Investigating the Role of Neuronal Oscillations in Tactile Temporal Perception using Magnetoencephalography and Transcranial Alternating Current Stimulation

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Glossary

ANOVA	analysis of variance
CTC	Communication through Coherence
EEG	electroencephalography
FDI	first dorsal interosseus
MEG	magnetoencephalography
rmANOVA	repeated measures analysis of variance
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SOA	stimulus onset asynchrony
SQUIDS	superconductive quantum interference devices
STDP	spike-timing dependent plasticity
tACS	transcranial alternating current stimulation
TMS	transcranial magnetic stimulation
VPL	ventral posterior lateral nucleus
VPM	ventral posterior medial nucleus

Summary

Neuronal oscillations are a ubiquitous phenomenon in the brain. They occur in different frequency bands which have been attributed to different functions. Alpha oscillations (8 – 12 Hz) have been related to inhibition or excitability of a brain area. It has been shown that the power of prestimulus alpha oscillations in the primary somatosensory cortex (S1) negatively correlates with temporal tactile discrimination. Furthermore, gamma oscillations (40 – 150 Hz) have been related to the processing of stimuli. This thesis builds upon these results by (1) studying the role of poststimulus gamma power in relation to prestimulus alpha power and tactile temporal discrimination by using magnetoencephalography (MEG). And (2) by studying the causal role of alpha power on tactile temporal discrimination by using transcranial alternating current stimulation (tACS).

A tactile temporal discrimination task was used in which participants received two subsequent electrical stimuli to their left index finger with different stimulus onset asynchronies (SOAs). After finger stimulation, participants respond whether they perceived one or two stimuli. At specific SOAs, perception between one or two stimuli varies despite identical physical stimulation. Therefore, this task offers the possibility to study the effects of neuronal oscillations on temporal tactile discrimination.

In the first study, participants performed the tactile temporal discrimination task while brain activity was measured with MEG. It was hypothesized that poststimulus gamma power correlates positively with tactile temporal discrimination and negatively with prestimulus alpha power. However, data showed that poststimulus gamma power does not correlate with temporal tactile discrimination. Additionally, the data revealed a U-shaped relation between prestimulus alpha power and poststimulus gamma power. That is, both low and high prestimulus alpha power were related to high poststimulus gamma power whereas intermediate alpha power was related to low gamma power. Given that poststimulus gamma power was high at alpha power levels that relate to either the perception of mainly one stimulus or the perception of mainly two stimuli, it is concluded that high gamma power represents unambiguous stimulus processing rather than veridical processing. At intermediate alpha power, perception varied the most between one and two stimuli. Given that gamma power was low at intermediate alpha power, low gamma power could represent ambiguous processing.

In the second study, participants performed the tactile temporal discrimination task while and after tACS at 10 Hz, 5 Hz and sham was applied on primary somatosensory cortex. It

was hypothesized that tACS at 10 Hz decreases tactile temporal discrimination ability. However, no influence of tACS at 10 Hz was found on temporal tactile discrimination. Thus, it could be that alpha power is not causally related to tactile temporal discrimination or the setup used in this thesis was not able to modulate tactile temporal discrimination. Given both negative and positive results in the tACS literature, methodological issues are discussed in this thesis. It is concluded that a negative results adds to the literature by providing a tACS setup that is unable to modulate tactile temporal discrimination. Knowledge of negative results is crucial given the many degrees of freedom in the planning of tACS experiments.

In conclusion, this thesis contributes to the research of neuronal oscillations in the somatosensory domain by showing that (1) prestimulus alpha power is related to poststimulus gamma power and (2) even though tACS is known as a method to modulate neuronal oscillations and study causality, no change in temporal tactile discrimination performance was found.

Zusammenfassung

Neuronale Oszillationen sind ein universelles Phänomen im Gehirn. Neuronale Oszillationen kommen in verschiedenen Frequenzbändern vor, welchen bestimmte Funktionen zugeordnet werden konnten. Alpha-Oszillationen (8 – 12 Hz) sind an der Regulation der Hemmung und Exzitabilität eines Gehirnareals beteiligt. Es wurde gezeigt, dass das Leistungsspektrum von alpha-Oszillationen vor der Stimulation im primären somatosensorischen Kortex negativ mit der zeitlichen taktilen Diskriminierung korreliert. Gamma-Oszillationen (40 – 150 Hz) hingegen wurden mit der Verarbeitung von Stimuli assoziiert. Diese Arbeit baut auf diesen Ergebnisses auf: (1) Es wird die Rolle von poststimulären Gamma-Oszillationen in Zusammenhang mit prästimulären Alpha-Oszillationen und der taktilen temporären Diskriminierung mithilfe der Magnetoenzephalographie (MEG) untersucht. (2) Es wird die kausale Rolle von Alpha-Oszillationen auf die taktile temporäre Diskriminierung mithilfe der transkraniellen Wechselstromstimulation (tACS) untersucht.

Im Paradigma zur zeitlichen taktilen Diskriminierung in dieser Arbeit bekommen Probanden zwei aufeinanderfolgende elektrische Reize an den linken Zeigefinger mit unterschiedlichen Zeitabständen. Im Anschluss an die Stimulation am Finger gaben die Probanden an, ob sie ein oder zwei Stimuli wahrgenommen haben. Bei bestimmten Zeitabständen der Stimuli variiert die Wahrnehmung zwischen einem und zwei Stimuli trotz gleich bleibender physikalischer Stimulation. Trotz physikalisch gleich bleibender Stimulation variiert die Wahrnehmung der Probanden zwischen einem Stimulus und beiden Stimuli. Folglich bietet dieses Paradigma die Möglichkeit, den Einfluss neuronaler Oszillationen auf die zeitlichen taktilen Diskriminierung zu untersuchen.

In der ersten Studie führten Probanden das Paradigma durch während ihre Gehirnaktivität mit MEG gemessen wurde. Hypothese war, dass das poststimuläre Gamma-Leistungsspektrum positiv mit der taktilen temporären Diskriminierung korreliert und negativ mit dem prästimulären Alpha-Leistungsspektrum. Die MEG-Daten zeigten hingegen, dass das Leistungsspektrum der gamma-Oszillationen nicht mit der zeitlichen taktilen Diskriminierung korreliert. Außerdem hat sich ein U-förmiger Zusammenhang zwischen den Leistungsspektren der alpha- und gamma-Oszillationen gezeigt. Das heißt, dass sowohl ein relativ hohes als auch ein niedriges Leistungsspektrum der alpha-Oszillationen ein relativ hohes Leistungsspektrum der gamma-Oszillationen aufwiesen. Nur bei einem intermediären Leistungsspektrum der alpha-Oszillationen war das

Leistungsspektrum der gamma-Oszillationen niedrig. Das Gamma-Leistungsspektrum war somit hoch, wenn das Alpha-Leistungsspektrum mit der Wahrnehmung von entweder hauptsächlich einem Stimulus oder hauptsächlich zwei Stimuli assoziiert war. Folglich könnte ein hohes Gamma-Leistungsspektrum eher an einer eindeutigen Stimulusverarbeitung beteiligt sein anstatt an veridikaler Verarbeitung. Bei intermediärem Alpha-Leistungsspektrum variierte die Wahrnehmung am meisten zwischen einem Stimulus und zwei Stimuli. Das Gamma-Leistungsspektrum war bei intermediärem Alpha-Leistungsspektrum am niedrigsten und könnte somit eine uneindeutige Stimulusverarbeitung repräsentieren.

In der zweiten Studie wurde führten Probanden das oben beschriebene Paradigma durch während und nachdem tACS mit 10 Hz, 5 Hz und sham am primären somatosensorischen Cortex appliziert wurde. Hypothese war, dass tACS mit 10 Hz die Fähigkeit, die zwei Stimuli zu diskriminieren verschlechtert im Vergleich zu tACS-Bedingungen. Es wurde allerdings kein Einfluss von tACS mit 10 Hz auf die Fähigkeit zur taktilen temporären Diskriminierung festgestellt. Somit könnte es sein, dass das Alpha-Leistungsspektrum keine kausale Rolle in der taktilen temporären Diskriminierung hat. Andererseits könnte es auch sein dass die hier genutzte tACS-Konfiguration nicht geeignet war die taktilen temporären Diskriminierung zu beeinflussen. Da es in der tACS-Literatur sowohl positive als auch negative Ergebnisse gibt, werden in dieser Arbeit methodische Aspekte diskutiert. Es wird geschlussfolgert, dass das negative Ergebnis zur Literatur beiträgt, indem eine tACS-Konfiguration gezeigt wird, welche die taktile temporäre Diskriminierung nicht moduliert. Das Wissen von negativen Ergebnissen ist relevant in der tACS-Forschung aufgrund der vielen Freiheitsgrade, die das Planen von tACS-Experimenten beinhaltet.

Zusammenfassend behandelt diese Arbeit neuronale Oszillationen in der somatosensorischen Domäne. Es wird gezeigt, (1) dass alpha-Oszillationen vor der Finger-Stimulation mit gamma-Oszillationen nach der Finger-Stimulation zusammenhängen. Außerdem wird gezeigt, (2) dass tACS mit 10 Hz keinen Einfluss auf die Fähigkeit der taktilen temporäre Diskriminierung hat, obwohl tACS eine häufig benutzte Methode ist um neuronale Oszillationen zu modulieren und Kausalität zu erforschen,

1. Introduction

Perception is the fundamental process that lets us interact with the external world. An adequate functioning of perception is essential for both survival and well-being.

In the nervous system, perception operates basically in three stages:

1. Reception of the stimulus
2. Transmission to the brain
3. Processing in the brain.

Information from the external world is acquired with the sensory organs. In humans, the sensory organs are specific for different kinds of stimuli. For example, the sensory organ for vision is the eyes or for touch the skin. These sensory organs contain receptors which are sensitive to a specific type of stimulus energy (Gardner & Johnson, 2013a). For example, receptors in the retina of the eye are sensitive to electromagnetic energy (photoreceptors) whereas receptors in the skin are sensitive to mechanical energy (mechanoreceptors). The receptors are the first interaction of the human body with the external, incoming stimulus.

This signal is then transmitted to the brain. In vision, for example, the signal is transmitted from the eye via the optical nerve to the brain. In touch, the signal is transmitted via intermediate hubs, e.g., the spinal cord (see chapter 1.1).

Finally, the signal is processed in the brain. Generally, the brain serves as an information processing unit that integrates information from both internal and external sources of the organism. This information processing is realized by the communication between neurons in different brain areas and on different time scales. One key factor for communication between neurons are periodic fluctuations of neuronal activity which are hence called neuronal oscillations (Buzsáki & Watson, 2012).

Despite being fundamental for interaction with the external world, the neuronal mechanisms of perception are yet not fully understood. Specifically, the role of neuronal oscillations for perception is still under debate. In this thesis, the main focus will be to study the influence of neuronal oscillations on perception. In the first part, the relation between neuronal oscillations in different frequency bands (i.e., alpha and gamma oscillations, see chapter 1.3) during tactile perception will be investigated. In the second part, alpha oscillations will be modulated noninvasively to study their functional role on tactile perception.

1.1 Anatomical pathways in tactile perception

Tactile perception can be broadly defined as the processing of external stimuli coming in contact with the skin.

Sensory reception of the stimulus is mediated by mechanoreceptors in the skin that react to mechanical stimulation (Fig. 1). The skin contains different kinds of mechanoreceptors, which are sensitive to different kinds of stimulation, e.g. pressure, distortion. From these mechanoreceptors, the sensory information is transmitted via afferent nerve fibers to the spinal cord via action potentials (Gardner & Johnson, 2013b). In contrast to mechanical stimuli, which activate mechanoreceptors, electrical stimuli (which are used in this work) are suggested to directly stimulate the afferent nerve fibers (Kaczmarek et al., 1991).

The signal from the mechanoreceptors or nerve fibers enters the spinal cord on the site ipsilateral to the stimulation at the dorsal root (Fig. 1). From there, the signal is transmitted to the medulla where it crosses the midline of the central nervous system (called decussation). Thus, the signal is now further transmitted on the site contralateral to the stimulation. If the initial stimulus originated from the face, the signal is transmitted to the ventral posterior medial nucleus (VPM) of the thalamus. If the stimulus originated from the rest of the body, the signal is transmitted to the ventral posterior lateral nucleus (VPL) (Hendry & Hsiao, 2008). From the thalamus, the sensory signal is further transmitted to the primary somatosensory cortex (S1). S1 is somatotopically organized. That is, every region in S1 corresponds to a certain body part (Amaral, 2013). For example, if a stimulus is received at the left index finger, the signal is finally transmitted to the index finger region of the right S1. From S1, the signal can be processed via two streams in the cortex: a dorsal stream and a ventral stream. The ventral stream leads from S1 to the secondary somatosensory cortex (S2) and further to the insula. From the insula the signal is transmitted to the amygdala and (over the entorhinal cortex) to the hippocampus (Gardner, 2008). Furthermore, the ventral stream leads to the superior temporal gyrus, in which the integration of signals from different sensory modalities takes place (Hendry & Hsiao, 2008).The dorsal stream leads from S1 to the posterior parietal cortex and from there to the premotor cortex and supplementary motor cortex. The dorsal stream is involved in integrating somatosensory information into motor action (Gardner, 2008; Hendry & Hsiao, 2008).

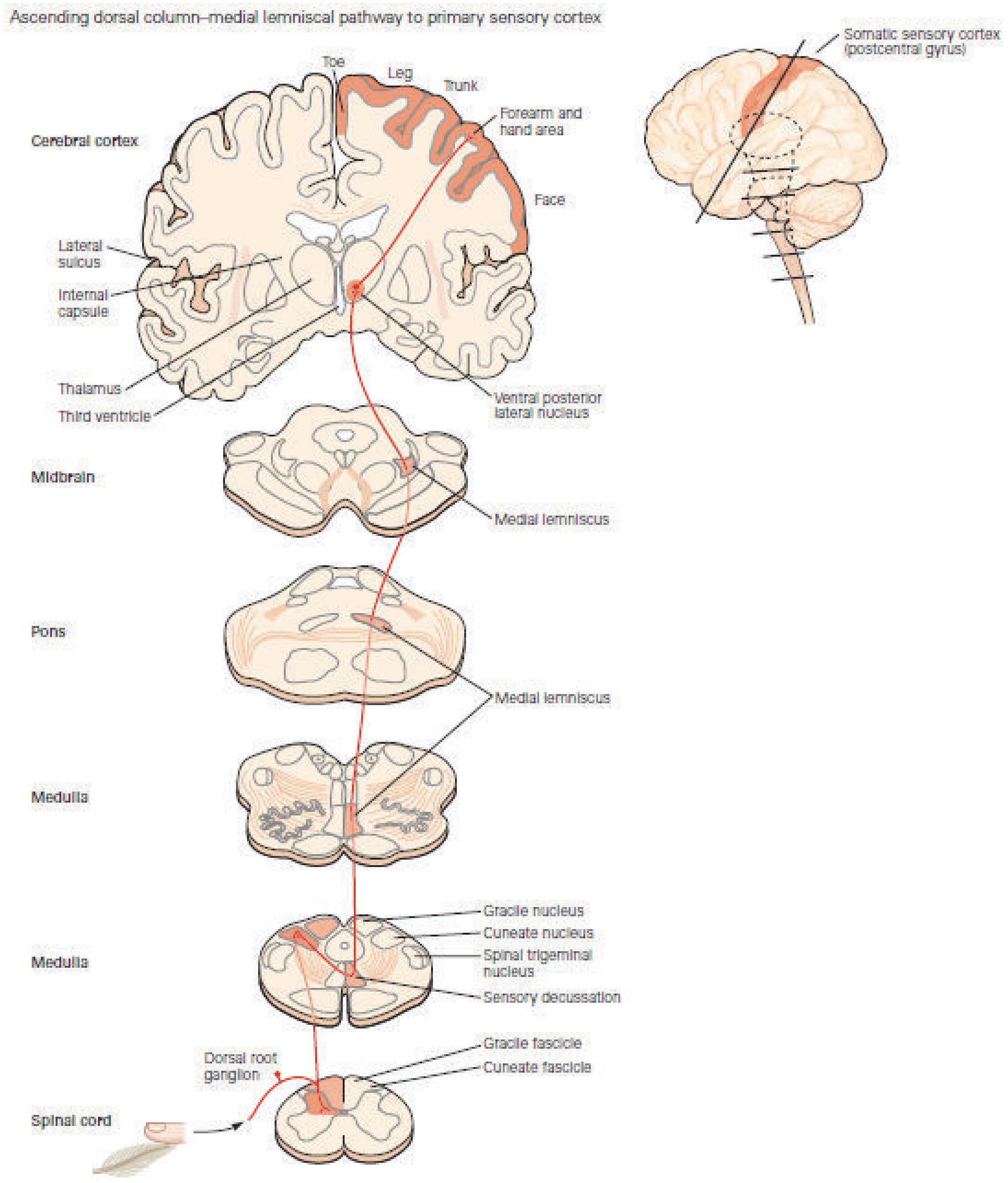

Figure 1. The somatosensory system. Pathway in the somatosensory system from the entrance of afferent neurons into the spinal cord up to the primary somatosensory cortex.

Taken with permission from Kandel et al. (2013).

1.2 Behavioral aspects in tactile perception

The signal is transmitted via the pathways mentioned in the previous chapter only if the intensity of the stimulus reaches a specific threshold. If the stimulus intensity is below this threshold, the signal will not be consciously detected. If stimulus intensity is near this threshold, the stimulus will sometimes be detected while sometimes it will be missed (so called near-threshold stimuli). Such near-threshold stimuli can be used to study the neuronal mechanisms of conscious perception. Participants are presented a stimulus and have to respond whether or not they detected the stimulus. Such tasks are usually labeled detection tasks. Then neuronal activity can be compared between detected and missed stimuli. This might give information about the neuronal mechanisms of stimulus detection. However, even if the stimulus intensity is high enough to be detected (i.e., supra-threshold), participants can differ in their ability to discriminate between multiple stimuli. The spatial and temporal resolution of tactile perception is also restricted by specific thresholds. If the spatial or temporal distance between two stimuli is below this specific threshold, these two stimuli cannot be discriminated and will be perceived as one stimulus (e.g., Gardner & Johnson, 2013c; Baumgarten et al., 2016). Tasks that test the ability to discriminate between multiple stimuli will be called discrimination tasks.

The spatial resolution depends on the distance of the mechanoreceptors (Goldstein, 2010). For example, in the finger tips, the distance between mechanoreceptors is smaller than the distance of mechanoreceptors in the upper arm. Consequently, the spatial resolution is better in the finger tips than in the upper arm (Nolan, 1982).

The temporal resolution between two stimuli is much less understood and seems to be more dependent on activity in the brain. One example is the auditory gap detection. Here, two bursts of sounds are presented and participants have to indicate which burst contains a gap (Phillips, 1999). Studies found that auditory gap detection depends on neuronal activity in the thalamus and the auditory cortex (Anderson & Linden, 2016; Weible et al., 2014). In the somatosensory domain, the ability to discriminate between two subsequent tactile stimuli depends on activity in the somatosensory cortex (Baumgarten et al., 2016).

In both detection and discrimination tasks, perception can differ on trial-to-trial basis despite physical identical stimuli. This fact implies that the processing of stimuli depends not only on the stimulus parameters, but also on internal mechanism (Lange et al., 2014). Previous studies suggest that these internal mechanisms are represented in different brain states (Baumgarten et al., 2015, 2016; Hanslmayr et al., 2007; Lange et al., 2012;

Linkenkaer-Hansen et al., 2004; Mathewson et al., 2009; van Dijk et al., 2008; Zhang & Ding, 2010). Therefore, these tasks using identical stimuli but varying perception offer the opportunity to study the underlying internal mechanisms of tactile perception.

In this work, mechanisms underlying temporal discrimination will be investigated. Therefore, the following of this thesis will be mainly focused on temporal discrimination. In temporal discrimination, varying perception can also be found despite identical stimulation. If two stimuli are apart for a specific time interval, perception varies between one or two stimuli over time (Baumgarten et al., 2016). Therefore, this varying perception has to result from internal mechanisms rather than from the unchanging external stimulation (Lange et al., 2014). Thus, presenting the two stimuli within this time interval is helpful to study the internal mechanism of temporal discrimination.

1.3 Neuronal Oscillations in the brain

Sensory information arrives in the brain. This information leads to neuronal activity in the receiving neurons as well as in the neurons connected to the receiving neurons. These neurons communicate constantly with each other (Buzsáki & Watson, 2012). A key factor in neuronal communication are neuronal oscillations (for review, see Buzsáki & Watson, 2012). Neuronal oscillations are the periodic fluctuations of neuronal activity (Buzsáki & Watson, 2012).

Neuronal oscillations occur in different frequencies. Thus, neuronal activity fluctuates at different rates. Therefore, neuronal oscillations can act on different time scales and therefore might provide a mechanism of the brain for neuronal communication on different time scales (Buzsáki & Watson, 2012).

Neuronal oscillations were found in vertebrates and invertebrates (Bosman et al., 2014; Bosman & Aboitiz, 2015), suggesting a universal mechanism of neuronal information processing.

1.3.1 Origin of neuronal oscillations

Neuronal oscillations result from the constant flux of electrically charged ions (mainly K^+, Na^+ and Ca^{2+}) between the intracellular and the extracellular medium. This creates an electric potential along the cell membranes that moves along the neurons, hence giving rise to an electric current. This electric current induces a magnetic field orthogonal to the electric field.

This current moves along the axon of a neuron until it reaches the presynapse. Here, voltage-dependent Ca^{2+}-channels open which leads to the release of neurotransmitters into the synaptic cleft. The neurotransmitters dock onto receptors of the postsynapse which leads to change in conformation of receptor-dependent ion-channels. Depending on the neurotransmitter and the ion-channel, this can either lead to an excitatory or inhibitory response in the postsynapse. In case of an excitatory response, the postsynaptic membrane depolarizes, whereas it hyperpolarizes at an inhibitory response. A depolarization leads the potential to come closer the threshold potential needed to activate action potential in the axon. A hyperpolarization decreases the potential, shifting it away from the threshold potential.

A network of neurons consists of excitatory and inhibitory neurons. The interaction between excitatory and inhibitory neurons leads to an oscillatory pattern of neuronal activity (Wang, 2010). Hence, neuronal oscillations are fluctuations in neuronal excitability (Fries, 2005; Jensen et al., 2014; Thut et al., 2012).

The activity of each neuron leads to a small electromagnetic field. If the activity of many neurons synchronizes and overlaps temporally and spatially, their individual electromagnetic field result in an overall stronger electromagnetic field. This electromagnetic field can be measured transcranially by EEG or MEG. The synchronized overlap of electromagnetic fields is mainly the case for postsynaptic dendritic activity (Hall et al., 2014). Axonal action potentials only play a minor role in generating neuronal oscillations. The electromagnetic fields action potentials produce are of a very short duration (< 2 ms). During this short time window, neurons rarely fire synchronously during low-frequency oscillations (Buzsáki et al., 2012). Thus, the electric fields of action potentials rarely overlap, which leads to an overall electric field too small to be detectable.

1.3.2 Characterizing neuronal oscillations

Neuronal oscillations are characterized by three different parameters: frequency, power, and phase.

