The role of influencing factors on the outcome of transcranial alternating current stimulation

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 Herrn Heiko Ivo Stecher

geboren am 02.01.1985 in Bremen

Gutachter: Prof. Dr. Christoph Siegfried Herrmann

Weitere Gutachterin: Prof. Dr. Lisa Marshall

Tag der Disputation: 03.05.2019

Table of Contents

List of Figures

List of Tables

List of Abbrevations

AIC	Akaike Information Criterion
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
DBS	Deep Brain Stimulation
ECOG	Electrocorticogram
EEG	Electroencephalogram
GAMM	Generalized Additive Mixed regression Model
IAF	Individual Alpha Frequency
MEG	Magnetoencephalogram
fMRI	functional Magnetic Resonance Imaging
LTD	Long Term Depression
LTP	Long Term Potentiation
NIBS	Non-Invasive Brain Stimulation
NTBS	Non-invasive transcranial brain stimulation
SSEP	Steady State evoked Potential
STDP	Spike-Timing Dependent Plasticity
tACS	transcranial Alternating Current Stimulation
tDCS	transcranial dicect current stimualtion

Outline

The functional role of oscillatory electric activity in the brain has been the subject of debate since its first discovery. The use of different recording methods has shown a connection between changes in rhythmic activity and cognitive functioning. These observations could only reveal correlative links, not a causal relationship. The emergence of brain stimulation techniques has opened the way for intervention approaches, in which brain activity is modulated and the behavioral outcome measured. Transcranial alternating current stimulation (tACS) is one of these techniques that is seeing widespread use, as it is noninvasive and frequency-specific. Especially the alpha(α)-band, a dominant rhythm of electric brain activity, has been the subject of many studies to explore the capabilities of tACS. Past studies have shown that tACS, when frequency-tuned to the endogenous alpha frequency, can cause sustained power increases after the stimulation has ended. The occurrence of these aftereffect is, however, not universal. A deeper understanding under which conditions this aftereffect appears is important for the further use of tACS as a tool in research and therapy. This dissertation aims to explore how environmental factors and stimulation parameters affect the occurrence of post-stimulation aftereffects in the α-band.

The first chapter covers the basics of rhythmic brain activity and its measurement via electroencephalography (EEG), and gives an overview over known functional links between cognitive functions and specific brain rhythms. Further, it introduces the established techniques of non-invasive brain stimulation, and provides a review on the suspected principle by which tACS influences neuronal activity. It concludes with a presentation of established literature and derives open questions regarding different factors that influence the occurrence of aftereffects. The second chapter contains a peer-reviewed study exploring the role of ambient illumination on the progression of α-power and the aftereffects of α-tACS during a visual vigilance task. Chapter 3 covers a peer-reviewed study on the aftereffect of α-tACS, following four blocks of stimulation of different lengths. The fourth chapter summarizes the results of both studies and discusses the implications of the findings for future studies.

Chapter 1

General Introduction

Oscillatory electric activity of the brain has been one of the first features to be discovered within the human EEG. While at first thought to be only an epiphenomenon of the brain's electrical activity, years of research have shown a close link between behavior and certain changes of brain oscillations. It has often been debated whether this link is merely of correlative nature or if it represents a causal relationship, thereby implying a functional role of brain oscillations for behavioral processes. The emergence of brain stimulation methods facilitates the investigation of this issue. By the deliberate manipulation of brain oscillations, while measuring the behavioral and physiological outcome, the functional role of these oscillations can be uncovered. This manipulation can be achieved by using rhythmic brain stimulation methods like transcranial alternating current stimulation (tACS). Apart from effects that occur during the stimulation, many studies have also shown lasting physiological effects, which can be tracked in the EEG. The observation of physiological effects during the stimulation is difficult due to the severe artifacts introduced by the stimulation. Therefore, the lasting changes are of particular interest to gain an understanding of the processes that take place during the stimulation in the underlying neural networks. Moreover, understanding and inducing persistent effects is a prerequisite for clinical approaches that aim at the treatment of ailments, characterized by abnormal brain activity. While many studies successfully showed aftereffects of stimulation in the EEG, it is unclear which parameters lead to their occurrence. Rhythmical electrical stimulation in the α-band has repeatedly been shown to produce a lasting increase in the band power of the stimulated frequency. The employed ranges of stimulation duration, stimulation amplitude and cognitive tasks, were however quite narrow. The influence of the stimulation's duration and the dependency of the mental state on the formation of a stable aftereffect are sparsely explored. Changes in alpha activity, in particular are prone to many environmental factors. The understanding how these factors influence the outcome of the

stimulation are crucial for the mastery of the method of rhythmic stimulation in the exploration of brain oscillations. In the following, brain rhythms shall be introduced regarding their origin, their features and their presumed role. Based on that, a short overview on their exploration using stimulation-based intervention methods is given. Subsequently, open issues with tACS as a tool for research are pointed out and how they are addressed in the presented studies.

1.1 Brain oscillations in the EEG

The most common and cost efficient method to measure oscillatory brain activity is the EEG. It was first studied in humans by Hans Berger (Berger, 1929). He also offered the first description of oscillatory activity, later coined alpha and beta rhythms, and its changes, dependent on behavior (Berger, 1929; Niedermeyer and Silva, 2004). The EEG records brain activity by employing a differential amplifier to amplify the voltage between a scalp electrode and a neutral reference electrode from which the voltage difference between the reference electrode and a ground electrode is subtracted (Luck, 2005). This ensures that the electric potential caused by brain activity near the scalp electrode can be measured against the potential at a neutral reference site, without interference from ambient electrical activity (Luck, 2005; Nunez and Srinivasan, 2006). The signal of the EEG is mainly composed of the activity of post synaptic potentials of pyramidal cells in the neocortex (Luck, 2005). The activity picked up by a single electrode represent synaptic activity in the range of millions of neurons (Nunez and Srinivasan, 2006).

While an EEG has the disadvantage of a poor spatial resolution of around 10 cm^2 per electrode (Buzsáki et al., 2012), it is far less expensive than other methods of measuring brain activity like functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) and it is not invasive in contrast to Electrocorticography (ECoG) or deep probes. In order to gain information on brain functions from a recording, it is necessary to understand that the voltages at a certain location is a summation of the electric field of different dipoles within the brain (Buzsáki et al., 2012). These dipoles are generated by synchronous activity of pyramidal neurons in a column within the cortex (Jackson and Bolger, 2014). The excitation of a postsynaptic neuron causes a voltage difference between dendrites and the rest of the neuron. This causes a dipole that can be measured at a scalp electrode if the neuronal column is aligned tangential towards it. The voltage deflection at a particular location, however, represent a superposition of all currents within the brain, attenuated and distorted by the different types of tissues within the head (Buzsáki et al., 2012). In order to determine which brain region constitutes the origin of a measured sig-

nal, it is necessary to solve the so-called inverse problem (Grech et al., 2008). Following the solving of the forward problem – given the known tissue conductance of the individual anatomy, which is the scalp voltage distribution resulting from a theoretical dipole inside the brain – the inverse problem is solved to calculate the probable position of a dipole from a given voltage distribution. Different approaches for this source reconstruction employ the use of dipole fitting or spatial filtering methods like beamformers, dependent on whether single or distributed sources are required (Grech et al., 2008). Even with the dipole localized, the information regarding the functional neural circuits remain unknown and assertions towards their functionality should be made with caution (Cohen, 2017).

One apparent feature in the EEG are event related potentials (ERP). They consist of slow characteristic deflections, following discrete events (Luck, 2005), like the appearance of a visual stimulus. But apart from those restricted slow potentials, there is also a multitude of different electrical rhythms within the human EEG, either continuous or evoked and short lasting. Oscillatory properties can already be found in isolated thalamic (Steriade et al., 1993; Steriade and Deschenes, 1984), hippocampal (Buzsáki, 2002; Marshall et al., 2002) and neocortical (Silva et al., 1991) neurons. On a large scale oscillatory activity in the brain can emerge from a number of different mechanisms like recurrent networks of inhibitory and excitatory neurons, pacemaker cells, resonance and membrane oscillations (Pevzner et al., 2016; Steriade et al., 1990; Wang, 2010). The amplitudes of the existing rhythms generally follow a 1/f-spectrum (Penttonen and Buzsáki, 2003; Singer, 1993). It has long been argued, that these oscillations might offer a self-generated temporal code, by which neuron populations in widely separated sites might synchronize their activity in order to bind feature encoding activity (Singer, 1993; Fries, 2005). In this concept, fast oscillations synchronize a small, local population of neurons, while slow oscillations with high amplitudes can recruit spatially distributed neurons in distant brain areas (Buzsáki and Draguhn, 2004; Penttonen and Buzsáki, 2003). Even in the absence of direct synaptic connections, the strong fields generated by synchronized activity of a large population of neurons, may influence the behavior of neighboring neurons by ephaptic effects (Buzsáki et al., 2012).

The most dominant rhythms have been named in the sequence of their discovery using Greek letters and are usually defined as the α-rhythm ranging from 8-13 Hz, the β-rhythm ranging from 14-40 Hz, the γ-rhythm denoting frequencies above 40 Hz, the slow δ-rhythm in the range of below 4 Hz and the θ-rhythm ranging from 4-8 Hz (Noachtar et al., 1999). The definition of the exact borders might differ (cf. with Nunez and Srinivasan, 2006) and represent a rather arbitrary division (Buzsáki, 2006), irrespective of functional differences across different species. The different rhythms have all been associated with certain cognitive

functions (Başar et al., 1999, 2001; Buzsáki, 2006; Herrmann et al., 2016a; Ward, 2003). In the following, the major brain rhythms and their functional connection are shortly introduced:

The most distinct oscillations in the EEG is the alpha rhythm in posterior brain areas. It was originally considered to be an idling rhythm, representing deactivated cortical areas (Pfurtscheller et al., 1996a). Today, it is known that it is also closely associated with visual processing (Busch et al., 2009; Ergenoglu et al., 2004; Hanslmayr et al., 2005; Iemi et al., 2017), attention (Sauseng et al., 2005) and short term memory (Palva and Palva, 2007; Jensen, 2002). Generally, alpha is assumed to play a controlling role in cortical processing by inhibiting task-irrelevant regions of the brain (Jensen and Mazaheri, 2010; Klimesch et al., 2007). A similar rhythm in the same frequency range can be found in the sensorimotor areas of the brain, which is generally denoted mu, rolandic or wicked-rhythm (Chatrian et al., 1959). It is characterized by being blocked (desynchronized) at the onset of planned or reflexive movement or even during imagined movements (Pfurtscheller et al., 2006). As with the posterior alpha, the occurrence of the mu-rhythm is thought to reflect an inhibition of the respective areas, when attention is directed somewhere else (Salmelin et al., 1995).

The beta rhythm, analog to the rolandic mu-rhythm, can be found in precentral areas and shows blocking by movement onset. The mu-rhythm's arch-like shape (Pfurtscheller, 1981) causes a harmonic frequency in the beta range, so one might assume that beta is no individual rhythm. But a component of the beta rhythm can be distinguished from the harmonic activity by its more anterior topography and its faster rebound to synchronization after movement (Pfurtscheller et al., 1997), proving that it is indeed an independent brain rhythm. Early theories suspected an idling of motor areas (Pfurtscheller et al., 1996b), similar to early presumptions about alpha. Beta oscillations show a high coherence to the contralateral EMG of muscle oscillations as well as coherent activity between motor and somatosensory regions, suggesting a role in integrating proprioceptive feedback in order to recalibrate the movement system (Baker, 2007). A current theory suggests that beta activation represents the signaling of a status quo within the sensorimotor system, while an expected change of the state causes a lower beta coupling (Engel and Fries, 2010). Within the perceptual system, beta desynchronization can be seen in response to visual stimuli, when a motoric response needs to be prepared, while the withholding of the response causes a fast rebound (Zhang et al., 2008). More recent studies also explore a possible role of the beta band as base for time estimation (Kononowicz and van Wassenhove, 2016; Wiener et al., 2018) and a role of beta-desynchronization during episodic memory formation(Hanslmayr et al., 2016).

The gamma band has been thoroughly studied in the context of perceptual binding, originally in the

cortex of animals (Eckhorn et al., 1988; Gray and Singer, 1989). The local high frequency oscillations are thought to provide a mode, by which neuronal populations in early sensory areas can encode responses for integration in later areas (Fries, 2009; Singer and Gray, 1995). In this concept, the perceptual features of distributed cells which require grouping in later areas are not bound by convergence (summation of axonal connections in one target cell) but by dynamic binding due to synchronized activity (Singer, 1999). In recent years, a multitude of studies has linked gamma activity to a variety of cognitive functions such as attention (Hanslmayr et al., 2007; Herrmann and Knight, 2001; Womelsdorf et al., 2007) and memory (Herrmann et al., 2004; Palva et al., 2005).

The slow delta waves are mainly associated with deep sleep (Steriade et al., 1990) and the developing brain (Knyazev, 2012), but there is also evidence for an involvement in cognitive functions (Başar et al., 2001). An increase in delta power is found during cognitive tasks that require concentration, like short term memory, mental calculation and semantic tasks (Harmony, 2013). Other studies found a delta response in the oddball paradigm suggesting a connection to decision-making and signal matching (Başar-Eroglu et al., 1992). One interpretation of the delta wave is that of an evolutionary old function, involved in reward and defense behavior (Knyazev, 2012).

The theta band is a slow rhythm that dominates the activity in the hippocampus (Steriade et al., 1990), originating possibly within the medial septum (Colgin, 2013). Its function seems to be closely associated with memory and learning processes (Kahana et al., 2001). Theta synchronization can be observed in the encoding of new information (Klimesch, 1999), the process of navigation (Ekstrom et al., 2005) and directed attention (Missonnier et al., 2006). Theta seems to be heavily involved in the induction of long term potentiation (LTP) (Larson et al., 1986), thereby providing the timing necessary for synaptic changes during learning (Colgin, 2013; Klimesch, 1999).

As the variety of links between frequencies and different functions show, it is not reasonable to suggest a one on one correspondence between a single function and a singular activity band (Herrmann et al., 2016b). Many functions arise from an interplay of activities of different frequencies, to name a few examples: The top down process of attention seems particularly controlled by a reciprocal interaction between gamma and alpha, where high alpha synchronization suppresses gamma activity in non-attended areas (Jensen and Mazaheri, 2010). Visual perception is involved with a low amount of alpha synchronization, but high phase coupling within the beta and gamma band (Hanslmayr et al., 2007). Mental arithmetic enhances phase synchronization among the alpha, beta and gamma band (Palva et al., 2005). Within

the short term memory, performance seems to be determined by the nature of the theta-gamma coupling (Lisman and Jensen, 2013). Such interactions between different frequencies can take different forms like phase-amplitude, phase-phase, phase-frequency or amplitude-amplitude couplings (Canolty and Knight, 2010; Osipova et al., 2008; Palva et al., 2005). One current notion is that cognition emerges from neural circuits with specific frequencies acting on the individual neuronal levels and on long-range connections (Siegel et al., 2012; von Stein and Sarnthein, 2000; Ward, 2003).

Many of the associations of oscillations with cognitive functions were drawn from fundamental brain research. There is also a broad range of clinical research, where different neuropsychiatric disorders have been linked to abnormal brain oscillations (Başar and Güntekin, 2008; Uhlhaas and Singer, 2006, 2012). Disorders which involve failed modulation of attention and working memory, like schizophrenia and attention deficit hyperactivity disorder (ADHD) show atypical gamma and alpha band activity. Schizophrenia is also characterized by overall low alpha-power (Sponheim et al., 2000), decreased evoked gamma activity in negative symptoms and increased gamma activity during positive symptoms (Herrmann and Demiralp, 2005). Patients with ADHD show a pronounced alpha asymmetry (Hale et al., 2009) and increased gamma band responses in auditory attention (Yordanova et al., 2001) and visual memory tasks (Lenz et al., 2008). Alzheimer's patients show decreased evoked coherence in the alpha and beta bands (Schnitzler and Gross, 2005) as well as an overall higher level of delta activity (Hier et al., 1991). In movement disorders like Parkinson's disease, activity in the beta-range often shows an irregular behavior (Schnitzler and Gross, 2005). Furthermore, there is evidence that mood disorders like bipolar disorders (Özerdem et al., 2008) or major depression (Fingelkurts et al., 2006) involve abnormal oscillatory activity. These clinical findings support the link between cognitive functions and brain oscillations and suggest a possible therapeutic approach based on the alteration of endogenous oscillations (Antal and Paulus, 2013; Thut et al., 2012).

The links between brain oscillations and cognitive functions introduced thus far stem from passive observation. The coincidence of rhythmic brain activity and function can only prove a correlation and does not imply a causal relationship with certain observed behavior. The oscillatory activity might simply be a byproduct of a hitherto unknown process or the function itself. The proof that a cognitive function arises from a certain oscillatory activity requires the implementation of an intervention study. In an intervention study, one variable is manipulated (the independent variable, here the brain oscillation) and the outcome on another variable (the depend variable, here the cognitive function) measured (Thut et al., 2012; Bergmann et al., 2016; Herrmann et al., 2016a). A causal link between the independent and the dependent variable

can be established by such an approach. This requires a method of direct, target-specific interference with ongoing brain oscillations.

1.2 Noninvasive brain stimulation

The targeted manipulation of brainwaves can be achieved by a variety of methods. The most direct approaches, like deep brain stimulation (DBS) (Perlmutter and Mink, 2006), are invasive and involve breaking the skin-barrier. Such invasive methods obviously require well-considered surgery, which naturally limits the applicability as a tool for fundamental research and ordinary therapy. A different apparent approach would be pharmacological interventions. However, pharmacological agents, while less invasive than surgery, have mostly widespread physiological consequences and partially unknown side effects. It is rather unlikely that their actions can be limited to a specific neural circuitry or neurons of a specific activity band. This renders the pharmacological approach unsuitable for intervention studies on very specific brain oscillations. Another approach is the rhythmic sensory stimulation (Herrmann et al., 2016a). The rhythmic presentation of a sensory stimulus, e.g. a short flash of light, elicits a response in the brain activity called a steady state evoked potential (SSEP). In the visual domain, it could be shown that visual flicker stimulation causes resonance in certain neural oscillators (Herrmann and Knight, 2001). Recently, it was shown that endogenous brain oscillations like the posterior alpha rhythm can be successfully entrained (i.e.: made synchronous to external rhythm) by visual flicker stimulation (Notbohm et al., 2016). Similar phenomena exist in the auditory domain (Picton et al., 2003) and in somatosensory perception (Vlaar et al., 2015). Rhythmic sensory stimulation is, however, inherently limited to sensory cortices of the brain, and the stimulation passes through different levels of pre-processing (Thut et al., 2011b).

The most novel and promising approaches are combined under the term ‘non-invasive transracial brain stimulation’ (NTBS) (Bergmann et al., 2016) and encompass the methods of transcranial magnetic stimulation (TMS) and transcranial current stimulation (TCS). Both methods have decisive advantages over the other approaches: They are rather inexpensive and non-invasive, offer good targeting of distinctive brain areas, drive neurons actively and can be shaped by variety of desired waveforms (Herrmann et al., 2016a; Paulus et al., 2013; Thut et al., 2011b).

TMS

Pioneering work was conducted by Merton and Morton (1980) who used high-voltage stimulation of the brain to provoke muscle switches and phosphenes. This approach of transcranial electric stimulation (TES), however proved to be quite painful and is nowadays seldom used in awake participants, though it still finds it use in clinical settings (Paulus et al., 2013). In order to find a pain-free methods to achieve brain stimulation, Barker et al. (1985) conceived the method of TMS in 1985. In TMS a current in one or more coils close to the scalp creates a strong magnetic field (2-3 Tesla), which in turn induces a current flow in the brain tissue, depolarizing neuronal membranes and causing action potentials (Ilmoniemi et al., 1999). The voltage in the coil usually has a monophasic or biphasic sinusoidal shape and lasts for about 100 μs (Hallett, 2007). Multiple pulses can be delivered in high succession to achieve a rhythmic stimulation. Such a rhythmic stimulation has been shown to successfully entrain ongoing α-oscillations (Thut et al., 2011b) as well as modulate cognitive functions like perception (Romei et al., 2010) and memory (Sauseng et al., 2009).

TCS

In TCS an electric current is directly applied to the scalp via at least two electrodes, either in the shape of sponges soaked in saline solution, carbonized rubber electrodes fixed to the scalp using conductive paste or Ag/AgCl-electrodes, filled with electrolyte gel (Antal et al., 2017). In contrast to the aforementioned clinical TES (Merton and Morton, 1980), the voltages are considered sub-threshold, meaning the induced current in the neuronal tissue is below the threshold necessary to provoke an action potential (Bikson et al., 2006; Paulus et al., 2013). Usually a current of $\sim$ 1-2 mA is applied, but most of it is shunted through the skin, resulting in an effective voltage gradient in the range of 0.2-0.5 V/m at the neuronal layer (Antal and Herrmann, 2016).The low strength of the electric field is believed to affect neuronal firing by modulation of the membrane potential of neurons, thereby changing its processing of synaptic input as well as changing the synaptic plasticity (Bikson et al., 2006). TCS includes the methods of transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and transcranial alternating current stimulation (tACS) (seldom, oscillatory tDCS (otDCS)). In tDCS, a static electric field is applied between anode and cathode. This has generally been shown to lead to excitation below the anode and inhibition below the cathode (Nitsche and Paulus, 2001), enabling the specific manipulation of activity in cortical areas. tDCS has now become a widely established method for research and therapeutic applications (Nitsche

et al., 2008). tACS and tRNS represent more novel methods, but work on similar principles. In their cases the applied electric field is alternating, i.e. the location of the anode and cathode changes over time. In the case of tACS, the underlying current is usually sinusoidal (albeit other waveforms are possible see e.g. (Dowsett and Herrmann, 2016; Marshall et al., 2006), whereas in tRNS, the intensity and frequency follows a random white noise spectrum (Antal and Herrmann, 2016). The effect of tACS effect on brain activity seems to be based on the coherent alignment of spike timing of neurons within the induced electric field, thereby shifting dynamic network activity towards the frequency of the stimulation. This effect has been repeatedly demonstrated in modelling approaches and in in-vivo and in-vitro animal studies (Ali et al., 2013; Fröhlich et al., 2010; Ozen et al., 2010; Reato et al., 2010). For tRNS, the mechanism is less clear as the skull actually acts as a low-pass filter for the high-frequency-proportion of the stimulation signal, but it has been suggested, that the added noise might sporadically enhance sub-threshold activity by stochastic resonance (Antal and Herrmann, 2016; Moss et al., 2004).

The successful application of all NTBS-methods requires a precise targeting of the relevant brain areas. The magnetic field of TMS undergoes few distortions by the individual anatomy of the scalp (Zhi-De Deng et al., 2009), but modelling studies have shown that heterogeneity and anisotropy of the brain tissue can still effect the current distribution (Miranda et al., 2003). For TCS the differences in conductivity of the different head compartments greatly influence the applied electric field (Miranda et al., 2006). Similar to the inverse problem in EEG source analysis, a preferably precise head model is necessary to calculate the amount and direction of current that is created by a certain stimulation protocol. The optimal electrode montage for the stimulation of a targeted brain region can be calculated by using multi-compartment finite element models. This can even be done for a single individual if anatomical MRI-data is available (Neuling et al., 2012b). In order to further optimize the focality of an effect, a multitude of electrodes with individual voltages and locations can be used, an approach which is usually coined HD (High Definition)-TCS (Dmochowski et al., 2011; Kuo et al., 2013).

The exploration of the functional role of a specific brain region requires a method, which effects can be targeted at a specific frequency (Thut et al., 2011a). Of the introduced NTBS-methods, only rTMS and tACS fulfill this criterion. RTMS has the advantage of a high focality and is less influenced by individual anatomical differences, like skull thickness and skin conductivity, but it requires expensive equipment with high power consumption and is rather limited in the available shapes of applied waveforms (Paulus et al.,

2013). Particularly problematic however is the fact that the pulses' shapes span a very wide range of frequencies (Herrmann et al., 2016a), thereby influencing not only the targeted frequency but a multitude of brain rhythms. The effects of tACS, in contrast, can be limited to a single frequency and its (sub-)harmonics, if a sinusoidal waveform is applied. This makes the method of tACS the prime candidate for the further research on brain oscillations. In order to understand how rhythmic stimulation is able to alter ongoing oscillations in their frequency, phase or amplitude, it is necessary to give a more profound introduction into the assumed underlying mechanism. The most plausible mode of action by which rhythmic stimulation is able to modulate a brain oscillation is generally believed to be entrainment (Herrmann et al., 2016a; Thut et al., 2011a). In physics, entrainment is the term used to describe the phenomenon of synchronization between two oscillators of similar frequency when coupled (see Pikovsky et al., 2002, for a general introduction of the concept). This coupling enables them to exchange a small amount of their force, which can act decelerating or accelerating dependent on the phase-difference between the systems until synchronization is reached. When the coupling is unidirectional, as is the case with tACS, the system can be simplified to one driving oscillator with fixed frequency and one driven oscillator with its own eigenfrequency, which can be entrained by the driver, under the right circumstances. In this case, synchronization is dependent on the proximity of the driver's frequency to the eigenfrequency and the driving force, as specified by the strength of the driver and the coupling strength. If the driver's frequency deviates too far from the eigenfrequency, a strong driving force is necessary to synchronize the driven oscillator to the driver's frequency, while a minimal amount of force is required if the frequencies match. Within a space of frequency-deviation and driving strength, this region of synchronization is called the Arnold tongue (see Figure 1.1 A). In the case of tACS, the applied electric field constitutes the external driver that influences an endogenous brain rhythm (the driven oscillator) via a mode of weak coupling (see Figure 1.1 B). Assuming that tACS has a rather weak driving force, the endogenous brain rhythm will synchronize to the frequency of tACS, if the driving frequency is within the region of synchronization around the eigenfrequency of the brain rhythm (Figure 1.1 C). This implies that a successful tACS-based intervention of brain activity needs to be very close to the brain-frequency of interest (or its harmonics).

