

# Frequency-specific transcranial neuromodulation of alpha power alters visuospatial attention performance

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## ABSTRACT

Transcranial alternating current stimulation (tACS) at 10 Hz has been shown to modulate spatial attention. However, the frequency-specificity and the oscillatory changes underlying this tACS effect are still largely unclear. Here, we applied high-definition tACS at individual alpha frequency (IAF), two control frequencies (IAF+/-2Hz) and sham to the left posterior parietal cortex and measured its effects on visuospatial attention performance and offline alpha power (using electroencephalography, EEG). We revealed a behavioural and electrophysiological stimulation effect relative to sham for IAF but not control frequency stimulation conditions: there was a leftward lateralization of alpha power for IAF tACS, which differed from sham for the first out of three minutes following tACS. At a high value of this EEG effect (moderation effect), we observed a leftward attention bias relative to sham. This effect was task-specific, i.e., it could be found in an endogenous attention but not in a detection task. Only in the IAF tACS condition, we also found a correlation between the magnitude of the alpha lateralization and the attentional bias effect. Our results support a functional role of alpha oscillations in visuospatial attention and the potential of tACS to modulate it. The frequency-specificity of the effects suggests that an individualization of the stimulation frequency is necessary in heterogeneous target groups with a large variation in IAF.

## 1. Introduction

As the number of visual stimuli in the visual world exceeds the processing capacity of our brain, we have to filter the visual input. *Visuospatial attention* - a form of visual attention - helps us to select stimuli for enhanced processing based on their location in space (Posner 1980a, Posner, 1980b; Downing 1988; Johnson et al. 1991). It thereby acts as an attentional filter enabling us to prioritize some stimuli over others. A visuospatial attention *bias* describes the tendency to pay more attention towards one side in space compared to the other side.

On a neuronal level, visuospatial attention biases are associated with an interhemispheric asymmetry in oscillatory alpha (7–13 Hz) power over posterior sites (Newman et al. 2013; Marshall et al. 2015; Lasaponara et al. 2019). Similarly, dynamical shifts of visuospatial attention

to either hemifield lead to a lateralization of occipitoparietal alpha power with higher alpha power ipsilateral to the attentional locus (Sauseng et al. 2005; Thut 2006; Gould et al. 2011; Händel et al. 2011). In this context, it has been postulated that alpha oscillations could serve as an attentional inhibition mechanism, enabling the selective processing of relevant stimuli by suppressing distracting incoming sensory information (Kelly et al. 2006; Klimesch et al. 2007; Jensen and Mazaheri 2010). However, based on correlational electroencephalography (EEG) data it is difficult to draw definitive conclusions about the functional relevance of alpha oscillations. It remains possible that alpha oscillations are an epiphenomenon, a by-product of another attentional mechanism. To demonstrate a direct relationship between alpha oscillations and visuospatial attention, it is necessary to modulate alpha power and show that this leads to a change in visuospatial attention performance. Note

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that we refrain from claiming causality as the term ‘causal’ suggests that we found the origin of a cascade of processes leading up to a certain outcome. As this is not possible using neuromodulation paradigms, we use the term ‘functional’ instead, thereby referring to a process that modulates a given outcome but is not necessarily causally relevant for it.

Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation technique, which uses alternating electrical currents to increase the power of brain oscillations (Thut et al. 2011; Herrmann et al. 2013; Lakatos et al. 2019). Numerous studies have reported effects of tACS on perception (Helfrich et al. 2014; Riecke et al. 2015; Graaf et al. 2020), cognitive functions (Polanía et al. 2012; Chander et al. 2016; Kasten and Herrmann 2017) as well as motor control and learning (Antal et al. 2008; Pogosyan et al. 2009; Joundi et al. 2012; Wach et al. 2013; Pollok et al. 2015; Cappon et al. 2016; Krause et al. 2016; Leunissen et al. 2017; Schilberg et al. 2018; Heise et al. 2019) (for a recent review see (Cabral-Calderin and Wilke 2020)). Furthermore, experiments that combine tACS with EEG indicate that alpha power over both hemispheres can be enhanced through medial occipitoparietal tACS at alpha frequency (Zaehle et al. 2010; Neuling et al. 2013; Vossen et al. 2015). Building upon these findings, we recently applied high-definition (HD) tACS at 10 Hz to the left posterior parietal cortex (PPC) with the aim of modulating the visuospatial attention locus. In line with our hypothesis, we demonstrated that tACS at 10 Hz induces a visuospatial attentional leftward bias relative to sham (Schuhmann et al. 2019). Even more recently, this effect was extended by Kasten and colleagues (Kasten et al. 2020) who showed that the effect of tACS at alpha frequency on the visuospatial attentional locus is inverse to the effect of tACS at gamma frequency and can only be found during left but not right hemispheric stimulation. Similar effects were reported in the auditory domain by Wöstmann and colleagues (2018) as well as Deng, Reinhart and Choi (2019) who found an ipsilateral shift of auditory spatial attention during unilateral tACS at 10 Hz. This suggests that alpha oscillations indeed play a causal role in attentional control (Worden et al. 2000; Sauseng et al. 2005; Kelly et al. 2006; Thut 2006; Klimesch et al. 2007; de Graaf et al. 2013).