Past research led to the classification of neuronal oscillations into different frequency bands. Each frequency band has been assigned specific functions in cognition, movement or perception. The frequency bands are: delta (< 2 Hz), theta (4 – 7 Hz), alpha (8 – 12 Hz), beta (15 – 30 Hz) and gamma (30 – 90 Hz) (Singer, 2013). The upper and lower bounds of these frequency bands are not strictly set and can differ between studies. For example, a study reported alpha oscillations in the range of 7 – 14 Hz (Haegens et al., 2014) and gamma oscillations were reported to have an upper bound of 150 Hz (Ray et al., 2008) or even 200 Hz (Fitzgerald & Watson, 2018).

Besides the frequency, the power of neuronal oscillations can give information about neuronal networks. The power of neuronal oscillations is the square of the amplitude. Each neuron transmits the electrical current with a specific frequency and amplitude. The resulting amplitude of the network is the sum of the amplitudes of the current of each individual neuron. Therefore, the amplitude and thus the power increases when the synchronized activity between neurons increases or when more neurons are included in this neuronal network.

Typically, power is smaller if the frequency is higher. Power is related to frequency f by a factor of $1/f^n$ with $n = 1 – 2$ (Buzsáki et al., 2012). The reason for this relation is twofold. First, low frequency oscillations are found in larger neuronal networks than high frequency oscillations. A reason for this is that longer time windows of low frequency oscillations allow for the recruitment of more neurons (Buzsáki et al., 2012). Second, dendrites act like a low-pass filter, attenuating signals with lower frequency much less than signals with higher frequency which results from the serial capacitance of the bilipid cell membrane (Buzsáki et al., 2012).

The phase describes the position within a cycle of an oscillation. Given that neuronal oscillations are fluctuations in neuronal excitability (Buzsáki & Watson, 2012), the phase refers to the state of excitability within an oscillation with a specific frequency.

In this thesis, the focus will be on neuronal oscillations in the alpha and gamma band. Therefore, the following chapters will describe specifically alpha and gamma oscillations.

1.3.3 The functional role of alpha oscillations

Alpha oscillations are the most prominent oscillation and were the first type of neuronal oscillations to be discovered in 1929 by Hans Berger (Berger, 1929). Berger found that the amplitude of occipital alpha oscillations increased when eyes were closed compared to when eyes were open.

A first interpretation was that with eyes open, visual stimuli are processed in the occipital cortex whereas there is no processing when the eyes are closed. This led to the conclusion that alpha oscillations represent an idling state in which cortical processing is decreased (Adrian & Matthews, 1934). At first, this was seen as a bottom-up process, that is, the visual stimuli reaching the eyes led to a decrease in alpha power. However, another result was found that alpha amplitude also decreases when the eyes were opened in a dark room (Moosmann et al., 2003). Thus, it is not merely the incoming light that led to the increase of alpha amplitude, but also an internal, top-down mechanism (Klimesch, Sauseng, & Hanslmayr, 2007; Moosmann et al., 2003).

In line with alpha oscillations representing an idling state of the brain area, various results showed that alpha power decreases during perceptual, judgment and memory tasks as well as in voluntary movement (for review see Pfurtscheller & Lopes da Silva, 1999). Here, the decrease was stronger the more demanding the task was (for review see Pfurtscheller & Lopes da Silva, 1999).

However, the notion of cortical idling came into question with later results, especially by a closer look at a memory scanning task. It was found that both an increase and a decrease of alpha power occur during this task. In the memory scanning task, participants have to memorize a string of characters. After a retention interval, a single character is shown and participants have to indicate whether this character was in the string shown before. The memorization consists of either the same string of characters over trials or the characters vary over trials (Klimesch et al., 2007). Only if the string of characters varied over trials, alpha power increased during the encoding and the retention interval (Klimesch, Doppelmayr, Schwaiger, Auinger, & Winkler, 1999). Klimesch et al. (1999) interpret this result that if strings vary, character strings from previous trials have to be blocked. The character strings from the previous trial are suggested to be blocked by alpha oscillation. Alpha oscillations therefore adopt an active inhibitive role, rather than the more passive idling role (Klimesch et al., 2007). When the single character is shown after the retention interval, alpha power decreases in both conditions, i.e., whether the memorization consisted of the same string or varied strings (Klimesch et al., 1999; Klimesch et al., 2007). The idea of alpha oscillations playing an active role is also strengthened by the result that alpha power increased the more information had to be remembered (Jensen, Gelfand, Kounios, & Lisman, 2002; Klimesch et al., 1999; Schack, Klimesch, & Sauseng, 2005; Tuladhar et al., 2007).

The inhibitive role of alpha oscillations is thought to gate information processing to relevant brain areas (Jensen & Mazaheri, 2010). By inhibiting task-irrelevant brain areas, the signal-to-noise ratio increases in relevant brain areas (Klimesch, 2012).

In line with this, alpha oscillations play a critical role in attention.

In a visuospatial attention task, the direction to which the participants have to attend is cued before the stimulus is shown. Here, prestimulus alpha power was shown to be lower in the hemisphere contralateral to the cued direction compared to the pre-cue baseline (Thut et al., 2006; Worden et al., 2000). Also, the higher this alpha power decrease was, the better did participants perform in a visual target detection task (Thut et al., 2006). In another task, the sensory modality was cued (either visual or auditory; Foxe, Simpson, & Ahlfors, 1998). Here, if the auditory modality was cued, parieto-occipital alpha power was increased compared to when the visual modality was cued. This result indicates that alpha oscillations are influenced by attention because the visual cue already influenced modulations in alpha power without presenting the auditory stimulus.

1.3.4 The functional role of gamma oscillations

Different functions have also been associated with gamma oscillations.

One of the first interpretations of the role of gamma oscillations was feature binding, that is, the combination of different features of a stimulus are combined into a coherent perception (Gray, König, Engel, & Singer, 1989; Singer & Gray, 1995). Gamma power increases during perception of meaningful percepts compared to meaningless percepts (Freunberger et al., 2007; Rodriguez et al., 1999).

Gamma oscillations have also been related to attention. Gamma power increases in sensory areas contralateral to the attended stimulus. This increase was found in visual (Fries et al., 2008; Müller et al., 2000; Siegel et al., 2008), somatosensory (Bauer et al., 2006; Haegens et al., 2010; Haegens, Nácher, Hernández, et al., 2011), and auditory cortex (Ahveninen et al., 2013).

Furthermore, gamma oscillations have been related to higher order functions such as working memory (Haegens et al., 2010). In a working memory task, participants received a series of pulses to their right hand (Haegens et al., 2010). After a retention interval, another series of pulses was delivered to either the left or right hand. Participants should respond whether the frequency of the latter series of pulses was higher or lower than the first series. Haegens et al. found that gamma power was increased in S1 contralateral to the stimuli and in S2 bilateral. Furthermore, frontal gamma power correlated with behavioral performance. As such, the functional role of gamma oscillations is regarded as engagement of neuronal networks in information processing (Jensen & Mazaheri, 2010). An influential model for this processing is described by the "Communication through Coherence" (CTC) hypothesis (Fries, 2005, 2015).

The CTC hypothesis states that groups of neurons communicate with each other by selectively aligning their excitability phases such that the presynaptic neurons fire in the phase with highest excitability of the postsynaptic neurons (Fries, 2015). Irrelevant postsynaptic groups of neurons (i.e., neurons that should not relay the signals) will receive the signal in a phase with low excitability. Therefore, they will not relay the signal. This principle allows for effective, precise and selective communication among groups of neurons (Fries, 2015). Thus, gamma oscillations are suggested to relate to an activated state of neuronal networks (Fries, 2009).

1.4 Alpha and gamma oscillations in perception

As described in the previous chapters, alpha and gamma oscillations have crucial roles in cortical processing. In perception, cortical processing of the stimulus is the final step after reception of the stimulus and transmission of the stimulus to the brain. In this chapter, the roles of alpha and gamma oscillations in perception will be described.

1.4.1 Alpha power in perception

In perception tasks, alpha power before the stimulation influences perception (i.e, prestimulus alpha power).

Spatial attention decreased alpha power contralateral to the attended side. This was shown in the visual and somatosensory domain (Baumgarten et al., 2016; Foxe et al., 1998; Thut et al., 2006; Worden et al., 2000). This alpha decrease was also shown to be behaviorally relevant (Baumgarten et al., 2016; Kelly et al., 2009; Thut et al., 2006; van Dijk et al., 2008, 2010).

Even without explicit modulation of spatial attention, several studies found that prestimulus alpha power is correlated with detection/discrimination ability. This correlation was found across different modalities.

In the visual domain, many studies find a negative correlation between alpha power and detection/discrimination ability. That means, with low alpha power, participants were better in detection tasks than with high alpha power (Achim et al., 2013; Ergenoglu et al., 2004).

In discrimination tasks, participants could better discriminate with lower prestimulus alpha power than with higher alpha power (Roberts et al., 2014; van Dijk et al., 2008).
Similarly, in the somatosensory domain, studies also found a linear relationship between alpha power and perception. That is, participants could better detect (Schubert et al., 2009; Weisz et al., 2014) or discriminate tactile stimuli (Baumgarten et al., 2016) with lower alpha power. Furthermore, with lower alpha power, participants could better temporally discriminate stimuli when there is a temporal offset between two stimuli (Baumgarten et al., 2016).

It should be that noted that in the somatosensory domain, some studies also found an inverted U-shaped relation between alpha power and detection/discrimination ability (Lange et al., 2012; Linkenkaer-Hansen et al., 2004; Zhang & Ding, 2010). That is, in those studies, intermediate alpha power led to better detection/discrimination ability whereas low and high alpha power led to worse ability.

As such, low alpha power was interpreted as representing a state of better perceptual acuity (Hanslmayr et al., 2007; Mathewson et al., 2009; Romei et al., 2010; van Dijk et al., 2008; Wyart & Tallon-Baudry, 2008). However, later studies questioned this interpretation. In line with the perceptual acuity interpretation, Lange et al. (2013) found that low alpha power led to better discrimination in a visual discrimination task (i.e., higher visual acuity). In contrast to that result, they also found that low alpha power led to a higher chance of illusory perception in a visuo-tactile illusion task (i.e., lower or less veridical visual acuity). Lange et al. interpreted their results that alpha power indexes excitability of sensory cortex rather than acuity.

In line with this result, studies found that both hits and false alarms increase with lower alpha power (Iemi et al., 2017; Limbach & Corballis, 2017).

1.4.2 Gamma power in perception

In contrast to alpha power, gamma power seems to be more prominent after stimulation (i.e, poststimulus gamma power).

In spatial attention tasks, poststimulus gamma power increases contralateral to the attended side. This was also found in the visual (Gruber et al., 1999; Müller et al., 2000; Wyart & Tallon-Baudry, 2008) and somatosensory domain (Bauer et al., 2006; Haegens et al., 2010).

Gamma power was also shown to be behaviorally relevant. In a visual task, monkey's reaction time correlated with gamma power in visual cortex (Womelsdorf et al., 2006) . A similar result was obtained in humans in an MEG study. In a visual change detection task, participants could react faster with higher gamma power in visual cortex (Hoogenboom et al., 2010). Similarly, in somatosensory cortex, gamma power was found to correlate with performance in a detection task (Meador et al., 2002).

In another study, Siegle et al. (2014) used optogenetics to entrain gamma oscillations in mice. They found that mice could detect vibrissal deflections better with higher gamma power. The use of optogenetics to modulate gamma power provides support that gamma power is causally involved in perceptual performance.

In conclusion, prestimulus alpha and poststimulus gamma power play a role in perception. Their modulatory patterns, however, seem to be diametrical. Whereas prestimulus alpha power decreases contralateral to the stimulus, poststimulus gamma power increases contralateral to the stimulus.

1.5 Magnetoencephalography (MEG)

Neuronal oscillations can be noninvasively measured by magnetoencephalography (MEG) or electroencephalography (EEG). The ionic flux across neuronal cell membranes creates an electromagnetic field. EEG measures the electrical part of this field whereas MEG measures the magnetic part. This results in the two methods measuring different parts of neuronal currents. Whereas EEG measures neuronal current orthogonal to the skull, MEG measures neuronal current tangential to the skull (Pollok & Schnitzler, 2010). Because the electromagnetic fields originate directly from neuronal activity, EEG and MEG measures neuronal activity directly instead of indirectly like functional magnetic resonance imaging which measures blood oxygen level dependent contrast.

EEG and MEG have different advantages. For example, EEG can be applied more easily and flexible due to the EEG not needing a cooling system and magnetically shielded room (see below). MEG however has a better spatial resolution which is on the millimeter scale (Hämäläinen et al., 1993). Two main factors determine the spatial resolution of MEG: (1) the penetrability of the magnetic fields through tissue and (2) the distance of the magnetic source to the sensor. The tissue surrounding the brain, like the skull, skin or the cerebral liquor have different electrical conductivity. This distorts the electrical signal that reaches from the brain to the sensor. Magnetic fields are less distorted by the electrical conductivity of the brain surrounding tissue, leading to a less-distorted magnetic signal reaching the sensor and thus to a higher spatial resolution (Baillet et al., 2001; Hall et al., 2014).

The second factor that influences the spatial resolution of MEG is the distance of the sensor from the source of neuronal magnetic field. In general, the farther away the signal is from the sensor, the lower is the signal-to-noise ratio, leading to a more distorted signal that reaches the sensor.

Furthermore, the magnetic fields from the brain are very small and are within the range of 10^{-15} Tesla. Therefore, very sensitive sensors are needed to measure those fields. These sensors are called superconductive quantum interference devices (SQUIDS). To ensure superconductivity of the SQUIDS, they have to be kept at low temperatures (below 4.2 K). This low temperature is realized by a liquid helium Dewar (Fig. 2).

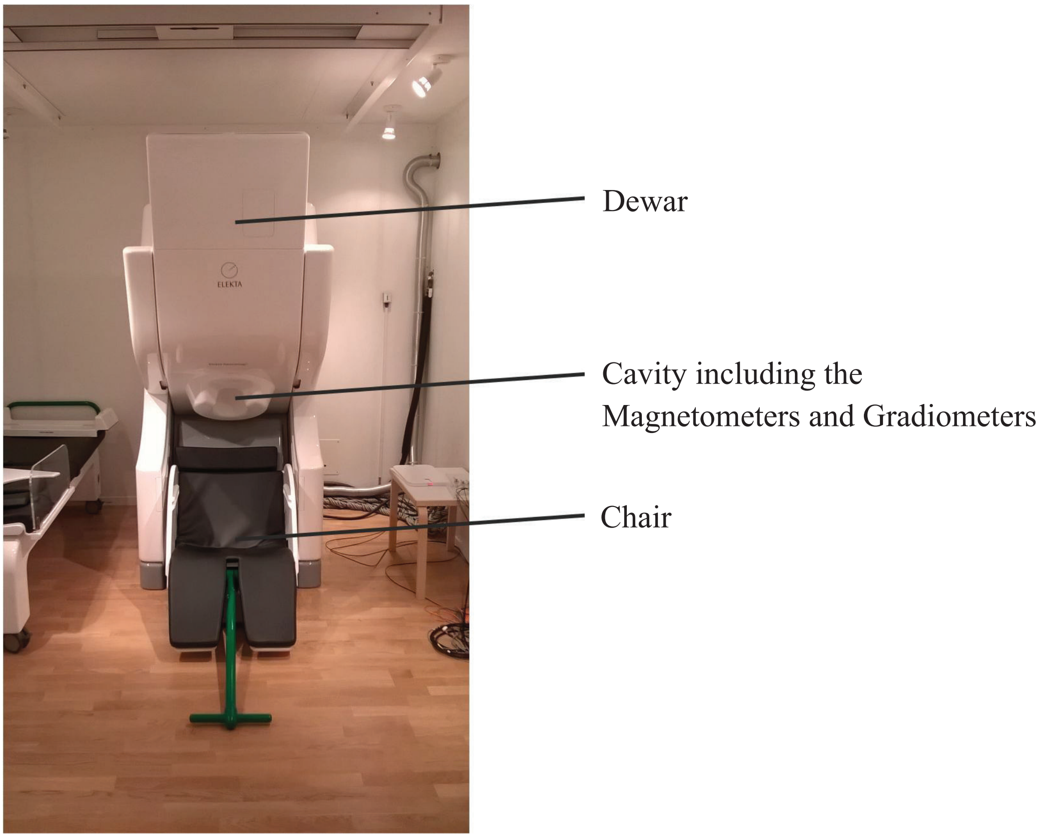

Figure 2. The MEG System used in this work (Elekta Neuromag Vector View 306 Channel MEG system (Elekta Oy, Helsinki, Finland)).The participant is seated in the chair with their head in the cavity. Within the cavity are the magnetometers and gradiometers which measure the magnetic field. The cooling system contains liquid helium to keep the SQUIDS at 4.2 K for adequate functionality (Self-made photo).

To reduce noise from external magnetic fields from surrounding electrical devices or the earth's magnetic field, the MEG is located in a magnetically shielded room. However, noise also comes from the human body itself because different parts of the human body produce magnetic fields of different strength. For example, heartbeat or eye and muscle movement produce magnetic fields leading to artifacts in the measurement of neuronal activity. Therefore, rejection of these artifacts is a crucial part of the analysis of the raw data. The Elekta Neuromag MEG of the university hospital Düsseldorf was used in this work (Fig. 2), consisting of 306 channels. These channels are divided into 102 triplets. Each triplet consists of 1 magnetometer and 2 planar gradiometers, whereby the gradiometers form an orthogonal pair (Fig. 3). The magnetometers are single coils which measure the absolute magnetic field whereas the gradiometers within the triplet measure the spatial gradient of the field. The magnetometers are prone to noise that passes the magnetically shielded room and to noise from inside the magnetically shielded room. The latter include the noise of the human body and mechanical vibrations of the Dewar (Hämäläinen et al., 1993).

The gradiometers reduce distant noise because gradiometers measure the gradient between the closely aligned coils (Hämäläinen et al., 1993). The gradient of a distant magnetic field is close to zero, whereas the gradient of a close magnetic field shows a greater difference. Therefore, the difference in measurement from these two coils results mainly from the close source, i.e., the human brain (Hämäläinen et al., 1993).

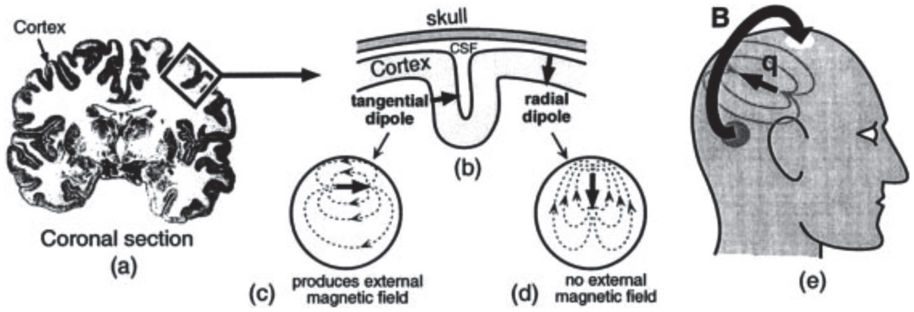

Figure 3. The cortex consists of numerous gyri and sulci (a). This convoluted structure of the cortex leads to electrical currents tangential and radial to the skull (b). Because the magnetic field is orthogonal to the electrical current, only tangential currents will produce will produce magnetic fields that are external to the skull (c,d). Given that the magnetic field rotates around the electrical current, the magnetic field first exits and then enters the skull (e). This magnetic field is measurable with MEG. Taken with permission from Vrba & Robinson (2001).

1.6 Modulation of neuronal activity with transcranial alternating current stimulation (tACS)

Methods that simultaneously measure brain activity and behavior can only find a correlation between these two variables. To find a causal relation, techniques have been developed that can modulate brain activity. If an induced change in brain activity leads to a change in behavior (or psychological variables in general), this indicates that a specific brain activity causes this behavior. Transcranial stimulation techniques offer the possibility to noninvasively modulate brain activity. They offer an expansion to MEG and EEG to study the causal influence of neuronal oscillations.

One of these techniques is transcranial alternating current stimulation (tACS). tACS is used in thesis and will be described in the following chapters.

1.6.1. Transcranial Alternating Current Stimulation (tACS)

Transcranial alternating current stimulation is a method in which two electrodes are placed on the head. These electrodes are connected to an electric generator. Through these electrodes, an alternating current is applied on the skull. If the current is of sufficient strength, the current will reach through the skull to the brain (Fig. 4) (for review see Herrmann, Rach, Neuling, & Strüber, 2013).

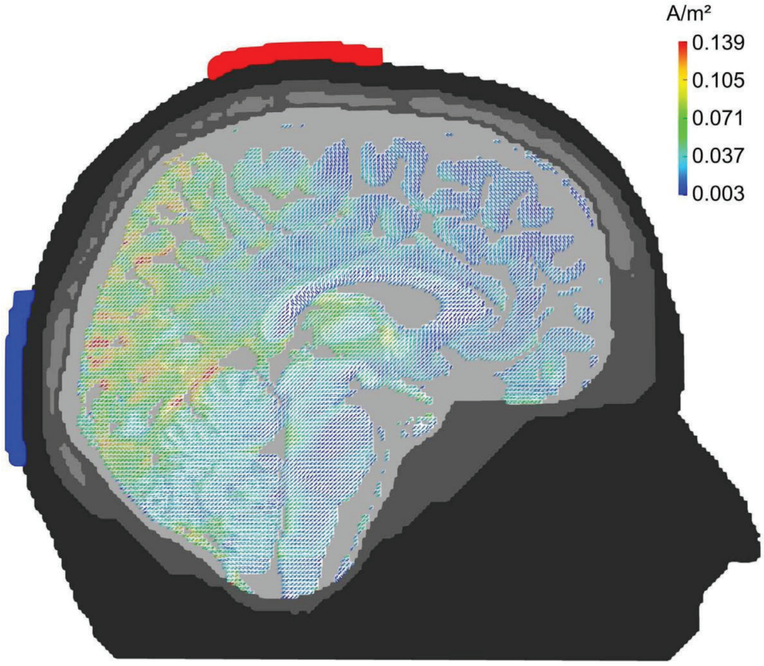

Figure 4. Electric current from tACS electrodes reaches the brain. Neuling, Wagner et al. (2012) modeled the electric current which originates from the tACS electrodes and found that the current reaches the brain. Therefore, tACS can be assumed to modulate brain activity. Taken from Neuling, Wagner, et al. (2012) (Creative Commons Attribution License).

To allow the current to run to the brain, the resistance has to be kept as low as possible. To this end, the electrodes are put into sponges soaked into a conductive liquid. These sponges are then fixated on the head by, e.g., a rubber band. Here, one electrode is placed above the area of interest where a modulation is desired (called the "stimulation electrode"). The other electrode is placed above an area which does presumably not affect the behavioral outcome to not distort the results (called the "reference electrode"; Fig. 5).