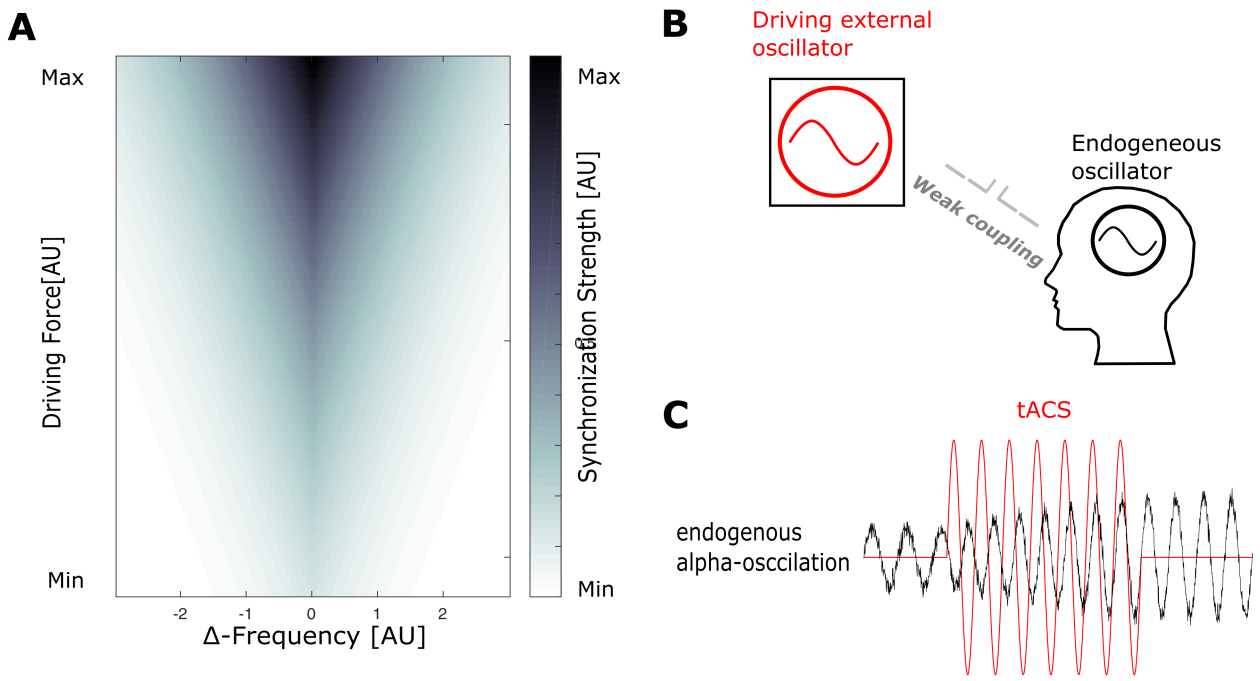

Figure 1.1: Entrainment of brain oscillations (A) An Arnold Tongue: a theoretical region of synchronization where a driven oscillator synchronizes to a driving oscillator. The x-axis denotes the deviation between the driving frequency and the eigenfrequency of the driven oscillator. The y-axis depicts the force the drivers exerts on the driven oscillator. The shaded triangular area depicts the region of synchronization between driver and driven oscillator. For a single driven oscillator this would be binary (sync. or not sync.), but in the case of neuronal oscillations the amount of neurons that are synchronized to the driver can vary. Not shown are additional tongues at harmonic frequencies of the eigenfrequency. **(B)** tACS constitutes a strong driving external oscillator, which drives a specific brain rhythm, an endogenous oscillator, by weak coupling. **(C)** A population of neurons follows a self-sustained oscillation, the synchronous activity creates a local field potential, measurable in the EEG as an alpha-oscillation. During tACS the neurons shift their activity towards the rhythm of the external driving frequency. As more neurons synchronize to the new frequency the overall amplitude in the EEG increases.

TACS as a tool for the alteration of endogenous brain rhythms in their phase, amplitude or frequency has been successfully used by a multitude of studies. The role of amplitude was demonstrated in the α-band for visual detection (Brignani et al., 2013) and mental rotation performance (Kasten et al., 2018; Kasten and Herrmann, 2017) and in the β-band for motor functions (Feurra et al., 2011b; Pogosyan et al., 2009). Phase-dependency of cognitive functions were shown for the θ-band in a delayed discrimination task (Polanía et al., 2012), in the α-band for auditory detection (Neuling et al., 2012a) and in the γ-band for ambiguous motion perception (Helfrich et al., 2014a). The relevance of frequency was explored for short-term memory using tACS-based θ-down regulation (Vosskuhl et al., 2015) and for auditory temporal resolution using γ-manipulation (Baltus et al., 2018). Additionally, the role of phase-dependent theta-gamma-coupling could recently been demonstrated for the spatial working memory by employing a cross-frequency tACS-protocol (Alekseichuk et al., 2016). While all these behavioral findings strongly

support the presumption of a functional role of brain oscillations, they alone are not sufficient to prove their causal relevance for cognitive functions, as they lack evidence that indeed electrophysiological activity was altered in the presumed way (Herrmann et al., 2013). Therefore, it is necessary to explore the physiological changes caused by tACS. This however is quite difficult, due to the large electrical artifact that the stimulation introduces to all recorded data (Herrmann and Strüber, 2017). In some cases, the artifact can be averted by analyzing brain rhythms that are sufficiently far away from the stimulation frequency (Helfrich et al., 2014a, 2016), but this obviously represents a rather limited application. Other approaches use template subtraction (Helfrich et al., 2014b) or beamforming approaches (Neuling et al., 2015; Ruhnau et al., 2016) in an attempt to suppress the artifact and recover physiological effects within the data. These approaches, however, remain problematic, due to the stimulation artifact contaminating the data (Kasten et al., 2018; Mäkelä et al., 2017; Noury et al., 2016).

The majority of the studies introduced so far explored the *online*-effects of tACS, meaning they measured alterations in cognitive functions during the tACS-intervention. However, many studies have shown that the tACS can also induce *offline* or *after-effects*, outlasting the stimulation (see Veniero et al., 2015, for an elaborate overview). These aftereffects have been found in different bands, resulting from different stimulation protocols. Short lived-physiological effects have been found after as little as 5 min of tACS (Garside et al., 2014) in the δ-band. For longer stimulation durations, lasting effects of up to 70 minutes in the α-band (Kasten et al., 2016) or even up to hours in the slow-wave range (Reato et al., 2013) were found. Apart from these physiological changes, also lasting behavioral modulations could be shown (Kasten and Herrmann, 2017). The origin of these aftereffects is not fully understood. It has been demonstrated by Vossen et al. (2015) that they are not a manifestation of entrainment echoes. Although there is an argument that lasting effects might arise due to specific network states (Alagapan et al., 2016), the prevalent notion sees them as an effect of spike timing dependent plasticity (STDP) (Vossen et al., 2015; Zaehle et al., 2010). Entrained spiking during stimulation leads to processes of long term potentiation (LTP) in those synapses that correspond to the entrained frequency, while long term depression weakens synapses that are part of recurrent neuronal loops of different timing. Recently a study study of Wischnewski et al. (2018) could show that aftereffects were abolished, when an NMDAR antagonistic drug was administered. As NMDAR-receptors are the primary receptors that permit plasticity at the synapses (see Chapter 4 for an elaborate overview), these findings strongly support the notion that aftereffects of stimulation are indeed caused by synaptic plasticity.

Aftereffects are of major interest for two reasons: First, as the exploration of online effects of tACS

remains problematic, aftereffects can offer much needed physiological evidence in the exploration of the functional role of brain oscillations. Secondly, the induction of lasting cognitive changes are the main prerequirement in using NTBS for clinical applications where therapeutic long-term effects are desired and indeed first research in therapeutic tACS-based interventions is conducted (Mellin et al., 2018). Therefore, the initial goal is to get a better understanding on the occurrence of aftereffects as a groundwork for further intervention studies.

1.3 Introduction to published articles

Many studies on the aftereffects of tACS were conducted on the α-rhythm. The α-rhythm as a study subject has some defining advantages, which makes it a prime research candidate over the other bands. In an awake relaxed subject, posterior alpha activity is usually spontaneous and continuous and does not need to be evoked by discrete stimuli or cognitive operations (Bazanova and Vernon, 2014), which would add additional dependent variables to an experimental design. This makes the α-band a self-sustained, internal oscillation on which modulation by entrainment can be tested in the absence of other factors. Additionally, the high-power of the α-rhythm makes it easily determinable from the raw-scalp EEG, with a minimal amount of preprocessing. Previous α-tACS studies could show physiological aftereffects in the α-band of the EEG-post stimulation, when participants conducted simple vigilance tasks (Kasten et al., 2016; Neuling et al., 2013, 2015; Vossen et al., 2015; Zaehle et al., 2010), but also when more demanding cognitive tasks were employed (Kasten and Herrmann, 2017). The occurrence of the aftereffect is however inconsistent. Physiological aftereffects of enhanced power following tACS were absent in studies employing short stimulation durations like intermittent trains of 1-s or 3-s (Strüber et al., 2015; Vossen et al., 2015), experimental conditions with high endogenous α-activity like closed eyes (Neuling et al., 2013) or on average low stimulation amplitudes (Kasten et al., 2018). Accordingly, this raises the question, which factors may have an influence on the outcome of stimulation.

From the previous studies, two factors can be derived, which most likely effect the outcome of tACS: the duration of stimulation and the current mental state of a participant. The following studies aim to independently explore the effect of these factors in otherwise established experimental designs, so that in combination they can provide a better explanation as to why an aftereffect of α-tACS might occur in some stimulation protocols while remaining absent in other seemingly comparable approaches. In the following chapters, both studies are presented in the order of conductance. This is done, as the research aim of

the second study was derived from the first studies results. The actual order of publication was however reversed.

The first study, introduced in chapter 2, was published in Frontiers in Psychology as part of the research topic Non-Invasive Brain Stimulation Effects on Cognition and Brain Activity: Positive Lessons from Negative Findings. The study intended to explore the minimal necessary stimulation duration for an aftereffect in the α-band to occur. Most of the aforementioned studies employed comparable stimulation protocols, with $\sim$ 1 mA amplitude and durations ranging from 10 minutes (Zaehle et al., 2010) to 20 minutes (Kasten et al., 2016; Neuling et al., 2013) in continuous blocks and intermittent stimulation (Vossen et al., 2015). Shorter stimulation durations, however, like intermittent 1-s blocks (Strüber et al., 2015) or 3-s blocks (Vossen et al., 2015) yielded no effect. In order to narrow down the range of minimal stimulation-lengths the study employed a sequence of tACS blocks of different durations with intermittent windows of EEG-recording. The vigilance task as well as the stimulation intensity and electrode montage were adapted from previous successful attempts (Kasten et al., 2016; Zaehle et al., 2010). Stimulation durations spanned 1 to 10 minutes, to cover a range that proved effective in tACS-studies of other frequencies (Veniero et al., 2015). The results failed to show an effective stimulation duration below 10 minutes and also failed to replicate earlier findings (Zaehle et al., 2010).

The second study, introduced in chapter 3, was published in Frontiers in Human Neuroscience. Inspired by the results of the first study, it investigates the role of environmental factors by which the first study deviated from established protocols. Spontaneous α-activity is greatly modulated by the illumination that a participants experiences (Min et al., 2013), as are lasting changes in activity (Cram et al., 1977; Paskewitz and Orne, 1973). As previous research has shown that the occurrence of tACS effects in the α-band is state dependent (Neuling et al., 2013; Ruhnau et al., 2016) the experiment was designed in a way that the role of ambience illumination during the stimulation was examined.

Chapter 2

Study I: Absence of Alpha-tACS Aftereffects in Darkness Reveals Importance of Taking Derivations of Stimulation Frequency and Individual Alpha Variability Into Account

Heiko I. Stecher[1] and Christoph S. Herrmann[1,2,*]

[1]Experimental Psychology Lab, Department of Psychology, European Medical School, Cluster for Excellence "Hearing for All", Carl von Ossietzky University, Oldenburg, Germany

[2]Research Center Neurosensory Science, Carl von Ossietzky University, Oldenburg, Germany

[*]Corresponcence:

Christoph S. Herrmann

christoph.herrmann@uni-oldenburg.de

Keywords: transcranial alternating current stimulation (tACS), EEG, aftereffect, alpha oscillations, replication, tES reliability

Published in Frontiers in Psychology 20 June 2018

2.1 Abstract

Transcranial alternating current stimulation (tACS) has found widespread use as a basic tool in the exploration of the role of brain oscillations. Many studies have shown that frequency-specific tACS is able to not only alter cognitive processes during stimulation, but also cause specific physiological aftereffects visible in the electroencephalogram (EEG). The relationship between the emergence of these aftereffects and the necessary duration of stimulation is inconclusive. Our goal in this study was to narrow down the crucial length of tACS-blocks, by which aftereffects can be elicited. We stimulated participants with αtACS in four blocks of 1-, 3-, 5-, and 10-min length, once in increasing and once in decreasing order. After each block, we measured the resting EEG for 10 min during a visual vigilance task. We could not find lasting enhancement of α-power following any stimulation block, when comparing the stimulated groups to the sham group. These findings offer no information regarding the crucial stimulation duration. In addition, this conflicts with previous findings, showing a power increase following 10 min of tACS in the alpha range. We performed additional explorative analyses, based on known confounds of (1) mismatches between stimulation frequency and individual alpha frequency and (2) abnormalities in baseline α-activity. The results of an ANCOVA suggested that both factor explain variance, but could not resolve how exactly both factors interfere with the stimulation effect. Employing a linear mixed model, we found a significant effect of stimulation following 10 min of α-tACS in the increasing sequence and a significant effect of the mismatch between stimulated frequency and individual alpha frequency. The implications of these findings for future research are discussed.

2.2 Introduction

Transcranial alternating current stimulation, in which weak electrical oscillating currents are administered by electrodes placed directly on the scalp, has emerged as a non-invasive technique for brain stimulation. Its role as a tool in clinical therapy and basic brain research is being investigated, as it is believed to interact directly with endogenous brain oscillations (Antal and Paulus, 2013; Herrmann et al., 2013). This could enable the direct exploration of their functional role (Thut et al., 2012). tACS has been shown to successfully alter behavioral processes like cognition (Vosskuhl et al., 2015; Kasten and Herrmann, 2017), perception (Feurra et al., 2011b; Helfrich et al., 2014b; Strüber et al., 2014), motor behavior (Feurra et al., 2013) and ongoing oscillations (Helfrich et al., 2014a; Neuling et al., 2015; Ruhnau et al., 2016). It has

been postulated that tACS directly interferes with endogenous oscillations by entrainment (Thut et al., 2011a; Reato et al., 2013; Herrmann et al., 2016a).

Aside from online-effects (occurring 'during' the stimulation) many studies have also shown physiological aftereffects, persisting even after the stimulation has ended (see Veniero et al., 2015). The exact nature of these aftereffects is unclear, and Vossen et al. (2015) it has been shown that these aftereffects are not likely to be a manifestation of entrainment. It has been suggested, that they are caused by spike time dependent plasticity (STDP) (Zaehle et al., 2010; Vossen et al., 2015), causing long-term-potentiation (LTP) or long-term-depression (LTD). The α-band in the electroencephalogram (EEG) is a frequency in which robust aftereffects of power-enhancement have been found. Effects have been found following 10-min (Zaehle et al., 2010) and 20-min (Neuling et al., 2013) of tACS at individual alpha frequency (IAF). It has been shown that these aftereffects persist for up to 70 min post-stimulation (Kasten et al., 2016). Comparable effects were also observed with intermittent protocols of a cumulative length of 11–15 min, if the single trains had a duration of at least 8 s (Vossen et al., 2015). By contrast, intermittent protocols of 1-s trains and a cumulative duration of 10 min did not yield any effects (Strüber et al., 2015). As of yet, the duration (and amplitude) of α-tACS required to produce lasting physiological effects is unknown. However, dependency on duration is implied if the aftereffect originates from synaptic strengthening, due to LTP/LTD, between the relevant neuronal networks. An understanding of the duration and the occurrence of lasting effects is essential for future experimental protocols and for dosages for therapeutic approaches.

In this study, we intended to find the range of crucial α-tACS durations necessary for the elicitation of measurable aftereffects, by observing the band-power in the EEG following tACS-blocks of different lengths, in a sham-controlled study. To this end, we employed an exploratory cascade design of increasing durations of α-stimulations. In order to partially control for effects of time and carry-over effects of one block to the next, we also used a reverse sequence. Since 10 min of tACS has been shown to elicit aftereffects in the α-band (Zaehle et al., 2010), we used a 10-min block of stimulation as a starting point. This enabled the study to serve as a replication of the results found by Zaehle et al. (2010). Sleep studies utilizing 5-min of δ-oscillatory direct current stimulation (otDCS) were also successful in eliciting short-lasting aftereffects (Marshall et al., 2006; Garside et al., 2014). These results suggest that 5-min might be a promising duration where aftereffects in the α-band are still measurable. Additionally, we tested 3- and 1-min durations. To look for immediate short-lasting effects, we included a 10-min observation window of EEG following each application of stimulation. We hypothesized that we would find at least one observation window, where the power is significantly more enhanced than in the sham condition.

2.3 Material and Methods

2.3.1 Participants

Fifty right-handed volunteers, who reported no neurological or psychiatric disorders, aged 18–30 (25 ♀) participated in the study. All participants had normal or corrected-to-normal vision and were recruited from the student body of the Carl von Ossietzky University Oldenburg. All gave written consent and received a monetary compensation for their participation. The design of the study was approved by the ethics committee ('Komission für Forschungsfolgenabschätzung und Ethik') of the Carl von Ossietzky Universität Oldenburg and was in accordance with the declaration of Helsinki. Due to technical problems, the data of five participants was discarded from the analysis and the measurements were redone with new participants. To each stimulation group, 15 participants were assigned, while 15 participants received sham-stimulation. During the analysis, one additional participant showed an average increase in a-power exceeding 4 s of the total sample's z-scored values and was excluded from the statistical analysis. The resulting sham group (N = 14, 8 ♀) had an average age of 23.8 years ($\pm$ 3.6). The stimulation group with an increasing sequence (N = 15, 8 ♀) had an average age of 24.0 years ($\pm$ 2.4), while the stimulation group with a decreasing sequence (N = 15, 8 ♀) had an average age of 23.8 years ($\pm$ 2.8).

2.3.2 EEG

The EEG data was acquired at an acquisition rate of 10 kHz, using an actiCHamp amplifier (Brain Products GmbH, Gilching, Germany) with 23 active electrodes. The electrodes were placed according to the international 10–10 system, omitting the sites of the stimulation electrodes (see Figure 2.1 C). Fp1 served as reference. A vertical EOG-channel was recorded by one electrode placed under the right eye. Pycorder software (Brain Products GmbH, Gilching, Germany) was used for recording. All impedances were below 10 kΩ before starting the experiments.

2.3.3 Electrical Stimulation

Transcranial alternating current stimulation was administered in accordance with previous studies (Neuling et al., 2013; Kasten et al., 2016; Stecher et al., 2017), with a maximum posterior stimulation [simulated using SimNIBS 2.0 (Thielscher et al., 2015); see Figure 2.1 C,D]. This constitutes a different montage to 10-min α-tACS study of Zaehle and colleagues, who used a PO9/PO10-montage. We employed a

Neuroconn DC Plus Stimulator (Neuroconn, Ilmenau, Germany) and two carbonized rubber electrodes, sized 5 cm x 7 cm and 4.5 cm x 4.5 cm. The smaller electrode was placed at Oz and the larger one at Cz. They were fixed to the scalp using Ten20 conductive paste (D.O. Weaver, Aurora, CO, United States). It was ensured that impedances were below 10 kΩ, before participants received a stimulation current at 1 mA to confirm they experienced neither pain nor irritation. From experience, this intensity is also below the threshold for phosphenes in the employed electrode configuration, although participants were not specifically asked about them and none gave any indication of perceiving any phosphenes. The sinusoidal stimulation signal was computed in MATLAB 2012b (The MathWorks Inc., Natick, MA, United States) and generated by a digital-to-analog converter (DAQ NI USB 6229, National Instruments, Austin, TX, United States), which drove the stimulator via remote access. The total duration of stimulation was 18 min. In the sham condition, the stimulation was faded out to 0 mA after 30 s. The stimulation protocol differed from previous studies (Zaehle et al., 2010; Neuling et al., 2013; Kasten et al., 2016) by employing a fixed amplitude of 1 mA in contrast to using a sub-sensation-threshold stimulation.

2.3.4 Experimental Procedure

At the start of each session, participants were informed and the tACS and EEG electrodes were prepared. After preparation, participants were told to keep their eyes open and to relax, while a 3 min resting EEG was recorded. From this recording the individual alpha frequency was determined by computing the peak frequency between 7.5 and 12 Hz in the raw recording of electrode Pz. For this determination no filtering or artifactprocessing was applied.

During the main experiment, the participants were seated in a dark room, with a monitor as a sole light source. To maintain a stable level of vigilance, participants had to conduct a visual vigilance task, which required them to fixate a white cross on a monitor, and respond to a 500 ms rotation of the cross by pressing a button with their right index finger (Figure 2.1 B). This visual vigilance task was in accordance with previous studies on α-tACS aftereffects (Zaehle et al., 2010; Vossen et al., 2015; Kasten et al., 2016; Stecher et al., 2017). The main experiment consisted of a 3 min baseline and four stimulation blocks of varying length, each followed by a 10 min observation block (see Figure 2.1 A). The stimulation block sequence was 1-, 3-, 5-, and 10-min in the increasing-sequence-group and in the reverse order for the decreasing-sequence group.

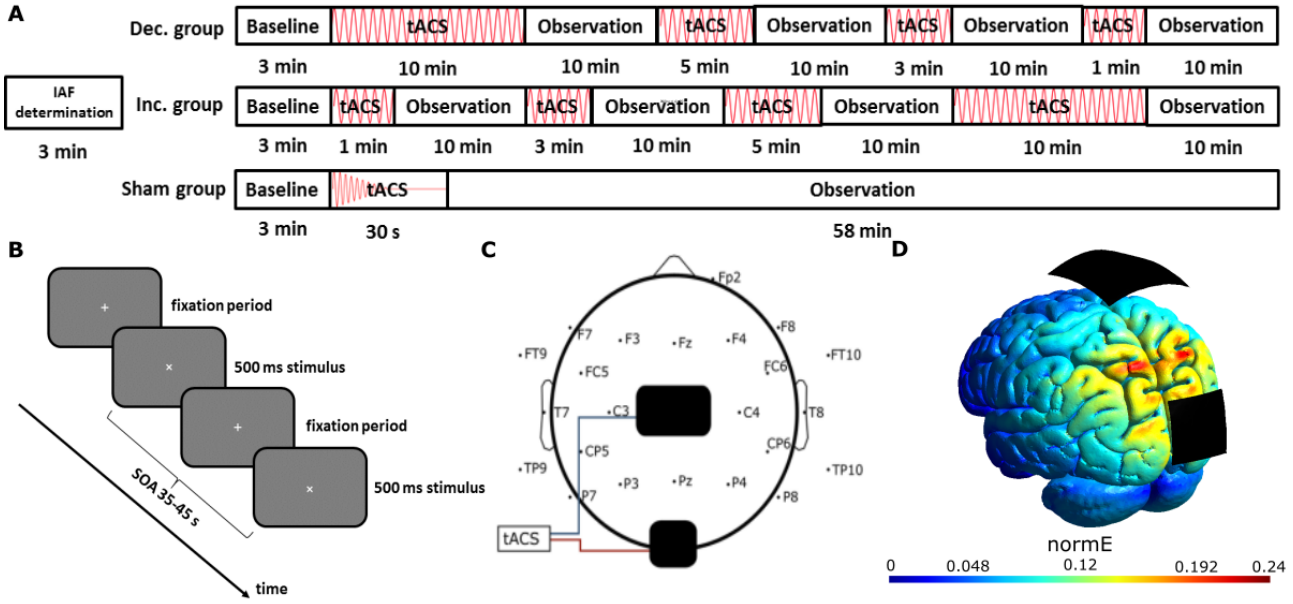

Figure 2.1: Experimental setup. **(A)** Time course of the experiment: the IAF of each participant was determined in a 3-min resting EEG. Afterwards, participants of all groups had to conduct a visual vigilance task for 58 min, while they received either sham stimulation or four blocks of stimulation in decreasing or increasing sequence, each followed by a 10-min window of no-stimulation. **(B)** Visual Vigilance task: Each participant had to fixate a small white cross in the center of a gray screen. Every 35–45 s, the fixation cross was rotated by 45 ° for 500 ms, and the participants had to respond by pressing a button using their right index finger. **(C)** Electrode configuration: EEG was recorded using 23 electrodes, placed according to the international 10–10 system, referenced against Fp1. tACS electrodes were placed at Cz and Oz. **(D)** Current simulation using SIMNIBS: simulation of the stimulation's electric field strength, covering the posterior brain areas.

2.3.5 Data Analysis

Data processing was carried out using MATLAB 2012b and the Fieldtrip toolbox (Oostenveld et al., 2011). The continuous EEG data was down-sampled to 1000 Hz, high-pass filtered above 0.5 Hz and low-pass filtered below 48 Hz. EEG data was then cut into segments starting 30 s after stimulation and ending 30 s before stimulation, resulting in a 3 min baseline block and four segments of 9 min length for both stimulation groups. For both stimulation groups, corresponding parts of the data from the sham group were selected. The data was then re-referenced to combined Fp1/Fp2 electrodes to prevent lateralization of effects due to the asymmetrical reference site during the recording and then further subdivided into 1-s trials. These trials were then used in an ICA approach for the manual removal of components containing vertical or horizontal eyemovements. Trials containing voltage differences of more than 200 mV were rejected as artifacts to clear out DC- distortions and strong muscle-artifacts. The first 66% of artifact free trials of each segment were used to compute the mean α-power (IAF $\pm$ 2 Hz as determined in the last post-stimulation

segment) for each block using a Hanning window with 2-s zero padding. This percentage was the minimal number of trials, necessary to avoid omitting further participants. For post-stimulation power analysis, the data of the four post-stimulation segments were then normalized to the power in the baseline-segment.

2.3.6 Statistics

Statistical analysis was performed by using MATLAB, SPSS 24.0 (IBMCorp, Armonk, NY, United States) and the software package R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) employing the nmle-package (Pinheiro et al., 2016) and the piecewise SEM-package (Lefcheck, 2016). The combined stimulation groups were tested against the sham group for differences in adverse effects by using a Wilcoxon–Mann–Whitney-*U* test. Awareness of stimulation was tested by using a Chi-squared test. For accuracy and reaction times in the vigilance task, the stimulation groups were pooled and tested against the sham group with a two-sided *t*-test. Accuracy and reaction times were evaluated using ANOVAS with the 3 - level factor group. Groups were checked for differences in baseline α-power by employing Mann–Whitney-*U* tests. The change of α-power post-stimulation was tested by employing a repeated measures ANOVA with the between subject factor group (stim/sham) and the within-factor time (observation windows 1, 2, 3, 4) for both stimulation groups against the corresponding time-segments of the sham group. All *p*-values were Greenhouse-Geisser corrected, when the assumption of sphericity was violated.

