pavel, M., Mathan, S., & Cohen Kadosh, R. (2022). Blinding efficacy and adverse events following repeated transcranial alternating current, direct current, and random noise stimulation. *Cortex*, *154*, pp. 77–88. https://doi.org/10.1016/j.cortex.2022.05.015

Spooner, R. K., & Wilson, T. W. (2023). Spectral specificity of gamma-frequency transcranial alternating current stimulation over motor cortex during sequential movements. *Cerebral Cortex*, *33*(9), pp. 5347–5360. https://doi.org/10.1093/cercor/bhac423

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*, Article Number: 984, pp. 1-9. https://doi.org/10.3389/fpsyg.2018.00984

Stecher, H. I., Pollok, T. M., Strüber, D., Sobotka, F., & Herrmann, C. S. (2017). Ten Minutes of α-tACS and Ambient Illumination Independently Modulate EEG α-Power. *Frontiers in Human Neuroscience*, *11*, Article Number: 257, pp. 1-10. https://doi.org/10.3389/fnhum.2017.00257

Strüber, D., & Herrmann, C. S. (2020). Modulation of gamma oscillations as a possible therapeutic tool for neuropsychiatric diseases: A review and perspective. *International Journal of Psychophysiology*, *152*, pp. 15–25. https://doi.org/10.1016/j.ijpsycho.2020.03.003

Summala, H. (1996). Accident risk and driver behaviour. *Safety Science*, *22*(1-3), pp. 103–117. https://doi.org/10.1016/0925-7535(96)00009-4

Takeuchi, N., & Izumi, S.-I. (2021). Motor Learning Based on Oscillatory Brain Activity Using Transcranial Alternating Current Stimulation: A Review. *Brain Sciences*, *11*(8). Article Number: 1095, pp. 1-20. https://doi.org/10.3390/brainsci11081095

Thompson, L., Khuc, J., Saccani, M. S., Zokaei, N., & Cappelletti, M. (2021). Gamma oscillations modulate working memory recall precision. *Experimental Brain Research*, *239*(9), pp. 2711–2724. https://doi.org/10.1007/s00221-021-06051-6

van Bueren, N. E. R., Reed, T. L., Nguyen, V., Sheffield, J. G., van der Ven, S. H. G., Osborne, M. A., Kroesbergen, E. H., & Cohen Kadosh, R. (2021). Personalized brain stimulation for effective neurointervention across participants. *PLOS Computational Biology*, *17*(9), Article ID: e1008886, pp. 1-24. https://doi.org/10.1371/journal.pcbi.1008886

van Schouwenburg, M. R., Sligte, I. G., Giffin, M. R., Günther, F., Koster, D., Spronkers, F. S., Vos, A., & Slagter, H. A. (2021). Effects of Midfrontal Brain Stimulation on Sustained Attention. *Journal of Cognitive Enhancement*, *5*(1), pp. 62–72. https://doi.org/10.1007/s41465-020-00179-z

van Veen, S., Vink, P., Franz, M., & Wagner, P.-O. (2020). Enhancing the Vigilance of Car Drivers:a Review on Fatigue Caused by the Driving Task and Possible Countermeasures. In P. Vink (eds) *Advances in Social and Organizational Factors, 9.* AHFE International Confernce, USA. 12 pages. https://doi.org/10.54941/ahfe100364

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*, Article Number: 952, pp. 1-14. https://doi.org/10.3389/fpsyg.2017.00952

Vosskuhl, J., Strüber, D., & Herrmann, C. S. (2018). Non-invasive Brain Stimulation: A Paradigm Shift in Understanding Brain Oscillations. *Frontiers in Human Neuroscience*, *12*, Article Number: 211, pp. 1-19. https://doi.org/10.3389/fnhum.2018.00211

Ward, N., Hussey, E., Gaspar, J., & Kramer, A. (2017). Distracted driving and high-definition tDCS. *Brain Stimulation*, *10*(4), conference abstract #23, p. e27. https://doi.org/10.1016/j.brs.2017.04.027

Warm, J. S., Parasuraman, R., & Matthews, G. (2008). Vigilance requires hard mental work and is stressful. *Human Factors*, *50*(3), pp. 433–441. https://doi.org/10.1518/001872008X312152

References

Wascher, E., Getzmann, S., & Karthaus, M. (2016). Driver state examination--Treading new paths. *Accident; Analysis and Prevention*, *91*, pp. 157–165. https://doi.org/10.1016/j.aap.2016.02.029