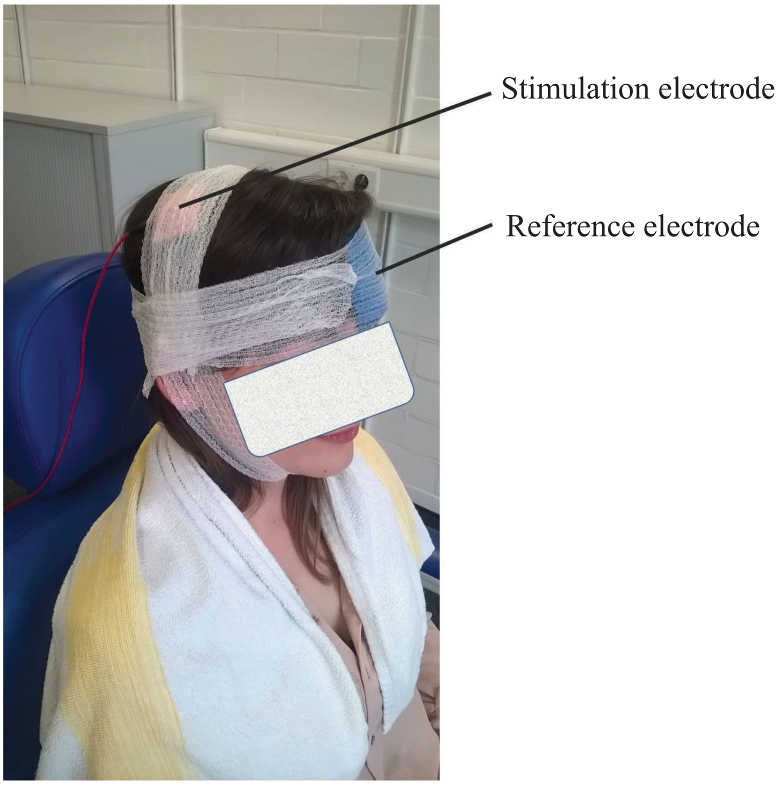

Figure 5. tACS Setup. The stimulation electrode stimulates the desired area. The reference electrode is placed on an area that does likely not interfere with the experimental task (Self-made photo).

The alternating current of tACS offers the possibility to use different frequencies for the stimulation. tACS leads to an entrainment of neuronal oscillations, that is, neuronal oscillations temporally align with the frequency of tACS (Thut et al., 2011; Vossen et al., 2015). This entrainment can also lead to an increase in power of neuronal oscillations with the respective frequency (Helfrich, Schneider, et al., 2014; Voss et al., 2014). For example, one study applied 40 Hz tACS to the frontal cortex during sleep while simultaneously measuring EEG (Voss et al., 2014). The authors found that tACS increased endogenous gamma oscillations. Another study applied 10 Hz tACS to parieto-occipital cortex while measuring EEG simultaneously (Helfrich, Schneider, et al., 2014). They found that alpha power was increased during tACS. These results are in favor of an increase of power of endogenous oscillations during tACS.

The generation of the power increase by applying tACS is described by a combination of the external applied tACS with the internal fluctuations of the brain (Zaehle et al., 2010). Typically, the higher the amplitude of the endogenous individual frequency, the more likely will tACS at the same frequency lead to a noticeable power increase in that frequency. For example, tACS in the alpha range leads to the best behavioral results when tACS is applied at individual alpha frequency (Kurmann et al., 2018).

This is further elucidated by the Arnold's tongue principle (Ali et al., 2013; Kurmann et al., 2018). The Arnold's tongue principle states that the lower the stimulation intensity, the less likely will tACS entrain frequencies outside the endogenous frequency. With tACS, this can result in a tradeoff between the stimulation intensity high enough to cause entrainment, but low enough to be within the safety conditions.

In addition to effects during tACS, studies have also shown a power increase after tACS. Zaehle et al. (2010) showed that alpha power was enhanced 3 minutes after tACS compared to before tACS. Neuling et al. (2013) found that alpha power was still enhanced 30 minutes after stimulation. It has been suggested that the after effects of tACS are due to spike-timing dependent plasticity (STDP) (Vossen et al., 2015). STDP refers to the concept that a synapse is either strengthened or weakened depending on the presynaptic input. Vossen et al. (2015) showed that the synaptic changes can persist after the stimulation.

1.6.2 Behavioral effects of tACS

tACS has been shown to have an effect on behavior. For example, Sliva et al. (2018) used tACS at alpha frequencies on S1 which led to an impairment in tactile detection of near-threshold stimuli. Other studies also used tACS to modulate performance in different domains, such as in motor (Feurra, Bianco, et al., 2011; Joundi et al., 2012; Pogosyan et al., 2009), perceptual (Kar & Krekelberg, 2014; Laczó, Antal, Niebergall, Treue, & Paulus, 2012; Neuling, Rach, Wagner, Wolters, & Herrmann, 2012), and higher cognitive function tasks (Santarnecchi et al., 2013).

By contrast, Gundlach et al. (2016) did not find an effect of alpha power on tactile detection with tACS at alpha frequencies. However, they found that detection thresholds varied with the phase of tACS. In general, effects of tACS on behavior are inconclusive as some studies did not find an effect of tACS on behavior (Brignani et al., 2013; Gundlach et al., 2016; Sheldon & Mathewson, 2018; Veniero et al., 2017). In line with this, one study performed the same tACS experiment twice with different results (Veniero et al., 2017). In the first experiment, they found an effect of tACS on behavior, but they could not replicate the effect in the second experiment.

2 Aims of the thesis

The first aim of this thesis is to investigate the role of alpha and gamma power on tactile temporal discrimination. As described in chapter 1.4, prestimulus alpha and poststimulus gamma power play a role in both detection and discrimination in the visual as well as in the somatosensory domain. Their effects were shown to be diametrical. However, the direct relation between prestimulus alpha and poststimulus gamma power is still unclear. Thus, the first aim of this thesis is to investigate the relation between prestimulus alpha power and poststimulus gamma power.

The second aim of this thesis is to investigate the causal role of alpha power and tactile temporal discrimination. As described in chapter 1.4.1 there is ample evidence of a correlation between alpha power and perception. For example, one study found that prestimulus alpha power and tactile temporal discrimination correlate negatively (Baumgarten et al., 2016). The causal role of alpha power on tactile temporal discrimination is still elusive. TACS is a useful method to modulate neuronal oscillations and study causal influence on behavior. As described in chapter 1.6, tACS has been used to modulate alpha power. Thus, in this study, tACS is used to study the causal role of alpha power on tactile temporal discrimination.

In summary, two questions will be investigated in this thesis:

1. What is the relation between prestimulus alpha power and poststimulus gamma power in tactile temporal discrimination?
2. Is prestimulus alpha power causally involved in tactile temporal discrimination?

To investigate these questions, a task was applied in which participants received two electrical stimuli to their left index finger with varying time intervals (stimulus onset asynchrony [SOA]). Participants should respond whether they perceived both stimuli or only one stimulus.

Study 1:

Study 1 investigated the relation between prestimulus alpha power and poststimulus gamma power. MEG data from a previous study was used in which participants performed the tactile temporal discrimination task (Baumgarten et al., 2016). A potential correlation between prestimulus alpha power and poststimulus gamma power was investigated. Hypothesis was that prestimulus alpha power and postimulus gamma power will correlate negatively.

Study 2:

Study 2 investigated a possible causal role of alpha power on tactile temporal discrimination. To this end, a tactile temporal discrimination task was used before, during, and after tACS at 10 Hz has been applied. Hypothesis was that tACS at 10 Hz will increase alpha power. This increase in alpha power should decrease discrimination ability. That means, participants should more often perceive one stimulus at a specific SOA when tACS has been applied compared to when tACS has not been applied.

3. Study 1: U-shaped Relation between Prestimulus Alpha-band and Poststimulus Gamma-band Power in Tactile Temporal Perception in the Human Somatosensory Cortex (Wittenberg et al., 2018, Journal of Cognitive Neuroscience)

3.1 Introduction

Study 1 (Appendix 1) investigated the relation between prestimulus alpha power, poststimulus gamma power and tactile temporal discrimination.

Prestimulus alpha power has been found to correlate with varying perception despite identical stimulation (Lange et al., 2012; Linkenkaer-Hansen et al., 2004; van Dijk et al., 2008). For example, lower prestimulus alpha power relates to better detection of visual near-threshold stimuli (Hanslmayr et al., 2007; van Dijk et al., 2008) or better discrimination between two subsequent tactile stimuli (Baumgarten et al., 2016). As such, prestimulus alpha oscillations were interpreted as a state of excitability or inhibition of a brain area (Jensen & Mazaheri, 2010; Klimesch et al., 2007; Lange et al., 2013). Here, low alpha power represents a state of lower inhibition or higher excitability. This influences neuronal processing and perception of ambiguous stimuli (Lange et al., 2013, 2014; Thut et al., 2006). Additionally, alpha power is modulated by attention (Foxe et al., 1998). In spatial attention, alpha increases ipsilateral and/or decreases contralateral to the attended side (Thut et al., 2006; Worden et al., 2000). A decrease contralateral and/or an increase ipsilateral to the attended side also correlated with better behavioral performance (Kelly et al., 2009; Thut et al., 2006). Moreover, a decrease in alpha power before the stimulus (i.e., prestimulus) correlated with better detection of the the stimulus (Ergenoglu et al., 2004). Poststimulus gamma power is also modulated by spatial attention. In both visuospatial and tactilospatial attention, gamma power increases contralateral to the stimulus (Bauer et al., 2006; Haegens et al., 2010; Haegens, Nácher, Hernández, et al., 2011; Müller et al., 2000; Siegel et al., 2008). Also, gamma power correlates with better behavioral performance (Hoogenboom et al., 2010; Womelsdorf et al., 2006).

In summary, prestimulus alpha and poststimulus gamma power show a diametrical pattern in regards to behavioral performance and attention. Their direct relation, however, is still unclear. Given the diametrical pattern, the hypothesis in this study was that prestimulus alpha power and poststimulus gamma power are negatively correlated.

3.2 Methods

The data included 12 of the 16 participants that were recorded in a previous study (Baumgarten et al., 2016; see below for exclusion criteria for four participants). Participants conducted a tactile temporal discrimination task. For this task, participants received two consecutive electrical stimuli to their left index finger. The stimulus onset asynchrony (SOA) between the two electrical stimuli was the intermediate SOA, which was individually determined in a pre-experiment. At the intermediate SOA, responses are about a 1:1 ratio between the perception of one and two stimuli (Baumgarten et al., 2016). The varying responses despite physically identical stimulation must therefore be dependent on internal brain states. One marker of brain states are neuronal oscillations. Thus, the intermediate SOA offers the possibility to study the role of neuronal oscillations on tactile temporal discrimination.

After electrical stimulation, participants then responded whether they perceived one or two stimuli. During the experiment, brain activity was measured with MEG.

Prestimulus alpha power (8 – 12 Hz) and poststimulus gamma power (40 – 150 Hz) were analyzed.

Prestimulus alpha power was analyzed in somatosensory-parietal sensors contralateral to finger stimulation (the same sensors were used as in Baumgarten et al., 2016).

In a previous study, an effect of prestimulus alpha power and tactile temporal discrimination was found (Baumgarten et al., 2016). To study the influence of prestimulus alpha power on poststimulus gamma power, the same sensors and time window as in Baumgarten et al. (2016) were used. Thus, prestimulus alpha power was analyzed in somatosensory-parietal sensors contralateral to finger stimulation in the time window of 0.9 – 0.25 s before the first stimulus. In these sensors and time window, alpha power was averaged from 8 Hz to 12 Hz.

Poststimulus gamma power was analyzed in sensors relating to S1 contralateral to finger stimulation in the time window of 0 – 0.2 s after the first stimulus. To identify these sensors, sensors showing the M50 component were identified. The M50 component is known to originate from S1 (Iguchi et al., 2005).

For gamma power, the frequency ranges with highest power were determined individually. To this end, power for each frequency and each time point between 0-0.2 s after the first stimulus was determined relative to a prestimulus baseline (0.6 – 0.2 s before the first stimulus) within the 40 – 150 Hz band by means of an independent *t* test. Within the

40 – 150 Hz band, peaks of the calculated *t*-values were determined. Then the gamma range with highest power was determined by taking the width of the peak at its half height. To include a peak, two criteria were applied:

1) A minimum peak height relative to neighboring points to distinguish narrow-band gamma activity from a possible broadband signal (i.e., extending into lower frequency bands) as a response to stimulus onset.
2) A minimum threshold to ensure that gamma power is high enough to not be confused with noise fluctuations.

After applying these two criteria, gamma power of three participants did not reach the minimum threshold and were thus excluded. A further participant was excluded for showing a broadband signal extending into the lower frequencies.

To investigate the relation between alpha or gamma power and mean responses, all trials were sorted from low to high power with respect to either alpha or gamma power for each participant. For each participant, trials were separated into five bins with each bin having equal amount of trials. The responses for each trial within a bin were averaged to obtain mean responses for each bin. Then, mean responses for each bin were normalized to the mean response across all bins. After that, mean responses within each bin were averaged across participants. Finally, linear and quadratic regression analyses were performed between alpha power and mean responses, and gamma power and normalized mean responses, respectively.

A similar procedure was applied to investigate the relation between prestimulus alpha power and poststimulus gamma power. Here, trials were separated into bins with respect to prestimulus alpha power for each participant. Within each bin, poststimulus gamma power was averaged across all trials. This average gamma power was then normalized to the average of gamma power across all bins. Then, gamma power within each alpha power bin was averaged across participants. Linear and quadratic regression analyses were performed between alpha power bins and normalized mean gamma power.

Additionally, to exclude that a possible relation between alpha and gamma power is due to covarying noise levels, signal-to-noise ratios were calculated. To this end, the same procedure that was used for calculating poststimulus gamma power was applied to a time window for which no modulations of gamma power but only noise fluctuations were expected (0.5 – 0.3 s before the first stimulus, i.e., prestimulus gamma power). Signal-to-noise ratios were then computed by dividing poststimulus gamma power and prestimulus gamma power for each trial and participant. The same analyses as for relation between alpha power bins and poststimulus gamma power were carried out for the signal-to-noise ratios.

3.3 Results

The result of Baumgarten et al. (2016) was reproduced. There was a negative linear correlation between prestimulus alpha power and mean responses (Appendix 1, Fig. 2A). By contrast, there was no correlation between poststimulus gamma power and mean responses (Appendix 1, Fig. 2B).

There was a quadratic (U-shaped) relation between prestimulus alpha power and poststimulus gamma power. That is, gamma power was highest for both high and low alpha power, whereas gamma power was lowest for intermediate alpha power (Appendix 1, Fig. 3). Signal-to-noise ratios indicated that this result is not explained by noise fluctuations within the alpha and gamma band.

Combining this result with mean responses means that high gamma power is related to the perception of either one or two stimuli depending on if alpha power is high or low (Appendix 1, Fig. 4). With intermediate alpha power and low gamma power, there was no clear preference between the perception of one or two stimuli.

3.4 Discussion

Study 1 comprises two main results. First, whereas perception correlated with prestimulus alpha power, perception did not correlate with poststimulus gamma power. Second, there was a U-shaped relation between prestimulus alpha power and poststimulus gamma power. Gamma oscillations are considered as signal processing in a brain area (Fries, 2005, 2015). As such, better perception of both stimuli was expected for higher gamma power in S1. Most studies that found a positive correlation between gamma power and perception near-threshold stimuli for which participants had to indicate whether or not they perceived a stimulus (Gross et al., 2007; Meador et al., 2002; Siegle et al., 2014). By contrast, in study 1 supra-threshold stimuli were used which always included the perception of at least one stimulus. Given that gamma power represents signal processing, perception of both one and two stimuli include gamma power indicating the processing of at least one stimulus.

There can be different explanations why there was not a difference in gamma power between the perception of one or two stimuli. One explanation could be that a possible difference in gamma power might be too small to be detected by the method used in this study. Another explanation can be that the discrimination between one or two stimuli might be processed in higher cortical areas than S1 (Haegens et al., 2010; Haegens, Nácher, Hernández, et al., 2011). Therefore, a difference in gamma power was not found in S1. A further explanation might be found in the U-shaped relation between prestimulus alpha power and poststimulus gamma power (see below).

The U-shaped relation between prestimulus alpha power and poststimulus gamma power might be due to gamma power not leading to veridical perception but unambiguous perception. By regulating excitability or inhibition, prestimulus alpha power gates the stimuli to the perception of either one or two stimuli. If alpha power is either low or high, this leads to the unambiguous perception of two or one stimuli, respectively. This unambiguous perception is in line with confidence ratings in Baumgarten et al. (2016). In Baumgarten et al. confidence was rated high in two cases: (1) when alpha power was high and one stimulus was perceived, or (2) when alpha power was low and two stimuli were perceived. Thus, gamma power might be associated with higher confidence.

By contrast, gamma power was low at intermediate alpha power. At intermediate alpha power, neither perception of one or two stimuli is preferred. Thus, perception is ambiguous and gamma power is low.

The U-shaped relation between prestimulus alpha power and poststimulus gamma power offers an alternative explanation why gamma power was not related to discrimination between one or two stimuli. If prestimulus alpha power determines the perception of either one or two stimuli, then averaging across all alpha power states (to analyze gamma power) will also average across perception of both one or two stimuli.

3.5 Conclusion

The main result of study 1 is a U-shaped relation between prestimulus alpha power and poststimulus gamma power in tactile temporal discrimination. Gamma power was high when alpha power was low or high, whereas gamma power was low when alpha power was intermediate.

Low or high prestimulus alpha power gates perception to either one or two stimuli, respectively. Both these states lead to high gamma power. Thus, high gamma power might be related to unambiguous perception rather than veridical perception.

4. Study 2: 10 Hz tACS Over Somatosensory Cortex Does Not Modulate Supra-Threshold Tactile Temporal Discrimination in Humans

(Wittenberg et al., 2019, Frontiers in Neuroscience)

4.1 Introduction

Several studies found a relation between alpha power and perception. In the visual and the somatosensory domain, low alpha power correlates with better ability in detection or discrimination tasks (Baumgarten et al., 2016; Haegens, Nácher, Luna, et al., 2011; Hanslmayr et al., 2007; Linkenkaer-Hansen et al., 2004; van Dijk et al., 2008). One example, which is the most relevant for study 2, is that tactile temporal discimination between two stimuli is better at lower alpha power than at higher alpha power (Baumgarten et al., 2016). These results are mostly of correlative nature, that is, the causal influence of alpha power on perception remains unclear. One method to study the causal influence of neuronal oscillations is transcranial alternating current stimulation (tACS). With tACS an alternating current is applied to the scalp which can modulate neuronal oscillations (Antal & Paulus, 2013). tACS has been shown to increase alpha power during and after it has been applied in the visual domain (Helfrich, Schneider, et al., 2014; Kasten, Dowsett, & Herrmann, 2016; Neuling et al., 2013; Ruhnau et al., 2016; Zaehle et al., 2010). By contrast, one study showed a decrease in alpha power after tACS in the somatosensory domain (Gundlach et al., 2017).

Additionally, tACS has been used to successfully modulate performance in behavioral tasks including perceptual tasks (Feurra, Bianco, et al., 2011; Helfrich, Knepper, et al., 2014; Joundi et al., 2012; Kar & Krekelberg, 2014; Laczó et al., 2012; Neuling, Rach, et al., 2012; Pogosyan et al., 2009; Santarnecchi et al., 2013).
Thus, in study 2 (Appendix 2) tACS was used to study the causal influence of alpha power on tactile temporal discrimination. The hypothesis of study 2 was that tACS at 10 Hz will modulate alpha power and thereby modulate discrimination ability during and after tACS.

4.2 Methods

17 participants were included in this study. Similar to study 1, participants conducted a tactile temporal discrimination task in which they received two consecutive electrical stimuli to their left index finger. Stimuli were applied with different SOAs (0, 20, 30, 40,

50, 60, 70, 80, 90, 100, 110, 130 ms). After finger stimulation, participants were asked to respond whether they perceived one or two stimuli (Appendix 2, Fig. 1B).

Participants conducted the task on three different days (Appendix 2, Fig. 1A). The days differed only in the applied tACS frequency (10 Hz, 5 Hz, or sham). On each day, participants conducted the task three times: before (pre), during (peri), and 25 min after (post) tACS. The order of the applied frequency was randomized across participants and double-blinded.

tACS was applied by placing the stimulation electrode over the right primary somatosensory cortex (S1) and the reference electrode over the left orbit (Appendix 2, Fig. 1C). S1 was localized by neuronavigation (LOCALITE, Sankt Augustin, Germany). Additionally, the stimulation electrode was placed on the head to minimally overlap with the right primary motor cortex (M1) to avoid stimulation of the finger muscle. The stimulation of the finger muscle might be misjudged for a stimulus from the finger electrode and thus interfere with the task. To this end, M1 was localized with TMS by inducing twitching of the left first dorsal interosseus (FDI). By moving the TMS coil posterior from the FDI, a spot was found where hand twitching stopped. At this spot, the anterior border of the stimulation electrode was placed. tACS was applied by two 5 cm × 7 cm electrodes at 1 mA for a maximum of 10 min, leading to a current density of 28.57 $\mu A/cm^2$ and a total charge of 0.017 C/cm^2. If a participant finished the paradigm before 10 min, tACS was terminated. This led to an average stimulation time of 8.20 ± 0.13 min (mean ± SEM).

Mean responses (averaged over participants) were determined for each frequency (10 Hz, 5 Hz, sham), session (pre, peri, post), SOA and subject. Then, a three-way repeated measures ANOVA (rmANOVA) with factors *Frequency*, *Session*, and *SOAs* was calculated. This analysis yielded no significant result. Furthermore, the first and the second half of the trials for the peri session for tACS at 10 Hz were compared to investigate if it takes some time until possible tACS effects occurred.

Additional analyses were then performed to check whether this non-significant results was caused by high intra- or interindividual variability. High intra- or interindividual variability can lead to a high variance in the data which will then cause a non-significant result. Another reason for a non-significant result could be potential “noise” in the data due to including data points which are irrelevant to the hypothesis.

To account for a possible intra- or inter-individual variability, two normalizations were performed.

Intra-individual differences might occur due to different individual performances on different days. Thus, in the first normalization, responses in the peri and post session were normalized with respect to the pre session of the respective day (called “relative to the pre session”).

In the second normalization, individual mean responses were transformed to a scale between 0 and 1 to account for inter-individual differences (called “relative to minimum-maximum”).

A final analysis was conducted to include only data points for which an effect might be especially expected *a priori*. To this end, the intermediate SOA was taken into account. The intermediate SOA is the SOA in which the perception of one and two stimuli occurs at about equal amounts. Baumgarten et al. (2016) found in their MEG study that alpha power correlates with mean responses at intermediate SOAs of ~25 ms. Thus, in study 2, a possible effect of alpha power on mean responses might be at SOAs around ~25 ms or at individual intermediate SOAs (the average intermediate SOA in study 2 was at ~54 ms). As such, a possible effect was investigated at individual intermediate SOAs, an SOA of 20 ms, 30 ms, or by combining the individual mean responses at SOAs of 20 ms and 30 ms.

All statistical analyses were first carried out in a frequentist framework. Given that these analyses yielded no significant results (see chapter 4.3), the same analyses were carried out in a Bayesian framework to test whether the results were in favor of the null hypothesis (i.e., that tACS at 10 Hz has no effect on tactile temporal discrimination).

4.3 Results

Frequentist rmANOVA resulted in no main effects for factors *Frequency* and *Session* and no interaction effects for the interactions *Frequency* × *Session*, *Frequency* × *SOAs* or *Frequency* × *Session* × *SOAs* (Appendix 2, Fig. 2). Bayesian rmANOVA provided results in favor of the null hypothesis of no effects. Additionally, there was no difference between the first and the second half of the trials during the peri session for tACS at 10 Hz. Similarly, no significant results were obtained when mean responses were normalized relative to the pre session or relative to minimum-maximum. Again, Bayesian analyses revealed evidence in favor of the null hypothesis.