2.4 Results

2.4.1 Behavioral Results

Stimulation did not cause side effects or behavioral differences in the vigilance task: rating of the adverse effects of tACS did not differ between the pooled stimulation groups and the sham group (all p <0.05). Participants of the stimulated groups did not think they were stimulated more frequently than shamparticipants (stim: 12.12%, sham: 23.53%, χ^2_1 = 1.086, p = 0.297). Neither accuracy nor reaction times in the vigilance task showed differences between stimulation and the sham group (accuracy: t_{42} = 0.248, p = 0.805; reaction times: t_{42} = 0.506, p = 0.615).

2.4.2 EEG Results

Standard Analysis

The baseline a-power neither differed between the increasingsequence (median = 2.651) and the sham group (median = 2.704), as tested with a Wilcoxon–Mann–Whitney-*U* test [*Z* = 0.414, *p*(uncorrected) = 0.678] , nor between the decreasing-sequence (median = 1.745) and the sham group (median = 2.704) [*Z* = 0.720, *p*(uncorrected) = 0.472]. The baseline power is plotted in Figure 2.2 A–C for all groups (blue lines), relative to the IAF as determined from the last post-stimulation EEG-segment (see below). The individual spectra for all participants can be found in the Supplemantary Figures 2.5 - 2.7.

As the IAF can show variability within participants and the initial determination can be faulty (Vossen et al., 2015; Stecher et al., 2017), we checked if the individual stimulation frequency (ISF) as determined before the stimulation matched the IAF after stimulation. We calculated the mismatch between the ISF and the alpha peak in the last observational window, which we consider the 'true' IAF for every participant (see Figure 2.2 D). The ISF and IAF only matched in 20 out of 44 participants.

Post-stimulation effects were analyzed using a standard approach like in comparable studies (Neuling et al., 2013; Kasten et al., 2016). A Shapiro–Wilk test showed that neither the data of the increasing-sequence (0.876, p <0.001) nor the decreasing-sequence (0.949, p <0.001) was normally distributed. We employed an ANOVA in absence of a non-parametric equivalent, even though sample size of n <30 is normally not assumed to be robust against such a violation. We used two repeated measures ANOVAs to test the increasing-sequence tACS group and the decreasing-sequence tACS groups independently against the sham group. In the comparison of the increasing-sequence and the sham groups, we found a main effect of *time* ($F_{3,81}$ = 14.031, p <0.001, χ^2 = 0.342), whereas the factor *group* ($F_{1,27}$ = 0.174, p = 0.680, η = 0.006) and the interaction *time* $\times$ *group* ($F_{3,81}$ = 1.950, p = 0.151, η^2 = 0.067) remained non-significant. In the comparison of the decreasing-sequence and the sham groups, we also found a significant main effect of *time* ($F_{3,81}$ = 7.010, p = 0.002, η^2 = 0.206), and no significant effects of the factor *group* ($F_{1,27}$ = 0.1728, p = 0.682, η^2 = 0.006) and the interaction *time* $\times$ *group* ($F_{3,81}$ = 0.233, p = 0.794, η^2 = 0.009). The general increase in relative a-power for both the tACS and the sham groups can be seen in Figure 2.3 (confer with Supplementary Figure 2.4 in the Supplementary Material, showing no short-term effects for smaller time-windows). The relative power of each EEG-windows of both tACS groups is plotted with the power ofthe respective windows of the sham-group. Note that the increaseseems to be limited to the alpha-band range (see Figures 2.2 A-C).

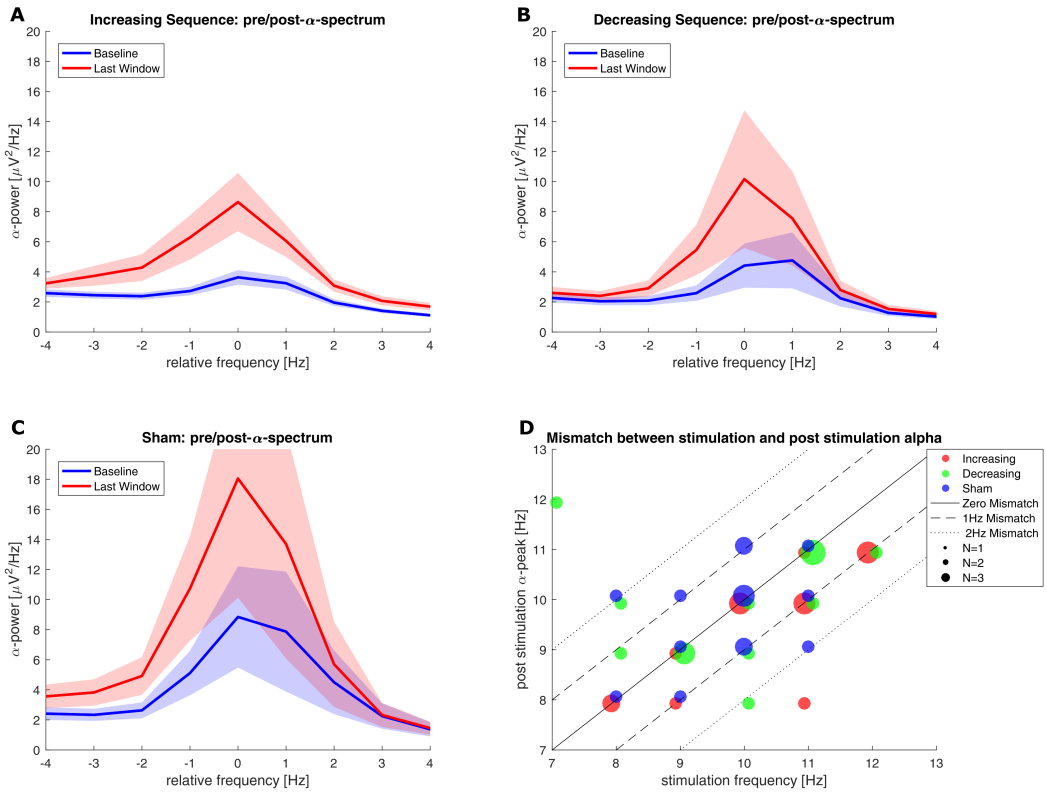

Figure 2.2: Parietal power-spectra in the α-range before stimulation and at the end of the recording and mismatch between stimulated frequency and individual alpha frequency. **(A–C)** Mean posterior alpha power for the increasing-sequence group, decreasing-sequence group, and sham-group. Power is taken from the baseline period (blue) and from the last 9 min of the recording (red). The frequency axis is centered around IAF as determined in the last 9 min window. Shaded areas show the standard error of the mean. **(D)** Frequency mismatch scatterplot: The stimulation frequency vs. the 'true' IAF as determined in the last 9 min of recording is plotted. The dot size denotes number of participants. The solid line marks the zero-mismatch diagonal. Dashed and dotted lines mark the areas of $\pm$1 Hz and$\pm$2 Hz.

Exploratory Analysis

Due to unexplained discrepancies between published reports and the results of our standard analysis approach, we performed an additional analysis to uncover confounding factors. Previous tACS studies in the a-range show that the power-enhancement relative to sham correlated with the negative mismatch between the stimulated frequency and true IAF (Vossen et al., 2015). Additionally it could be shown that the inclusion of such a mismatch as a factor explains observed variance when modeling power-enhancement (Stecher et al., 2017). The large variance in the baseline a-power (see Figures 2A–C, albeit not significantly different between groups) encouraged us to test, whether baseline-power might influence the capacity for post-stimulation enhancement. For this reason, we included both the factors *frequency mismatch* as well

as *baseline power* as covariates to a repeated measure ANCOVA. This did not lead to different results in the case of the decreasing sequence condition compared to sham, revealing no significant main effect of *time* ($F_{1,75}$ = 1.767, *p* = 0.180, η^2= 0.066), no significant effects of the factor *group* ($F_{1,25}$ = 0.199, *p* = 0.659, η^2= 0.008), or the interaction *time* $\times$ *group* ($F_{3,75}$ = 1.578, *p* = 0.570, η^2= 0.023). In the case of the increasing sequence, however, the inclusion of the covariates not only revealed the above-mentioned significant main effect of *time* ($F_{1,75}$ = 6.471, *p* = 0.018, η^2= 0.206), but also a significant interaction of *time* $\times$ *group* ($F_{3,75}$ = 4.134, *p* = 0.009, η^2 = 0.142). The interaction of *time* $\times$ *basepower* showed a trend ($F_{3,75}$ = 2.703, *p* = 0.051, η^2= 0.098), while the factor *group* ($F_{1,25}$ = 0.931, *p* = 0.344, η^2= 0.036) and the interaction *time* $\times$ *mismatch* did not reach significance ($F_{3,75}$ = 1.478, *p* = 0.227, η^2= 0.056). However, the resolution of the interaction *time* $\times$ *group*, employing post hoc one-way ANCOVAs for every timepoint between groups, did not yield any significant differences between groups at any timepoint (T1 group: $F_{1,25}$ = 0.031, *p* = 0.862, η^2= 0.001; T2 group: $F_{1,25}$ = 0.148, *p* = 0.704, η^2= 0.006; T3 group: $F_{1,25}$ = 0.1966, *p* = 0.173, η^2= 0.073; T4 group: $F_{1,25}$ = 2.452, *p* = 0.130, η^2 = 0.89; all *p*-values uncorrected).

We then tested if a random mixed effect model, which allows inter-subject variability would be better suited to explain our results. Initially we created a saturated model that predicted alpha power from the fixed effects of 9 time points per post-stimulation window, 4 blocks, 2 groups and effects of frequency-mismatch, basepower as well as their interactions and random effects for each participants ID. This did not yield any significant factors and the high-level interactions would be hard to interpret. Therefore, we omitted the factor of time and started with a minimal model, which only contained the hypothesis-relevant factors block (poststimulation window) and group (tACS or sham). Thereby the model is equivalent to the initial ANOVA, but allowed a random effect of participant's ID. To this minimal model, we added effects of the factors mismatch and basepower as different combinations with the other two factors and compared the Akaike Information Criterion of the resulting model to the minimal model. For the increasing sequence comparison, a model containing an interaction of block and mismatch, described by equation 2.1 resulted in a lower AIC that the minimal model.

$$\begin{aligned}\alpha =& \beta_0 + \beta_1 group1 + \beta_2 block2 + \beta_3 block3 + \beta_4 block4 + \beta_5 group1 \times block2 \\ &+ \beta_6 group1 \times block3 + \beta_7 group1 \times block4 + \beta_7 group1 : block2 \\ &+ \gamma_{0,ID} + \epsilon\end{aligned} \tag{2.1}$$

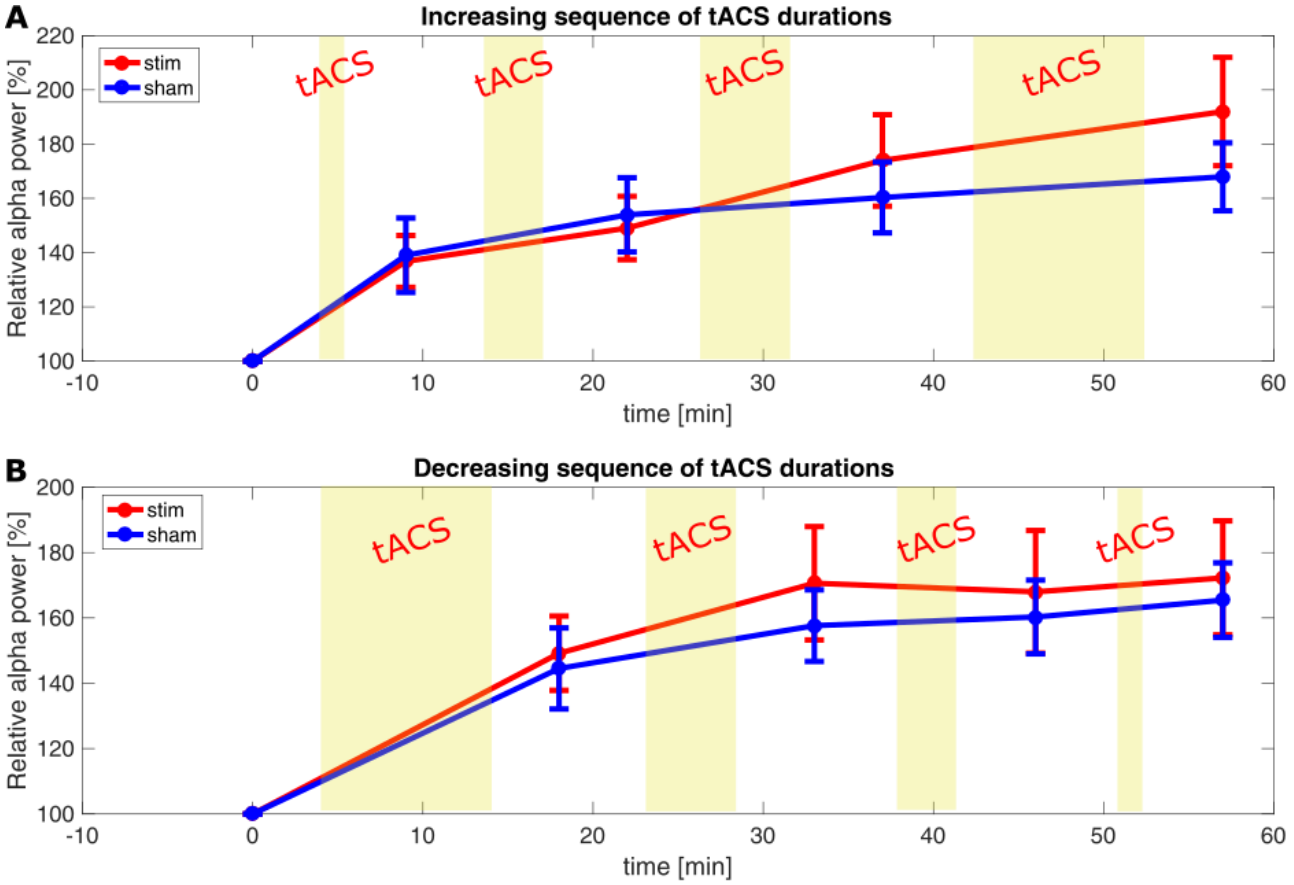

Figure 2.3: Relative parietal α–power post-stimulation. **(A)** Time-course of α-power relative to baseline, comparing increasing-sequence stimulation group (red) and sham (blue). Each point represents the average power of a 9-min observation window. Yellow bars represent blocks of stimulation. Error bars depict the standard error of the mean. **(B)** Time-course of α–power relative to baseline, comparing decreasing-sequence stimulation group (red) and sham (blue): each point represents the average power of a 9-min observation window. Yellow bars represent blocks of stimulation. Error bars depict standard error of the mean.

For the decreasing-sequence comparison, all additions to the minimal model resulted in an increase in AIC, so that the minimal model equation **??** was chosen for further analysis.

$$\begin{aligned}\alpha =& \beta_0 + \beta_1 group1 + \beta_2 block2 + \beta_3 block3 + \beta_4 block4 + \beta_5 group1 \times block2 \\ &+ \beta_6 group1 \times block3 + \beta_7 group1 \times block4 + \gamma_{0,ID} + \epsilon\end{aligned} \tag{2.2}$$

The resulting equations 2.1 and **??** predict the α-power for the fixed effects β, the random effects γ and the residual error ϵ. The estimators of the final model for the increasing-sequence condition are listed in Table 2.1, showing a significant effect of the factor block at the levels 2, 3, and 4, denoting a general increase in alpha power over time.

The significant interactions of the stimulation group with the fourth block, implies a significant increase

Table 2.1: Increasing transcranial alternating current stimulation (tACS)-sequence: result summary of linear mixed effect model.

Parameter	Coefficents β	SE(β)	*t*	*p*
(β_0)Intercept	145.019	17.709	8.189	<0.001
(β_1)Group1	0.021	25.092	0.001	0.999
(β_2)Block2	17.489	6.042	8.894	0.004
(β_3)Block3	32.302	6.042	5.346	<0.001
(β_4)Block4	45.992	6.042	7.611	<0.001
(β_5)Group1:Block2	2.899	8.686	0.334	0.739
(β_6)Group1:Block3	13.656	9.092	1.502	0.134
(β_7)Group1:Block4	25.443	9.733	2.614	0.009
(β_8)Mismatch:Block	-4.618	2.243	-2.056	0.040

Coefficient estimates for the fixed effects, standard Error SE(β), t-value t and significance level p. The model's has marginal R^2 of 0.074 and a conditional R^2 of 0.669

Table 2.2: Decreasing transcranial alternating current stimulation (tACS)-sequence: result summary of linear mixed effect model.

Parameter	Coefficents β	SE(β)	*t*	*p*
(β_0)Intercept	157.086	17.118	9.177	<0.001
(β_1)Group1	-7.063	5.096	-0.302	0.765
(β_2)Block2	15.761	5.096	83.093	0.020
(β_3)Block3	25.778	5.0962	5.058	<0.001
(β_4)Block4	29.945	5.096	5.876	<0.001
(β_5)Group1:Block2	-0.512	6.963	-0.074	0.941
(β_6)Group1:Block3	-4.837	6.963	-0.695	0.487
(β_7)Group1:Block4	-5.525	6.963	-7.794	0.428

Coefficient estimates for the fixed effects, standard Error SE(β), t-value t and significance level p. The model's has marginal R^2 of 0.074 and a conditional R^2 of 0.669

in α-power following 10 min of α-tACS. The significant interaction of mismatch and block represents a negative slope of α-power increase over blocks, due to large mismatches. In Table 2.1, the results of the decreasing-sequence condition are shown. While a significant effect of the factor block on α-power can be seen, the factor group has no effect.

2.5 Discussion

2.5.1 General Discussions and Discrepancies

When we used the standard statistical approach, our results showed no significant effect of stimulation on post-stimulation power in the alpha band, neither in an increasing nor in a decreasing sequence of stimulation durations. Only a general increase of power over time was found, as was expected for a long monotonous task in darkness. We would have expected to replicate previous findings of a power increase following 10 min of a-tACS (Zaehle et al., 2010) with a subsample of our data. The first post-stimulation measure in the decreasingsequence conditions strongly mimics the setup of Zaehle et al. (2010), despite the different montage of stimulation electrodes. Taking the effect sizes from their results into considerations (one-sided t-test on post-stimulation α–power, with a desire statistical power of 80% results in a sample size of 15 participants per group) our sample size should have been sufficiently large to expect a significant effect of stimulation at the first time-point for the respective group. One possible explanation for the discrepancy might be that the effect sizes in previously published a-tACS studies with small samples were overestimated, which would leave our study severely underpowered.

Another possible explanation is that our protocol was altered from the established procedures by unconsidered factors. When compared to other studies in our lab that employed a similar task (Zaehle et al., 2010; Neuling et al., 2013; Kasten et al., 2016), the natural increase of a-power within our unstimulated group is remarkably high. Indeed neither Neuling et al. (2013) nor Zaehle et al. (2010) found a significant increase in the α-power within the sham groups, while Kasten et al. (2016) found a mean increase by 40% only after 90 min post-stimulation – a value, which was already reached as early as 8 min post-stimulation in our experiment. When looking for systematic differences in the setups, we noticed that our experiment was conducted in complete darkness with the monitor as the sole source of light in the laboratory, whereas the setups of the aforementioned studies (Zaehle et al., 2010; Neuling et al., 2013; Kasten et al., 2016) included ambient light sources. In a recent study (Stecher et al., 2017), we could show that the level of ambient light significantly influences the rise of alpha power within the first 25 min of recording, while stimulation-related effects only emerged after that. Thus, we suggest that in the case of the current study any tACS-induced aftereffects in the early stimulation blocks might have been masked by the darkness-induced huge increase in α-power. In the decreasing-sequence condition, this likely could have prevented the replication of an aftereffect following the 10-min stimulation.

Additionally, our exploratory analysis employing covariatesand a linear mixed effect model showed

that ISF/IAF-mismatch and random differences in baseline a-power explain variance. The LMEM even showed a significant increase of α-power following 10 min of tACS, when employed as the last stimulation block. This finding may indicate that both mismatch and individual variability in alpha power pose potential confounds, individually influencing the post-stimulation development of α-power. Our results suggest that the standard approach of repeated measures ANOVAs and ANCOVAs may not always be the best choice for small datasets, and that data showing high inter-individual variability might be explored better by using mixed effect models.

It is unclear, which tACS duration at IAF and 1mA is necessary to elicit aftereffects, but our results indicate that future studie need to be designed in a way that better controls for confounding factors.

2.5.2 Limitations and Points to Consider

Other researchers have already discovered how individual brain anatomy might influence the efficiency of non-invasive brain stimulation (Krause and Cohen Kadosh, 2014; Veniero et al., 2017). Therefore, tACS studies should, whenever possible, consider the individual anatomy, taken from neuroimaging approaches, for precise placement of electrodes and choice of stimulation parameters (Bergmann et al., 2016). We think three limitations inherent in our design illustrate the importance of additional points to consider in future research:

First limitation: Minor differences in our environmental factors might have had a large independent effect on our measured outcome variable. We did not consider differences in environmental illumination when designing our study as a partial replication of previous results (Zaehle et al., 2010). Especially when studying a-activity, it is important to recognize all additional factors, which might independently induce changes, such as illumination (Min et al., 2013; Stecher et al., 2017), task induced fatigue (Cajochen et al., 1995; Oken et al., 2006) or memory load (Jensen, 2002; Tuladhar et al., 2007). All protocols should incorporate stable, replicable conditions with minimal influence on the measured outcome-variable and the states of the stimulated networks should be carefully considered (Fertonani and Miniussi, 2017). Additionally, as the control treatment consisted of a sham-stimulation it is unclear if the perception of consistent stimulation might have altered the behavior in the stimulated groups. This could be circumvented in future studies by employing control frequencies, which can also prove the frequency-specificity of tACS.

Second limitation: Since it is believed that the aftereffects of tACS are caused by LTP/LTD-processes due to entrainment during stimulation (Zaehle et al., 2010; Vossen et al., 2015), the physics of entrainment

(Pikovsky et al., 2002) require a close frequency-match between endogenous oscillation and the exterior driving frequency. Even though our protocol involved an adjustment of the stimulation frequency to the IAF, our post hoc analysis revealed that we missed the right frequency in nearly half the cases, with maximum deviations of up to 5 Hz (mean deviation in stimulated groups: 0.7 Hz). This poor estimation is probably caused by the short and unprocessed resting recording that we employed to find the posterior α-peak. Future studies should take better care in finding the true IAF by using a longer recording, and employing advanced methods for the processing of EEG-data, like basic artifact rejection and independent component analysis. The overall information regarding the relationship between successful stimulation and matching the IAF is quite sparse; only two studies so far have looked into eventual mismatches (Vossen et al., 2015; Stecher et al., 2017). Therefore, it might prove beneficial for future tACS studies to execute post hoc explorations of stimulation-frequency mismatches to get a better understanding of its effects.

Third limitation: The standard ANOVA as employed by previous studies (Neuling et al., 2013; Helfrich et al., 2014a; Vossen et al., 2015; Kasten et al., 2016) assumes small inter-individual variability in the distribution of α-power and enhancement. Additionally, confounding factors that might influence the susceptibility toward tACS are seldom explored, negating their capability to explain additional variance. Even though an ANOVA is often thought to be robust against violations of its general assumptions, it might be beneficial for some studies to use mixed-effect models that enable the modeling of the effects of additional factors while simultaneously allowing for more inter-individual variability.

2.6 Author Contributions

HS and CH designed the study and wrote the article. HS acquired and analyzed the data.

2.7 Funding

This work was supported by DFG (Deutsche Forschungsgemeinschaft) Special Priority Program to CSH (SPP1665 HE 3353/8-2).

2.8 Supplementary Material

2.8.1 Supplemetanry Figures

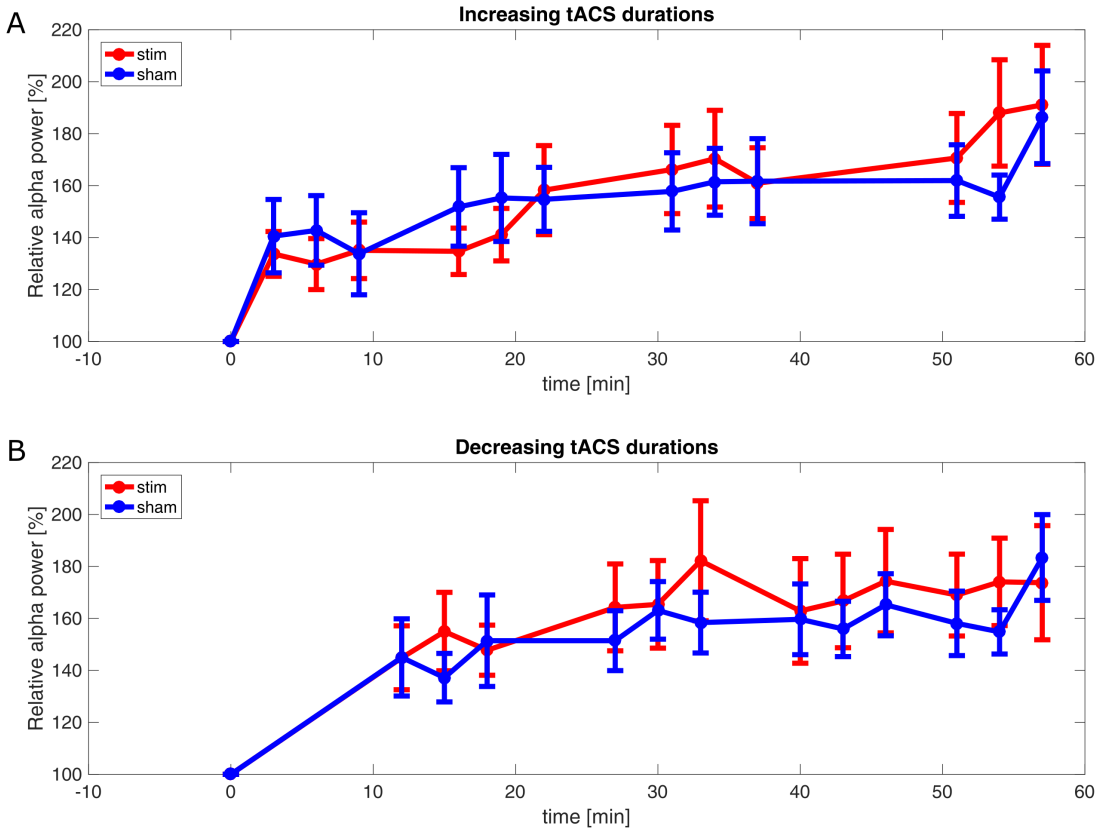

Figure 2.4: Relative parietal α-power post stimulation (A) Time-course of α-power relative to baseline, comparing increasing-sequence stimulation group (red) and sham (blue). Each point represents the average power of a 3-min observation window. Error bars depict the standard error of the mean.**(B)** Time-course of α-power relative to baseline, comparing decreasing-sequence stimulation group (red) and sham (blue): Each point represents the average power of a 3-min observation window. Error bars depict standard error of the mean.