Wei, J., Zhang, Z., Yao, Z., Ming, D., & Zhou, P. (2021). Modulation of Sustained Attention by Theta-tACS over the Lateral and Medial Frontal Cortices. *Neural Plasticity*, *2021*, Article ID: 5573471. 12 pages. https://doi.org/10.1155/2021/5573471

Wessel, M. J., Draaisma, L. R., Boer, A. F. W. de, Park, C.-H., Maceira-Elvira, P., Durand-Ruel, M., Koch, P. J., Morishita, T., & Hummel, F. C. (2020). Cerebellar transcranial alternating current stimulation in the gamma range applied during the acquisition of a novel motor skill. *Scientific Reports*, *10*(1), Article Number: 11217. 12 pages. https://doi.org/10.1038/s41598-020-68028-9

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

Wu, L., Liu, T., & Wang, J. (2021). Improving the Effect of Transcranial Alternating Current Stimulation (tACS): A Systematic Review. *Frontiers in Human Neuroscience*, *15*, Article Number: 652393, pp. 1-16. https://doi.org/10.3389/fnhum.2021.652393

Yamaguchi, T., Svane, C., Forman, C. R., Beck, M. M., Geertsen, S. S., Lundbye-Jensen, J., & Nielsen, J. B. (2020). Transcranial Alternating Current Stimulation of the Primary Motor Cortex after Skill Acquisition Improves Motor Memory Retention in Humans: A Double-Blinded Sham-Controlled Study. *Cerebral Cortex Communications*, *1*(1), Article ID: tgaa047, pp. 1-11. https://doi.org/10.1093/texcom/tgaa047

Zanto, T. P., Jones, K. T., Ostrand, A. E., Hsu, W.-Y., Campusano, R., & Gazzaley, A. (2021). Individual differences in neuroanatomy and neurophysiology predict effects of transcranial alternating current stimulation. *Brain Stimulation*, *14*(5), pp. 1317–1329. https://doi.org/10.1016/j.brs.2021.08.017

Zhu, X., Ren, Y., Tan, S., & Ma, X. (2023). Efficacy of transcranial alternating current stimulation in treating chronic insomnia and the impact of age on its effectiveness: A multisite randomized, double-blind, parallel-group, placebo-controlled study. *Journal of Psychiatric Research*, *170*, pp. 253–261. https://doi.org/10.1016/j.jpsychires.2023.12.037

Declaration

I have completed the work independently and used only the indicated facilities. This dissertation is my own work. All the sources of information have been acknowledged by means of complete references. The dissertation as a whole or in parts has not been submitted to assessment in a doctoral procedure at another university. This dissertation has neither as a whole nor as a part been published apart from those parts where this is explicitly indicated. I am aware of the guidelines of good scientific practice of the Carl von Ossietzky University Oldenburg and I observed them when preparing this dissertation. I confirm that I have not availed myself of any commercial placement or consulting services in connection with my promotion procedure.

_____

Birte Sofie Löffler

Bremen, 25 January 2024

CV

Birte S. Löffler (M.A.)

Research interests

human-machine interaction, psychology, neurophysiology, biomimetics, medical technology, engineering design

Academic career

Throughout assistance in teaching, supervision of students´ work and guidance in practical courses and seminars

05/2021 – 12/2023
Scientific research assistant, Study program Biomimetics & Biomimetics Innovation Center (B-I-C), City University of Applied Sciences, Germany
Public Relations

02/2015 – 10/2018
Scientific research assistant / CSE scholar in subproject "the car that cares", Division of Systems in Medical Engineering, University Oldenburg
Research area: Potential of transcranial alternating current stimulation for applied contexts (basis for PhD)

11/2013 – 12/2014
Scientific research assistant in "TAAndem-Project", Human-Machine Systems Engineering Group, University of Kassel, Germany
Research area: Development of a further education for people working in the context of AAL (Ambient Assisted Living), E-Learning, Age-simulation suits and gait analysis

05/2008 – 11/2008
Scientific research assistant, Study program Biomimetics, City University of Applied Sciences Bremen, Germany
Research area: Role models from nature as inspiration for non-toxic antifouling strategies

Education

10/2008 - 07/2013
Master program „Engineering Design", University of Applied Sciences Magdeburg-Stendal
05/2012-10/2012 Master-Thesis at Ovesco Endoscopy AG, Tübingen, Germany:
Thesis: Design of a biomimetic capsule for colonoscopy