In a further analysis, only mean responses at the intermediate SOA, the SOA of 20 ms, 30 ms, or the combined individual mean responses at SOAs 20 ms and 30 ms were taken into account. Here, mean responses did no differ at peri 10 Hz tACS when compared to pre 10 Hz tACS, peri Sham tACS, or peri 5 Hz tACS (Appendix 2, Fig. 3). Results of Bayesian statistics were in favor of the null hypothesis that there is no difference between the above mentioned comparisons.

Similarly, mean responses at post 10 Hz tACS did not differ from mean responses at pre 10 Hz tACS, post Sham tACS, or post 5 Hz tACS. Results of Bayesian statistics were either inconclusive or in favor of the null hypothesis.

4.4 Discussion

No evidence was found that tACS at 10 Hz influences tactile temporal discrimination with frequentist statistics. Using Bayesian statistics, most results were in favor of the null hypothesis that there is no difference between tACS at 10 Hz compared to control conditions. Only if specific SOAs were chosen from the post session, Bayesian statistics were either in favor of the null hypothesis or inconclusive, thus providing no evidence for an effect of tACS at 10 Hz on tactile temporal discrimination.

There can be different reasons for this null result.

A potential reason could be that neuronal oscillations were not entrained. Given that no neuronal oscillations were measured, this remains a possibility. However, other studies found a modulation of alpha power during (Helfrich, Schneider, et al., 2014; Ruhnau et al., 2016) and after tACS (Kasten et al., 2016; Neuling et al., 2013; Zaehle et al., 2010). These studies were in the visual domain, but also in the somatosensory domain, a modulation of alpha power was found after tACS (Gundlach et al., 2017). It could be that the current density used in study 2 was too low to modulate alpha power. However, other studies showed a modulation of neuronal oscillations with a current density similar to the one used in study 2 (Moliadze, Atalay, Antal, & Paulus, 2012; Neuling et al., 2015; Ruhnau et al., 2016). Given that these studies were in the visual domain, it could be that in the somatosensory domain higher current densities are needed to modulate neuronal oscillations. However, using a higher current density was discarded because at a higher current density, tACS at alpha frequency over S1 can elicit tactile sensations (Feurra, Paulus, et al., 2011). These tactile sensations might be misjudged for a stimulus from the finger electrode in study 2 and therefore distort behavioral results.

Another potential problem might be the chosen tACS frequency. Some studies applied tACS at individual alpha frequencies based on the peak of individual alpha oscillations

(Cecere et al., 2015; Gundlach et al., 2016). Other studies applied tACS at a fixed frequency within the alpha band for all subjects (Brignani et al., 2013; Kar & Krekelberg, 2014; Sheldon & Mathewson, 2018). In study 2, a fixed frequency of 10 Hz was used for all participants because of two reasons: 1) Tactile temporal discrimination did not correlate with individual endogenous alpha power (Baumgarten, Schnitzler, et al., 2017); 2) In a previous study, tactile temporal discrimination correlated with the power of the alpha frequency averaged across all participants instead of the power at individual alpha frequencies (Baumgarten et al., 2016).

It could be that this fixed frequency contributed to the null effect of study 2. According to the Arnold's tongue principle, a low current density only modulates a small frequency band around the endogenous frequency if the applied frequency is similar to the endogenous frequency (Herrmann et al., 2016; Kurmann et al., 2018). By contrast, the modulated frequency band is wider for higher current densities (Herrmann et al., 2016; Kurmann et al., 2018). Therefore, it could be that in participants whose endogenous peak alpha frequency differs too much from 10 Hz, alpha power was not sufficiently entrained in those participant to have an effect on tactile temporal discrimination. Alternatively, it could be that the mechanisms of tactile temporal discrimination are not modulated by 10 Hz but by another frequency within the alpha band. Due to the Arnold's tongue principle, this other frequency was not entrained given the low current density. However, as mentioned above, a higher current density might lead to tactile sensation (Feurra, Paulus, et al., 2011) which could be misjudged for a stimulus from the finger electrode and distort the behavioral result.

There are mixed results of the effects of tACS on perception. Some studies reported a modulation of perception by tACS (Brignani et al., 2013; Gundlach et al., 2016; Neuling, Rach, et al., 2012; Veniero et al., 2017) whereas others studies did not (Brignani et al., 2013; Gundlach et al., 2016; Sheldon & Mathewson, 2018; Veniero et al., 2017). Especially in the somatosensory domain, results are unclear. One study reported that tACS at alpha frequencies decreased detection ability (Sliva et al., 2018). By contrast, another study did not find an effect of alpha power when using tACS at alpha frequencies on tactile detection (Gundlach et al., 2016). However, they found that the detection rates depended on the phase of tACS. Both of these studies used a detection task where near-threshold stimuli were either perceived or not perceived. By contrast, study 2 used supra-threshold stimuli that were always perceived but participants had to discriminate between the perception of either one or two stimuli. There might be different underlying processes between detection and discrimination. Given that previous studies found that tactile temporal discrimination correlates with alpha power but with the phase of beta frequencies (Baumgarten et al., 2015, 2016), study 2 focused on the analysis of power modulations with tACS at alpha frequencies. In line with a possible difference between detection and discrimination, a study found that tACS at alpha frequencies affects detection but not discrimination in the visual domain (Brignani et al., 2013). Thus, there could be a similar pattern in the somatosensory domain.

Given these problems concerning the correct tACS setup, this study does not conclude that alpha power has not a causal role in tactile temporal discrimination.

Experiments with tACS comprise many degrees of freedom in the setup (e.g., electrode placement, stimulation frequency, current density, and the combination these factors). Additionally, there are individual differences in the impact of tACS due to anatomical differences like the gyral depths or thickness of the skull (Nitsche et al., 2008; Opitz et al., 2015). And even if the parameters are unchanged, results cannot always be replicated even within one study (Veniero et al., 2017). This results in a large search space for finding the optimal setup for tACS experiments (Kar & Krekelberg, 2014). Study 2 adds to this by providing a tACS setup that is unable to modulate tactile temporal discrimination.

4.5 Conclusion

In conclusion, study 2 provides a tACS setup that does not modulate tactile temporal discrimination. Given the remaining difficulties in setting up a tACS experiment, the result of study 2 could be explained by either the tACS setup is insufficient to entrain alpha power or that alpha power is not causally involved in tactile temporal discrimination.

5. General Discussion

In this thesis, the role of alpha and gamma power was investigated in tactile temporal discrimination. To this end, two studies were conducted: 1) In study 1, MEG data was analyzed to study the relation of prestimulus alpha power and poststimulus gamma power in a tactile temporal discrimination task. The results revealed that prestimulus alpha power in somatosensory-parietal areas and poststimulus gamma power in the primary somatosensory cortex (S1) had a U-shaped relation. That is poststimulus gamma power was highest at both low and high prestimulus alpha power whereas poststimulus gamma power was lowest at intermediate prestimulus alpha power. Prestimulus alpha power also correlated negatively with tactile temporal discrimination (as in Baumgarten et al., 2016). Moreover, poststimulus gamma power in S1 did not correlate with tactile temporal discrimination. 2) In study 2, tACS with a frequency of 10 Hz was applied to study a possible causal role of alpha power on tactile temporal discrimination. tACS at 10 Hz over S1 did not modulate tactile temporal discrimination neither during nor after tACS was applied.

The results presented in this thesis were unexpected. Except for the negative correlation between prestimulus alpha power and temporal tactile discrimination, different results were expected in study 1. Predictions for study 1 were based on the hypothesis that gamma power is related to stimulus processing (Fries, 2005, 2015; Jensen & Mazaheri, 2010). Thus, it was expected that higher poststimulus gamma power increases the ability to discriminate between the two stimuli. Given that higher prestimulus alpha power decreases the ability to discriminate between the two stimuli (Baumgarten et al., 2016), a negative correlation between prestimulus alpha power and poststimulus gamma power was expected. Instead, there was a U-shaped relation between alpha power and gamma power and no correlation between gamma power and tactile temporal discrimination. The results of study 1 indicate that poststimulus gamma power in S1 is not related to tactile temporal discrimination. As described earlier, a possible explanation might be that gamma power in S1 is only related to the detection but not to the discrimination of tactile stimuli (see chapter 3.4 and Appendix 1). Additionally, gamma power in S1 might be related to unambiguous perception of either one or two stimuli rather than veridical perception of the physically present stimuli.

In study 2, no correlation was found between tACS at 10 Hz and tactile temporal discrimination. This negative result in study 2 was also unexpected. Previous studies indicated that tACS at alpha frequencies modulates endogenous alpha power (Gundlach et al., 2017; Helfrich, Schneider, et al., 2014; Kasten et al., 2016; Neuling et al., 2013; Ruhnau et al., 2016; Zaehle et al., 2010). Given the negative relationship between alpha power and tactile temporal discrimination (Baumgarten et al., 2016), the modulation of alpha power was expected to modulate tactile temporal discrimination. Different reasons could explain why no modulation of tactile temporal discrimination occurred during or after applying tACS. These reasons included the possibility of no entrainment of alpha power due to low current density, 10 Hz not being the right frequency to affect discrimination, or alpha power in S1 not being causally related to tactile temporal discrimination (see chapter 4.4 and Appendix 2).

Study 2 provides a tACS setup that does not modulate tactile temporal discrimination which is important in light of the many degrees of freedom in setting up a tACS experiment and the mixed results of tACS on perception (see chapter 4.4 and Appendix 2).

The results of study 2 can have implications on the results of study 1. Here, two different cases can be considered whether or not alpha power in the stimulated area is causally involved in tactile temporal discrimination.

In the first case, prestimulus alpha power is causally involved in tactile temporal discrimination but the tACS setup used in study 2 was unable to modulate tactile temporal discrimination. In this case, the functional role of prestimulus alpha power is to gate the processing of the stimuli (Jensen & Mazaheri, 2010). This gating influences the perception of the stimuli (see chapter 3.4 and Appendix 1). Given the U-shaped relation between alpha and gamma power found in study 1, both high and low prestimulus alpha power lead to high poststimulus gamma power. Thus, a tACS setup which modulates tactile temporal discrimination should also modulate poststimulus gamma power. At low levels of endogenous alpha power, increasing alpha power with tACS should lead to a decrease of gamma power. By further increasing alpha power with tACS, gamma power should decrease until an intermediate alpha power level is reached. At high levels of endogenous alpha power, further increasing alpha power with tACS should lead to an increase in gamma power.

In the second case, the tACS setup used in study 2 was able to modulate alpha power but did not modulate tactile temporal discrimination because prestimulus alpha power is not causally involved in tactile temporal discrimination. If alpha power does not influence tactile temporal discrimination, then another factor is likely to cause the ability to discriminate two stimuli with different stimulus onset asynchronies (SOAs, i.e., the temporal interval between two stimuli). One likely candidate is the cycle of beta oscillations. A previous study found that tactile temporal discrimination changes if both stimuli occur in the same beta cycle or in different beta cycles (Baumgarten et al., 2015). If both stimuli fall within the same beta cycle, only one stimulus is perceived. If the two stimuli fall into different beta cycles, both stimuli are perceived. The authors could also modulate tactile temporal discrimination by adding a stimulus below perceptual threshold before presenting the two stimuli above perceptual threshold (Baumgarten, Königs, et al., 2017). This modulation occurred in a rhythm within the beta frequencies, supporting the hypothesis that the beta cycle in S1 has a key role in tactile temporal discrimination. Thus, it could be that the beta cycle is the main causal factor whereas alpha power only has a minor or no role in tactile temporal discrimination.

If prestimulus alpha power in somatosensory areas has no causal role in tactile temporal discrimination, the correlation between alpha power and tactile temporal discrimination could be the result of another factor. For example, both alpha power and perceptual performance have been shown to be related to attention (Foxe et al., 1998; Posner, 1980; Posner et al., 1980; Thut et al., 2006; Worden et al., 2000). Furthermore, attention can fluctuate which can influence perceptual performance (Adam & deBettencourt, 2019; Esterman et al., 2014). Alpha power is also known to be influenced by attention (Foxe et al., 1998; Thut et al., 2006; Worden et al., 2000). Thus, a hypothesis could be that the linear correlation between prestimulus alpha power in S1 and tactile temporal discrimination is a result of different levels of attention for each trial.

Poststimulus gamma power in S1 could be related to the unambiguous perception as described above. Contrary to the hypothesis of unambiguous perception seems to be that gamma power is typically linearly related to spatial attention (Bauer et al., 2006; Fries et al., 2008; Haegens et al., 2010; Müller et al., 2000; Siegel et al., 2008). However, in the tasks used in both studies in this thesis, spatial attention is always directed to one side (left). Therefore, it can be expected that gamma power in contralateral S1 is relatively high for each trial if it were compared to not directing attention to the left side. Thus, the gamma power for both the perception of one or two stimuli is already relatively high. Given that no relation between gamma power and discrimination ability was found, there seems to be no linear relation between gamma power and discrimination at this high gamma power level.

In study 1, no correlation between poststimulus gamma power in S1 and tactile temporal discrimination could be found. In study 2, tACS at 10 Hz did not modulate tactile temporal discrimination. In general, studies have failed to replicate results from previous studies in psychology (Nissen et al., 2016; Open Science Collaboration, 2015). One reason for this may be a bias towards the publishing of new positive results (Nissen et al., 2016). Publishing negative results in tACS experiments shows that conclusions about causality can be premature if only positive results were published. Additionally, negative results can be a motivating factor to search for reasons why other studies found positive results. One example is the recent study of Asamoah et al. (2019) in the motor domain. They found that tACS led to a stimulation of peripheral nerves in the skin which then caused entrainment in cortical areas. Therefore, a positive result in the motor domain in a tACS experiment might not be caused by solely the stimulation of a brain area but also due to peripheral nerve stimulation. Thus, it would be interesting if there are also positive results in the somatosensory domain that were caused by factors other than direct cortical stimulation. Both studies in this thesis have been published and add to the understanding of neuronal oscillations and its research methodology. This is especially true for study 2 given the diverging results of tACS on perception (see chapter 4.4 and Appendix 2).

In summary, using a tactile temporal discrimination task, the present work revealed a U-shaped relation between prestimulus alpha power and poststimulus gamma power. Additionally, poststimulus gamma power in S1 is not related to tactile temporal discrimination. Poststimulus gamma power might be related to unambiguous perception whereas prestimulus alpha power acts as a gateway between the perception of either one or two stimuli.

This hypothesis requires a causal role of alpha power in tactile temporal discrimination. A causal role of alpha power was investigated with a tACS experiment. This tACS experiment could not modulate tactile temporal discrimination with a stimulation frequency within the alpha band. Methodological challenges in tACS research were discussed which prevent a premature conclusion about a non-causal role of alpha power. Hence, a tACS setup was provided that does not modulate tactile temporal discrimination but further research is needed regarding the causal role of alpha power.

6. Outlook

Both studies offer the possibility for further research.

For study 1, the hypothesis that poststimulus gamma power in S1 has a role of unambiguous perception could be tested. One possible approach might be using different SOAs: one SOA that leads to the clear perception of one stimulus (i.e., an SOA of 0 ms), one SOA that leads to a clear perception of two stimuli, and an intermediate SOA. Here, poststimulus gamma power should be lower at the intermediate SOA than at the SOAs that lead to a clear perception of either one or two stimuli.

One approach for both studies is the combination of tACS with EEG or MEG (e.g., Helfrich, Schneider, et al., 2014; Herring et al., 2019; Zaehle et al., 2010). Here, brain activity could be measured while and after tACS at alpha frequencies is applied to test whether endogenous alpha and gamma power is modulated. In study 2, brain activity was not measured. Measuring alpha power would help to clarify whether the tACS setup modulated alpha power. For study 1, it could be measured whether poststimulus gamma power is influenced by tACS at alpha frequencies. This would offer an indication whether alpha and gamma power in tactile temporal discrimination are causally related. It should be noted that tACS during EEG/MEG leads to artifacts in the EEG/MEG measurement. Thus, an approach of simultaneous EEG/MEG and tACS would need to reject those artifacts. Methods for artifact rejection have been subject of previous research (e.g., Helfrich, Schneider, et al., 2014; Herring et al., 2019).

As mentioned above, the beta cycle could play a key role in tactile temporal discrimination (Baumgarten et al., 2015). This could also be tested with tACS. One possible approach could make use of the individual beta frequency. tACS could be applied with the individual beta frequency as well as with frequencies higher and lower than the individual beta frequency (similar to the approach within the alpha band done by Cecere et al., 2015 or Herring et al., 2019). This would lead to shortened or lengthened beta cycles, respectively. If the beta cycle has a causal role in tactile temporal perception, shortened beta cycles should lead to an increased perception of two stimuli compared to perception at the individual beta frequency. In turn, lengthened beta cycles should lead to an increased perception of one stimulus.

7. References

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8. Erklärung

Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist.“

Die Dissertation wurde in der vorliegenden oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den

Marc Wittenberg

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10. Appendix

This work is based on:

Appendix 1:

Wittenberg, M. A., Baumgarten, T. J., Schnitzler, A., & Lange, J. (2018).
U-shaped Relation between Prestimulus Alpha-band and Poststimulus Gamma-band Power in Temporal Tactile Perception in the Human Somatosensory Cortex.
Journal of Cognitive Neuroscience, *30*(4), 552–564. https://doi.org/10.1162/jocn_a_01219

Impact factor (2018): 3.029
Personal Contribution: 75%, hypothesis formulation, data analysis, data interpretation, manuscript writing and revision

Appendix 2:

Wittenberg, M. A., Morr, M., Schnitzler, A., & Lange, J. (2019).
10 Hz tACS Over Somatosensory Cortex Does Not Modulate Supra-Threshold Tactile Temporal Discrimination in Humans.
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U-shaped Relation between Prestimulus Alpha-band and Poststimulus Gamma-band Power in Temporal Tactile Perception in the Human Somatosensory Cortex

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Abstract

■ Neuronal oscillations are a ubiquitous phenomenon in the human nervous system. Alpha-band oscillations (8–12 Hz) have been shown to correlate negatively with attention and performance, whereas gamma-band oscillations (40–150 Hz) correlate positively. Here, we studied the relation between prestimulus alpha-band power and poststimulus gamma-band power in a suprathreshold tactile discrimination task. Participants received two electrical stimuli to their left index finger with different SOAs (0 msec, 100 msec, intermediate SOA, intermediate SOA ± 10 msec). The intermediate SOA was individually determined so that stimulation was bistable, and participants perceived one stimulus in half of the trials and two stimuli in the other half. We measured neuronal activity with magnetoencephalography (MEG). In trials with intermediate SOAs, behavioral performance correlated inversely with prestimulus alpha-band power but did not correlate with poststimulus gamma-band power. Poststimulus gamma-band power was high in trials with low and high prestimulus alpha-band power and low for intermediate prestimulus alpha-band power (i.e., U-shaped). We suggest that prestimulus alpha activity modulates poststimulus gamma activity and subsequent perception: (1) low prestimulus alpha-band power leads to high poststimulus gamma-band power, biasing perception such that two stimuli were perceived; (2) intermediate prestimulus alpha-band power leads to low gamma-band power (interpreted as inefficient stimulus processing), consequently, perception was not biased in either direction; and (3) high prestimulus alpha-band power leads to high poststimulus gamma-band power, biasing perception such that only one stimulus was perceived. ■

INTRODUCTION

Even in the absence of external sensory input, the brain is constantly active. Thus, neuronal activity is constantly fluctuating (Buzsáki & Draguhn, 2004). Incoming stimuli can therefore impinge on different levels of neuronal activity (i.e., brain states) at different times. These brain states can influence the processing of stimuli (Iemi, Chaumon, Crouzet, & Busch, 2017; Lange, Keil, Schnitzler, van Dijk, & Weisz, 2014; Weisz et al., 2014; Keil, Müller, Ihssen, & Weisz, 2012; Jensen & Mazaheri, 2010).

One prominent marker of brain states is neuronal oscillation. Neuronal oscillations refer to rhythmic changes in activity of neuronal populations (Buzsáki & Watson, 2012). Thus, fluctuations of brain states can be reflected in fluctuations of these neuronal oscillations. Two prominent frequency bands are the alpha (8–12 Hz) and gamma band (40–150 Hz). It has been found that fluctuations in prestimulus alpha-band power correlate with varying perception despite physically identical stimulation (Lange, Halacz, van Dijk, Kahlbrock, & Schnitzler, 2012; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008; Linkenkaer-Hansen, Nikulin, Palva, Ilmoniemi, & Palva, 2004). For example, lower parieto-occipital alpha-band power increased participants' ability to detect near-threshold visual stimuli (van Dijk et al., 2008; Hanslmayr et al., 2007). Similarly, prestimulus alpha-band power in contralateral somatosensory-posterior areas was lower when participants could discriminate veridically between two subsequent tactile stimuli compared with trials where participants perceived stimulation as one single stimulus (Baumgarten, Schnitzler, & Lange, 2016). Given these results, it was suggested that prestimulus alpha oscillations reflect the excitability of a brain area, which in turn influences the neuronal processing and perception of ambiguous stimuli (Lange et al., 2014; Lange, Oostenveld, & Fries, 2013; Thut, Nietzel, Brandt, & Pascual-Leone, 2006). In addition, alpha-band power has been related to active inhibition of brain areas (Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). In line with the inhibition hypothesis, prestimulus alpha-band power is modulated by spatial attention, and such modulations of

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alpha-band power have been shown to affect perception (Thut et al., 2006; Worden, Foxe, Wang, & Simpson, 2000; Foxe, Simpson, & Ahlfors, 1998). In addition to prestimulus alpha-band power, the power of poststimulus gamma oscillations is also modulated by attention. In visuospatial attention tasks, poststimulus gamma-band power increases in the visual area contralateral to the stimulus (e.g., Händel, Haarmeier, & Jensen, 2011; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Siegel, Donner, Oostenveld, Fries, & Engel, 2008; Müller, Gruber, & Keil, 2000). Similarly, poststimulus gamma power in tactile spatial attention tasks increases in somatosensory areas contralateral to the attended side and can affect perception (Haegens, Nácher, Hernández, et al., 2011; Haegens, Osipova, Oostenveld, & Jensen, 2010; Bauer, Oostenveld, Peeters, & Fries, 2006). Finally, it was found that poststimulus gamma oscillations and behavioral performance are linked. For example, high gamma-band power in visual cortex relates to faster RTs (Hoogenboom, Schoffelen, Oostenveld, & Fries, 2010; Womelsdorf, Fries, Mitra, & Desimone, 2006). In the somatosensory domain, higher poststimulus gamma-band power in contralateral primary somatosensory cortex (S1) relates to increased stimulus detection (Siegle, Pritchett, & Moore, 2014; Meador, Ray, Echauz, Loring, & Vachtsevanos, 2002). Generally, gamma oscillations are discussed as the neuronal underpinnings of cortical information processing (Fries, 2005, 2009, 2015).

In summary, both prestimulus alpha and poststimulus gamma oscillations are associated with attention, neuronal processing, and behavioral performance. Prestimulus alpha-band power typically decreases with higher attention, and low alpha-band power is associated with higher behavioral performance. By contrast, poststimulus gamma-band power typically increases with higher attention and high gamma-band power is associated with higher behavioral performance. Given these similar, but also diametrical effects of prestimulus alpha-band power and poststimulus gamma-band power, we speculated that prestimulus alpha-band power and poststimulus gamma-band power are directly (negatively) correlated.

To this end, we studied the relation of prestimulus alpha-band power, poststimulus gamma-band power, and tactile perception in a suprathreshold tactile discrimination task. We hypothesized that poststimulus gamma-band power in primary somatosensory cortex (S1) is positively correlated with perception, whereas prestimulus alpha-band power is negatively correlated with perception. Consequently, when comparing alpha- and gamma-band power directly, we hypothesized to find a negative correlation between prestimulus alpha-band power and poststimulus gamma-band power.