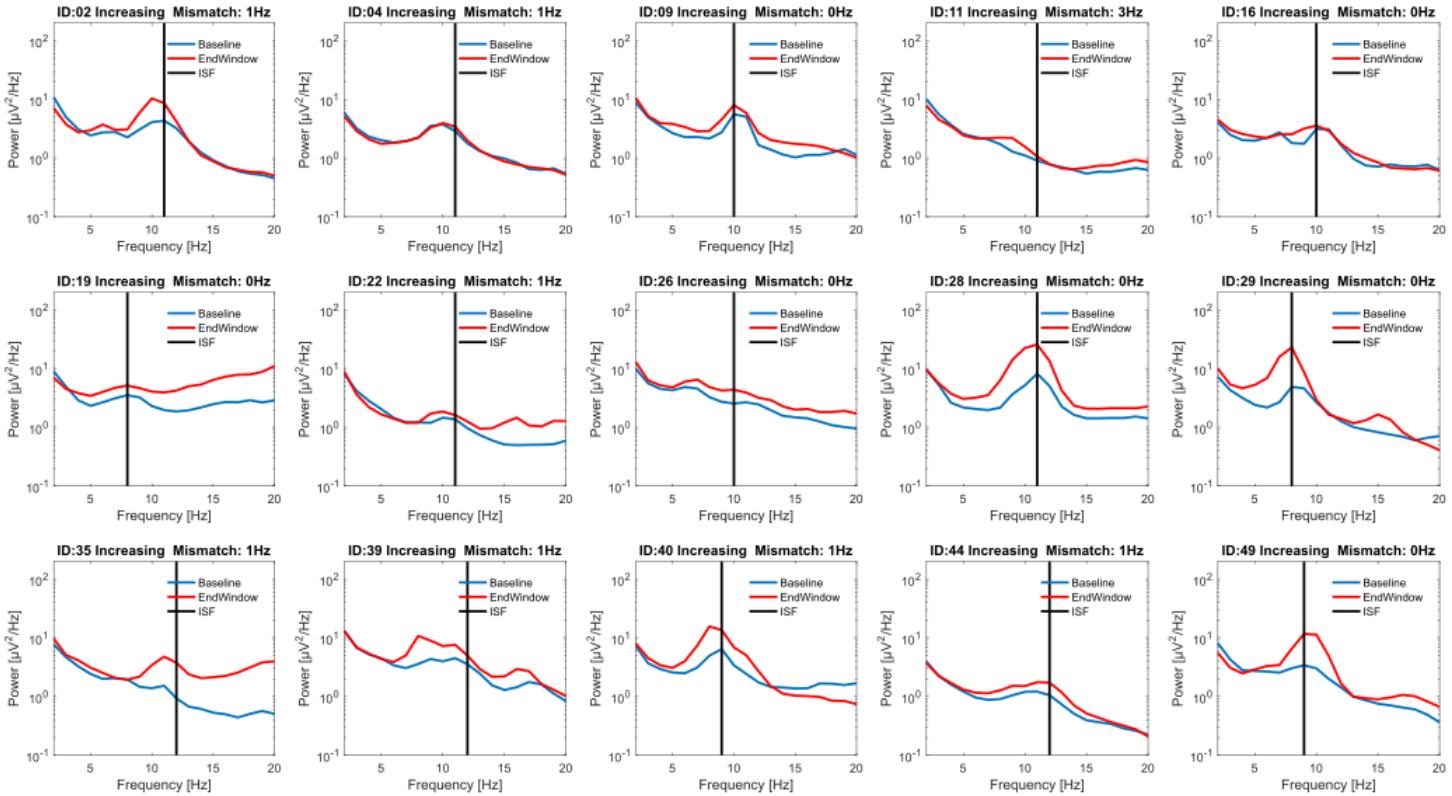

Figure 2.5: Posterior power spectra of all participants of the increasing-stimulation group are shown. The blue lines depict the power in the 3 min baseline before the first stimulation block, the red line depicts the power spectra in the last 9 min of the experiment. The black line marks the Individual stimulation frequency, that was determined before the start of the experiment from a raw 3 min recording of Pz. The mismatch between the IAF peak of the last 9 mine recording and the ISF is given in each subtitle.

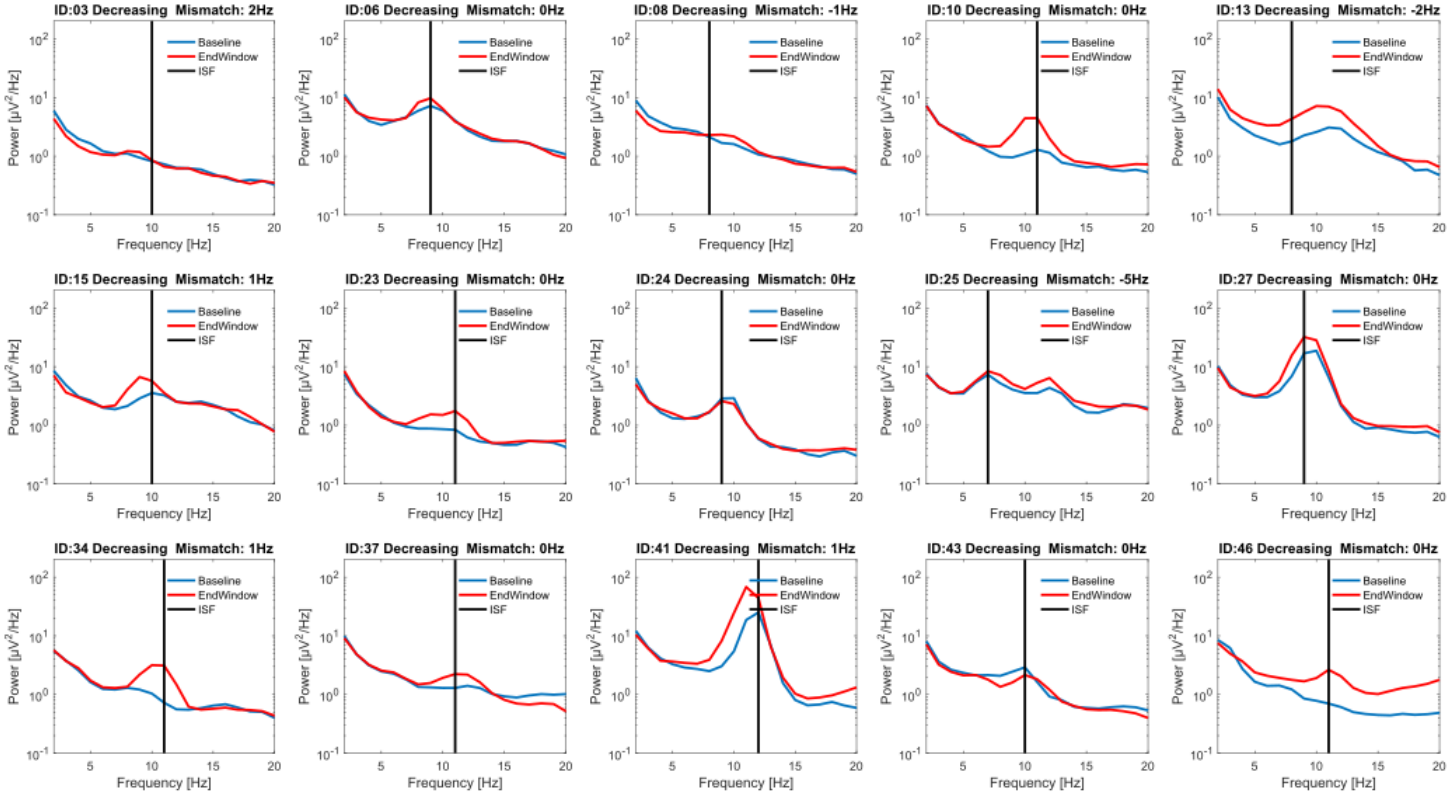

Figure 2.6: Posterior power spectra of all participants of the decreasing-stimulation group are shown. The blue lines depict the power in the 3 min baseline before the first stimulation block, the red line depicts the power spectra in the last 9 min of the experiment. The black line marks the Individual stimulation frequency, that was determined before the start of the experiment from a raw 3 min recording of Pz. The mismatch between the IAF peak of the last 9 mine recording and the ISF is given in each subtitle.

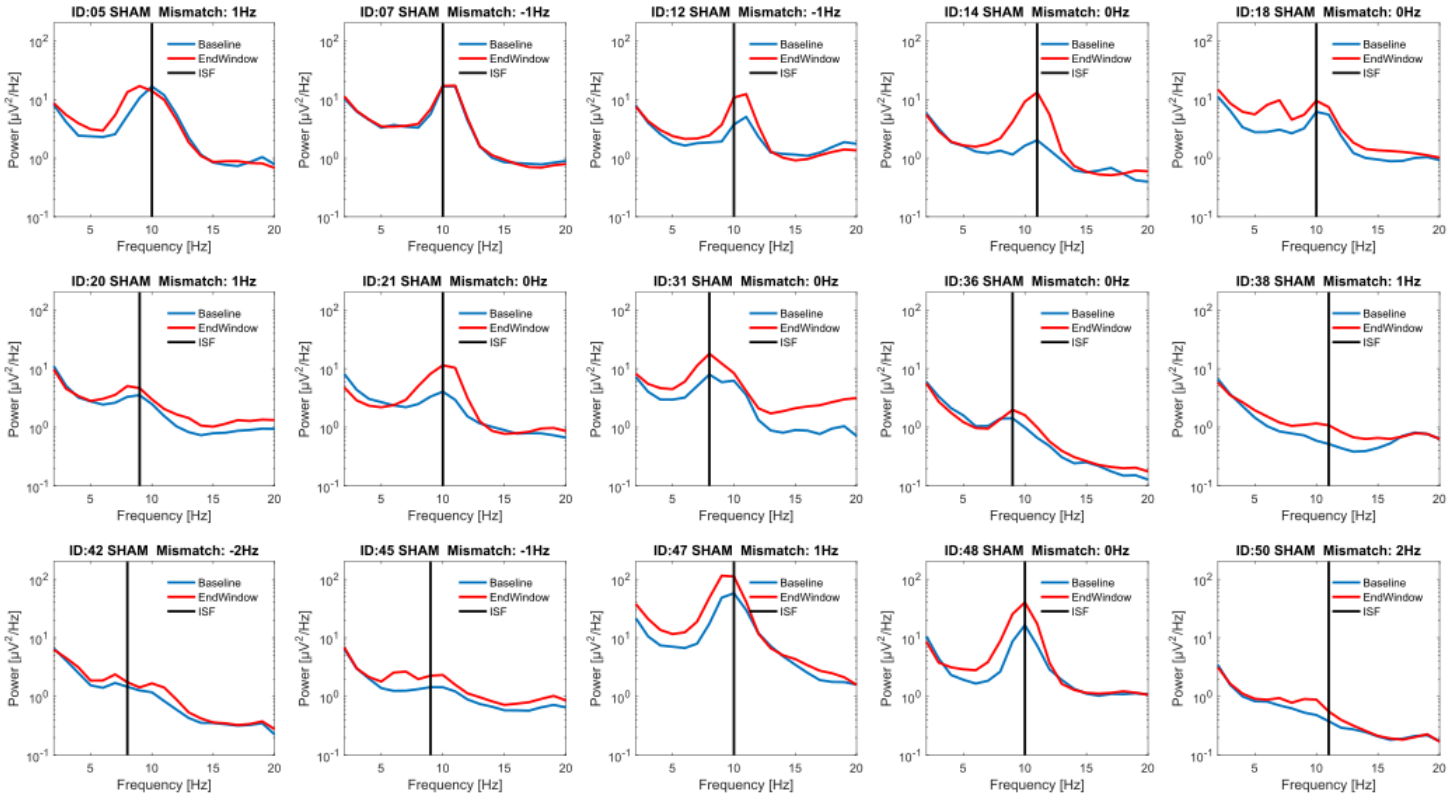

Figure 2.7: Posterior power spectra of all participants of the sham-stimulation group are shown. The blue lines depict the power in the 3 min baseline before the first stimulation block, the red line depicts the power spectra in the last 9 min of the experiment. The black line marks the Individual stimulation frequency, that was determined before the start of the experiment from a raw 3 min recording of Pz. The mismatch between the IAF peak of the last 9 mine recording and the ISF is given in each subtitle.

Chapter 3

Study II: Ten Minutes of α-tACS and Ambient Illumination Independently Modulate EEG α-Power

Heiko I. Stecher[1], Tania M. Pollok[1], Daniel Strüber[1,2], Fabian Sobotka[3] and Christoph S. Herrmann[1,2,*]

[1]Experimental Psychology Lab, Department of Psychology, European Medical School, Cluster for Excellence "Hearing for All", Carl von Ossietzky University, Oldenburg, Germany

[2]Research Center Neurosensory Science, Carl von Ossietzky University, Oldenburg, Germany

[3]Division of Epidemiology and Biometry, Department of Health Services Research, Carl von Ossietzky University, Oldenburg, German

[*]Corresponcence:

Christoph S. Herrmann

christoph.herrmann@uni-oldenburg.de

Keywords: transcranial alternating current stimulation (tACS), EEG, after effect, alpha oscillations

Published in Frontiers in Human Neuroscience 18 May 2017

3.1 Abstract

Transcranial alternating current stimulation (tACS) sees increased use in neurosciences as a tool for the exploration of brain oscillations. It has been shown that tACS stimulation in specific frequency bands can result in aftereffects of modulated oscillatory brain activity that persist after the stimulation has ended. The general relationship between persistency of the effect and duration of stimulation is sparsely investigated but previous research has shown that the occurrence of tACS aftereffects depends on the brain state before and during stimulation. Early alpha neurofeedback research suggests that particularly in the alpha band the responsiveness to a manipulation depends on the ambient illumination during measurement. Therefore, in the present study we assessed the brain's susceptibility to tACS at the individual alpha frequency during darkness compared to ambient illumination. We measured alpha power after 10 min of stimulation in 30 participants while they continuously performed a visual vigilance task. Our results show that immediately after stimulation, the alpha power in the illumination condition for both the stimulated and sham group has increased by only about 7%, compared to about 20% in both groups in the 'dark' condition. For the group that did not receive stimulation, the power in darkness remained stable after stimulation, whereas the power in light increased by an additional 10% during the next 30 min. For the group that did receive stimulation, alpha power during these 30 min increased by another 11% in light and 22% in darkness. Since alpha power already increased by about 10% without stimulation, the effect of illumination does not seem to have interacted with the effect of stimulation. Instead, both effects seem to have added up linearly. Although our findings do not show that illumination-induced differences in oscillatory activity influence the susceptibility toward tACS, they stress the importance of controlling for factors like ambient light that might add an independent increase or decrease to the power of brain oscillations during periods, where possible persistent effects of stimulation are explored.

3.2 Introduction

The nature of rhythmic brain activity has been the subject of research since the first use of electroencephalography. While many studies in the past have shown links between specific cognitive tasks and modulations in endogenous frequencies, most were limited to showing purely correlative relationships (Buzsáki and Draguhn, 2004). Recent intervention approaches of exploring the role of brain rhythms involve the external modulation of endogenous oscillation by non-invasive brain stimulation like visual flicker

(Notbohm et al., 2016), transcranial magnetic stimulation (TMS) (Thut et al., 2012) or transcranial electric stimulation (TES) (Neuling et al., 2013). Among these techniques, transcranial alternating current stimulation (tACS) has proven to be a viable tool that offers direct stimulation of targeted cortical areas in specific frequencies. TACS modulates activity in the cortex by applying sinusoidal currents (or other waveforms) at the scalp (Antal and Paulus, 2013; Herrmann et al., 2013). tACS is thought to cause its effects by interfering with naturally occurring oscillations of brain activity by the mechanism of entrainment [i.e., synchronization of one oscillator to an external one by weak coupling (Pikovsky et al., 2002)]. This has been shown in modeling approaches and animal studies (Fröhlich et al., 2010; Ali et al., 2013) and there is evidence that tACS can modulate frequencies in human EEG (Helfrich et al., 2014b; Cecere et al., 2015).

Many studies have demonstrated that tACS modulates perception (Brignani et al., 2013; Helfrich et al., 2014a; Strüber et al., 2014), short-term memory (Vosskuhl et al., 2015) and motor-excitability (Antal et al., 2008; Bergmann et al., 2009). Multiple studies have shown that tACS also creates persistent physiological effects, like elevated power or coherence of brain oscillations following oscillatory TES (see Veniero et al., 2015, for an elaborate summary). Most tACS studies used the alpha band to demonstrate aftereffects of stimulation. After 10 min of stimulation at occipito-parietal sites at the individual alpha frequency (IAF), Zaehle et al. (2010) reported a frequency specific elevation of alpha power in the EEG. When stimulating for 20 min, this aftereffect has been shown to persist for up to 70 min (Kasten et al., 2016).

The occurrence of stimulation induced effects, however, is not universal. Feurra et al. (2013) could show that excitation of motor evoked potentials was modulated by different tACS frequencies, dependent on mental state (motor imagery or quiescence). Exploration of online-tACS effects in MEG source space showed that phase coherence between resting state alpha and stimulation was increased during states with eyes open only, but not during states with eyes closed (Ruhnau et al., 2016). Another study also found the aftereffect of tACS to be dependent on the brain state. An EEG-experiment with stimulation at IAF produced a robust aftereffect of alpha power increase in participants with open eyes, whereas no such increase was found with eyes closed during the experiment (Neuling et al., 2013). The authors suggested that the alpha activity during closed eyes could be at an un-amplifiable ceiling level, or, alternatively, that the endogenous oscillation was too strong to be influenced by the weak current of tACS (Neuling et al., 2013). Yet another alternative could be that eyes-open and eyes-closed alpha likely involve different physiological mechanisms (Barry et al., 2007) –only one of which was entrained by tACS.

It has been shown that alpha activity with eyes open can be influenced by ambient illumination. For instance, bright illumination reduced alpha activity during a sustained attention task, whereas a dark envi-

ronment led to an increase in alpha activity (Min et al., 2013). Other early studies on alpha neurofeedback found a strong influence of ambient illumination on the effectiveness of alpha neurofeedback training. Paskewitz and Orne (1973) and Cram et al. (1977) could both show that ambient lighting yielded the biggest effect in alpha increase compared to darkness and bright illumination during a task of operant alpha production.

Taking the state dependency of tACS and the effect of illumination on alpha modulation into account, this study aims to explore how the aftereffect of tACS depends on the illumination-induced state of the endogenous alpha oscillation before, during and after stimulation. To this end, we measured alpha power before and after tACS while the participants executed a visual vigilance task in either a dimly illuminated or a dark room. We hypothesized that we will reproduce the known aftereffect (Zaehle et al., 2010) in a state of weak endogenous alpha during ambient illumination (Min et al., 2013), superimposed on the normal increase of alpha during prolonged states of wakefulness (Cajochen et al., 1995). In contrast, we expect a dark environment to result in stronger endogenous alpha which may not be susceptible to further enhancement via tACS, similar to the state of alpha during eyes-closed (Neuling et al., 2013; Ruhnau et al., 2016).

3.3 Material and Methods

3.3.1 Participants

Thirty-three right-handed volunteers (16 females with an average age of 23.8 years, SD = 5), participated in the study and gave their written informed consent to participate and have their results anonymously published and received a monetary compensation for their participation. All participants had normal or corrected to normal vision and reported no history of psychiatric or neurological diseases. The study protocol was designed and performed according to the declaration of Helsinki and was approved by the local ethics committee of the Carl von Ossietzky Universität Oldenburg. Two measurements were aborted due to failure to comply with experimental procedure. Data of one participant was omitted from further analyses due to an extreme alpha increase in the post-stimulation period (exceeding 3 σ of the whole sample's z-scored values). Aborted measurements were repeated with new participants.

3.3.2 EEG Recording

The EEG data was measured using a 32 channel actiCHamp amplifier (Brain Products GmbH, Gilching, Germany) with active electrodes in unipolar configuration. The reference electrode was placed at Fp1 and the ground electrode at FPz. Data was recorded using Pycorder (Brain Products GmbH, Gilching, Germany) at an acquisition rate of 10 kHz. Electrodes at 23 head locations according to the 10/10-system were used in the recording, leaving locations beneath the stimulation electrodes empty (see Figure 3.1 C). One electrode placed underneath the right eye served as a vertical EOG channel. No online filters were applied. Impedances were brought below 20 kΩ.

3.3.3 Electrical Stimulation

Transcranial alternating current stimulation was applied using a Neuroconn DC Plus Stimulator (Neuroconn, Ilmenau, Germany) and two rubber electrodes. A 5 cm $\times$ 7 cm electrode was placed on Cz, a second 4.5 cm $\times$ 4.5 cm electrode on Oz to achieve a maximum of posterior stimulation in accordance with previous experiments (see Figure 3.1 C Neuling et al., 2013; Kasten et al., 2016). The electrodes were affixed to the scalp using Ten20 conductive paste (D.O. Weaver, Aurora, CO, United States) and the impedances were brought below 10 kΩ (mean impedance 3.7 kΩ). Before starting the experiment, it was ensured that each participant was comfortable with a stimulation current of 1 mA peak to peak and did not experience pain, tingling or other unpleasant sensations. For each participant a sinusoidal stimulation at pre-determined IAF was applied. The signal was computed using MATLAB 2016b (The MathWorks, Inc., Natick, MA, United States), and generated using a DAQ-module Ni USB 6229 (National Instruments, Austin, TX, United States) at 10 kHz, then fed into the stimulator via its remote access port. The NiDAQ was externally clocked by the actiCHamp EEG amplifier. The total stimulation duration was 10 min. In accordance to previous studies (Neuling et al., 2013; Kasten et al., 2016), the stimulation started with a linear fade-in of 10 s from 0 to 1 mA amplitude and ended with a linear fade-out of 10 s. The sham stimulation consisted of a 10 s linear fade-in, 10 s of stimulation at 1 mA, followed by a 10 s linear fade-out.

3.3.4 Procedure

The experiment consisted of two separate sessions: one with ambient illumination in the lab and one without, in the following denoted ‘light’ and ‘dark.’ Every participant took part in both sessions (50% ‘light’ at first day, 50% ‘dark’ at first day) with an interval of at least 3 days between both sessions to avoid

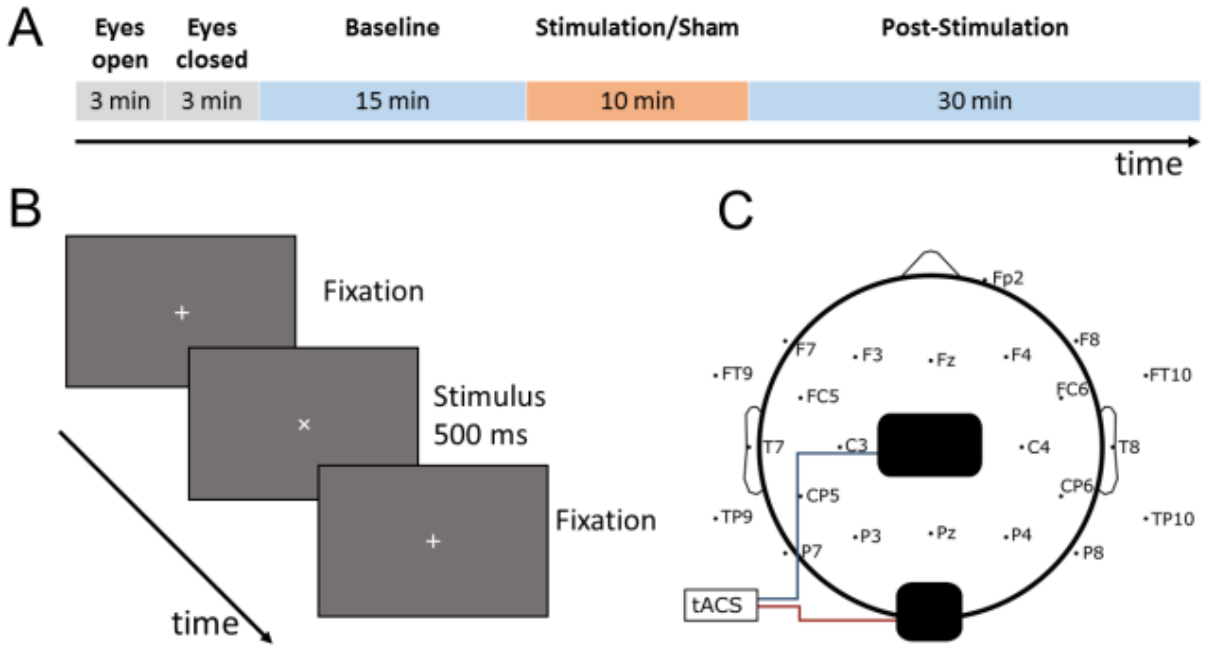

Figure 3.1: Experimental setup: (A) time course of the experiment: a single session started with two 3-min recordings to determine the individual alpha frequency (IAF) once with eyes open and once with eyes closed in a relaxed state. Following this, the participants had to conduct the visual vigilance task for a total duration of 55 min (15 min baseline, 10 min stimulation/sham, 30 min post-stimulation). 15 min after the start of the task, the participants received either 10 min of tACS or sham stimulation at their IAF with an amplitude of 1 mA. **(B)** Visual vigilance: the participants had to fixate a small cross in the middle of the screen during the whole experiment. Every 35–45 s the fixation cross rotated by 45° and stayed rotated for 500 ms. The participants had to detect this rotation and to respond by pressing a button with their right index finger. **(C)** Setup of the tACS electrodes and the EEG electrodes: a 5 cm × 7 cm electrode was placed on Cz and a smaller 4.5 cm × 7 4.5 cm electrode on Oz according to the international 10/10 system.

carry-over effects. During the session without ambient illumination, all light sources except the computer monitor for stimulus presentation were turned off. During the session with ambient illumination a 50 W spotlight, positioned in the ceiling thirty centimeters behind the participant, was switched on and dimmed to have an intensity of 500 lx at 1 m distance (height of the participant's head, see Figure 3.2). Participants were seated in a comfortable chair, 75 cm in front of a Samsung P2470H monitor running at 60 Hz. After preparation of the EEG cap and stimulation electrodes, each session started with a 3-min block resting-EEG with open eyes followed by a 3-min block resting EEG with eyes closed.