10/2004 – 03/2008
International Degree Program in Biomimetics (B.Sc.), University of Applied Sciences Bremen, Germany
07/2013-10/2013 Bachelor-Thesis at Max-Planck-Institute for Marine Biology, Bremen, Germany:
Thesis: The nitric oxide metabolism of bio-films in respect to their possible usage as role models for efficient energy harvesting
09/2006 – 01/2007
Internship Vision Touch and Hearing Research Centre in Brisbane, Australia:
Research area: Color vision of reef fish & the capability of stomatopods to see circular polarized light as inspiration for the enhancement of remote sensing technologies

09/2001 – 08/2004
Study program Jewellery – Linking Bodies, Gerrit Rietveld Academie, Amsterdam, The Netherlands

CV

Publications in Peer-reviewed Journals

Löffler, B. S.; Stecher, H. I.; Fudickar, S.; de Sordi, D. de; Otto-Sobotka, F.; Hein, A.; Herrmann, C. (2018): Counteracting the Slowdown of Reaction Times in a Vigilance Experiment With 40-Hz Transcranial Alternating Current Stimulation. *IEEE transactions on neural systems and rehabilitation 26* (10), pp. 2053–2061. https://doi.org/10.1109/tnsre.2018.2869471

Löffler, B. S.; Stecher, H. I.; Meiser, A.; Fudickar, S.; Hein, A.; Herrmann, C. S. (2023): Attempting to counteract vigilance decrement in older adults with brain stimulation. *Front. Neuroergonomics 4*, Article 1201702. https://doi.org/10.3389/fnrgo.2023.1201702.

Volkening, N.; Unni, A., Löffler, B. S.; Fudickar, S.; Rieger, J.W.; Hein, A. (2016): Characterizing the Influence of Muscle Activity in fNIRS Brain Activation Measurements. *IFAC-PapersOnLine 49* (11), pp. 084–088. https://doi.org/10.1016/j.ifacol.2016.08.013

Schreiber, F.; Loeffler, B.; Polerecky, L.; Kuypers, M. MM; de Beer, D. (2009): Mechanisms of transient nitric oxide and nitrous oxide production in a complex biofilm. *The ISME Journal 3,* pp. 1301–1313. https://doi.org/10.1038/ismej.2009.55

Chiou, T.-H-; Kleinlogel, S.; Cronin, T.; Caldwell, R.; Loeffler, B.; Siddiqi, A.; Goldizen, A.; Marshall, J. (2008): Circular Polarization Vision in a Stomatopod Crustacean. *Current Biology* 18, pp. 429–434. https://doi.org/10.1016/j.cub.2008.02.066

Conference contributions

Loeffler, B. S., Fudickar, S., Herrmann, C. S., Hein, A. (2016): Ein Blick in das Gehirn: Messung und Verbesserung der Fahrleistung älterer Autofahrender mit Hilfe von Neuroimaging und Elektrostimulation. In Wienrich, C.; Zander, T. O.; Gramann, K. (eds.*): Trends in Neuroergonomics. Proceedings of the 11th Berliner Workshop of Human-Machine Systems, Berlin, Germany, October 7-9, 2015*. Universitätsverlag der TU Berlin, Berlin, ISBN 978-3-7983-2803-7 (online), pp. 166 – 169

Heußner, M., Löffler, B., Schmidt, L. (2016): Design and Implementation of a Concept for Two-Way Exchange and Network Building of Professionals from Different Working Fields Within the Context of AAL. In: Wichert, R., Klausing, H. (eds) *Ambient Assisted Living. Advanced Technologies and Societal Change*. Springer, Cham, pp. 111-122. https://doi.org/10.1007/978-3-319-26345-8_10

Löffler, B.; Heußner, M.; Radziwill, M.; Schmidt, L. (2015): Weiterentwicklung eines E-Learning-Angebots für eine Weiterbildung von Berufstätigen aus dem sozialen und technischen Bereich unter Berücksichtigung von Spielmechaniken. In Verband der Elektrotechnik Elektronik Informationstechnik e. V. (eds.): *Technologie und Vernetzung für Gesundheit, Selbstständigkeit und Komfort: 8th AAL-Kongress, Frankfurt, Germany, April 29-30, 2015*. VDE-Verlag, Berlin, pp. 286–291. https://www.vde-verlag.de/proceedings-de/453901048.html, last accessed 2024-01-25