METHODS

We used data recorded by Baumgarten et al. (2016). Here, we give a concise description. More details on paradigm, participants and recordings can be found in Baumgarten et al. (2016).

Participants

We included 12 of the 16 right-handed participants (four men, mean = 26.0 years, *SD* = 5.3 years) measured by Baumgarten et al. (2016; see below for reasons for excluding four participants). Participants gave written informed consent in accordance with the Declaration of Helsinki and the Ethical Committee of the Medical Faculty, Heinrich-Heine-University Düsseldorf before participating in the experiment.

Participants had no known neurological disorders, no somatosensory deficits, and normal or corrected-to-normal vision.

Paradigm

Each trial began with a fixation dot in the center of the participant's visual field projected on the backside of a translucent screen (60 Hz refresh rate) positioned 60 cm in front of the participant. After 500 msec, this fixation dot decreased in luminance, indicating that the stimulation is about to be applied after a jittered period (900–1100 msec). Then, participants received two electrical stimuli (duration: 0.3 msec each) with different SOAs. Electrical stimuli were applied by electrodes located between the two distal joints of the left index finger. The amplitude of the pulses was individually determined so that stimulation was clearly perceived, but without being painful (stimulus amplitude: mean = 4.1, *SD* = 1.4 mA). In a premeasurement, the individual SOA was determined for which a participant veridically perceived two stimuli in ~50% of the trials (intermediate SOA, mean = 24.6 msec, *SD* = 6.2 msec). During the task, participants received stimulation with five different SOAs: 0 msec, 100 msec, intermediate SOA, intermediate SOA ± 10 msec. After stimulation, the fixation dot remained visible for another jittered period (500–1200 msec) to minimize motor preparation effects. By written instruction on the screen, participants were asked to report the number of perceived stimuli (either one or two) within 3000 msec via button press with the right index or middle finger. Again, to minimize motor preparation effects, configuration of the response buttons was randomized for each trial.

Each SOA was used in 50 trials. Only the intermediate SOA was used in 200 trials, resulting in 400 trials in total. Stimuli were presented in blocks. Each block consisted of 80 trials: 40 trials with intermediate SOA and 10 trials for each of the remaining SOAs. After each block, a self-paced break (~2 min) was included.

To familiarize participants with the task, a 5-min training phase with all five SOAs preceded the actual measurement. Before the measurement, participants received information about the task, but not about the purpose of the study or the different SOAs.

Presentation of the stimuli was done with Presentation software (Neurobehavioral Systems, Albany, NY).

Magnetoencephalography Measurement

A 306-channel whole-head magnetoencephalography (MEG; Neuromag Elekta Oy, Helsinki, Finland) was used to record brain activity at a sampling rate of 1000 Hz while participants performed the task. The MEG consisted of 102 pairs of orthogonal gradiometers and 102 magnetometers. For the analysis, only the gradiometers were taken into account. EOGs were measured to detect eye movements. EOG electrodes were placed at the outer sides of both eyes and above and below the left eye.

Data Preprocessing

Data were analyzed with custom-made scripts using Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) and Matlab (The MathWorks, Natick, MA).

Continuously recorded data were divided into trials. A trial started with the appearance of the fixation dot and ended with the press of the response button. The total number of trials was 400 with an average trial length of ~6 sec (4–8.6 sec). Power line noise at 50 Hz and its harmonics at 100 and 150 Hz were removed by a band-stop filter, and data were bandpass filtered between 2 and 250 Hz. For the filters, we used the default options implemented in FieldTrip, that is, we used an infinite impulse response zero-phase Butterworth filter of fourth order. A mean of 5.1 (*SEM* = 0.5) noisy channels were removed and reconstructed by interpolation of neighboring channels. Artifacts (muscle or eye movement, SQUID jumps) were removed semiautomatically by means of a *z*-score-based algorithm implemented in FieldTrip, followed by an additional visual inspection to remove artifacts (e.g., extensively noisy channels or channels still containing nondetected squid jumps, etc.). A mean of 104.1 (*SEM* = 9.1) trials were removed due to artifacts.

Other preprocessing steps were conducted according the respective analyses (see below).

Overview of Analysis Steps

We aimed to analyze the relation between prestimulus alpha-band power, poststimulus gamma-band power, and perception. Details on the analyses will be provided below. Here, we give a concise overview of the analysis steps performed. First, for each single trial prestimulus alpha-band power was determined by averaging power in a priori defined sensors, time range, and frequency band based on results of our previous study (Baumgarten et al., 2016). Second, for each single trial poststimulus gamma-band power was determined similarly by averaging power across sensors, time, and frequency. Here, sensors of interest were determined based on the topography of the M50, and frequency ranges were determined individually.

After performing these two steps, we could determine per participant and for each single trial one value for prestimulus alpha-band power, poststimulus gamma-band power, and perception, respectively. This enabled us to sort individual trials with respect to alpha-band power or gamma-band power. Then, we combined trials to bins, computed mean gamma-band power and/or mean perception in these bins. Finally, we tested by means of first- and second-order regression analyses a putative relation between the two variables (i.e., alpha- or gamma-band power, respectively, on the one side, and gamma-band power or perception, respectively, on the other side).

Time–Frequency Analysis

Time–frequency analysis (TFA) was performed for frequencies in the alpha (8–12 Hz) and gamma band (40–150 Hz) by means of discrete Fourier transformation on sliding time windows. For the following analyses, we only used trials with intermediate SOA. Before TFA, we removed the mean of the respective time period and the linear trend. We combined each pair of gradiometers by summing the spectral power of orthogonal gradiometers. The TFA was performed on 3000-msec data segments (−1000 to 2000 msec). If the data in a trial were shorter than 3000 msec (e.g., due to removed artifacts), the corresponding trial was zero-padded to 3000 msec.

The alpha-band (8–12 Hz) power was analyzed in steps of 1 Hz with a time window Δt of seven cycles of the respective frequency f ($\Delta t = 7/f$), moved in steps of 50 msec (Baumgarten et al., 2016). We used a single Hanning taper on each time window, resulting in spectral smoothing of $1/\Delta t$.

In our previous study, we found a significant effect of prestimulus alpha-band power on perception in a specific set of sensors and in the prestimulus time period (−0.9 to −0.25 sec, with 0 msec being the time point in which the first electrical stimulus occurred; Baumgarten et al., 2016). Here, we thus analyzed alpha-band power in the same sensors and the same time period. As in Baumgarten et al. (2016), we averaged alpha-band power from 8 to 12 Hz in this time window and in these sensors. These sensors are as follows: MEG1042+1043, MEG1112+1113, MEG1122+1123, MEG1312+1313, MEG0712+0713, MEG0722+0723, MEG1142+1143, MEG1132+1133, MEG1342+1343, MEG2212+2213, MEG2412+2413, MEG2422+2423, MEG2642+2643, MEG1832+1833, MEG2242+2243, MEG2232+2233, MEG2012+2013, MEG2442+2443, MEG2432+2433, MEG2522+2523, MEG2312+2313, MEG2322+2323, MEG2512+2513, MEG2342+2343, MEG2022+2023, MEG2212+2213, MEG2612+2613, MEG2222+2223.

The gamma band (40–150 Hz) was analyzed in steps of 5 Hz with a time window of 100 msec, moved in steps of 20 msec. Here, we used three Slepian tapers on each time window, resulting in spectral smoothing of ±20 Hz. We focused our analysis of gamma-band power on the right primary somatosensory cortex (S1 contralateral to stimulation site) by identifying five sensors showing maximum amplitude of the M50 (MEG1122+1123, MEG1132+1133, MEG1312+1313, MEG1342+1343, MEG1332+1333; see below for details on sensor selection). In the following analyses, we averaged gamma-band power over these five sensors. Furthermore, we only used trials with intermediate SOAs.

For the analysis of gamma-band power, we first determined individual frequencies showing maximal power. To this end, we calculated for each participant, for each time point between 0 and 200 msec, and for each frequency between 40 and 150 Hz the power relative to an averaged prestimulus baseline (−600 to −200 msec) by means of an independent *t* test.

Next, we averaged for each frequency the *t* values across all poststimulus time points (0–200 msec; Baumgarten, Schnitzler, & Lange, 2017; Cousijn et al., 2014). Individual gamma-band peaks were identified using Matlab's built-in function *findpeaks* (Baumgarten et al., 2017). Gamma ranges with maximum power were determined by taking the width of the gamma-band peak at its half height (as implemented in the function findpeaks; Figure 1A).

We used two inclusion criteria for a frequency to be identified as a peak frequency: First, to ensure that gamma-band activity was not just a broadband signal in response to stimulation onset but a clear narrow-band range, we defined a minimum peak height relative to neighboring points (i.e., setting in *findpeaks* the MinPeakProminence to a *t* value of 0.5). By this criterion, we had to exclude one participant because we could not ensure that a seeming gamma range was actually a broadband response across a wider range of frequencies, including the beta band (20–40 Hz, Participant 8 excluded; see Figure 1A). Second, to ensure that gamma ranges with highest power were sufficiently strong to be not confused with noise fluctuations, we set an absolute threshold of $t = 1$ (i.e., setting in *findpeaks* the MinPeakHeight to a *t* value of 1). By this criterion, we had to exclude three participants from further analyses (Participants 5, 13, and 15; see Figure 1A).

Selection of Sensors of Interest (Event-related Field Analysis)

We focused our analysis of gamma-band power on the right primary somatosensory cortex (S1 contralateral to stimulation site). To this end, we determined sensors showing maximum amplitude of the M50 component of the event-related field. The M50 component is known to originate from S1 after tactile stimulation (Iguchi, Hoshi, Tanosaki, Taira, & Hashimoto, 2005). To identify the M50, we first averaged the time domain data for each gradiometer and each participant separately. Next, gradiometer pairs were combined by adding the signal of all trials to the two orthogonal sensors using Pythagoras' rule. The evoked responses were then averaged across participants. We identified the M50 component by focusing on the time window 0.025–0.120 sec after stimulation. Finally, we determined five sensor pairs showing maximum amplitude of the M50 (MEG1122+1123, MEG1132+1133, MEG1312+1313, MEG1342+1343, MEG1332+1333).

Regression Analyses

For each participant, we sorted the trials with intermediate SOA from low to high power, either for the gamma band or the alpha band. Then, we divided the trials in five bins with equal number of trials in each bin. There were 30.0 ± 0.1 trials per bin. Note that the sum of trials in all bins is not 200 due to trials being removed in the preprocessing steps.

To determine a potential relation between oscillatory power and perception, we determined for each bin the mean responses per participant by averaging the number of "1" and "2" responses.

For each bin, we normalized mean responses according to the following procedure (Baumgarten et al., 2016; Lange et al., 2012; Jones et al., 2010; Linkenkaer-Hansen et al., 2004): We calculated the mean response for each participant for (a) each single bin and (b) across all bins. Then, for each single bin, we subtracted the mean response across all bins from the mean response from a single bin. The obtained result was then divided by the mean response across all bins.

Finally, we calculated for each bin mean responses (and *SEM*) across participants.

To reproduce the results of Baumgarten et al. (2016), we performed linear regression analysis between alpha-band power and perceptual responses. To determine a potential relation between prestimulus alpha-band power and poststimulus gamma-band power, we performed regression analyses (Baumgarten et al., 2016; Lange et al., 2012; Linkenkaer-Hansen et al., 2004). Because we a priori expected a linear relationship, we first performed a linear regression. In addition, we performed a post hoc quadratic regression analysis.

To determine a potential relation between alpha-band and gamma-band power, we determined for each alpha-band power bin the average gamma-band power per participant. Next, we normalized for each participant the mean gamma-band power relative to the mean gamma-band power across all bins. Finally, we calculated for each alpha-band power bin mean gamma-band power (and *SEM*) across participants.

To exclude the possibility that a correlation between alpha-band power and gamma-band power was induced by covarying noise levels in both frequency bands across

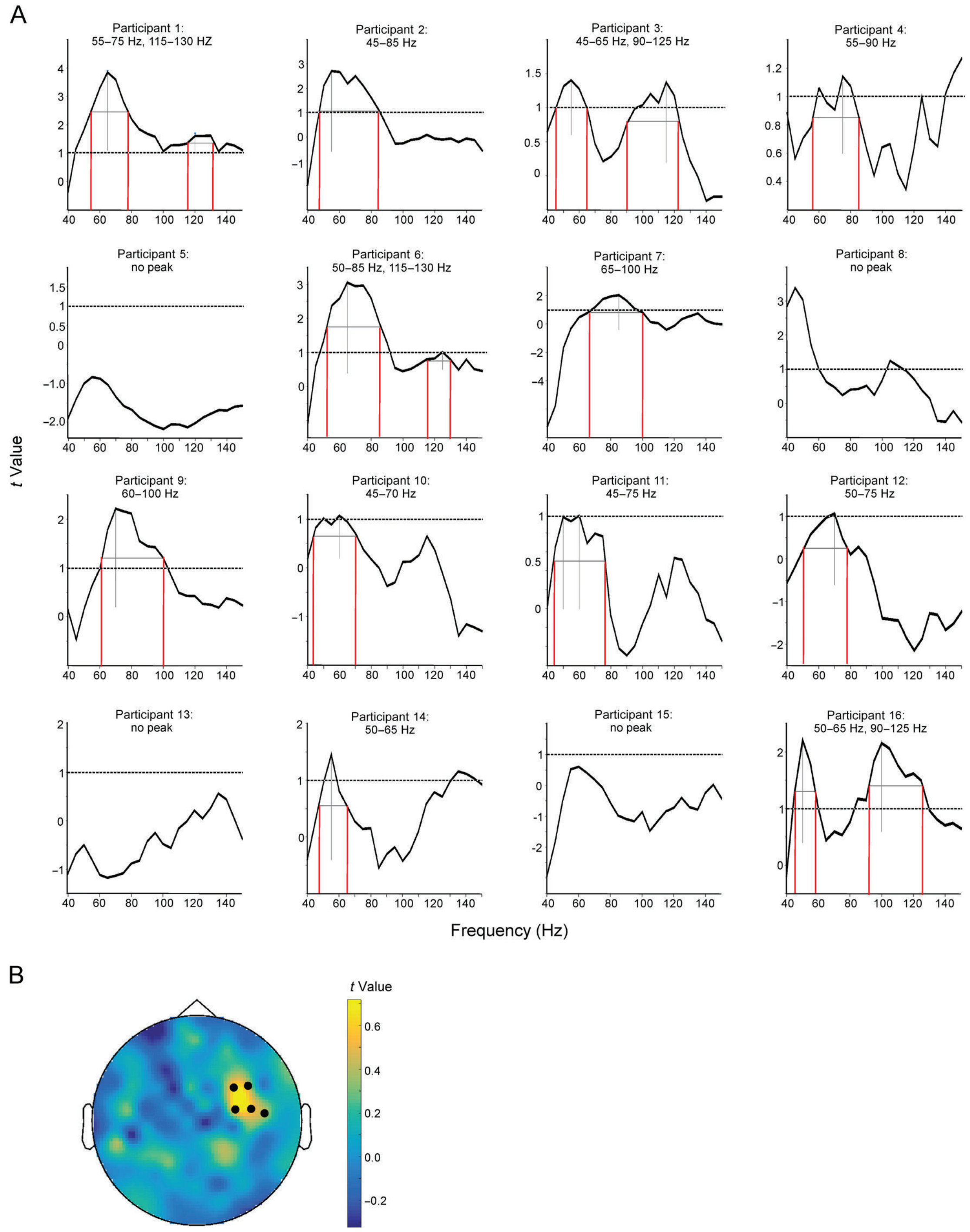

Figure 1. Poststimulus gamma-band activity. (A) Individual spectra in the gamma-band range (40–150 Hz). Spectra were determined by computing for each frequency (40–150 Hz) and time point (0–200 msec) t values (poststimulus vs. prestimulus activity) and then averaging t values across 0–200 msec. Peaks of each spectrum were determined using the Matlab function *findpeaks.* Dashed horizontal lines indicate the threshold ($t = 1$) for a peak to be recognized. Instead of peak frequencies, our analysis relied on narrow-band frequency ranges. Frequency ranges were determined by computing the width of the peak at its half height. Smaller gray lines indicate the relative height of the peak (Prominence in Matlab function *findpeaks*) and the width (Width at half prominence in Matlab function *findpeaks*). Red vertical lines indicate the frequencies at the half height, which determine the upper and lower limits of the gamma-band range used for subsequent analyses. Note that Participants 5, 13, and 15 had to be excluded from further analyses because their gamma peaks were below the threshold. Participant 8 had to be excluded from further analyses, because increased activity extended also to lower frequencies (not shown) so that we could not excluded that this activity was actually a broadband response to stimulation. (B) Topographical representation of gamma-band activity averaged across participants. For each participant, t values in the individual gamma-band ranges (see A) were averaged for each sensor. Next, the t values were averaged across participants. Black dots indicate the sensors of interest for gamma-band analysis, which were determined beforehand.

trials, we performed additional control analyses. To this end, we repeated the abovementioned analysis, but now with gamma-band power averaged across a different time window (but with identical length), for which we did not expect modulations of gamma-band power but just noise fluctuations (−500 to −300 msec).

Second, we computed signal-to-noise ratios (SNRs) by dividing for each participant and trial poststimulus gamma-band power (i.e., between 0 and 200 msec) and prestimulus gamma-band power (i.e., "noise" between −500 and −300 msec). Then, we repeated the abovementioned analysis for the SNRs.

All regression analyses were carried out using the Matlab built-in function *regstats.*

Statistical Analysis

We statistically compared perception across alpha- and gamma-band power bins, respectively. Likewise, we statistically compared gamma-band power across alpha-band power bins. First, we applied a Kolmogorov–Smirnov test to test for normality of the data for each bin. Kolmogorov–Smirnov tests showed that data in all bins significantly differed from a normal distribution (all ps $< .05$). To confirm and strengthen the significant linear or quadratic regression, we additionally performed planned post hoc Wilcoxon signed-ranked tests on the most extreme values, respectively. That is, for the significant linear regression between alpha-band power and perception, we compared Bins 1 and 5. For the significant quadratic regression between alpha-band power and gamma-band power, gamma-band power should be lower in alpha-band power Bin 3 relative to Bins 1 and 5. To this end, we applied one-sided Wilcoxon signed-ranked tests to compare Bin 3 versus Bin 1 and Bin 3 versus Bin 5.

RESULTS

To investigate the relationship between prestimulus alpha-band power, poststimulus gamma-band power, and perception, we measured MEG while participants performed a tactile temporal discrimination task.

Behavioral Data

Participants received one or two stimuli with varying SOAs and had to report the number of perceived stimuli. When only one stimulus was presented, participants reported one stimulus in 94.3 ± 0.4% of all trials. When two stimuli were presented with an SOA of 100 msec, participants reported two stimuli in 97.0 ± 0.3% of all trials. In addition, we presented stimuli with a predetermined individual SOA for which participants were supposed to perceive half of the trials as one stimulus and the other half as two stimuli (intermediate SOA, mean = 24.6 msec, *SD* = 6.2 msec). As intended, participants perceived trials with this intermediate SOA as two stimuli in 59.9 ± 0.9% of the trials. Finally, stimuli with an intermediate SOA+10 msec were perceived as two stimuli in 82.1 ± 1.3% and stimuli with an intermediate SOA-10 msec were perceived as two stimuli in 27.2 ± 1.5%.

Individual Gamma Ranges with Highest Power

We analyzed for each participant's gamma ranges with highest power within 40–150 Hz. Twelve of the 16 participants showed narrow-banded gamma-band activity within the range of 40–150 Hz (Figure 1A). Four participants showed two different gamma ranges with highest power. Three participants had to be excluded because their gamma-band activity never reached the threshold of $t = 1$. One participant had to be excluded because of a broadband response that extended into lower frequencies. Thus, for this participant, we could not distinguish a clear narrow-banded range of gamma-band activity.

Relation of Prestimulus Alpha and Poststimulus Gamma-band Power to Perception

We divided all trials with the intermediate SOA in five bins with respect to prestimulus alpha-band or poststimulus gamma-band power, respectively, and computed mean perception rates per bin. We found a significant negative correlation between prestimulus alpha-band power bins and perception, $r(3) = 0.92$, $p = .03$ (Figure 2A).

That is, with lower prestimulus alpha-band power, participants more likely reported to perceive two stimuli. Wilcoxon sign-ranked tests showed a significant difference in perception between alpha-band power Bin 1 and Bin 5 ($z = 2.20$, $p = .03$).

By contrast, we found no significant correlation between poststimulus gamma-band power and perception for both linear, $r(3) = 0.04$, $p = .95$ (Figure 2B), and quadratic, $r(2) = 0.44$, $p = .80$, regression analyses.

Relation of Prestimulus Alpha and Poststimulus Gamma-band Power

We divided all trials with the intermediate SOA in five bins with respect to prestimulus alpha-band power and computed mean gamma-band power per bin. Regression analysis did not demonstrate a significant linear relationship between prestimulus alpha-band power and poststimulus gamma-band power, $r(2) = 0.22$, $p = .72$. However, regression analysis demonstrated a significant quadratic relationship between prestimulus alpha-band power and poststimulus gamma-band power, $r(2) = 0.98$, $p = .04$ (Figure 3).

That is, trials with high and low prestimulus alpha-band power showed the highest poststimulus gamma-band power. Trials with intermediate prestimulus alpha-band power showed the lowest poststimulus gamma-band power.

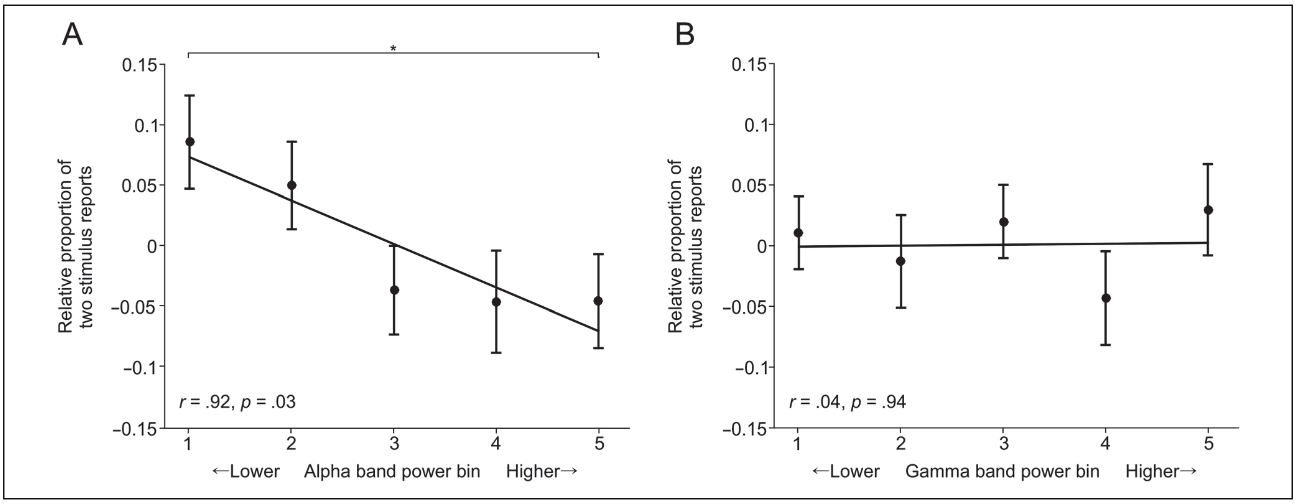

Figure 2. Regression analyses of oscillatory power and normalized temporal perceptual discrimination rate for (A) binned prestimulus alpha-band power (8–12 Hz, Bin 1 vs. Bin 5, $p = .03$) and (B) binned poststimulus gamma range with highest power. Insets show results of linear regression analyses (black lines). Higher number bins indicate higher spectral power. Error bars represent *SEM*.