The IAF for each participant was determined before the experiment by using the unfiltered 3 min recording during opened eyes, dividing it into 1-s epochs and scanning for the power peak between 8 and 12 Hz at electrode Pz. If the eyes-open recording did not yield a clear alpha peak (this was the case in 20 out of 60 measurements), we used the peak obtained from the eyes-closed recording as the stimulation

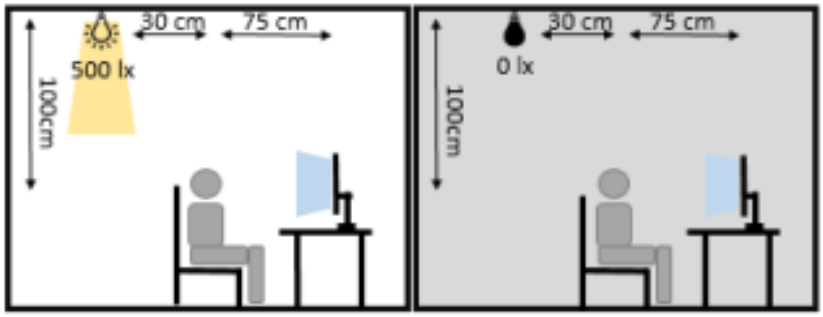

Figure 3.2: Illumination conditions during experimental sessions. The participant was seated 75 cm in front of the monitor. 30 cm behind and 100 cm above the participant's head, an LED spotlight was positioned. During the 'dark'-session the spotlight was turned off and the monitor constituted the only light source in the room. During the 'light'-session, the spotlight was turned on and produced 500 lx at a distance of 1 m.

frequency, since the frequency of the two peaks correlated significantly in the other 40 measurements (r = 0.63, p <0.001).

One session of the experiment lasted 55 min during which participants were required to fixate a white 7 mm fixation cross (0.535 vis. deg.), on a gray background (54 cd/m2). To keep the participants alert, they had to indicate rotations of the fixation cross (45°, 500 ms duration) occurring every 35–45 s by pressing a button with their right index finger (Figure 3.1 B).

Visual stimulation and timing of the experiment were controlled with the Psychophysics toolbox (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) for MATLAB. EEG was recorded throughout the complete duration of the session. The first 15 min served as a pre-stimulation measurement, followed by a 10-min block of stimulation or sham-stimulation and 30 min of post-stimulation measurement (Figure 3.1 A).

Fifty percent of the participants were randomly assigned to receive sham-stimulation. The resulting gender distribution was eight females in the stimulation group and seven in the sham group. The mean age of the resulting stim group was 24.2 years (SD : 4.4) and 24.3 years (SD : 5.6) in the sham group. Each participant took part in both sessions on different days with two contrasting illumination conditions, with 50% being randomly assigned to start with the second condition on the first day. The second session for each participant always took place at the same time of day as the first session. In both the sham and stimulation group, seven participants were measured in the morning and eight in the afternoon. After each session, participants filled out an adverse effect questionnaire (Brunoni et al., 2011) to indicate whether they experienced any of the common 10 side effects: headache, neck pain, skin irritation, tingling, itching, burning sensation, reddening of the skin, tiredness, trouble concentrating, and mood changes. In addition, it was asked whether they believed to have received stimulation. Participants rated the intensity of each

effect on a scale from one to four (1 – none, 2 – mild, 3 – moderate, 4 – severe) and whether they attributed the occurrence to the stimulation (1 – no, 2 – remote, 3 – probable, 4 – definite).

3.3.5 Data Processing

The EEG data was down-sampled to 500 Hz, high-pass filtered at 1 Hz and low-pass filtered at 100 Hz and re-referenced to a combined Fp1/Fp2 reference using MATLAB and the Fieldtrip toolbox (Oostenveld et al., 2011). Subsequently, the data was cut into two baseline blocks with a length of 5 min (15–10 min and 5-0 min before stimulation) and 30 blocks after stimulation of 1 min each. Eye blinks and eye movement artifacts were removed from the data, using an independent component analysis by manually rejecting the respective components. The blocks were then subdivided into 1-s segments and further DC-jumps and strong muscle artifacts were rejected by identifying all segments that presented a difference between minima and maxima of at least 150 μV. The first 270 artifact-free segments of the baseline blocks and 55 artifact-free segments of each block after stimulation were then used for further analysis. FFT-spectra were calculated for each segment using a Hanning window with 2 s zero-padding. FFT-spectra were then averaged across all segments for each block.

To compensate for a shift in the IAF over the course of the session since the initial determination of the stimulation frequency, the IAF for the post-stimulation power was determined by scanning for the power peak between 8 and 12 Hz in steps of 0.5 Hz at electrode Pz, averaged over the whole 30 min after the stimulation. The mean power of the IAF $\pm$ 2 Hz band averaged over all parietal electrodes was then used for further analysis.

According to the laws of synchronization (Pikovsky et al., 2002), even for a mismatch between stimulation frequency and IAF, we would still expect entrainment of the endogenous alpha oscillation, albeit weaker than with a mismatch of zero as has been shown in visual flicker experiments (Schwab et al., 2006). Such a mismatch can also influence the aftereffect of tACS (Vossen et al., 2015). To include the effects of small mismatches on the aftereffect, we added the factor mismatch to our analysis. As the relationship between strength of entrainment and frequency is non-linear (Notbohm et al., 2016) with the strongest entrainment centered on the eigenfrequency of the driven oscillator, we used only the absolute value of the mismatch.

3.3.6 Statistical Analysis

Statistical analysis was performed using SPSS 24.0 (IBMCorp, Armonk, NY, United States) and R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) employing the mgcv-package (Wood, 2017). Behavioral data analysis was conducted on accuracy (i.e., percent correct responses) and reaction times with a repeated measures ANOVA on the within-subjects factors *time* (baseline, stimulation, 0–15 min after stimulation, 16–30 min after stimulation) *illumination* ('light' vs. 'dark') and the between-subjects factor *group* (stimulation vs. sham). Greenhouse–Geisser correction was applied where appropriate. Differences in adverse effect between stimulation and sham group were tested using a Wilcoxon-Mann-Whitney-*U* test. Differences in answering the question of believing to have received stimulation were assessed using a Chi-squared test.

Changes in alpha power before stimulation were explored by comparing the absolute power values of the average 15–10 min (baseline 1) before stimulation onset with the average of 5–0 min (baseline 2) before stimulation onset in a repeated measures ANOVA with the within-subjects factor *time* (baseline 1 vs. baseline 2) and *illumination* ('light' vs. 'dark'), pooled over stimulation and sham group.

For the analysis of the aftereffect, all power values were normalized to the second baseline (5–0 min before stimulation). We explored the development of alpha power over time in the post-stimulation period by using a generalized additive mixed regression model (GAMM) in order to account for inter-subject variability and for time being a continuous, multi-level variable. The time period after the end of stimulation for which the aftereffect was analyzed lasted 30 min. If alpha values from 1800 spectra (30 min times 60 s) were entered into an ANOVA as a factor time with 1800 levels, this would most likely not yield significant results due to the huge number of degrees of freedom. Previous studies have circumvented this problem by averaging over adjacent time seconds in order reduce the number of levels in the ANOVA (Neuling et al., 2013; Kasten et al., 2016). A GAMM, however, adequately takes the multi-level factor time into account. As the distribution of the alpha values was strictly positive and right-skewed, a Gamma likelihood with an identity link was used in the model. The factors time, illumination, stimulation, frequency-mismatch, and day of measurement (1st or 2nd) were included as covariates and all pairwise interaction terms were constructed in order to gain a saturated model as a starting point. Three-way interactions were not considered because their interpretation is problematic. From this saturated initial model, we performed a manual model selection based on the Akaike Information Criterion (AIC) to obtain the optimal regression predictor with respect to model fit and complexity (See Supplementary Table 3.2 for a selection of tested

models). Further, the model included a random effect for a participant's ID, a random effect of time and a random effect of illumination. As multiple data points were collected subsequently for each individual, we needed to assume a dependency between measurements of the same participant. For the random effects, we applied an auto-correlated covariance structure of order 1 per ID and illumination scenario.

3.4 Results

3.4.1 Behavioral Results

The participants reached an average accuracy of 91.2% (SD: 8.8%) in the vigilance task with an average reaction time of 503 ms (SD : 125 ms), indicating high vigilance of the participants throughout the study. A repeated measures ANOVA with the between factor group and the within factors illumination and time (baseline, stimulation, 0–15 min after stimulation, 16–30 min after stimulation) did not show significant differences in reaction times between groups (*group*: $F_{1,28}$ = 0.828, *p* = 0.371, η^2 = 0.029; *illumination*: $F_{1,28}$ = 0.042, *p* = 0.840, η^2 = 0.001; *time*: $F_{3,26}$ = 2.202, *p* = 0.094, η^2 = 0.073; *group* $\times$ *time*: $F_{3,26}$= 0.520, *p* = 0.587, η^2 = 0.018; *illumination* $\times$ *time*: $F_{3,26}$= 2.318, *p* = 0.81, η^2 = 0.076; *group* $\times$ *illumination*: $F_{1,28}$ = 1.987, *p* = 0.170, η^2 = 0.066; *group* $\times$ *illumination* $\times$ *time*: $F_{3,26}$ = 0.579, *p* = 0.630, η^2 = 0.020). A repeated measures ANOVA with the same factors on accuracy revealed a significant effect of time and a significant interaction between *ambience* and *time* (*group*: $F_{1,28}$ = 0.036, *p* = 0.85, η^2 = 0.001; *illumination*: $F_{1,28}$ = 2.217, p = 0.148, η^2 = 0.073; *time*: $F_{3,26}$ = 23.161, *p* <0.001, η^2 = 0.453; *group* $\times$ *time*: $F_{3,26}$= 0.170, *p* = 0.855, η^2 = 0.006; *illumination* $\times$ *time*: $F_{3,26}$= 4.448, *p* = 0.013, η^2 = 0.137; *group* $\times$ *illumination*: $F_{1,28}$ = 0, *p* = 0.990, η^2 = 0; *group* $\times$ *illumination* $\times$ *time*: $F_{3,26}$ = 0.303, *p* = 0.823, η^2 = 0.011). In order to resolve the illumination $\times$ time interaction, we performed two-sided t-tests comparing the accuracy between illumination conditions in each block. Uncorrected results showed a difference at the last block of time (baseline: t_{58} <0.01, p = 1.000, *d* <0.01; stimulation: t_{58} = -0.876, *p* = 0.385, *d* = 0.230; post1 : t_{58} = 1.77, *p* = 0.081, *d* = 0.465; post2 : t_{58} = 2.04, *p* = 0.045, *d* = 0.537). After applying FDR-correction, this effect did not survive (baseline: p = 1.000; stimulation: *p* = 0.513; post1 : *p* = 0.164; post2 : *p* = 0.164). The time course of accuracy, as depicted in Figure 3.3 suggests a general decrease of accuracy over time. In order assess the effect of fatigue, we tested the mean single-subject correlations of accuracy and block number against zero. This revealed that accuracy declined with time passed throughout the experiment [t_{29} = -5.8917, *p* <0.01].

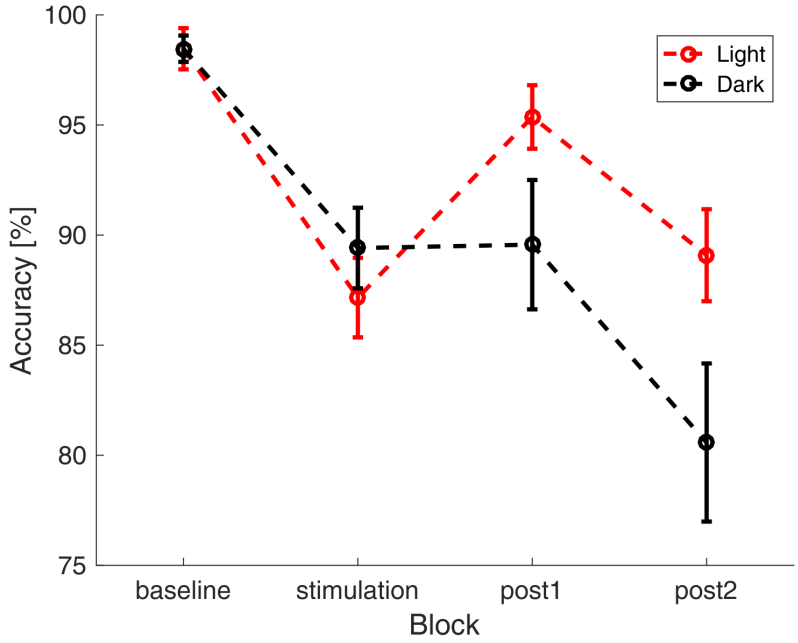

Figure 3.3: Accuracy in the visual vigilance task over time. Average accuracy in the four different blocks of the experiment (baseline, stimulation, 0–15 min after stimulation, 16–30 min after stimulation). The data was pooled over both stimulation and sham group. In red the results during the 'light'-condition are depicted, black depicts the 'dark'-condition. The error bars show the standard error of the mean.

The answers to the questions whether participants believed to have received stimulation did not differ significantly between groups (stim: 76.67%, sham: 66.67%, χ^2_1 = 0.739, p = 0.39). The response to the items on the adverse effect questionnaire did not show a significant difference between stimulation and sham group (Mann-Whitney-U test: all p <0.05). This indicates that the blinding was successful. Most frequently reported symptoms were tiredness (85%), trouble concentrating (76.67%) and tingling (40%). Only tingling was on average attributed to the stimulation (mean score: 2.5).

3.4.2 Pre-stimulation Alpha-Increase

Analyses revealed a significant main effect of *time* ($F_{1,29}$ = 12.202, p = 0.002, η^2 = 0.296), whereas the factor *illumination* ($F_{1,29}$ = 0.002, p = 0.961, η^2 <0.001) and the interaction *time* $\times$ *illumination* ($F_{1,29}$ = 3.13, p = 0.088, η^2 = 0.097) did not reach significance, indicating a similar increase of pre-stimulation alpha power from baseline 1 to baseline 2 for both illumination conditions (Figure 3.4).

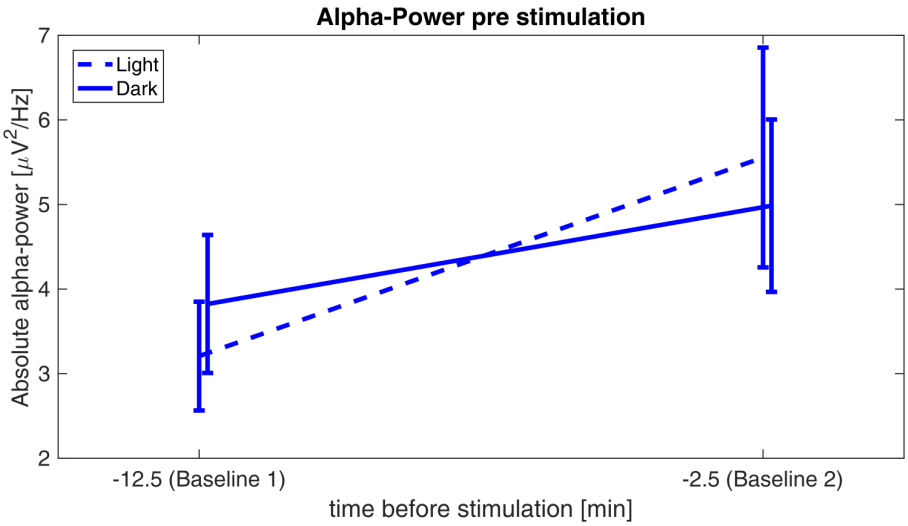

Figure 3.4: Alpha-power before stimulation. Absolute alpha power before stimulation: power values are averaged over the first 5 min (baseline 1) of the experiment and 5 min before onset of the stimulation (baseline 2) for the sessions in 'light' (dashed) and in 'dark' (solid).

3.4.3 Aftereffect

Evaluation of the mismatch between stimulation-frequency and the IAF of the measurement's last minute revealed that the initial estimation deviated on average 0.7 Hz in the 'light'-group and 0.8 Hz in the 'dark'-group with rare mismatches up to $\pm$2.5 Hz as can be seen in Figure 3.5. To control for effects of the mismatch, it was added as a factor to the GAM-model.

The final model contained the fixed effects factor *illumination* and the interactions *illumination* $\times$ *frequency-mismatch*, *illumination* $\times$ *time* and *stimulation* $\times$ *time* as well as the random effects factors *time* and *illumination*. All other factors and interactions have been removed in order to gain a model of minimal AIC.

The final model predicts relative alpha power post-stimulation according to the following equation:

$$\begin{aligned}\alpha =& \beta_0 + \beta_1 illum + \beta_2 illum \times mmatch + \beta_3 illum \times time + \beta_4 stim \times time + \gamma_{0,ID} \\ &+ \gamma_{1,ID} \times time + \gamma_{1,ID} \times illum + \epsilon\end{aligned} \tag{3.1}$$

All β-coefficients represent fixed effects, whereas γ-coefficients represent random effects. The coefficients β_0, β_1, β_2, γ_0, γ_2 describe the intercept (i.e., the power of the alpha activity immediately after the end of the stimulation period) of the post-stimulation alpha time course depending on the conditions of

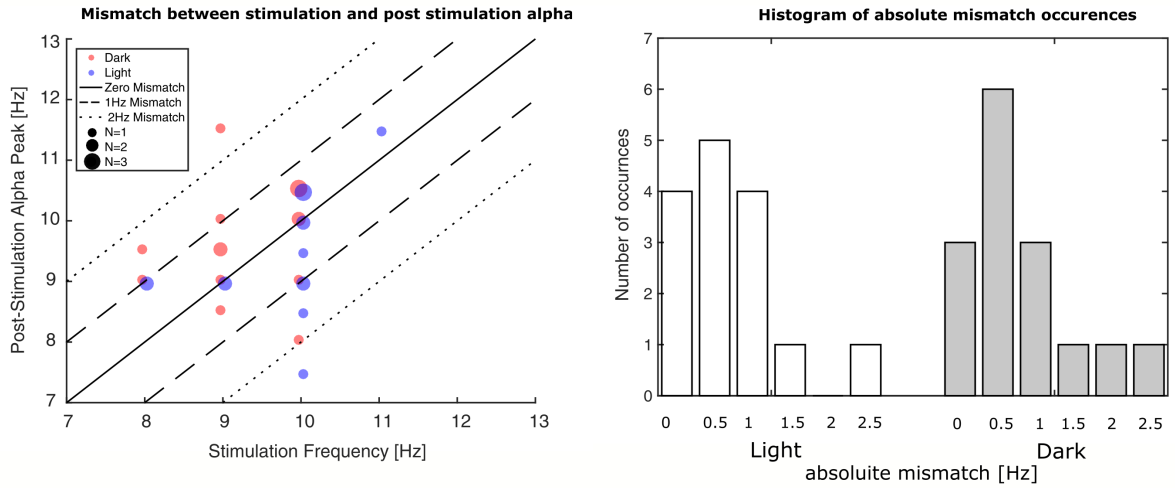

Figure 3.5: Occurrences of mismatches between stimulation frequency and post-stimulation alpha frequency. (A) Plot of stimulation frequency vs. post-stimulation IAF. The smallest dots represent single participants, whereas the bigger dots represent two or three participants. Blue dots represent participants in the 'light' condition; red dots represent participants in the 'dark' condition. The solid line depicts zero mismatch between stimulation frequency and post-stimulation IAF; the dashed lines depict the areas of $\pm$1 Hz and $\pm$2 Hz deviation. **(B)** Histograms depict number of occurred frequency mismatches between stimulation frequency and post-stimulation IAF. Left bars: 'light' condition; right bars: 'dark' condition. The mismatch is shown in absolute deviations in Hz in accordance with their inclusion in the GAMM-based analysis.

illumination, *stimulation*, and the *mismatch* between stimulation frequency and IAF as well as random individual effects. The coefficients β_3, β_4, and γ_1 describe the slope (i.e., increase in alpha power over time), depending on stimulation, illumination and the random individual effects, while ϵ describes the residual error.

The estimators of the final model are listed in Table 3.1, demonstrating a significant effect of illumination on alpha power and significant interactions of *illumination* $\times$ *time* and *stimulation* $\times$ *time*. The final model has a marginal R^2 of 0.078, measuring the determination of the fixed effects and a conditional R^2 of 0.999, measuring the determination of both the fixed and the individual random effects. In Figure 3.6 A, B, the smoothed time course of the measured power change for a 'dark' and 'light' ambience are depicted, whereas Figure 3.6 C shows the resulting predictions of the model for linear alpha increase in the different groups, omitting the effect of frequency-mismatch which did not reach significance.

Immediately after the end of stimulation, both stimulation and sham group in the 'dark' condition showed a higher increase in alpha power by 20% compared to baseline (general intercept β_0). In contrast to this, brighter illumination only shows a smaller increase in alpha power of about 7% within both the stimulation and the sham group (β_0 + intercept due to illumination β_1). Within the 30 min post-stimulation period, the alpha power in the sham group remained stable during darkness, whereas alpha power in the 'light'

Table 3.1: Result summary of final generalized additive mixed model.

Parameter	Coefficients β	SE(β)	*t*	*p*
(β_0)Intercept	120.900	4.782	25.285	<0.001
(β_1)Illumination	-13.183	6.284	-2.098	0.036
(β_2)Illumination $\times$ Freq.Mismatch	10.965	7.583	1.446	0.148
(β_3)Illumination $\times$ Time	0.337	0.155	2.180	0.029
(β_4)Stimulation $\times$ Time	0.366	0.171	2.133	0.033

Coefficient estimates β for the fixed effects, standard Error SE(β), t-value t and significance level p. The model's has marginal R^2 of 0.078 and a conditional R^2 of 0.999.

condition increased by an additional 0.337% per minute (slope caused by illumination β_3). In the stimulated groups, the stimulation leads to a general increase of power over time by 0.366% per minute in darkness (slope caused by stimulation β_4). Within the stimulated group in 'light' this adds up to the illumination-based increase to an increase of 0.7% per minute (slope β_3+ β_4), resulting in ultimately higher alpha power within the stimulated group, compared to the respective sham group (See Supplementary Figure for a plot containing all individual trajectories).

While we did not test whether our effects are frequency specific, grand average of the power spectra averaged over the total 30 min of post-stimulation show that the differences between conditions are closely confined to the immediate vicinity of the alpha peak, as can be seen in Figure 3.7.

3.5 Discussion

In this study, we assessed whether 10 min of stimulation at IAF produces an aftereffect of elevated alpha power as has been reported previously for longer stimulation durations. Moreover, we explored the impact of ambient illumination on the occurrence of this aftereffect. Our results show that 10 min of tACS led to an aftereffect in alpha power similar to earlier findings of Zaehle et al. (2010), who found an aftereffect of increased alpha power within the first three min after stimulation. Extending the findings of Zaehle et al. (2010), our results demonstrate a linear increase of alpha power within thirty min after stimulation. Furthermore, our results show that the alpha power immediately after the end of the stimulation period (tACS/sham) depends on ambient illumination level.

We found that the expected decrease of alpha activity in a bright environment (Min et al., 2013) was not present within the first 15 min of our recordings (baseline 1 to baseline 2). Instead, illumination seems to

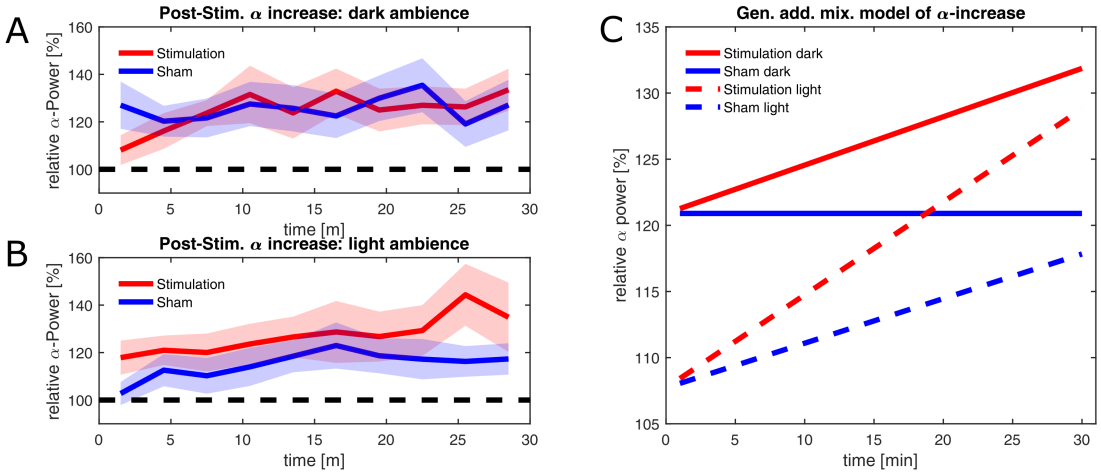

Figure 3.6: Alpha-power changes post-stimulation. (A) Time course of the relative alpha power during the 30 min after stimulation in the 'dark' condition. **(B)** Time course of the relative alpha power during the 30 min after stimulation in the 'light' condition. Alpha-power is relative to baseline 2, averaged over three min. Stimulation group is shown in red and sham group is shown in blue. The dashed black line represents baseline power. The shaded areas depict standard error of the mean. **(C)** Time course of alpha power as fitted with a GAMM with the fixed effects of time, stimulation and illumination, omitting random effects and the non-significant effect of frequency mismatch. The blue lines depict the sham groups; the red lines depict the stimulation groups. Solid lines depict power in darkness, while dashed lines depict the power in the 'light' condition. The letters 'i' indicate the intercepts of the time course of alpha, resulting from the coefficient β_0 in darkness, and the coefficients β_0+β_1 in light. The letters 's' indicate the slopes of the time course of alpha, resulting from the coefficients β_3 and β_4 (power change over time) in light and due to stimulation, respectively. For stimulation in ambient light, coefficients β_3 and β_4 add up, leading to the steepest increase of alpha over time.

take effect during the stimulation period (tACS/sham), resulting in reduced alpha power at the beginning of the post-stimulation period, i.e., the time course of alpha power after stimulation starts at different levels for the 'dark' and the 'light' condition. Our results suggest that in the absence of stimulation, there is a general increase in alpha activity in ambient light which is absent in a dark environment. A general increase in alpha activity over time was to be expected, as the continuous task causes increasing mental fatigue, which is a well-known effect (Daniel, 1967; Cajochen et al., 1995; Boksem et al., 2005; Oken et al., 2006).