Heußner, M.; Loeffler, B. S.;Schmidt, L (2015): AAL-Weiterbildung für Pflege und Handwerk: Ergebnisse des ersten Pilotdurchlaufs. In Verband der Elektrotechnik Elektronik Informationstechnik e. V. (eds.): *Technologie und Vernetzung für Gesundheit, Selbstständigkeit und Komfort: 8th AAL-Kongress, Frankfurt, Germany, April 29-30, 2015.* VDE-Verlag, Berlin, 2015, pp. 254–259. https://www.vde-verlag.de/proceedings-de/453901042.html, last accessed 2024-01-25

Heußner, M.; Loeffler, B. S., Schmidt, L. (2015): Untersuchung eines Alterssimulationsanzugs mittels geriatrischer Bewegungstests und Ganganalyse. In Gesellschaft für Arbeitswissenschaft e. V. (eds.): VerANTWORTung für die Arbeit der Zukunft: 61th Kongress der Gesellschaft für Arbeitswissenschaft, Karlsruhe 2015. GfA-Press, Dortmund. pp. 1-6 (B.2.5). https://gfa2015.gesellschaft-fuer-arbeitswissenschaft.de/inhalt/B.2.5.pdf, last accessed 2024-01-25

Löffler, B. S., Schostek, S., Melbert, M., Schurr, M .O. (2015): Optimierung eines Kapselendoskops nach Vorbild des Wasserkäfers: Die Biokapsel. In: Kesel, A. B. (ed.*): Bionik: Patente aus der Natur - Innovations- und Nachhaltigkeitspotenziale für Technologieanwendungen. Proceedings of the 7th congress of Biomimetics; University of Applied Sciences Bremen, Bremen, Germany, October 24-25, 2014*. GTBB e.V. & Bionik-Innovations-Centrum, Saarbrücken / Bremen, pp. 242 – 248

Heußner, M.; Loeffler, B. & Schmidt, L. (2014): Design and Evaluation of a Further Education for Persons Working in AAL Context. *Biomedical Engineering 59* (S1), pp. S422+. https://www.degruyter.com/journal/key/bmte/59/s1/html, last accessed 2014-01-25

Löffler, B. & Schmidt, L. (2014): Potential der Simulation von Einschränkungen mit Hilfe eines Alterssimulationsanzuges für arbeitsplatzgestaltende Maßnahmen in einer älter werdenden Gesellschaft. In Böckelmann, I.; Lorenz, A.; Sammito, S. & Darius, S. (eds.): *Forum Arbeitsphysiologie: 18. Symposium Arbeitsmedizin und Arbeitswissenschaft für Nachwuchswissenschaftler*, Magdeburg, 2014. Otto-von-Guericke-Universität Magdeburg: 2014, pp. 25

CV

Editorial work

Kesel, A. B.; Löffler, B. S. (2023): Bionik: Patente aus der Natur - Innovations- und Nachhaltigkeitspotenziale für Technologieanwendungen. Proceedings of the 10th congress of Biomimetics. *University of Applied Sciences Bremen, Bremen, Germany, May 12-13, 2023*. GTBB e.V. & Bionik-Innovations-Centrum, Saarbrücken / Bremen

Competitions

1. prize: Best scientific poster at the 7th congress of Biomimetics: Gesellschaft für technische Biologie und Bionik e.V. (GTBB), October 24-25, 2014, Bremen, Germany

1. prize: Design of the „Jugend filmt Bionik"-Trophy: future vision gGmbH, German Museum, September 30, 2011, Munich, Germany

Acknowledgements

First, thank you to Prof. Dr.-Ing. Andreas Hein, Prof. Dr.-Ing. Christoph S. Herrmann and Heiko Stecher for your support, long endurance and enabling me to finally finish this project.

Then many thanks in more detail go out to Heiko Stecher for his support in the laboratory, in discussions, in online conferences and home office meetings. You have been a great help! And to Christoph, you have been a great supervisor. And to Prof. Hein for your encouragement to finish this project and your effectiveness and reminding me to be effective.

Thank you also to all colleagues form the Division of Assistance Systems and Medical Device Technology, so many nice people, talks and “Diss-Klausuren”.

Thank you also to Horst-Dieter Selent for believing in me and giving me support.

Thank you to my family and friends, we will all be relieved once this is finished!