Wilcoxon signed-rank tests revealed a significant difference in gamma-band power between alpha-band power Bins 1 and 3 ($z = -2.00$, $p = .02$), that is, bins with low prestimulus alpha-band power showed significantly higher poststimulus gamma-band power than trials with intermediate prestimulus alpha-band power. Wilcoxon sign-ranked tests also revealed a significant difference of poststimulus gamma-band power between alpha-band power Bins 3 and 5 ($z = -1.84$, $p = .03$), that is, bins with high prestimulus alpha-band power showed significantly higher poststimulus gamma power than trials with intermediate prestimulus alpha-band power. Gamma-band power in the intermediate alpha-band power bin is therefore significantly lower than in the bin with highest or lowest alpha-band power, respectively.

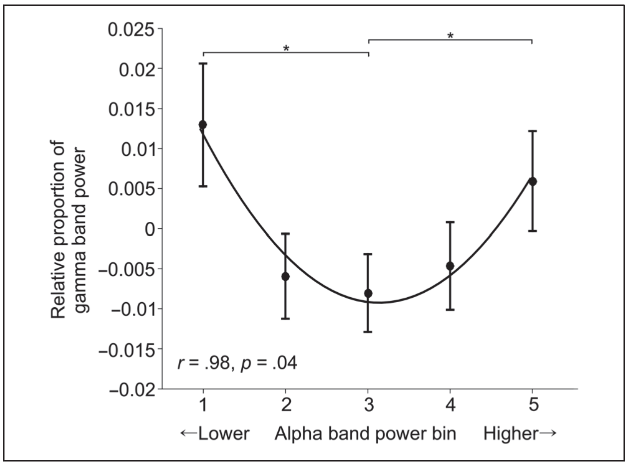

Figure 3. Regression analysis of binned prestimulus alpha-band power (8–12 Hz) and poststimulus gamma range with highest power. Inset shows result of quadratic regression analysis (black line). Higher number bins indicate higher spectral power. Error bars represent *SEM*. Bin 3 vs. Bin 1, $p = .02$; Bin 3 vs. Bin 5, $p = .03$.

Control analyses revealed that this result could not be explained by common noise fluctuations in the alpha and gamma bands (Figure A1).

Figure 4 combines and summarizes the results above; with low prestimulus alpha and high poststimulus gamma-band power, participants more often perceived two stimuli. By contrast, with high poststimulus gamma-band power but with high prestimulus, alpha-band power participants more often perceived one stimulus. Finally, with intermediate alpha-band power and low poststimulus gamma-band power, participants had no clear preference for either perception (Figure 4).

DISCUSSION

We analyzed data from a previous temporal tactile discrimination task in which participants received one or two tactile stimuli with varying SOAs (Baumgarten et al., 2016). We analyzed neuronal activity recorded with MEG with respect to the relation of prestimulus alpha-band power, poststimulus gamma-band power, and tactile perception. We found a significant linear relationship between prestimulus alpha-band power and tactile perception. However, we did not find a significant correlation between poststimulus gamma-band power and tactile perception (Figure 2). Finally, we found a significant U-shaped relation between prestimulus alpha-band power and poststimulus gamma-band power (Figure 3). That is, for both lowest and highest prestimulus alpha-band power, we found the highest poststimulus gamma-band power. For intermediate prestimulus alpha-band power, we found the lowest poststimulus gamma-band power.

As in our original study (with 16 participants; Baumgarten et al., 2016), we also found a significant correlation between prestimulus alpha-band power and perception for the 12 participants in our present study. Our results are also in line with other studies reporting a linear relationship between

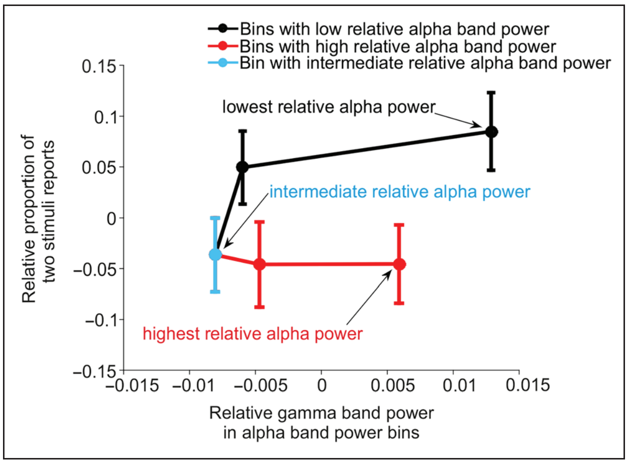

Figure 4. Combination and summary of results. Low prestimulus alpha-band power (8–12 Hz) and high poststimulus gamma-band power lead to increased perception of two stimuli. High prestimulus alpha-band power and high poststimulus gamma-band power lead to increased perception of one stimuli. Intermediate alpha-band power and low gamma-band power lead to no clear preference for either perception.

prestimulus alpha-band power in somatosensory areas and tactile perception (Lange et al., 2012; Jones et al., 2010).

Prestimulus alpha-band power and poststimulus gamma-band power were analyzed in predefined sensors of interest. Prestimulus alpha-band power was analyzed in sensors showing a significant effect of prestimulus alpha power on perception in our previous study (Baumgarten et al., 2016). Poststimulus gamma-band power was analyzed in sensors defined by the M50 component of evoked fields. Because we performed our analyses on sensor level, we can only indirectly infer the underlying cortical sources. In our previous study, we found that the alpha effect on perception originates from somatosensory and parietal cortical regions (Baumgarten et al., 2016). In addition, the M50 component is known to originate from primary somatosensory cortex (S1; Iguchi et al., 2005). Because the poststimulus gamma response in our task strongly overlapped with the sensors defined by the M50 component (Figure 1B), it seems likely that the effect of poststimulus gamma-band activity has the same origin as the M50 event-related field component, namely, S1. This interpretation is in line with previous studies showing that poststimulus gamma-band activity in response to tactile stimulation is typically found in (primary) somatosensory areas or in sensors putatively overlying somatosensory areas (Cheng et al., 2016; Siegle et al., 2014; Lange, Oostenveld, & Fries, 2011; Gross, Schnitzler, Timmermann, & Ploner, 2007; Bauer et al., 2006). In summary, this suggests that the cortical sources of prestimulus alpha-band power and poststimulus gamma-band power might overlap but also demonstrate differences.

We focused our analysis of poststimulus gamma-band power on the time period of 0–200 msec. This time window temporally coincides with evoked activity. Such evoked activity could induce broadband activity in the frequency domain that might be misinterpreted as gamma-band activity. However, except for one participant, our analysis of the individual gamma-band ranges revealed narrow-band poststimulus gamma-band power increases that did not extend into lower frequencies (Figure 1A). We are thus confident that our gamma-band activity is not due to broadband evoked responses.

Three participants did not show a reliable range of gamma-band activity and were thus excluded from the analyses. We can only speculate about the reason for the missing gamma-band activity. One reason might be a SNR of gamma-band activity too low to be detected. Moreover, these participants showed a decrease of gamma-band power in almost all frequencies. Such a decrease is highly unusual as it indicates increased prestimulus gamma-band power relative to the poststimulus period in almost all frequencies. Because of the unusual gamma-band activity and missing gamma range with highest power (according to our criteria, see above), we thus decided to exclude these participants from further analyses.

We have analyzed gamma-band activity in the range of 40–150 Hz. Many studies have used an upper limit lower than 150 Hz for gamma oscillations oscillations (Fries, Nikolić, & Singer, 2007; Bauer et al., 2006; Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006). However, several studies have shown that gamma-band activity can extend up to 150 Hz (Lange et al., 2011; Ray, Niebur, Hsiao, Sinai, & Crone, 2008; Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005). Therefore, we included gamma-band activity up to 150 Hz to not miss potentially important effects in the higher frequencies of the gamma band.

There has been an ongoing discussion about the nature of gamma-band oscillations. Several studies report increases of gamma-band power in narrow frequency bands in response to sensory stimulation (Krebber, Harwood, Spitzer, Keil, & Senkowski, 2015; Fries et al., 2007; Gross et al., 2007; Hoogenboom et al., 2006), arguing that gamma-band power reflects oscillatory activity. Other studies reported increases of gamma-band power in broadbands, spanning almost the entire gamma band (40 up to 200 Hz; e.g., Hermes, Miller, Wandell, & Winawer, 2015; Crone, Korzeniewska, & Franaszczuk, 2011). These studies often argue that the broadband response is unlikely of oscillatory nature but rather reflects asynchronous neuronal firing. In line with previous MEG/EEG studies, we found in our study poststimulus gamma-band responses in comparably narrow frequency bands. It seems interesting that narrow band gamma responses are often found in MEG and EEG studies, whereas broadband gamma responses are often reported in ECoG studies (e.g., Hermes et al., 2015; Lachaux et al., 2005). The nature of gamma-band power is thus far from conclusive, and thus, it is interesting and important to further elucidate the nature of gamma-band activity.

Previous studies reported increased somatosensory poststimulus gamma-band power in relation to improved tactile or nociceptive somatosensory perception (Siegle et al., 2014; Gross et al., 2007; Meador et al., 2002). Therefore, we hypothesized that poststimulus gamma-band power might correlate with perception in our tactile discrimination task. Contrary to our hypothesis, however, we did not find a significant correlation between poststimulus gamma-band power and perception. The reason for the apparent discrepancy between our study and previous studies might be found in the stimuli and tasks. Stimulus detection tasks can be near-threshold or suprathreshold. In near-threshold tasks, participants typically report whether or not they perceive a stimulus near perceptual threshold (e.g., Siegle et al., 2014; Weisz et al., 2014; van Dijk et al., 2008; Linkenkaer-Hansen et al., 2004). In suprathreshold tasks, stimuli are always above perceptual threshold, and thus, participants always perceive a stimulus but typically have to discriminate between different stimuli or perceptual states (e.g., Baumgarten et al., 2016; Peng, Hautus, Oey, & Silcock, 2016; Sato, Nagai, Kuriki, & Nakauchi, 2016; Lange et al., 2012).

Notably, the studies reporting a positive relation between poststimulus gamma-band power and perception used near-threshold stimuli and tasks. For example, detection of tactile near-threshold stimuli improved when participants exhibited higher poststimulus gamma-band power in contralateral S1 (Meador et al., 2002). Also, perceived pain around the pain threshold was accompanied by higher gamma-band power in S1 compared with unperceived pain stimuli (Gross et al., 2007). Entraining peristimulus neocortical gamma-band power optogenetically led to increased tactile stimulus detection in mice in a near-threshold detection task (Siegle et al., 2014). By contrast, we used a suprathreshold discrimination task. That is, participants always perceived a stimulus but their perception varied on a trial-by-trial basis between perceiving one or two stimuli. It has been suggested that neuronal oscillations in the gamma band are a fundamental process of neuronal communication and stimulus processing (e.g., Fries, 2005, 2015). Gamma oscillations are believed to be instrumental for efficient neuronal processing. That is, neuronal synchronization in the gamma band leads to efficient transmission of the sensory signal in the neuronal network and hence to an efficient stimulus processing (e.g., Womelsdorf & Fries, 2007). By contrast, lower gamma-band activity would then indicate that the sensory signal is transmitted less efficiently across the neuronal network and hence the signal is less efficiently processed, leading potentially to a less clear and potentially even ambiguous perception. In line with this hypothesis, low gamma-band power in a near-threshold detection task might indicate that the stimulus is insufficiently processed and thus not perceived. By contrast, high gamma-band power indicates efficient stimulus processing, leading to successful detection of the near-threshold stimulus (Siegle et al., 2014; Gross et al., 2007). In suprathreshold tasks, a stimulus is always strong enough to be sufficiently processed to result in successful perception. Therefore, a suprathreshold task should display high gamma-band power for all stimuli.

In our study, we used stimuli with identical physical characteristics (two suprathreshold stimuli with intermediate SOA), which differed only in participants' subjective perception. Gamma-band power was present in all trials, indicating efficient stimulus processing. However, the lack of a significant difference in gamma-band power between perceiving one or two stimuli suggests that the stimulus processing in S1 is largely independent of subjective perception in suprathreshold tasks. Subjective perception might be processed in other, higher cortical areas. For example, studies using working memory tasks in humans and monkeys found that vibrotactile stimulation induced gamma-band power in somatosensory areas. Somatosensory gamma-band power, however, did not differ between correctly and incorrectly perceived trials. Such differences between subjective perception and gamma-band power were found in higher areas (Haegens, Nácher, Hernández, et al., 2011; Haegens et al., 2010).

An alternative explanation for the lack of a significant correlation between poststimulus gamma-band power and perception might be that a potential correlation between gamma-band power and subjective perception might be too small to be detected with our paradigm or analysis approach. In addition, differences in gamma-band power might occur at different frequencies than analyzed in our study. However, we focused our analysis on individual frequency bands showing gamma-band power in response to stimulation, whereas other frequency bands showed only negligible gamma-band power, at all.

In contrast to our study in the somatosensory domain, studies in the visual domain reported that poststimulus gamma-band power correlated with subjective perception in suprathreshold tasks. These differences in gamma-band power, however, were typically found in higher visual areas, other than primary visual cortex. For example, if participants receive one visual stimulus accompanied by two tactile stimuli, they frequently perceive a second illusory visual stimulus (Shams, Kamitani, & Shimojo, 2000).

Studies have shown that, despite identical physical stimulation, poststimulus gamma-band power in parieto-occipital cortex correlated with participants' subjective perception of the illusion (Balz et al., 2016; Lange et al., 2011; Bhattacharya, Shams, & Shimojo, 2002). Moreover, poststimulus gamma-band power in somatosensory cortices was larger for congruent compared with incongruent visuotactile stimuli and correlated with shorter RTs (Krebber et al., 2015). Future studies might thus further investigate how gamma-band power correlates with tactile perception in suprathreshold tasks by studying other cortical areas or using methodological approaches that allow a finer spatial resolution, such as intracranial EEG or local field potential recording.

The main focus of our study was to study a potential relationship between prestimulus alpha and poststimulus gamma-band power. It has been shown that attention correlates negatively with prestimulus alpha-band power and positively with poststimulus gamma-band power in somatosensory areas (Haegens, Luther, & Jensen, 2012; Haegens, Nácher, Luna, Romo, & Jensen, 2011; Bauer et al., 2006). In addition, higher behavioral performance is associated with lower prestimulus alpha-band power and higher poststimulus gamma-band power (e.g., Baumgarten et al., 2016; Siegle et al., 2014). We thus hypothesized that prestimulus alpha and poststimulus gamma-band power negatively correlate on a trial-by-trial basis, a question that to our knowledge has never been directly investigated. In contrast to our hypothesis, we did not find a significant linear relationship. Rather, we found that prestimulus alpha and poststimulus gamma-band power show a quadratic relationship. That is, low but also high prestimulus alpha-band power was associated with high poststimulus gamma-band power, whereas intermediate levels of prestimulus alpha-band power were associated with low levels of poststimulus gamma-band power. In addition, in trials with low prestimulus alpha/high poststimulus gamma-band power, participants more often perceived two stimuli, whereas in trials with high prestimulus alpha/high poststimulus gamma-band power, participants perceived more often one stimulus (Figure 4). Furthermore, in trials with intermediate prestimulus alpha/low poststimulus gamma-band power, participants showed no preference for either perception.

Although this quadratic relation was shown to be significant, the overall effect sizes seem rather small. We can only speculate about the size of the effects. It might be that only a small fraction of neurons that elicit gamma-band activity are involved in the perception process and are modulated by prestimulus alpha-band power. This would lead to a comparably low SNR and thus small effect sizes. Another potential reason might be found in the overall lower SNR for higher frequencies. Such a low SNR might reduce potential effects. The effect sizes in our study are, however, comparable in size to effect sizes of gamma-band effects in other MEG studies (Yuan, Li, Liu, Yuan, & Huang, 2016; Krebber et al., 2015; Haegens et al., 2010).

We propose that low prestimulus alpha-band power reflects states of high excitability (Iemi et al., 2017; Lange et al., 2013; Thut et al., 2006). Therefore, stimuli will be efficiently processed during states of low prestimulus alpha-band power, resulting in the perception of two stimuli (Baumgarten et al., 2016).

The lower prestimulus alpha-band power, the higher was participants' confidence in their decision. In other words, stronger or more efficient processing of "two" stimuli is accompanied by lower alpha-band power (Baumgarten et al., 2016).

Such efficient stimulus processing should be reflected in high poststimulus gamma-band power (Fries, 2005, 2009).

Hence, we propose that low prestimulus alpha-band power will lead to high poststimulus gamma-band power, resulting in the perception of two stimuli (Figure 4, upper curve). On the other hand, high prestimulus alpha-band power reflects lower excitability or pulsed inhibition (Jensen & Mazaheri, 2010; Mathewson, Gratton, Fabiani, Beck, & Ro, 2009), leading to the perception of only one stimulus (Baumgarten et al., 2016).

The higher prestimulus alpha-band power, the higher was participants' confidence in their decision of "one" stimulus. In other words, stronger or more efficient processing of "one" stimuli was accompanied by higher alpha-band power (Baumgarten et al., 2016). Again, such efficient stimulus processing (despite leading to erroneous perception) should be reflected in high poststimulus gamma-band power (Fries, 2005, 2009). Thus, we propose that high prestimulus alpha-band power should also lead to high poststimulus gamma-band power. This way, however, high gamma-band power will result in the perception of one stimulus (Figure 4, lower curve). Finally, intermediate level of prestimulus alpha-band power will not bias perception in either direction, leading to lower or inefficient forwarding of the stimulus, which will be reflected in lower levels of gamma-band power.

This proposed model offers an alternative explanation why we did not find a significant correlation between gamma-band power and perception (Figure 2B). If prestimulus alpha-band power determines whether high poststimulus gamma-band power reflects the perception of one or two stimuli, then averaging across all prestimulus alpha states (as done in Figure 2B) will also average across both perceptions. Thus, ignoring the prestimulus alpha state and simply looking at poststimulus gamma states might give the wrong impression of no correlation between poststimulus gamma-band power and perception.

In conclusion, we found that prestimulus alpha-band and poststimulus gamma-band power show a quadratic relationship with both low and high prestimulus alpha power, leading to high poststimulus gamma-band power. Notably, the two states of high poststimulus gamma-band power are related to different states of perception. We propose a model in which prestimulus alpha-band power determines the computational and perceptual fate of a stimulus. If prestimulus alpha-band power is low, stimuli are efficiently processed, leading to more veridical perception in suprathreshold temporal discrimination tasks or near-threshold detection tasks. In such cases, poststimulus gamma-band power will be high, indicating efficient stimulus processing. If prestimulus alpha-band power is high, stimuli are inefficiently processed, leading to more incorrect perceptions in suprathreshold temporal discrimination tasks and no perception in near-threshold detection tasks. In suprathreshold temporal discrimination tasks, stimuli will still be processed, leading to high gamma-band power. In near-threshold detection task, nonperceived stimuli will not be processed, leading to no poststimulus gamma-band power.

APPENDIX

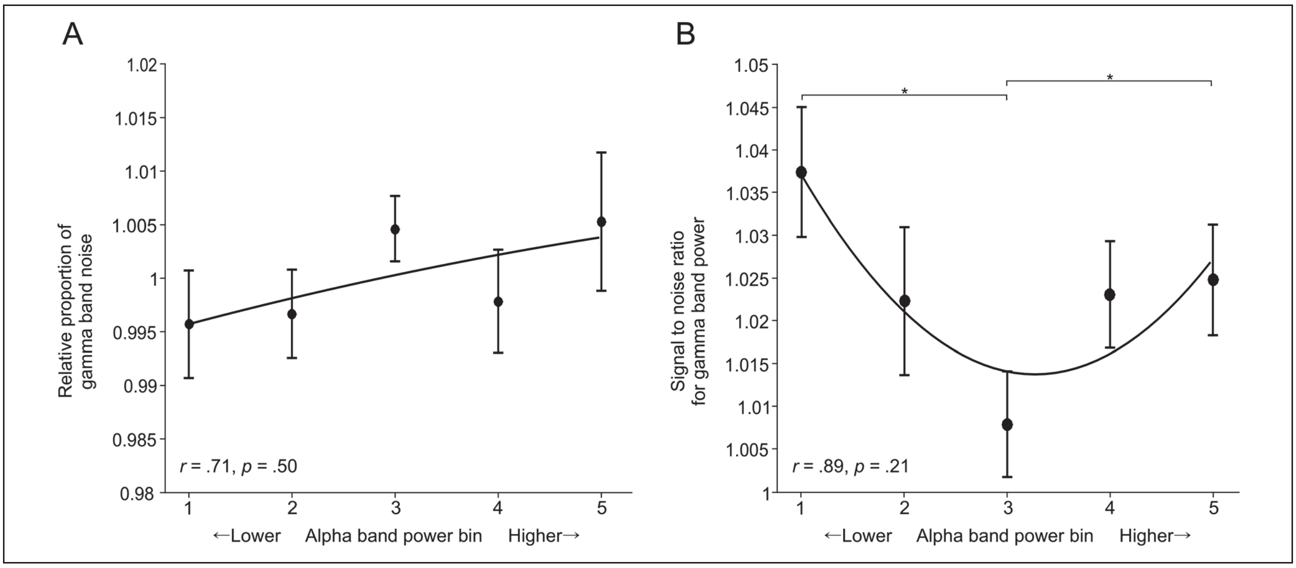

Figure A1. Regression analysis of binned prestimulus alpha-band power (8–12 Hz) and (A) prestimulus gamma-band noise or (B) SNR of gamma-band power. Inset shows results of quadratic regression analyses (black line). Higher number bins indicate higher spectral power. Error bars represent *SEM*. For (A): Bin 1 versus Bin 3, $p = .95$; Bin 3 versus Bin 5, $p = .48$. For (B): Bin 3 versus Bin 1, $p = .026$; Bin 3 versus Bin 5, $p = .002$.

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10 Hz tACS Over Somatosensory Cortex Does Not Modulate Supra-Threshold Tactile Temporal Discrimination in Humans

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Perception of physical identical stimuli can differ over time depending on the brain state. One marker of this brain state can be neuronal oscillations in the alpha band (8–12 Hz). A previous study showed that the power of prestimulus alpha oscillations in the contralateral somatosensory area negatively correlate with the ability to temporally discriminate between two subsequent tactile suprathreshold stimuli. That is, with high alpha power subjects were impaired in discriminating two stimuli and more frequently reported to perceive only one stimulus. While this previous study found correlative evidence for a role of alpha oscillations on tactile temporal discrimination, here, we aimed to study the causal influence of alpha power on tactile temporal discrimination by using transcranial alternating current stimulation (tACS). We hypothesized that tACS in the alpha frequency should entrain alpha oscillations and thus modulate alpha power. This modulated alpha power should alter temporal discrimination ability compared to a control frequency or sham. To this end, 17 subjects received one or two electrical stimuli to their left index finger with different stimulus onset asynchronies (SOAs). They reported whether they perceived one or two stimuli. Subjects performed the paradigm before (pre), during (peri), and 25 min after tACS (post). tACS was applied to the contralateral somatosensory-parietal area with either 10, 5 Hz or sham on three different days. We found no significant difference in discrimination abilities between 10 Hz tACS and the control conditions, independent of SOAs. In addition to choosing all SOAs as the independent variable, we chose individually different SOAs, for which we expected the strongest effects of tACS. Again, we found no significant effects of 10 Hz tACS on temporal discrimination abilities. We discuss potential reasons for the inability to modulate tactile temporal discrimination abilities with tACS.