We could not find evidence that tACS-aftereffect is dependent on illumination. It rather seems that tACS raises the total power level toward which the alpha activity converges, adding linearly to the illumination effect. It seems, that the endogenous alpha in our 'dark' condition did not reach a ceiling level above which a further elevation by tACS is no longer possible (Neuling et al., 2013), refuting our initial hypothesis. The ongoing vigilance task probably prevents the fatigue induced alpha activity from reaching a ceiling level that cannot be further increased.

It has been shown, that perception is linked to the activity in the alpha band (Ergenoglu et al., 2004; Hanslmayr et al., 2005; Thut et al., 2006). However, we only found a general decline in the participants'

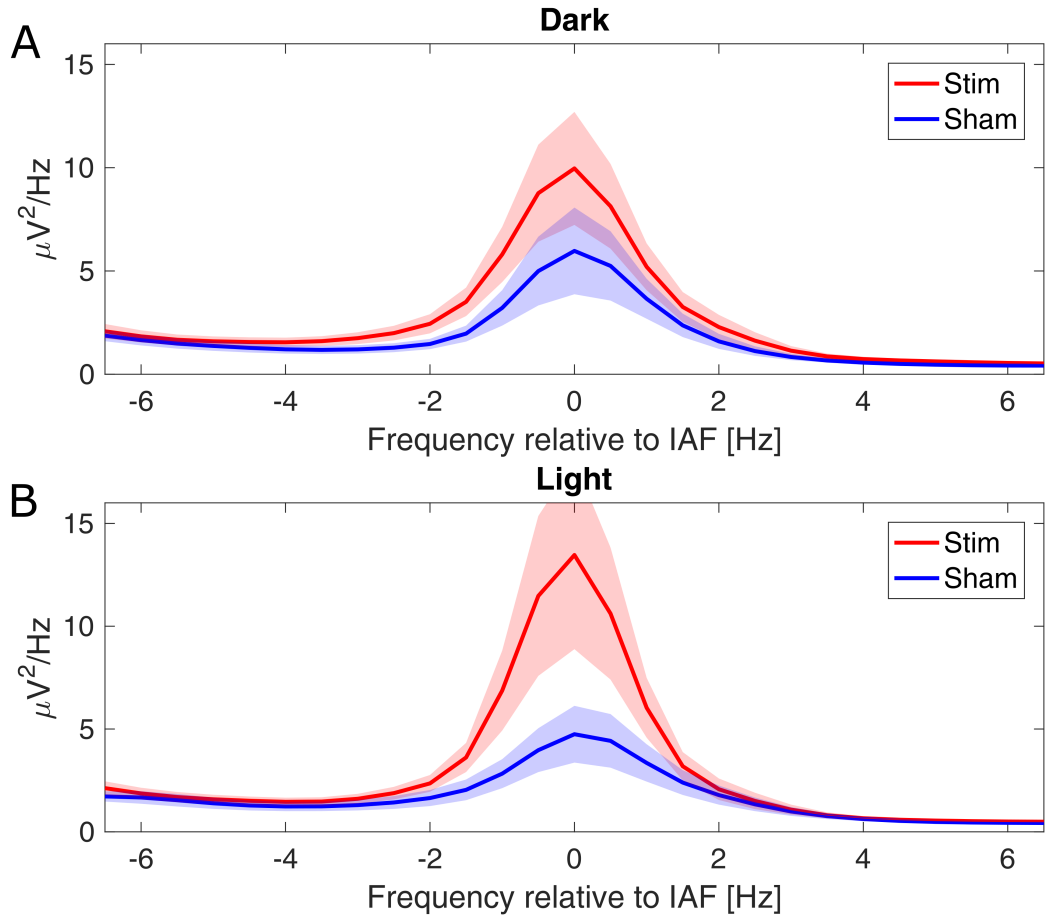

Figure 3.7: Power spectra post-stimulation Grand average power spectra of the mean alpha activity post-stimulation, centered on the IAF for each participant (peak power between 7.5 and 12 Hz). **(A)** In 'dark' **(B)** in 'light'. Shaded area shows the standard error of the mean.

accuracy over time in the vigilance task, which seemed to be independent of ambience illumination and stimulation. This is in line with an earlier study (Kasten et al., 2016), that used the same visual vigilance task. This effect is probably due to our stimuli being super-threshold and lasting several alpha-cycles, as they were merely designed to keep the participants in a state of sustained attention.

Our findings of a delayed increase in post-stimulation alpha power is in line with studies utilizing 20 min of tACS and a prolonged measurement of post-stimulation activity (Neuling et al., 2013; Kasten et al., 2016). Whereas numerous studies have suggested entrainment as a candidate mechanism during tACS (Neuling et al., 2012a, 2015; Helfrich et al., 2014b; Strüber et al., 2014; Witkowski et al., 2015), recent findings of Vossen et al. (2015) could show that the aftereffect is not a manifestation of entrainment echoes. Instead, their findings point toward spike-timing dependent plasticity (STDP, see Feldman, 2012) as the main factor for bringing up tACS aftereffects as was previously suggested by Zaehle et al. (2010). Accord-

ing to Veniero et al. (2015), STDP acts during the entrained state of tACS by causing synapses in recurrent neuronal networks of specific intrinsic frequencies to strengthen their connections by long term potentiation (LTP), whereas others are weakened by long term depression (LTD). Thus, it seems plausible to assume a two-stage process to be responsible for tACS aftereffects to occur: at first, entrainment is responsible for amplitude enhancements of brain oscillations during tACS. Second, if entrainment lasts sufficiently long, synaptic plasticity is induced resulting in prolonged amplitude enhancements after the end of stimulation. From this point of view, our findings suggest that the ambient illumination influences the natural increase or decrease of alpha activity, whereas the maximum capacity of the underlying networks for alpha activity can be strengthened by tACS.

It is currently unclear how long these changes persist. The natural increase in power during long-lasting experiments (>1 h), ultimately leads to the power of the unstimulated conditions catching up to the level of the stimulated condition, which masks the “real” stimulation effect, as reported by Kasten et al. (2016) for an aftereffect-duration of 70 min. This, however, does not necessarily mean that physiological changes induced by tACS have ceased at this point in time. A major problem in studying tACS aftereffects is the increase of alpha activity caused by fatigue. In order to better control this source of alpha increment, future studies might employ events that naturally diminish the alpha-activity in the post-stimulation period – like a marked change in illumination. This procedure could reveal if a stimulation-induced faster increase in alpha activity is still present and, thereby, help to disentangle fatigue-driven from tACS-induced alpha enhancements.

As the difference in brightness of the two illumination levels that we employed was relatively small, we cannot generalize tACS effect to more drastic differences in illumination like daylight vs. complete darkness. However, given that even small differences in illumination led to significant effects on the natural progression of alpha activity during a sustained task, we strongly suggest to take ambient illumination into consideration when designing alpha modulation studies.

Depending on the overall duration of the experiment and the length of the post-stimulation observation period, very low levels of illumination may raise the alpha activity to high levels, where aftereffects of tACS are no longer visible.

3.6 Author Contributions

HS, TP, DS, CH: designed the study; HS, TP: acquired the data; HS, FS, TP: analyzed the data; HS, TP, FS, DS, CH: wrote the article.

3.7 Funding

This work was supported by DFG (Deutsche Forschungsgemeinschaft) Priority Program 1665 to CH (SPP1665 HE 3353/8-1).

3.8 Supplementary Material

3.8.1 Supplementary Figures

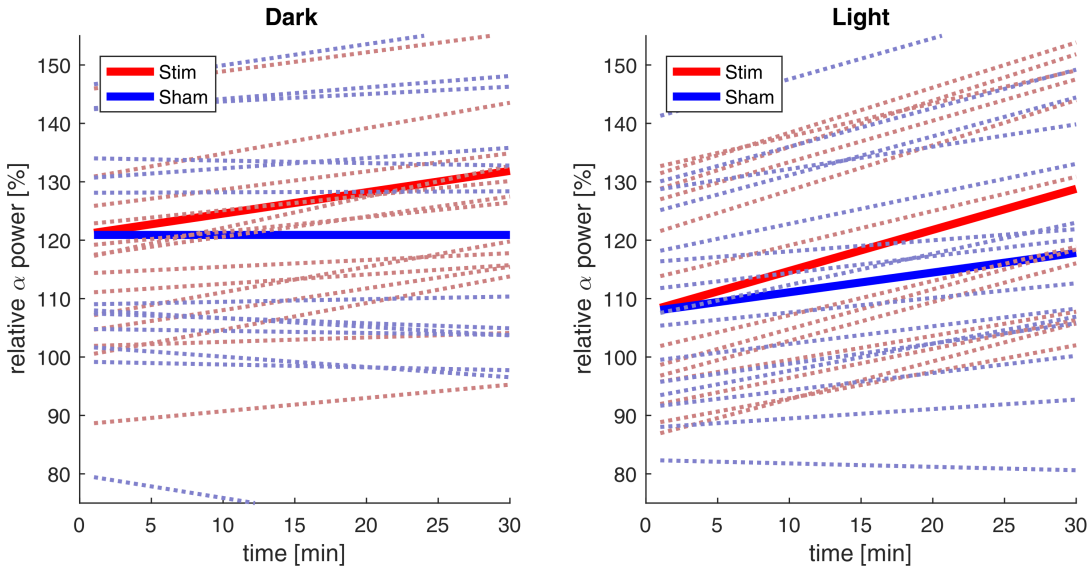

Figure 3.8: Time course of alpha power as fitted with a GAMM for the fixed effects (bold lines) and time course for each individual with the individual random effects (thin lines). Red are the stimulation groups; blue are the sham groups.

3.8.2 Supplementary Tables

Table 3.2: The table shows a selection of different generalized additive mixed models that were tested during the manual model selection process. In the Model column, the formulas with different selections of all factors and interactions are shown. The Random column shows the respective selection of random effects, while the Correlation column depicts the employed autocorrelation. For each tested model the Akaike information criterion is shown, which represents a relative measure for the quality of the model for the given dataset, where lower values represent less information loss. The final model, that was selected for our statistics can be found at the bottom.

Model	Random	Correlation	AIC
Mismatch:Illu + Illu + Illu:Time + Time:Stim	ID = $\sim$ Time, Illu = $\sim$ 1	-	177260.19
Mismatch:Illu + Illu + Illu:Time + Time:Stim	ID =$\sim$ 1	corAR1(form= $\sim$ Time| ID/Illu)	17892.16
Mismatch + Illu:Time:Stim	ID = $\sim$ Time, Illu = $\sim$ 1	corAR1(form= $\sim$ Time| ID/Illu)	17713.19
Mismatch:Illu + Illu + Illu:Time + Time + Stim + Time:Stim	ID = $\sim$e Time,Illu = $\sim$ 1	corAR1(form= $\sim$ Time| ID/Illu)	17709.53
Illu + Illu:Time + Time:Stim	ID = $\sim$ Time, Illu = $\sim$ 1	corAR1(form= $\sim$ Time| ID/Illu)	17707.90
Mismatch:Illu + Illu + Illu:Time + Time:Stim	ID = $\sim$ Time, Illu = $\sim$ 1	corAR1(form= $\sim$ Time| ID/Illu)	17707.83

Chapter 4

General Discussion

4.1 Summary

Intervention studies explore the functional role of brain rhythms by the targeted modulation of activity at specific frequencies. These modulations have been shown to lead to lasting physiological changes in some cases, while having no effects in other comparable study designs. As these lasting effects can have great value for the exploration of the functional role of brain rhythms as well as the development of therapeutic procedures, it is important to understand which factors allow their deliberate generation. The studies introduced in this thesis explored factors that might influence the physiological outcome of tACS in the α-band. The first study, introduced in Chapter 2, explored if shorter durations of stimulation, than those usually employed (Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015; Zaehle et al., 2010), were sufficient to induce physiological aftereffects. The study could not achieve its goal of finding a new minimal α-tACS duration and could not reproduce the known aftereffects following 10 minutes of stimulation. This motivated the second study, introduced in Chapter 3, in which it was tested if the previously shown aftereffect of 10 minutes of tACS might be dependent on the illumination condition during recording, which is known to influence endogenous α-activity. While the results did not show that the illumination affected the physiological aftereffect of tACS, they could demonstrate that dimmer illumination leads to a strong endogenous increase in α-power within the first minutes of recording, which might mask potential aftereffects in early recordings. This finding also offers a good explanation why in study 1 no aftereffect could be found following the 10 min tACS-block, when the block constituted the first in the sequence. It is noteworthy that in both studies a portion of band-power variance post-stimulation was explained due to the mismatch between pre-established stimulation frequency and later determined IAF.

4.2 Limitations

Both conducted studies were aimed at identifying factors that influence the occurrence of tACS-aftereffects. They were not meant to offer new insights into the physiological mechanisms taking place during stimulation or the exact nature of the aftereffects. For this reason, the studies focused on the effect of increased power of the stimulated band as the most prominent physiological after effect, although previous research also explored different effects, like increased phase locking (Helfrich et al., 2014b). Therefore, the studies contain a few limitations in their informative value if only considered on their own. First off, the studies employed no control conditions, except a sham group, and control analyses to test whether the effects are specific to stimulation-site, stimulation-frequency, targeted brain areas and frequency bands (Veniero et al., 2016). Such tests were conducted by a variety of past studies with the goal of exploring if tACS-effects indeed entailed the necessary properties associated with targeted entrainment. For instance, the *online* effect on cognitive functions was shown to be specific for a single stimulation frequency, while absent in other frequencies (Feurra et al., 2011c,a, 2013; Kanai et al., 2008). Other studies compared different electrode montages (Gundlach et al., 2016; Mehta et al., 2015) and could thereby show that behavioral *online* effects were site-specific. Studies on the *offline* effect of tACS demonstrated, that lasting modulations of EEG-activity were confined to the stimulated band (Helfrich et al., 2014a; Kasten et al., 2016; Vossen et al., 2015; Zaehle et al., 2010).

By design, both presented studies did not include a demanding cognitive task, which would allow the exploration of behavioral consequences. Therefore, their results offer no insights whether the physiological offline effect of increased band power is also associated with a functional component. Studies that explored the behavioral outcome following rhythmic stimulation are rather rare (see Veniero et al., 2015), but there are a few studies that found lasting effects. Following theta-burst rTMS (Marshall et al., 2015) could show impaired spatial attention outlasting the stimulation, while Rizk et al. (2013) could demonstrate a lasting effect in an visual exploration task. For tACS, sleep studies could show that slow-wave stimulation can have a short lasting effect on declarative memory (Garside et al., 2014; Marshall et al., 2006) and recently Kasten and Herrmann (2017) could show that the effect of α-tACS on mental rotation performance outlasted the stimulation. Additionally, the low demand of the visual vigilance task employed in both presented studies, enabled the participants to conduct individual different cognitive behavior to pass the time. Participants might have maintained attention on the task or reverted to other strategies like mind wandering (Braboszcz and Delorme, 2011) or counting time between stimuli which could have affected

their endogenous alpha-activity. Without a way of tracking the respective individually applied mental strategy, this could have added large inter individual variance to the results, which were only partly accounted for by using statistics which allow random effects of participants.

4.3 Implications

tACS in the α-band has been widely utilized in past research to successfully elicit online as well as offline effects. Lasting physiological effects of the stimulation were replicated multiple times for cumulative stimulation durations of $\sim$ 20 minutes (Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015), but seldom shown for shorter durations (Zaehle et al., 2010). In other studies such an aftereffect remained absent in some conditions (Neuling et al., 2013; Vossen et al., 2015) or altogether (Fekete et al., 2018; Sliva et al., 2018). For the successful application of tACS as a tool in brain research it is crucial to understand by which factors the occurrence of physiological aftereffects is influenced. The presented findings were aimed at closing some of the gaps in the knowledge by exploring if the factors of ambient illumination and stimulation duration interfere with the elicitation of aftereffects in the α-band. The results could successfully offer one explanation for the absence of aftereffects but failed to find a new minimal stimulation duration necessary for the elicitation of tACS aftereffects. The results also hinted at the factor of mismatching stimulation frequencies playing a significant role for the strength of aftereffects. The first presented study was meant to find a shorter tACS duration in the α-band, which is still sufficient to induce aftereffects, but failed to find a shorter minimal duration than the already known 10 minutes. Additionally, the results also failed to replicate previous findings following 10-min α-tACS. As the stimulation protocol were very comparable to other studies were tACS successfully elicited lasting effects, the findings imply that the effect of stimulation can be absent due to unconsidered differences in minor parameters. Thereby the study integrates into the line of other failed replications in the domain of tACS studies (Clayton et al., 2018; Fekete et al., 2018; Sliva et al., 2018; Veniero et al., 2017). Those studies have recently gained interest for their significance of offering a better understanding of the limits of the method of tACS and the requirements for its successful application. Research is now aimed at finding additional factors which impede stimulation effects from occurring. One factor which has been known to influence the outcome of stimulation is the mental state during stimulation. The state has previously been shown to influence the occurrence of stimulation effects in TMS (Silvanto et al., 2008). More recent studies, utilizing tACS, could also show that the occurrence of online effects is state dependent (Feurra et al., 2013; Ruhnau et al., 2016). Such a dependency was also

shown for offline effects of tACS (Alagapan et al., 2016; Neuling et al., 2013). This motivates the exploration of different mental states under which tACS is not-effective. Ambient illumination was considered one factor which sets the brain activity in a state where it could not be influenced, due to high endogenous alpha-activity (Min et al., 2013). The results of study 2, however, provide no evidence that illumination influences the elicitation of aftereffects. The results rather suggest that low illumination conditions will cause a strong increase in endogenous α-power over time, which can disturb the exploration of tACS effects if it coincides with the stimulation. As experiments involving the exploration of the α-rhythm, like the presented studies, usually employ cognitively non-demanding tasks, participants have a certain amount of freedom in their behavior. This sacrifices some amount of control over brain states un such experiments, making alpha not a primary candidate for exploration of state-dependency.

Another group of factors that are very likely to have an are factors which influence synaptic plasticity. As already mentioned in Chapter 1, there is plenty of evidence that synaptic plasticity is the cause of aftereffects following NTBS (Wischnewski et al., 2018). STDP is regarded as the mechanism of neuronal learning and development (Feldman, 2012; Markram, 1997). During learning, structural changes at the synapses between two neurons, which are associated by repetitive simultaneous activity strengthen the synaptic coupling between both as originally proposed by Hebbs (1949), and which is today often generally summarized as 'What fires together wires together' (Lowel and Singer, 1992). These effects of plasticity are on their own already very dependent on brain states (Ritter et al., 2015), as i.e. activity in the theta-band is known to affect LTP (Larson et al., 1986). But plasticity is also influenced by a multitude of other random factors, like sex, age, sleep/time of day, genetics and nicotine consumption (Ridding and Ziemann, 2010). These factors are difficult to control for in the average sample of participants and require an extensive individual exploration in their influence on stimulation effects. An understanding of their influence might then explain a portion of variance in the results of brain stimulation studies. Plasticity effects also offer a plausible explanation for the effect of stimulation frequency mismatches as found in the presented studies and by Vossen et al. (2015) synaptic changes are mainly mediated by NMDA-receptors (McBain and Mayer, 1994). In contrast to AMPA-receptors, which produce only a short lived amount of post-synaptic electric activity in response to a docking transmitter, NMDA-receptor act as a coincidence detectors (Bourne and Nicoll, 1993) as they integrate synaptic activity over time, by being partly voltage dependent. Long term potentiation at a synapse due to NMDA-gated calcium influx will occur if the postsynaptic membrane is depolarized shortly after synaptic release of Glutamate, which translates to a coincidence of the activity of the presynaptic cell to the activity of the postsynaptic neuron (Bourne

and Nicoll, 1993). If the Glutamate release of a spike repeatedly happens after the depolarization, and the presynaptic activity was thereby not causal for the postsynaptic activity, LTD processes will weaken the synapse (Feldman, 2012). When the generated electric field of tACS causes an accumulation of spikes in neurons that form recurrent loops, corresponding to the stimulation frequency, those synapses get strengthened as the spikes correspond to causal events. If the tACS frequency deviates far from the endogenous frequency of the network, no synaptic changes will happen or the network's synapses might get weakened (Vossen et al., 2015; Zaehle et al., 2010). In case of flawed estimation of the stimulation frequency, larger deviations from the true endogenous α-rhythm are expected to result in the absence or weaker physiological aftereffects. Moreover, while alpha activity has long been considered a stable frequency in individuals (Gasser et al., 1985; Kondacs, 1999; Salinsky et al., 1991), with high heritability (Posthuma et al., 2001), more recent research has shown that the frequency can be subject to state dependent shifts (Haegens et al., 2014; Mierau et al., 2017). Indeed, it is observable in recordings that, while some participants show a stable IAF, the peak frequency within the alpha-range can shift substantially in other participants (see Figure 4.1, for exemplary subjects. Unpublished data). In participants with such unstable peak frequencies, the endogenous rhythm might drift in and out the entrainment region during tACS, causing no stable plasticity effects to develop.

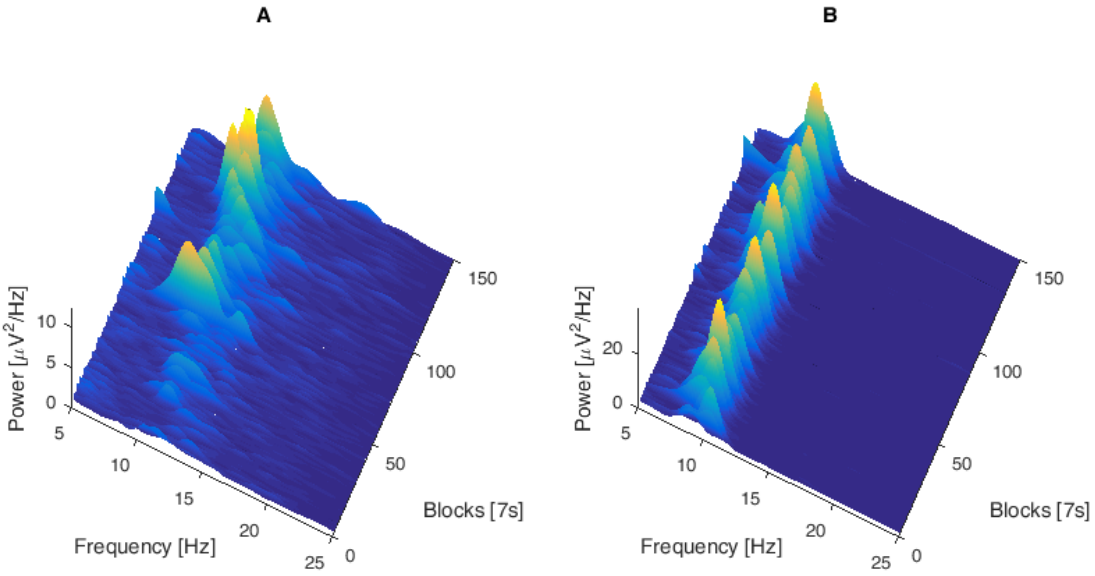

Figure 4.1: Individual alpha differences: Parietal EEG spectrograms of two different participants performing a visual luminance detection task. Each time point represents the average of a 7 seconds EEG-Block recorded with 8 seconds break in between. A: the alpha rhythm of the participant is unstable and deviates by up to 2 Hz. B: the participant shows a stable alpha rhythm with few frequency-deviations.

Vossen et al. (2015) discussed that a stimulation frequency slightly below the endogenous frequency should have the biggest effect on synaptic strengthening, as the spiking probability get shifted to a region of time where the spikes are detected as causal, whereas stimulation frequencies above the endogenous frequency may cause spikes preceding presynaptic events, thereby causing long term depression, weakening the recurrent loops at their eigenfrequency. This effect could be successfully demonstrated in their data as a correlation between the negative mismatch between IAF and stimulation frequency and the size of the aftereffect. The statistic models used in the studies in the presented studies in Chapters 2 and 3 employed the absolute value of the mismatch as a predictor variable and were therefore unfit to verify this concept. But as it is highly probable, given the known mechanisms of STDP (Markram, 1997),it should be considered in future tACS-experiments as a factor when the induction of physiological aftereffects is the main goal.

4.4 Future Study Designs

The preceding considerations and the results of the presented studies point at three main complications that might inhibit stimulation effects in otherwise reasonable experimental designs. The stimulation might be unsuitable to affect the targeted brain rhythm, individual factors might reduce the effects of plasticity at the target site, or the targeted rhythm might shift, thereby becoming unaffected by the employed stimulation. This offers a few lessons on the improvement of future tACS studies in general and the specific case of tACS targeted on the posterior α-rhythm. Employed standardized stimulation protocols might be unsuitable to affect the targeted brain rhythm at the targeted brain area in every participant, due to the huge inter individual variances in brain and skull anatomy (Krause and Cohen Kadosh, 2014). Effects of the stimulation might then be greatly increased by applying individualized stimulation protocols. This includes the precise localization of the targeted brain area and identification of the specific targeted brain rhythm (Bergmann et al., 2016). If anatomical data is available, the ideal electrode positions can be calculated by utilizing the most novel optimization approaches and toolboxes (Huang et al., 2018; Wagner et al., 2016). Secondly, the multitude of factors that might influence NTBS-induced plasticity, like, age, sex, nicotine consumption, sleep etc. (Ridding and Ziemann, 2010) should be acknowledged and particularly explored so that their individual effects on future results can be accordingly accounted for. Third, the emergence of endogenous changes in oscillatory activity, like shifting frequencies needs to be overcome. While this could be done by finding behavioral tasks that stabilize the rhythmic activity, this would severely limit the

scope of tACS as a method for the exploration of a wide variety of brain functions. Therefore, the best proposed method to approach this problem is the establishment of closed loop protocols that dynamically tune the stimulation parameters to the current endogenous activity (Bergmann et al., 2016; Boyle and Frohlich, 2013; Karabanov et al., 2016; Thut et al., 2017). In such designs the current brain activity is continuously

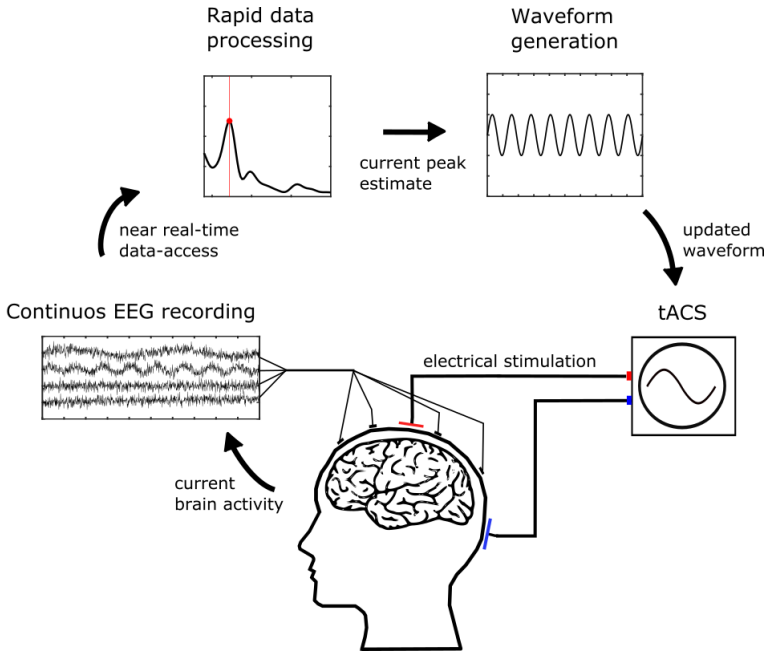

Figure 4.2: Proposed design for a closed loop tACS Experiment: A participants EEG is contiuosly recorded while the data is passed online to a processing routine. From the latest block of EEG activity, the current frequency of brain activity is determined by a rapid fourier transformation. The current frequency is than used to update the stimulation frequency accordingly for the next block of tACS.

measured by EEG or MEG. The most recent recorded data is accessed online with a minimal latency by a computer running a fast data processing program and used to determine the current activity state (i.e. the current frequency) in order to tailor an updated stimulation waveform, which is then directly feed into the transcranial stimulator (see Figure 4.2). Due to the electrical artifact, the recording during stimulation can not be used in the online processing. Therefore, such designs need to be intermittent, employing several short stimulation blocks, if the stimulation rhythm is close to the rhythm of interest. Dependent on the latency of the system and the length of the data that is used in every single iteration, such a system can react to changes in the range of seconds. Such a design has already been successfully employed in the targeted stimulation of sleep spindles (Lustenberger et al., 2016). In order to prove that found effects are specifically caused by the electrical stimulation at the targeted frequency and not due to somatosensoric perceptions, phosphenes or effects, unspecific to the employed waveform, future studies should, whenever

possible, include control conditions such as control frequencies outside the harmonics of the stimulated frequency (Pletzer et al., 2010) and control montages. To explore if the physiological aftereffects following stimulation are based in effects of plasticity future studies can also employ pharmacological agents, which influence plasticity effects, for example by the administration of NMDA-receptor agonists like dextromethorphane (Wischnewski et al., 2018) or even more potent substances like ketamine (Zorumski et al., 2016) or nitrous oxide (Jevtović-Todorović et al., 1998).

4.5 Conclusion

The presented studies were meant to explore the role of the factors of ambient illumination and the duration of applied stimulation on the occurrence of physiological aftereffects of elevated α-band power post tACS-intervention. The studies could successfully show that ambient illumination, while seemingly having no effect on the elicitation of aftereffects, is sufficient to induce changes in alpha activity that can mask the observation of stimulation-based effects. The other presented study failed to demonstrate a new minimal effective tACS duration and overall could only show an effect of tACS in one special case. This leaves the question which duration of tACS is enough for the elicitation of aftereffects still open. The discovery of short effective stimulation durations and a better understanding of the duration of the elicited aftereffects is highly interesting for future research and should be resolved swiftly. The utilization of shorter tACS blocks would enable the exploration of multiple conditions within fever and shorter experiments, thereby leading to a faster uncover of the effects of different factors on stimulation effects. The employment of sophisticated improvements in stimulation protocols can close the existing gaps in knowledge and render rhythmic noninvasive stimulation methods to a valuable tool in the research of brain functions and possible therapeutic approaches in the clinical settings.

References

Alagapan, S., Schmidt, S. L., Lefebvre, J., Hadar, E., Shin, H. W., and Fröhlich, F. (2016). Modulation of Cortical Oscillations by Low-Frequency Direct Cortical Stimulation Is State-Dependent. *PLOS Biology*, 14(3):e1002424.

Alekseichuk, I., Turi, Z., Amador de Lara, G., Antal, A., and Paulus, W. (2016). Spatial Working Memory in Humans Depends on Theta and High Gamma Synchronization in the Prefrontal Cortex. *Current Biology*, 26(12):1513–1521.

Ali, M. M., Sellers, K. K., and Frohlich, F. (2013). Transcranial Alternating Current Stimulation Modulates Large-Scale Cortical Network Activity by Network Resonance. *Journal of Neuroscience*, 33(27):11262–11275.

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., Cohen, L. G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M. S., Hamilton, R., Haueisen, J., Herrmann, C. S., Hummel, F. C., Lefaucheur, J. P., Liebetanz, D., Loo, C. K., McCaig, C. D., Miniussi, C., Miranda, P. C., Moliadze, V., Nitsche, M. A., Nowak, R., Padberg, F., Pascual-Leone, A., Poppendieck, W., Priori, A., Rossi, S., Rossini, P. M., Rothwell, J., Rueger, M. A., Ruffini, G., Schellhorn, K., Siebner, H. R., Ugawa, Y., Wexler, A., Ziemann, U., Hallett, M., and Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology*, 128(9):1774–1809.

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., and Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimulation*, 1(2):97–105.

Antal, A. and Herrmann, C. S. (2016). Transcranial Alternating Current and Random Noise Stimulation: Possible Mechanisms. *Neural Plasticity*, 2016:1–12.

Antal, A. and Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in human neuroscience*, 7(June):317.

Başar, E., Başar-Eroglu, C., Karakaş, S., Schürmann, M., Bas, E., Schurmann, M., Başar, E., Başar-Eroglu, C., Karakaş, S., Schürmann, M., Bas, E., and Schurmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *International Journal of Psychophysiology*, 39(2-3):241–248.

Başar, E., Başar-Eroğlu, C., Karakaş, S., and Schürmann, M. (1999). Are cognitive processes manifested in event-related gamma, alpha, theta and delta oscillations in the EEG? *Neuroscience Letters*, 259(3):165–168.

Başar, E. and Güntekin, B. (2008). A review of brain oscillations in cognitive disorders and the role of neurotransmitters. *Brain Research*, 1235:172–193.

Başar-Eroglu, C., Başar, E., Demiralp, T., and Schürmann, M. (1992). P300-response: possible psychophysiological correlates in delta and theta frequency channels. A review. *International Journal of Psychophysiology*, 13(2):161–179.

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current Opinion in Neurobiology*, 17(6):649–655.

Baltus, A., Wagner, S., Wolters, C. H., and Herrmann, C. S. (2018). Optimized auditory transcranial alternating current stimulation improves individual auditory temporal resolution. *Brain Stimulation*, 11(1):118–124.

Barker, A. T., Jalinous, R., and Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet (London, England)*, 1(8437):1106–7.

Barry, R. J., Clarke, A. R., Johnstone, S. J., Magee, C. A., and Rushby, J. A. (2007). EEG differences between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology*, 118(12):2765–2773.

Bazanova, O. M. and Vernon, D. (2014). Interpreting EEG alpha activity. *Neuroscience and Biobehavioral Reviews*, 44:94–110.

Berger, H. (1929). Über das Elektrenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten*, 87(1):527–570.

Bergmann, T. O., Groppa, S., Seeger, M., Molle, M., Marshall, L., and Siebner, H. R. (2009). Acute Changes in Motor Cortical Excitability During Slow Oscillatory and Constant Anodal Transcranial Direct Current Stimulation. *Journal of Neurophysiology*, 102(4):2303–2311.

Bergmann, T. O., Karabanov, A., Hartwigsen, G., Thielscher, A., Siebner, H. R., Ole, T., Karabanov, A., Hartwigsen, G., Thielscher, A., Roman, H., Bergmann, T. O., Karabanov, A., Hartwigsen, G., Thielscher, A., Siebner, H. R., Ole, T., Karabanov, A., Hartwigsen, G., Thielscher, A., Roman, H., Bergmann, T. O., Karabanov, A., Hartwigsen, G., Thielscher, A., and Siebner, H. R. (2016). Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives. *NeuroImage*, 140:4–19.

Bikson, M., Radman, T., and Datta, A. (2006). Rational modulation of neuronal processing with applied electric fields. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings*, pages 1616–1619.

Boksem, M. A. S., Meijman, T. F., and Lorist, M. M. (2005). Effects of mental fatigue on attention: An ERP study. *Cognitive Brain Research*, 25(1):107–116.

Bourne, H. R. and Nicoll, R. (1993). Molecular machines integrate coincident synaptic signals. *Cell*, 72(1001):65–75.

Boyle, M. R. and Frohlich, F. (2013). EEG feedback-controlled transcranial alternating current stimulation. In *2013 6th International IEEE/EMBS Conference on Neural Engineering (NER)*, pages 140–143. IEEE.

Braboszcz, C. and Delorme, A. (2011). Lost in thoughts: Neural markers of low alertness during mind wandering. *NeuroImage*, 54(4):3040–3047.

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*, 10:433–436.

Brignani, D., Ruzzoli, M., Mauri, P., and Miniussi, C. (2013). Is Transcranial Alternating Current Stimulation Effective in Modulating Brain Oscillations? *PLoS ONE*, 8(2):e56589.

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. *The International Journal of Neuropsychopharmacology*, 14(8):1133–1145.

Busch, N. A., Dubois, J., and VanRullen, R. (2009). The Phase of Ongoing EEG Oscillations Predicts Visual Perception. *Journal of Neuroscience*, 29(24):7869–7876.

Buzsáki, G. (2002). Theta oscillations in the hippocampus. *Neuron*, 33(3):325–340.

Buzsáki, G. (2006). *Rhythms of the Brain*. Oxford University Press.

Buzsáki, G., Anastassiou, C. A., and Koch, C. (2012). The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience*, 13(6):407–420.

Buzsáki, G. and Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science (New York, N.Y.)*, 304(5679):1926–9.

Cajochen, C., Brunner, D. P., Krauchi, K., Graw, P., and Wirz-Justice, a. (1995). Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep*, 18(10):890–894.

Canolty, R. T. and Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, 14(11):506–515.

Cecere, R., Rees, G., and Romei, V. (2015). Individual differences in alpha frequency drive crossmodal illusory perception. *Current Biology*, 25(2):231–235.

Chatrian, G. E., Petersen, M. C., and Lazarte, J. A. (1959). The blocking of the rolandic wicket rhythm and some central changes related to movement. *Electroencephalography and Clinical Neurophysiology*, 11(3):497–510.

Clayton, M. S., Yeung, N., and Cohen Kadosh, R. (2018). The Effects of 10 Hz Transcranial Alternating Current Stimulation on Audiovisual Task Switching. *Frontiers in Neuroscience*, 12(FEB):1–12.

Cohen, M. X. (2017). Where Does EEG Come From and What Does It Mean? *Trends in Neurosciences*, 40(4):208–218.

Colgin, L. L. (2013). Mechanisms and Functions of Theta Rhythms. *Annual Review of Neuroscience*, 36(1):295–312.

Cram, J. R., Kohlenberg, R. J., and Singer, M. (1977). Operant control of alpha EEG and the effects of illumination and eye closure. *Psychosomatic medicine*, 39(1):11–8.

Daniel, R. S. (1967). Alpha and theta EEG in vigilance. *Perceptual and motor skills*, 25(3):697–703.

Dmochowski, J. P., Datta, A., Bikson, M., Su, Y., and Parra, L. C. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of Neural Engineering*, 8(4).

Dowsett, J. and Herrmann, C. S. (2016). Transcranial Alternating Current Stimulation with Sawtooth Waves: Simultaneous Stimulation and EEG Recording. *Frontiers in Human Neuroscience*, 10(3):135.

Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M., and Reitboeck, H. J. (1988). Coherent oscillations: a mechanism of feature linking in the visual cortex? Multiple electrode and correlation analyses in the cat. *Biological cybernetics*, 60(2):121–30.

Ekstrom, A. D., Caplan, J. B., Ho, E., Shattuck, K., Fried, I., and Kahana, M. J. (2005). Human hippocampal theta activity during virtual navigation. *Hippocampus*, 15(7):881–889.

Engel, A. K. and Fries, P. (2010). Beta-band oscillations-signalling the status quo? *Current Opinion in Neurobiology*, 20(2):156–165.

Ergenoglu, T., Demiralp, T., Bayraktaroglu, Z., Ergen, M., Beydagi, H., and Uresin, Y. (2004). Alpha rhythm of the EEG modulates visual detection performance in humans. *Cognitive Brain Research*, 20(3):376–383.

Fekete, T., Nikolaev, A. R., Knijf, F. D., Zharikova, A., and van Leeuwen, C. (2018). Multi-electrode alpha tACS during varying background tasks fails to modulate subsequent alpha power. *Frontiers in Neuroscience*, 12(JUN).

Feldman, D. E. (2012). The spike timing dependence of plasticity. *Neuron*, 75(4):556–571.

Fertonani, A. and Miniussi, C. (2017). Transcranial Electrical Stimulation. *The Neuroscientist*, 23(2):109–123.

Feurra, M., Bianco, G., Santarnecchi, E., Del Testa, M., Rossi, A., and Rossi, S. (2011a). Frequency-Dependent Tuning of the Human Motor System Induced by Transcranial Oscillatory Potentials. *Journal of Neuroscience*, 31(34):12165–12170.

Feurra, M., Pasqualetti, P., Bianco, G., Santarnecchi, E., Rossi, A., and Rossi, S. (2013). State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters. *The Journal of Neuroscience*, 33(44):17483–17489.

Feurra, M., Paulus, W., Walsh, V., and Kanai, R. (2011b). Frequency specific modulation of human somatosensory: Cortex. *Frontiers in Psychology*, 2(FEB):1–6.

Feurra, M., Paulus, W., Walsh, V., and Kanai, R. (2011c). Frequency specific modulation of human somatosensory: Cortex. *Frontiers in Psychology*, 2(FEB):1–6.

Fingelkurts, A. A., Fingelkurts, A. A., Rytsälä, H., Suominen, K., Isometsä, E., and Kähkönen, S. (2006). Composition of brain oscillations in ongoing EEG during major depression disorder. *Neuroscience Research*, 56(2):133–144.

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, 9(10):474–480.

Fries, P. (2009). Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation. *Annual Review of Neuroscience*, 32(1):209–224.

Fröhlich, F., McCormick, D. A., Fröhlich, F., McCormick, D. A., Fröhlich, F., and McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron*, 67(1):129–143.

Garside, P., Arizpe, J., Lau, C.-I., Goh, C., and Walsh, V. (2014). Cross-hemispheric Alternating Current Stimulation During a Nap Disrupts Slow Wave Activity and Associated Memory Consolidation. *Brain Stimulation*, 8(3):520–7.

Gasser, T., Bächer, P., and Steinberg, H. (1985). Test-retest reliability of spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology*, 60(4):312–319.

Gray, C. M. and Singer, W. (1989). Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proceedings of the National Academy of Sciences*, 86(5):1698–1702.

Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., Xanthopoulos, P., Sakkalis, V., and Vanrumste, B. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of NeuroEngineering and Rehabilitation*, 5:1–33.

Gundlach, C., Müller, M. M., Nierhaus, T., Villringer, A., and Sehm, B. (2016). Phasic Modulation of Human Somatosensory Perception by Transcranially Applied Oscillating Currents. *Brain Stimulation*, 9(5):712–719.

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.

Hale, T. S., Smalley, S. L., Hanada, G., Macion, J., McCracken, J. T., McGough, J. J., and Loo, S. K. (2009). Atypical alpha asymmetry in adults with ADHD. *Neuropsychologia*, 47(10):2082–8.

Hallett, M. (2007). Transcranial Magnetic Stimulation: A Primer. *Neuron*, 55(2):187–199.

Hanslmayr, S., Aslan, A., Staudigl, T., Klimesch, W., Herrmann, C. S., and Bäuml, K. H. (2007). Prestimulus oscillations predict visual perception performance between and within subjects. *NeuroImage*, 37(4):1465–1473.

Hanslmayr, S., Klimesch, W., Sauseng, P., Gruber, W., Doppelmayr, M., Freunberger, R., and Pecherstorfer, T. (2005). Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. *Neuroscience Letters*, 375(1):64–68.

Hanslmayr, S., Staresina, B. P., and Bowman, H. (2016). Oscillations and Episodic Memory: Addressing the Synchronization/Desynchronization Conundrum. *Trends in Neurosciences*, 39(1):16–25.

Harmony, T. (2013). The functional significance of delta oscillations in cognitive processing. *Frontiers in Integrative Neuroscience*, 7(December):1–10.

Hebbs, D. G. (1949). The organization of behavior. *Wiely and Sons, New York, NY, USA*.

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.

Helfrich, R. F., Knepper, H., Nolte, G., Strüber, D., Rach, S., Herrmann, C. S., Schneider, T. R., Engel, A. K., Helfrich, R. F., Knepper, H., Nolte, G., Stru, D., Schneider, T. R., Engel, A. K., and Herrmann, C. S. (2014a). Selective Modulation of Interhemispheric Functional Connectivity by HD-tACS Shapes Perception. *PLoS Biology*, 12(12):e1002031.

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*, 24(3):333–339.

Herrmann, C. S. and Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clinical Neurophysiology*, 116(12):2719–2733.

Herrmann, C. S. and Knight, R. T. (2001). Mechanisms of human attention: event-related potentials and oscillations. *Neuroscience & Biobehavioral Reviews*, 25(6):465–476.

Herrmann, C. S., Munk, M. H., and Engel, A. K. (2004). Cognitive functions of gamma-band activity: Memory match and utilization. *Trends in Cognitive Sciences*, 8(8):347–355.

Herrmann, C. S., Murray, M. M., Ionta, S., Hutt, A., and Lefebvre, J. (2016a). Shaping Intrinsic Neural Oscillations with Periodic Stimulation. *Journal of Neuroscience*, 36(19):5328–5337.

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(June):1–13.

Herrmann, C. S. and Strüber, D. (2017). What Can Transcranial Alternating Current Stimulation Tell Us About Brain Oscillations? *Current Behavioral Neuroscience Reports*, 4(2):128–137.

Herrmann, C. S., Strüber, D., Helfrich, R. F., and Engel, A. K. (2016b). EEG oscillations: From correlation to causality. *International Journal of Psychophysiology*, 103:12–21.

Hier, D. B., Mangone, C. A., Ganellen, R., Warach, J. D., Van Egeren, R., Perlik, S. J., and Gorelick, P. B. (1991). Quantitative measurement of delta activity in Alzheimer's disease. *Clinical EEG Electroencephalography*, 22(3):178–182.

Huang, Y., Datta, A., Bikson, M., and Parra, L. C. (2018). ROAST: An Open-Source, Fully-Automated, Realistic Volumetric-Approach-Based Simulator For TES. In *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pages 3072–3075. IEEE.

Iemi, L., Chaumon, M., Crouzet, S. M., and Busch, N. A. (2017). Spontaneous Neural Oscillations Bias Perception by Modulating Baseline Excitability. *The Journal of Neuroscience*, 37(4):807–819.

Ilmoniemi, R. J., Ruohonen, J., and Karhu, J. (1999). Transcranial magnetic stimulation–a new tool for functional imaging of the brain. *Critical reviews in biomedical engineering*, 27(3-5):241–84.

Jackson, A. F. and Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: A review for the rest of us. *Psychophysiology*, 51(11):1061–1071.

Jensen, O. (2002). Oscillations in the Alpha Band (9-12 Hz) Increase with Memory Load during Retention in a Short-term Memory Task. *Cerebral Cortex*, 12(8):877–882.

Jensen, O. and Mazaheri, A. (2010). Shaping Functional Architecture by Oscillatory Alpha Activity: Gating by Inhibition. *Frontiers in Human Neuroscience*, 4(November):1–8.

Jevtović-Todorović, V., Todorović, S. M., Mennerick, S., Powell, S., Dikranian, K., Benshoff, N., Zorumski, C. F., and Olney, J. W. (1998). Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nature medicine*, 4(4):460–3.

Kahana, M. J., Seelig, D., and Madsen, J. R. (2001). Theta returns. *Current Opinion in Neurobiology*, 11(6):739–744.

Kanai, R., Chaieb, L., Antal, A., Walsh, V., and Paulus, W. (2008). Frequency-Dependent Electrical Stimulation of the Visual Cortex. *Current Biology*, 18(23):1839–1843.

Karabanov, A., Thielscher, A., and Siebner, H. R. (2016). Transcranial brain stimulation. *Current Opinion in Neurology*, 29(4):397–404.

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(May):245.

Kasten, F. H. and Herrmann, C. S. (2017). Transcranial alternating current stimulation (tACS) enhances mental rotation performance during and after stimulation. *Frontiers in Human Neuroscience*, 11(2):1–16.

Kasten, F. H., Maess, B., and Herrmann, C. S. (2018). Facilitated Event-Related Power-Modulations during Transcranial Alternating Current Stimulation (tACS) Revealed by Concurrent tACS-MEG. *Eneuro*, 5(June):ENEURO.0069–18.2018.

Kleiner, M., Brainard, D. H., Pelli, D. G., Broussard, C., Wolf, T., and Niehorster, D. (2007). What's new in Psychtoolbox-3? *Perception*, 36:S14.

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.

Klimesch, W., Sauseng, P., and Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews*, 53(1):63–88.

Knyazev, G. G. (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience and Biobehavioral Reviews*, 36(1):677–695.

Kondacs, A. (1999). Long-term intra-individual variability of the background EEG in normals. *Clinical Neurophysiology*, 110(10):1708–1716.

Kononowicz, T. W. and van Wassenhove, V. (2016). In Search of Oscillatory Traces of the Internal Clock. *Frontiers in Psychology*, 7(February):1–5.

Krause, B. and Cohen Kadosh, R. (2014). Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience*, 8.

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., and Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: A neurophysiological study. *Brain Stimulation*, 6(4):644–648.

Larson, J., Wong, D., and Lynch, G. (1986). Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Research*, 368(2):347–350.

Lefcheck, J. S. (2016). piecewiseSEM: Piecewise structural equation modelling in r for ecology, evolution, and systematics. *Methods in Ecology and Evolution*, 7(5):573–579.

Lenz, D., Krauel, K., Schadow, J., Baving, L., Duzel, E., and Herrmann, C. S. (2008). Enhanced gamma-band activity in ADHD patients lacks correlation with memory performance found in healthy children. *Brain Research*, 1235:117–132.

Lowel, S. and Singer, W. (1992). Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science*, 255(5041):209–212.

Luck, S. J. (2005). *An introduction to the event-related potential technique*. The MIT Press, Cambridge, MA.

Lustenberger, C., Boyle, M. R., Alagapan, S., Mellin, J. M., Vaughn, B. V., and Fröhlich, F. (2016). Feedback-Controlled Transcranial Alternating Current Stimulation Reveals a Functional Role of Sleep Spindles in Motor Memory Consolidation. *Current Biology*, 26(16):2127–2136.

Mäkelä, N. N., Sarvas, J., and Ilmoniemi, R. J. (2017). A simple reason why beamformer may (not) reduce TACS-induced artifact in MEG. *Brain stimulation*, 10(2017):e66–e67.

Markram, H. (1997). Regulation of Synaptic Efficacy by Coincidence of Postsynaptic APs and EPSPs. *Science*, 275(5297):213–215.

Marshall, L., Helgadóttir, H., Mölle, M., and Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, 444(7119):610–613.

Marshall, L., Henze, D. A., Hirase, H., Leinekugel, X., Dragoi, G., and Buzsaki, G. (2002). Hippocampal pyramidal cell-interneuron spike transmission is frequency dependent and responsible for place modulation of interneuron discharge. *Journal of Neuroscience*, 22(2):RC197.

Marshall, T. R., O'Shea, J., Jensen, O., and Bergmann, T. O. (2015). Frontal Eye Fields Control Attentional Modulation of Alpha and Gamma Oscillations in Contralateral Occipitoparietal Cortex. *Journal of Neuroscience*, 35(4):1638–1647.

McBain, C. J. and Mayer, M. L. (1994). N-methyl-D-aspartic acid receptor structure and function. *Physiological Reviews*, 74(3):723–760.

Mehta, A. R., Pogosyan, A., Brown, P., and Brittain, J. S. (2015). Montage matters: The influence of transcranial alternating current stimulation on human physiological tremor. *Brain Stimulation*, 8(2):260–268.

Mellin, J. M., Alagapan, S., Lustenberger, C., Lugo, C. E., Alexander, M. L., Gilmore, J. H., Jarskog, L. F., and Fröhlich, F. (2018). Randomized trial of transcranial alternating current stimulation for treatment of auditory hallucinations in schizophrenia. *European Psychiatry*, 51:25–33.

Merton, P. A. and Morton, H. B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature*, 285(5762):227.

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.

Min, B. K., Jung, Y. C., Kim, E., and Park, J. Y. (2013). Bright illumination reduces parietal EEG alpha activity during a sustained attention task. *Brain Research*, 1538:83–92.

Miranda, P. C., Hallett, M., and Basser, P. J. (2003). The electric field induced in the brain by magnetic stimulation: A 3-D finite-element analysis of the effect of tissue heterogeneity and anisotropy. *IEEE Transactions on Biomedical Engineering*, 50(9):1074–1085.

Miranda, P. C., Lomarev, M., and Hallett, M. (2006). Modeling the current distribution during transcranial direct current stimulation. *Clinical Neurophysiology*, 117(7):1623–1629.

Missonnier, P., Deiber, M. P., Gold, G., Millet, P., Gex-Fabry Pun, M., Fazio-Costa, L., Giannakopoulos, P., and Ibáñez, V. (2006). Frontal theta event-related synchronization: Comparison of directed attention and working memory load effects. *Journal of Neural Transmission*, 113(10):1477–1486.

Moss, F., Ward, L. M., and Sannita, W. G. (2004). Stochastic resonance and sensory information processing: A tutorial and review of application. *Clinical Neurophysiology*, 115(2):267–281.

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(April):1–12.

Neuling, T., Rach, S., Wagner, S., Wolters, C., and Herrmann, C. (2012a). Good vibrations: Oscillatory phase shapes perception. *NeuroImage*, 63(2):771–778.

Neuling, T., Ruhnau, P., Fuscà, M., Demarchi, G., Herrmann, C. S., and Weisz, N. (2015). Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *NeuroImage*, 118:406–413.