Keywords: transcranial alternate current stimulation, tactile discrimination, alpha oscillations, somatosensory, supra-threshold

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INTRODUCTION

Perception does not only depend on the incoming stimuli, but also on intrinsic neuronal activity (or so called brain states). This intrinsic neuronal activity fluctuates over time and from trial to trial. Recent studies have shown that such fluctuations of neuronal activity can substantially influence perception. Specifically, fluctuations of neuronal oscillatory activity in the alpha band

(∼8–12 Hz) correlate with perception of physical identical stimuli over time. For example, the ability to detect visual near-threshold stimuli improved with lower posterior prestimulus alpha band power (Hanslmayr et al., 2007; van Dijk et al., 2008). Similarly in the somatosensory domain, lower prestimulus alpha band power was related to better perception or discrimination of tactile stimuli (Linkenkaer-Hansen et al., 2004; Haegens et al., 2011; Lange et al., 2012; Baumgarten et al., 2016). Alpha oscillations are therefore interpreted as reflecting the excitability of a brain area, a decision bias or active inhibition of brain areas (Thut et al., 2006; Klimesch et al., 2007; Jensen and Mazaheri, 2010; Lange et al., 2013, 2014; Iemi et al., 2017; Limbach and Corballis, 2017). The evidence for a role of prestimulus alpha power, however, is mostly correlative. To provide causal evidence for an influence of alpha power on perception it is required to modulate alpha power and measure its impact on perception.

One potential method to modulate neuronal oscillations is transcranial alternating current stimulation (tACS). tACS is a method to non-invasively stimulate the brain with electrical activity of a given frequency (Antal and Paulus, 2013). It has been suggested that tACS with 10 Hz entrains the endogenous alpha band power in the stimulated brain area during stimulation (Helfrich et al., 2014b; Ruhnau et al., 2016). Alterations in alpha power have also been shown to outlast tACS, such that alpha power was increased after tACS (Zaehle et al., 2010; Neuling et al., 2013; Kasten et al., 2016). However, these studies were not conducted in the somatosensory domain. Recently, a study in the somatosensory cortex showed a decrease in alpha power after tACS (Gundlach et al., 2017). This opens the possibility to study the causal influence of alpha oscillations on brain functions. tACS over the sensory area areas has been used successfully to elicit sensations in the respective sensory domains (Abd Hamid et al., 2015). For example, Feurra et al. (2011b) used tACS to stimulate the primary somatosensory cortex and could elicit tactile sensations in the contralateral hand. Also, tACS has been successfully used to modulate performance in motor (Pogosyan et al., 2009; Feurra et al., 2011a; Joundi et al., 2012), perceptual (Laczó et al., 2012; Neuling et al., 2012; Helfrich et al., 2014a; Kar and Krekelberg, 2014), and higher cognitive function tasks (Santarnecchi et al., 2013).

Here, we aimed to use tACS to study a putative causal impact of alpha oscillations on tactile temporal perception. A recent study has shown that prestimulus alpha band (∼8–12 Hz) power significantly negatively correlated with subjects' ability to perceive two electro-tactile stimuli as two separate stimuli (rather than one single stimulus; Baumgarten et al., 2016). To this end, we stimulated the somatosensory cortex with tACS at 10 Hz (i.e., in the alpha band) while subjects performed a tactile temporal discrimination task (Baumgarten et al., 2016). We hypothesized that 10 Hz tACS entrains intrinsic alpha oscillations and thus modulates the power of these alpha oscillations. Subsequently, discrimination of two subsequent tactile supra-threshold stimuli is expected to be altered with 10 Hz tACS compared to sham stimulation and stimulation with a control frequency (5 Hz). We tested this hypothesis during stimulation and 25 min after stimulation had ended.

MATERIALS AND METHODS

Subjects

We measured 17 subjects (nine female; age: 25.4 ± 1.4 years; mean ± SEM; range: 18 to 41 years). All subjects were right-handed according to the Edinburgh Handedness Inventory (87.0 ± 3.4; mean ± SEM; Oldfield, 1971).

Exclusion criteria were history or family history of epilepsy, history of loss of consciousness, brain related injury, or other neurological or psychiatric disorders, high blood pressure, cardiac pacemaker or intracranial metal implantation, tinnitus, intake of central nervous system-affective medication, pregnancy, and impairments of the peripheral nerves in the left arm.

The experiment was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Heinrich-Heine-Universität Düsseldorf, Germany (Study No. 4965R). Prior to the experiment, subjects gave written informed consent.

Subjects were naïve with respect to the hypotheses and stimulation conditions. Subjects received 50€ after completion of the entire experiment.

Paradigm

The paradigm was modified after Baumgarten et al. (2016). Subjects received one or two electrical stimuli with different stimulus onset asynchronies (SOAs) on their left index finger. Subjects were asked to respond whether they perceived one or two stimuli.

Each trial began with a fixation dot which decreased in luminance after 500 ms, indicating the upcoming application of the stimuli (**Figure 1B**). After a jittered period of 500–700 ms, subjects received one or two stimulations to the left index finger (stimulation duration: 0.3 ms each) while viewing the fixation dot. Amplitude of the stimuli was individually determined such that subjects could clearly perceive the stimuli without being painful (2.1 ± 0.2 mA; mean ± SEM). After another jittered period of 300–800 ms showing the fixation dot, subjects were asked by written instruction on the screen to respond with their right hand by button press. In nine subjects, button press with the right index finger related to perception of two stimuli and button press with the right middle finger related to perception of one stimulus. In the other subjects, button press pattern was reversed such that a press with the right index finger related to perception of one stimulus and button press with the right middle finger related to perception to two stimuli.

We used the following SOAs: 0 (i.e., only one stimulus applied), 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 130 ms. Trials with SOAs 0, 110, and 130 ms were each presented in 10 trials whereas each of the other SOAs was presented in 20 trials. SOAs with only 10 trials were added so that subjects responded to SOAs that clearly allowed for a perception of either 1 or 2 stimuli. The lower number of stimuli was chosen to keep the duration of the experiment within the time limit for tACS safety conditions (see below). The different SOAs were presented in pseudo-random order.

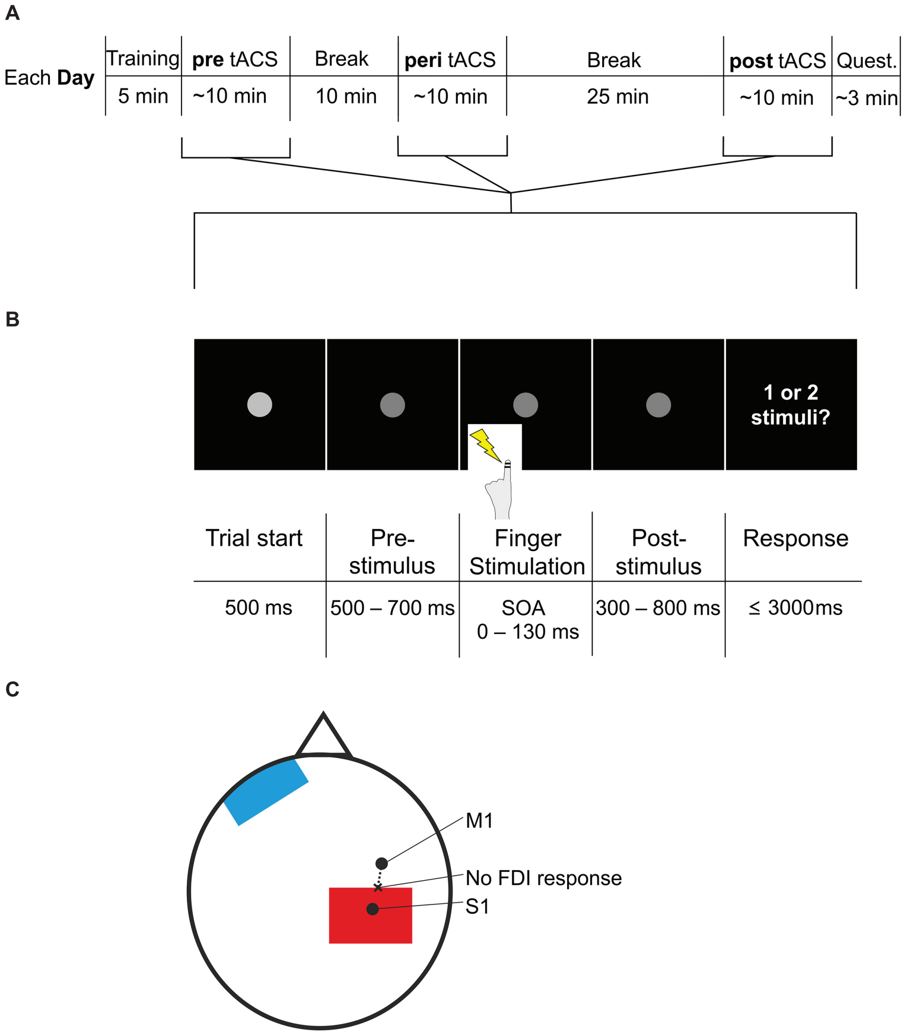

FIGURE 1 | Experimental procedure and paradigm. **(A)** The experiment started with a short training period. Next, participants conducted the task (*pre*, see **B**), followed by a 10 min break. Next, participants conducted the task again, now with additional tACS (*peri*), followed by a 25 min break. Finally, participants conducted the task for the third time, now again without tACS (*post*), followed by the questionnaire. Participants repeated the entire procedure on three different days. Each day differed only in stimulation frequency of tACS (10, 5 Hz, or sham) during the *peri* section. Quest., questionnaire. **(B)** The task used in the pre, peri, and post session (see **A**) started with a fixation point, which decreased in luminance after 500 ms. This darker fixation point was shown for a jittered period of 500–700 ms. The jittered period was followed by electric stimulation of the left index finger with varying SOAs (0, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 130 ms). After another jittered period of 300–800 ms showing the fixation point, participants were asked to respond whether they perceived one stimulus or two stimuli. Then the next trial started with the brighter fixation point. **(C)** Electrode placement. S1 was determined by neuronavigation. M1 was determined by the strongest FDI response when TMS was applied. Starting from M1, we applied TMS in steps of 0.5 cm moving to posterior (dashed line), until FDI response was no longer visible ("no FDI response"). At this spot we placed the most anterior border of the stimulation electrode (red). The reference electrode (blue) was placed on the contralateral forehead.

Subjects were asked to perform the experiment on 3 days, each separated by 1 week. On each day a different tACS frequency was applied: 10, 5 Hz, or sham. The order of tACS frequencies was randomized across subjects and double-blinded. For the double blinding, a person naïve to the experiment randomly selected the tACS frequency in each session and operated the DC stimulator during the experiment while the participants and the main experimenter who performed and analyzed the tACS experiment and communicated with the participants were unaware of the tACS frequency. Main experimenter and participants learned of the used tACS frequencies only after all three frequencies had been applied.

During each day, subjects performed the paradigm three times: pre (before tACS), peri (during tACS), and post (after tACS). The peri session started 10 min after pre session ended; the post-session started 25 min after the peri session ended (**Figure 1A**). The pre session was included as baseline performance of the paradigm. The post-session was included because it was shown that tACS effects can outlast the end of stimulation (Veniero et al., 2015). There is no consistent pattern, however, regarding the latency and duration of post-stimulation tACS effects (Veniero et al., 2015). While some studies report aftereffects a few minutes after the end of stimulation (e.g., Helfrich et al., 2014b), other studies report that aftereffects of 10 Hz tACS can last for 30 min (Neuling et al., 2013) or even start only 30 min after stimulation (Wach et al., 2013; see Veniero et al., 2015 for an overview). Most of these studies investigated tACS in the visual domain. Here, we aimed to investigate whether post-stimulation effects might be obtained in the somatosensory domain. Previous studies in the sensorimotor domain reported no effects of 10 Hz tACS directly after stimulation (Wach et al., 2013; Gundlach et al., 2016) and that aftereffects were visible only 30 min after stimulation (Wach et al., 2013). Therefore, we chose to study potential post-stimulation effects 25 min after tACS.

One session including all SOAs and repetitions lasted ∼8–10 min.

A training phase of 5 min was included at the beginning of each day to let subjects familiarize with the paradigm. This training phase included SOAs 0, 20, 40, 60, 80, 100, 130, 150 ms. 0 and 150 ms appeared three times as often as the other SOAs to familiarize subjects with the clear perception of 1 or 2 stimuli, respectively.

The paradigm was presented with the Presentation software (Neurobehavioral Systems, Albany, NY, United States). Electrical stimuli at the left index finger were delivered by a stimulus current generator (DeMeTec GmbH, Langgöns, Germany).

In summary, our study included three independent variables: *frequency* (sham, 5, 10 Hz), *session* (pre, peri, post), *SOAs* (0–130 ms).

The post-session of each day was followed by a short questionnaire. In this questionnaire, subjects were interviewed if they felt a sensation during the tACS. Also, they were asked whether they thought stimulation or sham was applied and how confident they were with their answer on a scale from 1 ("very unsure") to 10 ("very sure"). If they answered that stimulation had happened, then subjects were asked on their subjective impression of the stimulation frequency and their confidence in their judgment on a scale from 1 ("very unsure") to 10 ("very sure").

Transcranial Alternating Current Stimulation (tACS)

Transcranial alternating current stimulation was applied with two saline-soaked sponge electrodes (7 cm × 5 cm) on the skin surface (DC Stimulator Plus, NeuroConn, Ilmenau, Germany). The electrodes were held in place with a rubber band covering the whole electrode. One electrode was placed over the right somatosensory cortex similar to the area found in Baumgarten et al. (2016). The other electrode was placed over the left orbit. tACS was applied at 10 or 5 Hz with a current of 1 mA (peak-to-peak amplitude, sinusoidal waveform) for a maximum of 10 min leading to a current density of 28.57 $\mu A/cm^2$ and a total charge of 0.017 C/cm^2. Impedance was kept below 5 kΩ. These settings are within the boundary conditions of established safety protocols for transcranial direct current stimulation (Nitsche et al., 2003). Sham stimulation consisted of only 30 s stimulation with either 10 or 5 Hz. Each stimulation session included 10 s fade-in and 10 s fade-out time. If subjects finished the paradigm before 10 min, the stimulation was terminated, resulting in an average stimulation time of 8.2 ± 0.13 min (mean ± SEM).

Localization of Right Primary Motor and Somatosensory Cortex

Since Baumgarten et al. (2016) found a significant correlation between alpha power and tactile temporal discrimination in primary somatosensory cortex (S1) contralateral to stimulation, we aimed to stimulate contralateral (i.e., right) S1 with tACS.

To this end, the right S1 was localized by using neuronavigation (LOCALITE, Sankt Augustin, Germany) based on a standard MRI brain (MNI coordinates $x = 36$ mm, $y = -36$ mm, $z = 48$ mm; Bingel et al., 2004).

After locating S1 with neuronavigation, the tACS electrode can be placed differently on the located spot (i.e., electrode centered above spot or spot at the border of the electrode). We sought to place the electrode to minimally overlap with motor cortex to avoid stimulation of the finger muscle which might be misjudged for a stimulus from the finger electrodes and thus interfere with the task (**Figure 1C**). To this end, we localized the right primary motor cortex (M1) with TMS.

Right M1 was localized by inducing muscle twitching in the first dorsal interosseus (FDI) by means of TMS. TMS of the right motor cortex was performed using a standard figure of eight coil (MC-B70) connected to a MagPro stimulator (Medtronic, Minneapolis, MN, United States). We located the right FDI by placing the coil tangentially to the scalp with the handling pointing backward. We began by placing the coil 45° away from the head midline and vertical to the right periauricular point. Moving the coil anterior, posterior, medial, and lateral in ∼0.5 cm steps led to the localization with the maximal FDI motor response. This spot was determined as M1.

From M1 we applied TMS again posterior in ∼0.5 cm steps until hand twitching stopped. This point we determined as the posterior end of M1. Here, we placed the anterior border of the electrode.

S1 localized by neuronavigation was 2.8 ± 0.2 cm posterior to M1.

Data Analysis and Statistics

For data analysis we used custom MATLAB (The MathWorks, Natick, MA, United States) scripts.

For each frequency (5, 10 Hz, sham), session (pre, peri, post), SOA and subject, we determined mean responses across all repetitions. Next, for each frequency, session and SOA, individual mean responses were averaged across subjects.

In our main statistical analysis, we applied three-way repeated-measures ANOVA (rmANOVA, Trujillo-Ortiz, 2006) with factors *Frequency*, *Session* and *SOAs*, after testing for normality of the data by means of Shapiro–Wilk tests (BenSaïda, 2009, all *p*-values > 0.42). The main hypothesis was to test whether subjects' responses showed significant main effects of *Frequency* and/or *Session*, or significant interaction effects.

Since our main analysis did not reveal any relevant significant effects (see section "Results"), we performed additional statistical tests. These tests were performed to exclude the possibility that the non-significant results of the main analysis were caused by too low statistical power, by "noise" in the data due to the inclusion of data points that are irrelevant with respect to the hypothesis, or by too high intra- or inter-individual variability of responses.

The normalization was done in two different ways. In the first additional analysis, we normalized the data to minimize intra-individual variability.

The first normalization was based on the potential problem that individual performance might differ between different days in terms of absolute performance. We aimed to reduce intra-individual differences across days by normalizing the responses in the peri and post-sessions with respect to the pre session according to the formula:

$$r\_norm_{Freq,Session}(SOA) = \frac{r_{Freq,Session}(SOA) - r_{Freq,\mathrm{pre}}(SOA)}{r_{Freq,\mathrm{pre}}(SOA)} \tag{1}$$

with *r_norm* being the individual normalized mean response as a function of *SOA* for a given tACS frequency *Freq* (10, 5 Hz, Sham) and paradigm *Session* (pre, peri, post). *r* denotes the non-normalized response as a function of *SOA* for a given *Freq* and *Session*. This normalization results in a measure that can be described as "responses relative to the pre session."

In a second normalization, we sought to reduce inter-individual differences by transforming individual mean responses on a scale between 0 and 1 according to the following formula

$$r\_norm_{Freq,Session}(SOA) = \frac{r_{Freq,Session}(SOA) - r\_min_{Freq,Session}}{r\_max_{Freq,Session} - r\_min_{Freq,Session}} \tag{2}$$

with *r_norm* being the individual normalized mean response as a function of *SOA* for a given tACS frequency *Freq* (10, 5 Hz, Sham) and paradigm *Session* (pre, peri, post). *r* denotes the non-normalized response as a function of *SOA* for a given *Freq* and *Session*. *r_min* and *r_max* denote the non-normalized minimum and maximum, respectively, responses across all SOAs for a given *Freq* and *Session*. As mentioned above, this normalization results in responses normalized between 0 and 1.

As for the main analysis, we applied three-way repeated-measures ANOVA (rmANOVA, Trujillo-Ortiz, 2006) with factors *Frequency*, *Session* and *SOAs* on individual and normalized mean responses, again after confirming normality by means of Shapiro–Wilk tests (BenSaïda, 2009, all p-values > 0.12).

In the third and final analysis, we focused on *a priori* hypotheses for chosen SOAs for the statistical analysis. The *a priori* chosen SOAs were based on results of one of our previous studies (Baumgarten et al., 2016). This MEG study found an influence of alpha power on perception for intermediate SOAs at ∼25 ms. We speculated therefore that the effect of alpha power on perception is specific for SOAs of ∼25 ms, while all other SOAs are unaffected by changes in alpha power. To this end, we selected from our study only those SOAs that are close to 25 ms. That is, we chose the responses of the SOA at 20 and 30 ms, either separately or averaged across both SOAs. For statistical analyses, we applied either planned *t*-tests or Wilcoxon sign-ranked tests, depending on whether or not input data were normally distributed (again tested by means of Shapiro–Wilk tests; BenSaïda, 2009).

Alternatively, the effect of alpha power on response rates might not be specific for SOAs of 25 ms *per se*, but rather for individual intermediate SOAs (intermediate SOAs and SOAs of ∼25 ms coincide in Baumgarten et al., 2016). In the present study, the intermediate SOA was 54.1 ± 7.7 ms (mean ± SEM). If the influence of alpha power is specific for intermediate SOAs, we might expect an influence at ∼54 ms (the intermediate SOA). In this analysis, we therefore chose to analyze the effect of tACS on mean responses for the individual intermediate SOA.

In line with the statistical analyses above, we applied either planned *t*-tests or Wilcoxon sign-ranked tests, depending on whether or not input data were normally distributed (again tested by means of Shapiro–Wilk tests; BenSaïda, 2009).

For the statistical analysis of specific SOAs, we applied left-tailed tests when comparing mean responses at peri 10 Hz tACS against mean responses pre 10 Hz tACS, peri 5 Hz tACS, or peri sham tACS, respectively.

We used two-tailed tests when comparing mean responses at post 10 Hz tACS against mean responses pre 10 Hz tACS, post 5 Hz tACS, or post-sham tACS, respectively.

In addition, we used Bayesian statistics to test whether our data is in favor of the null hypothesis that there is no difference between 10 Hz tACS and control conditions. For all Bayesian tests we used the program JASP (JASP Team, 2018).

For non-normalized and normalized data, we calculated Bayesian repeated measures ANOVAs with factors *Frequency*, *Session*, and *SOAs*. For the interactions *Frequency* × *Session*, *Frequency* × *SOAs*, *Session* × *SOAs* and *Frequency* × *Session* × *SOAs* we calculated the Bayes Inclusion Factor ($\mathrm{BF}_{\mathrm{Inclusion}}$) based on matched models in JASP.

For our hypotheses for specific SOAs, we calculated Bayesian paired sample *t*-tests. As with our frequentist approach, we calculated left-tailed tests for peri tACS at 10 Hz vs. control conditions (i.e., mean responses at 10 Hz tACS smaller than mean responses at control conditions), and two-tailed tests for post-tACS at 10 Hz vs. control conditions. All Bayesian statistics were estimated based on a uniform prior distribution.

As an additional analysis we tested whether subjects that reported a flicker during tACS at 10 Hz showed a behavioral effect. To this end, we compared mean responses for peri tACS at 10 Hz vs. peri tACS at sham in line with above described analyses, but now only for subjects that reported a flicker sensation.

Given that tACS can have after-effects due to neuro-plastic changes (Veniero et al., 2015), we compared the first and the second half of the trials for peri tACS at 10 Hz by means of two-way repeated measures ANOVAs for non-normalized and normalized data with factors *SOAs* and *Half* (i.e., first or second half of the trials). Beforehand, we tested data for normality by means of Shapiro–Wilk tests. All data were normally distributed (all $p > 0.10$). Additionally, we calculated Bayesian repeated measures ANOVAs with factors *SOAs* and *Half*.

We also tested the first half against the second half of the trials for peri tACS at 10 Hz for the aforementioned specific SOAs. Depending on normality (tested by Shapiro–Wilk tests) we applied either planned *t*-tests or planned Wilcoxon sign-ranked tests. Additionally, we calculated Bayesian *t*-tests.

RESULTS

Questionnaire

All subjects tolerated tACS and TMS well. Four subjects felt a tingling sensation under the electrodes at the start of the stimulation. Four subjects reported a light burning under an electrode at the beginning of the stimulation while one of them felt the burning during the whole stimulation at 10 Hz. Two subjects reported a warming under an electrode.

Five subjects had a flickering effect in their visual field at 10 Hz tACS. Two subjects had the flickering only at the beginning of the stimulation while three subjects during the whole stimulation.

When 10 Hz tACS was applied, two of the 17 subjects correctly identified the 10 Hz frequency with a confidence rating of 7.0 ± 0.3 (mean ± SEM), only one of them reporting the flickering effect.

For the 5 Hz tACS frequency, five of the 17 subjects identified correctly the 5 Hz frequency with a confidence rating of 3.2 ± 0.9. For sham tACS, six of the 17 subjects identified correctly that sham tACS was applied with a confidence rating of 5.8 ± 0.6. Since all these values are below chance level, we evaluated the blinding procedure as successful.

General Effects of 10 Hz tACS on Tactile Perception

We measured perceptual responses in a temporal tactile discrimination task where subjects had to decide whether they perceived one or two electrical stimuli. We employed tACS at three different stimulation conditions: 10, 5 Hz, and sham. For each tACS frequency, subjects performed the paradigm three times: pre-, peri-, and post-tACS. Mean responses are shown in **Figure 2**. We tested the hypothesis that tACS at 10 Hz should modulate subjects' perception.

Three-way repeated measures ANOVA (rmANOVA) with factors *Frequency* (sham, 5, 10 Hz), *Session* (pre, peri, post), and *SOAs* (0–130 ms) revealed no significant main effects of *Frequency* [$F(2,32) = 0.78$, $p = 0.47$], *Session* [$F(2,32) = 1.67$, $p = 0.20$], nor interaction effects for *Frequency* × *Session* $F(4,64) = 0.64$, $p = 0.64$], *Frequency* × *SOAs* [$F(22,352) = 0.44$, $p = 0.99$], and *Frequency* × *Session* × *SOAs* [$F(44,704) = 0.72$, $p = 0.91$]. There was a significant main effect of *SOAs* [$F(11,176) = 59.59$, $p < 0.01$] which indicates that mean responses increase with increasing SOAs (**Figure 2**). There was also a significant interaction *Session* × *SOAs* [$F(22,352) = 2.29$, $p < 0.01$] which indicates that the increase of mean responses over SOAs differs between sessions independent of tACS frequency. However, the aim of our study was to investigate an effect of tACS frequency. Therefore, these two significant effects are irrelevant with respect to the main goal and will thus not further be discussed.

Bayesian repeated measures ANOVA with factors *Frequency*, *Session*, and *SOAs* revealed Bayes factors in favor of the null hypothesis that there is no difference in mean responses for the relevant main factors *Frequency* and *Session* and the interactions (*Frequency*: $BF_{10} = 0.11$, *Session*: $BF_{10} = 0.07$, *Frequency* × *Session*: $BF_{\text{Inclusion}} = 0.01$, *Frequency* × *SOAs*: $BF_{\text{Inclusion}} = 6.37 \times 10^{-6}$, *Session* × *SOAs*: $BF_{\text{Inclusion}} = 3.93 \times 10^{-5}$, *Frequency* × *Session* × SOAs: $BF_{\text{Inclusion}} = 8.89 \times 10^{-6}$). Only the factor *SOAs* revealed strong evidence for the alternative hypothesis ($BF_{10} = 6.50 \times 10^{346}$)˒ indicating that the factor SOA is an explanatory factor for the observed pattern of the data. Since this factor is of no relevance for the hypothesis of our study, we will not further discuss this finding.

Since the most relevant effects in the above analyses were not significant, we conducted further analyses to exclude several factors that might have hampered the main analyses. Our approaches included normalization approaches (to reduce intra- and inter-subjective variability) or using specific *a priori* hypotheses based on previous results (Baumgarten et al., 2016; see section "Materials and Methods").

Normalized Response Rates

We normalized data in two ways: in a first approach, we normalized individual mean responses relative to the pre session for each tACS frequency. In the second approach, we normalized individual mean responses relative to individual minimum and maximum mean responses.

Similar to the main analysis of non-normalized response rates, we only obtained significant results for the main factor *SOAs* [relative to pre: $F(11,176) = 2.83$, $p < 0.01$; relative to minimum-maximum: $F(11,176) = 61.56$, $p < 0.01$] and the interaction factor *Session* × *SOA* [relative to pre: $F(22,352) = 2.14$, $p < 0.01$; relative to minimum-maximum: $F(22,352) = 1.67$, $p = 0.03$]. Again, because these results are not relevant for our main goal, no *post hoc* analyses were carried out here.

We did not obtain significant results for main factors *Frequency* and *Session* nor for the interactions *Frequency* × *Session*, *Frequency* × *SOAs*, or *Frequency* × *Session* × *SOAs* (relative to pre: all $p > 0.08$; relative to minimum-maximum: all $p > 0.15$).

When data were normalized to the pre session, we obtained large Bayes factors for *Session* ($BF_{10} = 29913.82$) and *SOAs* ($BF_{10} = 3.80$). The large Bayes factor for the main factor Session most likely indicates a trivial result. Due to the normalization, all values in the pre session are set to "0" whereas the values in the peri and post-session are non-zeros. Bayesian analysis states that the model "Session" explains this difference better than a randomized model between all values. However, in this case this does not reveal a true difference between sessions *per se* but rather this is a result of our normalization procedure.

The main factor *Frequency* provides evidence for no difference between tACS frequencies ($BF_{10} = 0.02$). Also, the Bayes factors for the interactions provided strong evidence in favor of no effects (*Frequency* × *Session*: $BF_{\text{Inclusion}} = 0.06$, *Frequency* × *SOAs*: $BF_{\text{Inclusion}} = 4.83 \times 10^{-5}$, *Session* × *SOAs*:

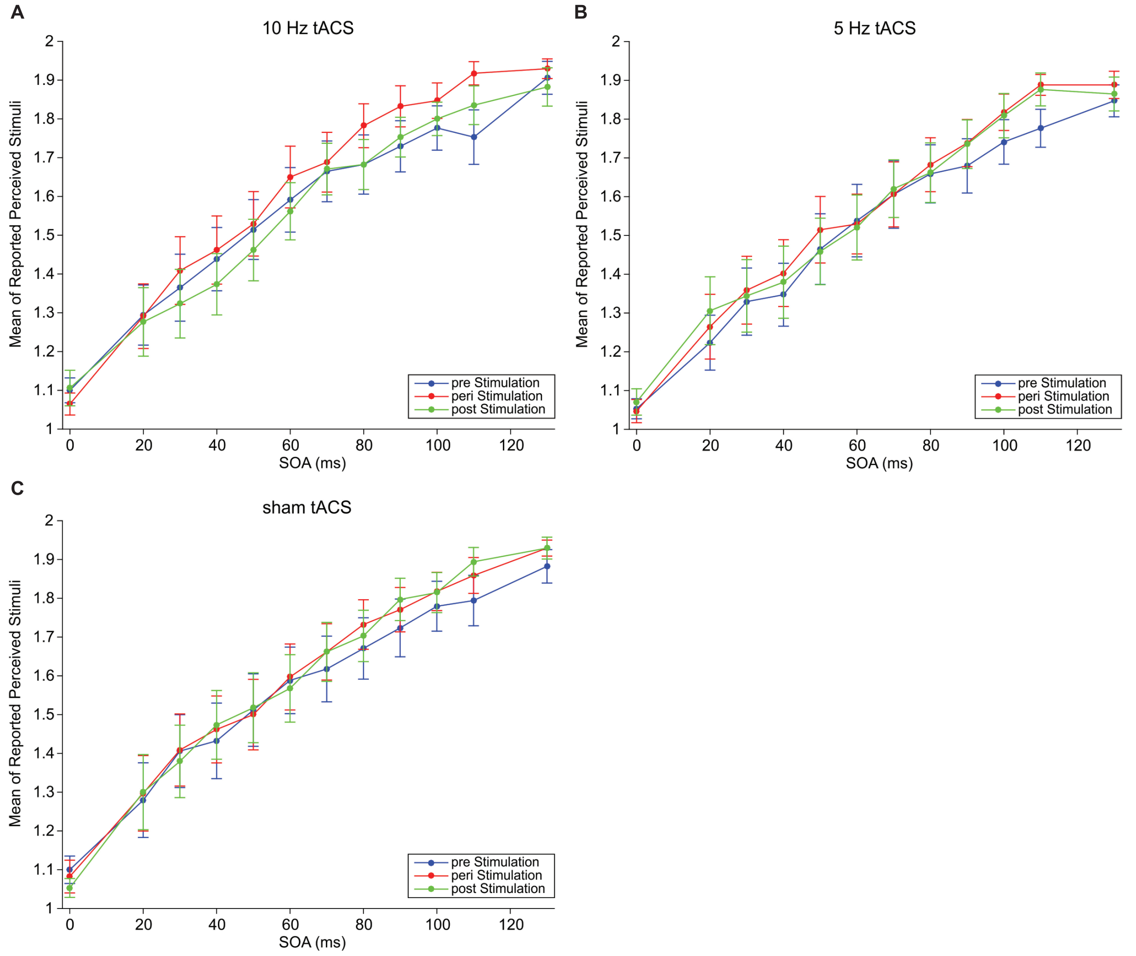

FIGURE 2 | Mean responses of perceived stimuli at different SOAs for **(A)** 10 Hz tACS, **(B)** 5 Hz tACS, and **(C)** sham tACS before (pre), during (peri), and 25 min after (post) stimulation. Error bars represent SEM.

$BF_{Inclusion} = 9.00 \times 10^{-4}$, *Frequency* × *Session* × *SOAs*: $BF_{Inclusion} = 2.82 \times 10^{-5}$).

When data was normalized relative to minimum-maximum, Bayesian repeated measures ANOVA revealed again Bayes factors in favor of the null hypothesis that there is no difference in mean responses for the relevant factors (*Frequency*: $BF_{10} = 0.02$, *Session*: $BF_{10} = 0.02$, *Frequency* × *Session*: $BF_{Inclusion} < 0.01$, *Frequency* × *SOAs*: $BF_{Inclusion} = 1.75 \times 10^{-5}$, *Session* × *SOAs*: $BF_{Inclusion} = 1.77 \times 10^{-5}$, *Frequency* × *Session* × *SOAs*: $BF_{Inclusion} = 9.82 \times 10^{-6}$). Only the factor *SOAs* provided strong evidence for an effect (*SOAs*: $BF_{10} = 1.31 \times 10^{399}$), indicating again that the factor *SOAs* is an explanatory factor for the observed pattern of the data. Since this factor is of no relevance for the hypothesis of our study, we will not further discuss this finding.

Comparison Between the First and Second Half of the Trials for 10 Hz tACS

To test whether tACS duration influences perception (e.g., due to neuro-plastic changes), we compared the first and the second half of the trials for the peri session of tACS at 10 Hz.

A two-way repeated measures ANOVA revealed neither a significant main effect for *Half* nor an interaction effect for *SOAs* × *Half* (all $p > 0.22$ for normalized and non-normalized data and for *a priori* chosen SOAs).

Bayesian statistics provided evidence for no difference between halves (all $BF_{10} < 0.20$, for normalized and non-normalized data). Results for the interaction *SOAs* × *Half* provided evidence for no interaction effects (all $BF_{Inclusion} \leq 0.23$).

A priori Hypotheses for the Effect of 10 Hz tACS on Tactile Perception at Intermediate SOAs

Here, we test the hypothesis that 10 Hz tACS might affect specifically intermediate SOA (i.e., SOAs for which subjects had mean responses of ∼1.5, i.e., no clear bias toward perception of "1" or "2").

Mean responses at peri 10 Hz tACS did not differ significantly from mean responses at pre 10 Hz tACS, peri Sham tACS or peri 5 Hz tACS (all $p > 0.54$; **Figure 3**). Bayesian statistics provided evidence for the null hypothesis of no effect of tACS (all $BF_{10} < 0.23$).

Likewise, mean responses at post 10 Hz tACS did not differ significantly from mean responses at pre 10 Hz tACS, post-Sham tACS or post 10 Hz tACS (all $p > 0.34$; **Figure 3**). Bayesian statistics provided either inconclusive results or evidence for the null hypothesis of no effect of tACS (all BF_{10} between 0.25 and 0.44).

Hypotheses for the Effect of 10 Hz tACS on Tactile Perception at SOAs 20 and 30 ms

A previous study reported a correlation of alpha power and perception at SOAs of ∼25 ms (Baumgarten et al., 2016). Therefore, we tested in this analysis that the causal effect of 10 Hz oscillations on temporal tactile perception might not be related to the intermediate SOA *per se*, but rather to an SOA of 20 to 30 ms.

Mean responses at peri 10 Hz tACS did not differ significantly from pre 10 Hz tACS, peri Sham tACS or peri 5 Hz tACS at an SOA of 20, 30 ms, or when responses of the SOAs at 20 and 30 ms where combined (all $p > 0.38$). Bayesian statistics provided evidence in favor of the null hypothesis (all $BF_{10} < 0.27$).

Likewise, mean responses at post 10 Hz tACS did not differ significantly from mean responses at pre 10 Hz tACS, post-Sham tACS or post 10 Hz tACS (all $p > 0.22$). Bayesian statistics provided either inconclusive results or evidence for the null hypothesis of no effect of tACS (all BF_{10} between 0.26 and 0.48).

Additional Analyses Only for Subjects That Reported a Flicker Sensation

When comparing mean responses for peri tACS at 10 Hz vs. peri tACS at sham only for subjects that reported a flicker sensation, there was no behavioral effect (all $p > 0.21$).

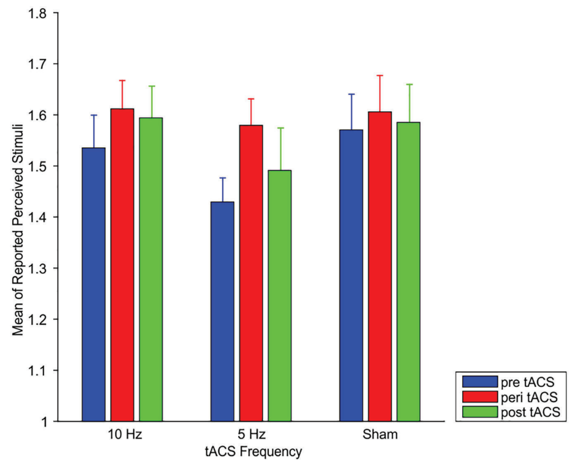

FIGURE 3 | Mean responses of perceived stimuli at the individual intermediate SOA for 10 Hz tACS, 5 Hz tACS, and sham tACS before (pre), during (peri), and 25 min after (post) stimulation. Error bars represent SEM.

DISCUSSION

We stimulated the somatosensory cortex with transcranial tACS while subjects performed a tactile discrimination task. Based on previous findings that reported a correlation between alpha power and tactile discrimination abilities (Baumgarten et al., 2016), we hypothesized that 10 Hz tACS would affect subjects' tactile perception. This way, we would provide evidence for a causal role of alpha power for tactile perception and add on the numerous studies reporting a correlation between (prestimulus) alpha power and perception. However, we found no significant effects of 10 Hz tACS on perceptual performance, neither when applied while subjects performed the task (i.e., peri tACS) nor did we find any aftereffects of stimulation (post-tACS).

That is, we did not find evidence for a causal role of alpha oscillations for tactile temporal discrimination. Bayesian statistics revealed that there is moderate to strong evidence in favor of the null hypothesis that mean responses with tACS at 10 Hz do not differ from control conditions. That is, our results are in favor that tACS at 10 Hz did not modulate tactile temporal discrimination. However, we do not conclude that 10 Hz or alpha power is not causally involved in tactile temporal discrimination. For such a conclusion there are still many factors to be considered as discussed below.

We will discuss in the following potential reasons and implications of this null result.

One potential reason might be that tACS at 10 Hz did not entrain neuronal oscillations. Since we did not measure neuronal activity in our study, we cannot exclude this possibility. Several previous studies, however, have shown that tACS in the alpha-band modulates neuronal oscillations. These studies have shown that alpha power is typically increased during tACS (Helfrich et al., 2014b; Ruhnau et al., 2016) as well as after tACS (Zaehle et al., 2010; Neuling et al., 2013; Kasten et al., 2016). In contrast to our study, these studies were not conducted in the somatosensory domain. In the somatosensory domain, recently, a decrease of alpha power after tACS at alpha frequencies was reported (Gundlach et al., 2017). One might argue that the current density we used may have been too low to entrain neuronal oscillations. Several studies, however, were able to entrain brain oscillations using similar current densities as we did (Moliadze et al., 2012; Neuling et al., 2015; Ruhnau et al., 2016). Since these studies were conducted in the visual domain, it might still be that in the somatosensory domain stronger current densities are needed to induce behavioral relevant entrainment. However, we refrained from using higher current densities because Feurra et al. (2011b) showed that tACS with a higher current density over S1 at alpha frequency elicited tactile sensations in the contralateral hand. Therefore, we used lower current density to minimize the possibility of inducing tactile sensations interfering with the task.

Another potential problem might be spatial inaccuracies in the stimulation so that our tACS did not entrain neuronal oscillations in S1. To exclude such a problem, we located S1 with two independent criteria (neuronavigation and no motor response with TMS) and we applied a large stimulation electrode. It seems thus unlikely that a putative entrainment did not affect S1.

In sum, although we have no direct measure of entrainment, we are confident that we entrained neuronal oscillations in the same area in which alpha power correlated with tactile discrimination in our previous study (Baumgarten et al., 2016).

Previous studies reported no unequivocal effects of tACS on perception. On the one hand, studies reported that tACS modulates perception (Neuling et al., 2012; Brignani et al., 2013; Gundlach et al., 2016; Veniero et al., 2017). On the other hand, several studies did not find an effect of tACS on perception (Brignani et al., 2013; Gundlach et al., 2016; Veniero et al., 2017; Sheldon and Mathewson, 2018). Specifically in the somatosensory domain, results are not clear. For example, Sliva et al. (2018) reported that tACS at alpha frequencies over somatosensory cortex lead to a decrease of performance in a tactile detection task of near-threshold stimuli. This decrease was reported for baseline corrected detection rates, but not for absolute detection rates. Thus, the putative effect of tACS may at least partially be explained by differences in baseline performances. In contrast, Gundlach et al. (2016) reported for a similar task that tACS at alpha frequencies did not affect mean detection rates. However, they reported that detection rates varied in a phasic manner, i.e., depending on the phase of tACS. Notably, these studies used detection tasks in which subjects had to report whether a stimulus near perceptual threshold was perceived. In our study, however, we used a discrimination task in which stimulation was always above perceptual threshold and subjects had to report whether they perceived one or two stimuli. Detection and discrimination tasks might be influenced by different processes. For example, our previous studies have shown that tactile discrimination tasks are influenced by power in the alpha frequencies, but the phase of beta frequencies (Baumgarten et al., 2015, 2016). Therefore, we focused our analysis on power modulations. In line with this hypothesis, Brignani et al. (2013) reported an effect of tACS at alpha frequencies in a visual detection task, while they could not find an effect of 10 Hz tACS in a visual discrimination task. Future studies might explore the differences between detection and discrimination tasks and how tACS might affect these tasks in more detail.

There is no clear consensus which frequency to use when tACS with "alpha frequencies" is applied. Whereas some studies used individual alpha frequencies, based on individual peak frequencies of neuronal oscillations in the alpha band (Cecere et al., 2015; Gundlach et al., 2016), others used a fixed frequency for all subjects (Brignani et al., 2013; Kar and Krekelberg, 2014; Sheldon and Mathewson, 2018). In the present study, we used a fixed frequency of tACS for all subjects. While this approach is easier to perform, especially since we did not measure neuronal oscillations, a fixed frequency might bear the downside that tACS does not match the "optimal" frequency in all subjects. According to the Arnold's tongue principle, low stimulation intensities only entrain the endogenous frequency in a small frequency band, whereas higher stimulation intensities can entrain a wider frequency band around the endogenous frequency (Herrmann et al., 2016; Kurmann et al., 2018). Therefore, it could be that we did not entrain alpha power in those subjects whose endogenous peak alpha frequency differs too much from 10 Hz to be entrained at the low stimulation intensity. However, Baumgarten et al. (2017) showed that tactile temporal discrimination does not correlate with individual alpha frequency of neuronal oscillations. In addition, several studies found an effect of tACS on detection using fixed frequencies (e.g., Brignani et al., 2013; Kar and Krekelberg, 2014). Finally, Baumgarten et al. (2016) reported an effect of alpha power on discrimination performances for one frequency, averaged across all subjects, rather than individual frequencies for each subject. Therefore, it seemed feasible for us to expect an effect of a fixed frequency for tACS. On the other hand, it could be that the mechanisms underlying tactile discrimination are not modulated by 10 Hz but other, neighboring frequencies within the alpha band. Given our low stimulation intensity, this potential alpha frequency might not be entrained due to the Arnold's tongue principle. As mentioned above, however, we were restricted to 1 mA stimulation intensities, because a higher stimulation intensity could have produced tactile sensations (Feurra et al., 2011b), which might be misjudged for a stimulus from the finger electrode and thus distort behavioral results.

One might argue that the control frequency of 5 Hz might affect alpha power similarly to 10 Hz stimulation (de Graaf et al., 2013). Given that we found no effect of tACS in our study at all, this limitation does not change the conclusion of this study.

Given that tACS can produce after-effects due to neuro-plastic changes (Veniero et al., 2015), we also investigated whether tACS at 10 Hz might have an effect only at a later time segment during the stimulation. To this end, we compared the first half of the trials to the second half of the trials during peri tACS at 10 Hz. We found no differences between the first and the second half of the trials. This result suggests that longer stimulation duration did not lead to stronger results.

In summary, in our study we were unable to modulate tactile discrimination by applying tACS at alpha frequencies contralateral to the tactile stimulation. Consequently, we were unable to provide evidence for a causal role of somatosensory alpha oscillations in tactile discrimination tasks. tACS experiments comprise many degrees of freedom (e.g., electrode placements, stimulation frequency, stimulation current density, task and combinations of all factors). Another problem is that tACS can have different effects on different individuals due to anatomical differences such as the gyral depth or the thickness of the skull (Nitsche et al., 2008; Opitz et al., 2015). These factors result in a large search space for optimal parameters for the tACS experiment, making it difficult to decide for the optimal setup with regard to the question investigated (Kar and Krekelberg, 2014). And even with identical parameters, sometimes results of an tACS experiment cannot be replicated, even within one study (Veniero et al., 2017).

We are, however, confident that we used a reasonable parameter space for the stimulation parameters to expect a modulation of discrimination abilities. Thus, we might conclude that this specific combination of experimental factors is unable to modulate tactile temporal discrimination, but that we cannot conclude whether alpha power has a causal role on tactile temporal discrimination. This null effect should thus offer new insights and increase knowledge about an adequate setup of tACS experiments and to further understand difficulties and sometimes inconsistent results in tACS studies. Nevertheless, additional studies are needed to investigate a potential causal role of somatosensory alpha oscillations in tactile discrimination tasks.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

MW and JL designed the study and analyzed the data. MW and MM collected the data. MW, MM, AS, and JL wrote the manuscript.

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

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