Neuling, T., Wagner, S., Wolters, C. H., Zaehle, T., and Herrmann, C. S. (2012b). Finite-Element Model Predicts Current Density Distribution for Clinical Applications of tDCS and tACS. *Frontiers in Psychiatry*, 3(September):1–10.

Niedermeyer, E. and Silva, F. H. L. D. (2004). *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. Lippincott Williams and Wilkins.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., Fregni, F., and Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, 1(3):206–223.

Nitsche, M. A. and Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, 57(10):1899–901.

Noachtar, S., Binnie, C., Ebersole, J., Mauguière, F., Sakamoto, A., and Westmoreland, B. (1999). A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report

form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalography and Clinical Neurophysiology.*, 52:21–41.

Notbohm, A., Kurths, J., and Herrmann, C. S. (2016). Modification of Brain Oscillations via Rhythmic Light Stimulation Provides Evidence for Entrainment but Not for Superposition of Event-Related Responses. *Frontiers in Human Neuroscience*, 10(February).

Noury, N., Hipp, J. F., and Siegel, M. (2016). Physiological processes non-linearly affect electrophysiological recordings during transcranial electric stimulation. *NeuroImage*, 140:99–109.

Nunez, P. L. and Srinivasan, R. (2006). *Electric Fields of the Brain: The neurophysics of EEG*. Oxford University Press.

Oken, B., Salinsky, M., and Elsas, S. (2006). Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clinical Neurophysiology*, 117(9):1885–1901.

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.

Osipova, D., Hermes, D., and Jensen, O. (2008). Gamma Power Is Phase-Locked to Posterior Alpha Activity. *PLoS ONE*, 3(12):e3990.

Ozen, S., Sirota, A., Belluscio, M. A., Anastassiou, C. A., Stark, E., Koch, C., and Buzsaki, G. (2010). Transcranial Electric Stimulation Entrains Cortical Neuronal Populations in Rats. *Journal of Neuroscience*, 30(34):11476–11485.

Özerdem, A., Güntekin, B., Tunca, Z., and Başar, E. (2008). Brain oscillatory responses in patients with bipolar disorder manic episode before and after valproate treatment. *Brain Research*, 1235(6):98–108.

Palva, J. M., Palva, S., and Kaila, K. (2005). Phase synchrony among neuronal oscillations in the human cortex. *The Journal of Neuroscience*, 25(15):3962–72.

Palva, S. and Palva, J. M. (2007). New vistas for α-frequency band oscillations. *Trends in Neurosciences*, 30(4):150–158.

Paskewitz, D. A. and Orne, M. T. (1973). Visual Effects on Alpha Feedback Training. *Science*, 181(4097):360–363.

Paulus, W., Peterchev, A. V., and Ridding, M. (2013). Transcranial electric and magnetic stimulation. In *Handbook of Clinical Neurology*, chapter Chapter 27. Elsevier B.V., 1 edition.

Pelli, D. G. (1997). The VideoToolbox software for visual psychophysics: transforming numbers into movies.

Penttonen, M. and Buzsáki, G. (2003). Natural logarithmic relationship between brain oscillators. *Thalamus and Related Systems*, 2(02):145.

Perlmutter, J. S. and Mink, J. W. (2006). Deep brain stimulation. *Annual review of neuroscience*, 29:229–57.

Pevzner, A., Izadi, A., Lee, D. J., Shahlaie, K., and Gurkoff, G. G. (2016). Making Waves in the Brain: What Are Oscillations, and Why Modulating Them Makes Sense for Brain Injury. *Frontiers in Systems Neuroscience*, 10(April):1–18.

Pfurtscheller, G. (1981). Central beta rhythm during sensorimotor activities in man. *Electroencephalography and Clinical Neurophysiology*, 51(3):253–264.

Pfurtscheller, G., Brunner, C., Schlögl, A., and Lopes da Silva, F. (2006). Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *NeuroImage*, 31(1):153–159.

Pfurtscheller, G., Stancák, A., and Edlinger, G. (1997). On the existence of different types of central beta rhythms below 30 Hz. *Electroencephalography and Clinical Neurophysiology*, 102(4):316–325.

Pfurtscheller, G., Stancák, A., and Neuper, C. (1996a). Event-related synchronization (ERS) in the alpha band - An electrophysiological correlate of cortical idling: A review. *International Journal of Psychophysiology*, 24(1-2):39–46.

Pfurtscheller, G., Stancák, A., and Neuper, C. (1996b). Post-movement beta synchronization. A correlate of an idling motor area? *Electroencephalography and Clinical Neurophysiology*, 98(4):281–293.

Picton, T. W., John, M. S., Dimitrijevic, A., and Purcell, D. (2003). Human auditory steady-state responses. *International journal of audiology*, 42(4):177–219.

Pikovsky, A., Rosenblum, M., Kurths, J., and Hilborn, R. C. (2002). Synchronization: A Universal Concept in Nonlinear Science. *American Journal of Physics*, 70(6):655–655.

Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., and Team, R. C. (2016). *nlme: Linear and Nonlinear Mixed Effects Models*. Number R package version 3.1-127.

Pletzer, B., Kerschbaum, H., and Klimesch, W. (2010). When frequencies never synchronize: The golden mean and the resting EEG. *Brain Research*, 1335:91–102.

Pogosyan, A., Gaynor, L. D., Eusebio, A., and Brown, P. (2009). Boosting Cortical Activity at Beta-Band Frequencies Slows Movement in Humans. *Current Biology*, 19(19):1637–1641.

Polanía, R., Nitsche, M. A., Korman, C., Batsikadze, G., and Paulus, W. (2012). The importance of timing in segregated theta phase-coupling for cognitive performance. *Current Biology*, 22(14):1314–1318.

Posthuma, D., Neale, M. C., Boomsma, D. I., and De Geus, E. J. C. (2001). Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation. *Behavior Genetics*, 31(6):567–579.

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2010). Low-Intensity Electrical Stimulation Affects Network Dynamics by Modulating Population Rate and Spike Timing. *Journal of Neuroscience*, 30(45):15067–15079.

Reato, D., Rahman, A., Bikson, M., and Parra, L. C. (2013). Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. *Frontiers in Human Neuroscience*, 7(October):1–8.

Ridding, M. C. and Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *Journal of Physiology*, 588(13):2291–2304.

Ritter, P., Born, J., Brecht, M., Dinse, H. R., Heinemann, U., Pleger, B., Schmitz, D., Schreiber, S., Villringer, A., and Kempter, R. (2015). State-dependencies of learning across brain scales. *Frontiers in Computational Neuroscience*, 9(February):1–21.

Rizk, S., Ptak, R., Nyffeler, T., Schnider, A., and Guggisberg, A. G. (2013). Network mechanisms of responsiveness to continuous theta-burst stimulation. *European Journal of Neuroscience*, 38(8):3230–3238.

Romei, V., Gross, J., and Thut, G. (2010). On the Role of Prestimulus Alpha Rhythms over Occipito-Parietal

Areas in Visual Input Regulation: Correlation or Causation? *Journal of Neuroscience*, 30(25):8692–8697.

Ruhnau, P., Neuling, T., Fuscá, M., Herrmann, C. S., Demarchi, G., and Weisz, N. (2016). Eyes wide shut: Transcranial alternating current stimulation drives alpha rhythm in a state dependent manner. *Scientific Reports*, 6(1):27138.

Salinsky, M., Oken, B., and Morehead, L. (1991). Test-retest reliability in EEG frequency analysis. *Electroencephalography and Clinical Neurophysiology*, 79(5):382–392.

Salmelin, R., Hámáaláinen, M., Kajola, M., and Hari, R. (1995). Functional Segregation of Movement-Related Rhythmic Activity in the Human Brain. *NeuroImage*, 2(4):237–243.

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A. A., Glennon, M., Gerloff, C., Birbaumer, N., and Hummel, F. C. (2009). Brain Oscillatory Substrates of Visual Short-Term Memory Capacity. *Current Biology*, 19(21):1846–1852.

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W. R., and Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, 22(11):2917–2926.

Schnitzler, A. and Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nature Reviews Neuroscience*, 6(4):285–296.

Schwab, K., Ligges, C., Jungmann, T., Hilgenfeld, B., Haueisen, J., and Witte, H. (2006). Alpha entrainment in human electroencephalogram and magnetoencephalogram recordings. *Neuroreport*, 17(17):1829–1833.

Siegel, M., Donner, T. H., and Engel, A. K. (2012). Spectral fingerprints of large-scale neuronal interactions. *Nature Reviews Neuroscience*, 13(February):20–25.

Silva, L., Amitai, Y., and Connors, B. (1991). Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons. *Science*, 251(4992):432–435.

Silvanto, J., Muggleton, N., and Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences*, 12(12):447–454.

Singer, W. (1993). Synchronization of Cortical Activity and its Putative Role in Information Processing and Learning. *Annual Review of Physiology*, 55(1):349–374.

Singer, W. and Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annual review of neuroscience*, 18(1):555–86.

Sliva, D. D., Black, C. J., Bowary, P., Agrawal, U., Santoyo, J. F., Philip, N. S., Greenberg, B. D., Moore, C. I., and Jones, S. R. (2018). A prospective study of the impact of transcranial alternating current stimulation on EEG correlates of somatosensory perception. *Frontiers in Psychology*, 9(NOV):1–17.

Sponheim, S. R., Clementz, B. A., Iacono, W. G., and Beiser, M. (2000). Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. *Biological Psychiatry*, 48(11):1088–1097.

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):1–10.

Steriade, M. and Deschenes, M. (1984). The thalamus as a neuronal oscillator. *Brain Research Reviews*, 8(1):1–63.

Steriade, M., Gloor, P., Llinás, R., Lopes da Silva, F., and Mesulam, M.-M. (1990). Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology*, 76(6):481–508.

Steriade, M., McCormick, D., and Sejnowski, T. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, 262(5134):679–685.

Strüber, D., Rach, S., Neuling, T., and Herrmann, C. S. (2015). On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. *Frontiers in Cellular Neuroscience*, 9(August):1–7.

Strüber, D., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., and Herrmann, C. S. (2014). Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. *Brain topography*, 27(1):158–71.

Thielscher, A., Antunes, A., and Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? *Conference proceedings : ... Annual*

International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference, 2015:222–5.

Thut, G., Bergmann, T. O., Fröhlich, F., Soekadar, S. R., Brittain, J. S., Valero-Cabré, A., Sack, A. T., Miniussi, C., Antal, A., Siebner, H. R., Ziemann, U., and Herrmann, C. S. (2017). Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. *Clinical Neurophysiology*, 128(5):843–857.

Thut, G., Miniussi, C., Gross, J., Miniussi, C., and Gross, J. (2012). The functional importance of rhythmic activity in the brain. *Current Biology*, 22(16):R658–R663.

Thut, G., Nietzel, A., Brandt, S. A., and Pascual-Leone, A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, 26(37):9494–502.

Thut, G., Schyns, P. G., and Gross, J. (2011a). Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Frontiers in Psychology*, 2(JUL):1–10.

Thut, G., Veniero, D., Romei, V., Miniussi, C., Schyns, P., and Gross, J. (2011b). Rhythmic TMS causes local entrainment of natural oscillatory signatures. *Current Biology*, 21(14):1176–1185.

Tuladhar, A. M., Ter Huurne, N., Schoffelen, J. M., Maris, E., Oostenveld, R., and Jensen, O. (2007). Parieto-occipital sources account for the increase in alpha activity with working memory load. *Human Brain Mapping*, 28(8):785–792.

Uhlhaas, P. J. and Singer, W. (2006). Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology. *Neuron*, 52(1):155–168.

Uhlhaas, P. J. and Singer, W. (2012). Neuronal Dynamics and Neuropsychiatric Disorders: Toward a Translational Paradigm for Dysfunctional Large-Scale Networks. *Neuron*, 75(6):963–980.

Veniero, D., Benwell, C. S., Ahrens, M. M., and Thut, G. (2017). Inconsistent effects of parietal α-tACS on Pseudoneglect across two experiments: A failed internal replication. *Frontiers in Psychology*, 8(JUN):1–14.

Veniero, D., Strüber, D., Thut, G., and Herrmann, C. S. (2016). Noninvasive Brain Stimulation Techniques Can Modulate Cognitive Processing. *Organizational Research Methods*, 22(1):116–147.

Veniero, D., Vossen, A., Gross, J., and Thut, G. (2015). Lasting EEG/MEG Aftereffects of Rhythmic Transcranial Brain Stimulation: Level of Control Over Oscillatory Network Activity. *Frontiers in cellular neuroscience*, 9(December):477.

Vlaar, M. P., van der Helm, F. C., and Schouten, A. C. (2015). Frequency Domain Characterization of the Somatosensory Steady State Response in Electroencephalography. *IFAC-PapersOnLine*, 48(28):1391–1396.

von Stein, A. and Sarnthein, J. (2000). Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *International Journal of Psychophysiology*, 38(3):301–313.

Vossen, A., Gross, J., and Thut, G. (2015). Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (α-tACS) Reflects Plastic Changes Rather Than Entrainment. *Brain Stimulation*, 8(3):499–508.

Vosskuhl, J., Huster, R. J., and Herrmann, C. S. (2015). Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. *Frontiers in human neuroscience*, 9(May):257.

Wagner, S., Burger, M., and Wolters, C. H. (2016). An Optimization Approach for Well-Targeted Transcranial Direct Current Stimulation. *SIAM Journal on Applied Mathematics*, 76(6):2154–2174.

Wang, X.-j. (2010). Neurophysiological and Computational Principles of Cortical Rhythms in Cognition. *Physiological Reviews*, 90(3):1195–1268.

Ward, L. M. (2003). Synchronous neural oscillations and cognitive processes. *Trends in Cognitive Sciences*, 7(12):553–559.

Wiener, M., Parikh, A., Krakow, A., and Coslett, H. B. (2018). An Intrinsic Role of Beta Oscillations in Memory for Time Estimation. *Scientific Reports*, 8(1):7992.

Wischnewski, M., Engelhardt, M., Salehinejad, M. A., Schutter, D. J. L. G., Kuo, M.-F., and Nitsche, M. A. (2018). NMDA Receptor-Mediated Motor Cortex Plasticity After 20 Hz Transcranial Alternating Current Stimulation. *Cerebral cortex*, (bhy160):1–8.

Witkowski, M., Garcia-Cossio, E., Chander, B. S., Braun, C., Birbaumer, N., Robinson, S. E., and Soekadar, S. R. (2015). Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS). *NeuroImage*, 140:89–98.

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., and Fries, P. (2007). Modulation of Neuronal Interactions Through Neuronal Synchronization. *Science*, 316(5831):1609–1612.

Wood, S. N. (2017). *Generalized Additive Models*. Chapman and Hall/CRC, New York.

Yordanova, J., Banaschewski, T., Kolev, V., Woerner, W., and Rothenberger, A. (2001). Abnormal early stages of task stimulus processing in children with attention-deficit hyperactivity disorder – evidence from event-related gamma oscillations. *Clinical Neurophysiology*, 112(6):1096–1108.

Zaehle, T., Rach, S., and Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One*, 5(11):13766.

Zhang, Y., Chen, Y., Bressler, S. L., and Ding, M. (2008). Response preparation and inhibition: The role of the cortical sensorimotor beta rhythm. *Neuroscience*, 156(1):238–246.

Zhi-De Deng, Lisanby, S., and Peterchev, A. (2009). Effect of anatomical variability on neural stimulation strength and focality in electroconvulsive therapy (ECT) and magnetic seizure therapy (MST). In *2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 682–688. IEEE.

Zorumski, C. F., Izumi, Y., and Mennerick, S. (2016). Ketamine: NMDA Receptors and Beyond. *Journal of Neuroscience*, 36(44):11158–11164.

Summary

Transcranial alternating current stimulation (tACS) is a novel, non-invasive method of manipulating the brain activity in a frequency specific manner. Its main use in basic research is the investigation of a proposed functional role of brain oscillations for cognitive processes. One substantial capability of tACS is the elicitation of persistent alterations of brain activity in specific bands. Particularly power-enhancement in the posterior α-band have repeatedly been shown to outlast the stimulation at the endogenous α-frequency.

However not every transcranial AC-stimulation within the alpha band leads to the occurrence of aftereffects. Particularly the role of the stimulation parameters and the influence of environmental factors on the aftereffect are unknown. To gain a better understanding of tACS as a tool in research and possibly clinical applications, it is necessary to gain deeper insights how additional factors might influence the outcome of the stimulation. The two studies introduced in this thesis explore the role of two controllable factors in established sham-controlled α-tACS experiments during visual vigilance tasks. In study 1, the α-power after four subsequent tACS-blocks of 1, 3, 5, and 10-minute durations in darkness was explored. Study 2 focused on the role of the environmental lighting conditions on the α-power in the post-stimulation EEG during an experiment containing 10-minute α-tACS stimulation.

Study 1 showed no aftereffects following the 1, 3 and 5-minute tACS-blocks. The 10-minute tACS blocks only led to an increase in power, when it constitutes the last block of the sequence. Study 2 showed that both a dark environment and tACS individually cause an increase in posterior α-power. The lighting condition itself, however, does not seem to influence the relative post-stimulation power increase over time but might mask effects in experiments with shorter EEG-recordings. Moreover, the results of both studies hint at a significant effect of the mismatch between the rapidly estimated stimulation frequency and the subsequently determined individual α-frequency on the outcome of the stimulation.

In summary, the results offer explanations, as to why some studies with largely similar experimental

setups might lead to the occurrence of lasting tACS-effects in some cases, while the effects might remain absent in other cases due to some minor differences in protocols. The implications for the design of tACS-studies are discussed and recommendations for improved protocols are introduced.

Zusammenfassung

Transkranielle Wechselstromstimulation (tACS) ist eine neue nicht invasive Methode Hirnaktivität frequenzspezifisch zu modulieren. In der Grundlagenforschung wird sie vor allem für die Untersuchung einer vermuteten Funktionellen Rolle von Hirnoszillationen für kognitive Prozesse eingesetzt. Eine wichtige Eigenschaft von tACS, ist die Erzeugung von bleibenden Veränderungen der Hirnaktivität in spezifischen Frequenzbändern. Insbesondere im α-Band konnten wiederholt Zunahmen der Power gezeigt werden, die nach einer Stimulation an der endogenen α-Frequenz bestehen blieben.

Allerdings führt nicht jede transkranielle AC-Stimulation im α-Band zum Auftreten solcher Nacheffekte. Insbesondere die Rolle der verschiedenen Stimulationsparameter und der Einfluss von Umgebungsfaktoren auf den Nacheffekt sind noch unerforscht. Um ein besseres Verständnis von tACS als Werkzeug in der Wissenschaft und als klinische Methode zu erlangen, ist es wichtig bessere Einblicke darin zu erhalten, wie diese Faktoren das Ergebnis einer Stimulation beeinflussen. Die zwei im Zuge dieser Dissertation vorgestellten Studien untersuchen die Rolle zweier kontrollierbarer Faktoren in etablierten sham-kontrollierten α-tACS Experimenten während Visueller Vigilanzaufgaben. In Studie 1 wurde die α-Power jeweils nach vier aufeinander folgenden tACS-Blöcken von 1,3,5 und 10 Minuten Länge in einer dunklen Umgebung untersucht. Studie 2 fokussierte sich auf die Rolle der Umgebungsbeleuchtung auf den Verlauf der Power im α-Band in einem Experiment mit 10-minütiger tACS-Stimulation.

Studie 2 zeigte keine Nacheffekte der Stimulation nach 1, 3 oder 5 Minuten Blöcken von tACS. Der 10 Minuten Block bewirkte nur dann einen Anstieg, wenn der Block der letzte in der Abfolge war. Die Ergebnisse von Studie 1 zeigen das sowohl eine dunkle Umgebung als auch tACS unabhängig zu einer Zunahme der posterioren α-Power führen. Der Faktor der Beleuchtung selber scheint selber nicht die Zunahme ab Power nach der Stimulation zu beeinflussen, aber könnte in Experimenten mit nur kurzer EEG-Aufzeichnung zu einer Maskierung der Effekte von tACS führen. Zusätzlich zeigen beide Studien, dass eine Abweichung zwischen der schnell abgeschätzten Stimulationsfrequenz und der nachträglich

genauer bestimmten individuellen α-Frequenz einen signifikanten Effekt auf den Ausgang der Stimulation zu haben scheint.

Zusammengefasst zeigen die Resultate Gründe auf, warum Studien mit größtenteils identischem experimentellem Aufbau in einigen Fällen zum Auftreten eines bleibenden Effektes von tACS führen, während in anderen Fällen durch kleine Abweichungen im Protokoll Nacheffekte ausbleiben. Die Bedeutung dieser Befunde für die Planung von tACS-Studien werden diskutiert und Vorschläge für verbesserte Protokolle vorgestellt.

Declaration of Authorship

I hereby confirm that Heiko Ivo Stecher contributed to the aforementioned studies as stated below:

Article: 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. *Front. Hum. Neurosci. 11, 1–10*

Author Contributions: HS, TP, DS, CH: designed the study; HS, TP: acquired the data; HS, FS, TP: analyzed the data; HS, TP, FS, DS, CH: wrote the article.

Article: Stecher, H. I., and 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. *Front. Psychol. 9, 1–9*

Author Contributions: HS and CH designed the study and wrote the article. HS acquired and analyzed the data.

Prof. Dr. Christoph S. Herrmann

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.

Heiko Ivo Stecher

Curriculum Vitae

PERSONAL DETAILS

Name:	Heiko Ivo Stecher
Address:	Ehlersdamm 42
	28307 Bremen, Germany
Phone:	+49 171 183 937 7
Email:	heiko.stecher@uni-oldenburg.de
Date of birth:	January the 2nd 1985
Place of birth:	Bremen, Germany

PROFESSIONAL EXPERIENCE

SINCE 2014	Research assistant
	Carl von Ossietzky University Oldenburg
	Department of Psychology | Experimental Psychology Lab
JUN – OCT 2012	Student assistant
	University of Bremen
	Institute for Theoretical Physics
MAY – JUL 2011	Internship(Lab-Rotation)
	University of Bremen
	Institute for Theoretical Physics
JAN – APR 2011	Internship(Lab-Rotation)
	Technical University Berlin
	Berlin BCI Group

EDUCATION

SINCE 2014	PhD candidate Psychology Carl von Ossietzky University Oldenburg
2009 – 2013	M.Sc. Neurosciences University of Bremen
2006 – 2009	B.Sc. Biology University of Bremen

PUBLICATIONS

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. *Front. Hum. Neurosci.* 11, 1–10

Stecher, H. I., and 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. *Front. Psychol.* 9, 1–9

Löffler, B. S., **Stecher, H. I.**, Fudickar, S., Sordi, D. De, Otto-sobotka, F., Hein, A., et al. (2018). Counteracting the Slowdown of Reaction Times in a Vigilance Experiment with 40 Hz Transcranial Alternating Current Stimulation. *IEEE Trans. Neural Syst. Rehabil. Eng.* 4320, 1–1.

Conference contributions:

Stecher, H. I., Pollok, T. M., Strüber, D., Sobotka, F., and Herrmann, C. S. (2017). The role of ambient illumination and stimulation duration on the aftereffect of α-band tACS. *Society for Neuroscience*, 2017, Washington, DC USA.

Reviewer activities

International Journal of Psychophysiology

TEACHING EXPERIENCE

Supervisor practical project 3 months

Does hemisphere-specific tACS modulate contrast detection? | Maximilian Jantzen, 2016

Determining the minimum stimulation duration to achieve after-effects in endogenous α-power with tACS | Tania M. Pollok, 2016

Does the tACS stimulation at the individual alpha frequency influence the visual detection performance? | Tea Kharebava, 2017

The causal role of alpha oscillations in human time perception | Jeanette Nischan, 2018

Supervisor Master Thesis 6 months

Long-term effects of five minutes transcranial alternating current stimulation (tACS) on oscillatory brain activity in the α-band | Tania M. Pollok, 2018

Acknowledgement

Abschließend möchte ich an diese Stelle den vielen Menschen danken, die mich in den letzten Jahren bei meiner Arbeit und der Erstellung dieser Dissertation unterstützt haben.

Mein Dank gilt **Christoph**, für die Möglichkeit meine Doktorarbeit in der Abteilung für Allgemeine Psychologie zu schreiben, der immer 5 Minuten gefunden hatte um sich neue Daten anzusehen und stets mit einer guten Idee aufwarten konnte.
Daniel, für die vielen hilfreichen Tipps beim Schreiben.
All den gegenwärtigen und ehemaligen Kollegen der Allgemeinen Psychologie, **Sabine**, **Andrea**, **Reiner**, **James**, **Jules**, **Esther**, **Maryam** und insbesondere:
Johannes, der mir alles über das Promovieren beigebracht hat, das ich nicht anderweitig gelernt habe.
Alina und **Annika**, dem Zentrum des Lebens in der AG.
Florian, für lange abendliche Diskussionen über Wissenschaft und Methoden für die ich gerne auch mal ein bis zwei Züge verpasste.
Fabian, für viele erdende Gespräche und die Klärung höchstwichtiger Fragen der Etymologie.
Anna, die mir in unseren kleinen Pausen mehr über Statistik beibrachte, als ich an einem ganzen Tag der Recherche hätte lernen können.
Tania, die so engagiert war, dass sie als Studentin tatsächlich die Arbeit des Betreuers reduzierte.
Meinen Koautoren **Birte** und **Fabian**, für eine höchst hilfreiche Einführung in die statistische Welt der gemischten Modelle.
Max, **Tea**, **Jeanette**, **Arnd** und den unzähligen anderen Studenten, mit denen ich in all den Jahren arbeiten durfte.
Cindy und **Paul**, die mit brutaler Ehrlichkeit einige meiner schlimmsten Satzkonstruktionen verhindert haben.

Acknowledgement

Meiner Familie für die fortwährende Unterstützung.
Und natürlich **Maylin**.

Es war mir eine Freude all meine Kollegen in dieser Zeit mit lebenswichtiger Energie in Form von Zucker zu versorgen. In den letzten drei Jahren habt ihr - ausgehend von einer Packung pro Woche - insgesamt 78108 $kcal$ oder 325680 kJ an Schokoladen zu euch genommen. Das reicht, nach meinen bescheidenen Berechnungen, um mit einem sparsamen Kleinwagen zwei mal von Bremen nach Oldenburg und zurück zu pendeln, oder aber um einen hartnäckigen Probanden mit einem Neuroconn Stimuluator DC Plus 41,3 Jahre unter Volllast zu stimulieren.

Auf meinem primären "To do"-Zettel verbleibt damit nur noch der letzten offene, hastig gekritzelte Punkt, dessen Bedeutung uns sich wohl für immer entziehen wird:

Nua equa tobbler