While these tACS studies on spatial attention show weak but fairly consistent behavioral stimulation effects, they did not include neuroimaging to verify the underlying neural effects. Spatial attention tasks can reveal information about the behavioural tACS effect, but EEG or magnetoencephalography (MEG) measurements in the same paradigm are necessary to confirm that the power of the targeted oscillation was indeed modulated as intended. Without such measurements, it is impossible to conclude with certainty that the behavioural tACS effects were driven by the assumed changes in oscillatory power. Showing electrophysiological effects of tACS is particularly relevant in the case of tACS studies in spatial attention, as there is, to our knowledge, no study that has revealed whether lateralized tACS leads to oscillatory power enhancements at the stimulation site, similar to central montages (Zaehle et al. 2010; Neuling et al. 2013; Vossen et al. 2015). Furthermore, the extent of the stimulation frequency-specificity of tACS has not yet been fully explored. The theoretical framework of synchronization (Pikovsky et al. 2002; Thut et al. 2011) predicts that external rhythmic stimulation (e.g. tACS) preferentially enhances an oscillation if it is applied at the intrinsic dominant frequency (e.g. individual alpha frequency (IAF)). In this case, tACS at IAF stimulates in phase with the intrinsic alpha oscillation and thereby progressively enhances alpha power (Fig. 2A). With increasing deviation of the stimulation frequency from the IAF, the stimulation effect is expected to diminish and to approach zero, which means that stimulation at frequencies above or below IAF are expected to result in weaker or no stimulation effects. However, while it has been proposed that tACS operates via synchronization of neural oscillations to the alternating current (Thut et al. 2011), we are not aware of any tACS experiment that tested the frequency-specificity of the tACS effect by comparing the effects of stimulation at the intrinsic dominant frequency to stimulation at close flanking control frequencies. A verification of the frequency-specificity

is not only relevant from a fundamental point of view but also for the use of tACS in heterogeneous target groups with a large variability in intrinsic frequencies.

Here, we tested the effect of left posterior parietal HD-tACS at alpha frequency on visuospatial attention performance and oscillatory alpha power in a heterogeneous group of healthy participants of various age groups spanning from adolescence to mature adulthood. We applied tACS at the individual alpha frequency (IAF), two control frequencies IAF $\pm$ 2 Hz (1.5 mA) as well as sham (placebo) stimulation for each approximately 40 min and every participant underwent all four stimulation conditions (IAF, IAF + 2 Hz, IAF - 2 Hz, sham) in separate sessions and randomized order (Fig. 2A). We used a high-definition (HD) ring electrode montage, which creates a focused electrical field and thereby allows for relatively spatially confined targeting of the left posterior parietal cortex (Fig. 2B) and minimizes the risk of retinal confounds. During stimulation, we assessed visuospatial attention performance with a spatial cueing (Fig. 2C) and a detection task (Fig. 2D). We measured the after-effects of tACS on alpha power with resting-state EEG recordings immediately before and after tACS (offline).

In the framework of the synchronization theory (Pikovsky et al. 2002; Thut et al. 2011), we predicted a frequency-specific effect of tACS on alpha power and visuospatial attention. More precisely, we hypothesized that only left posterior parietal tACS at IAF, but not at IAF $\pm$ 2 Hz, induces a leftward lateralization of alpha power as compared to sham, which in turn would result in a visuospatial attentional leftward bias (Fig. 2B). Furthermore, we anticipated an association between the neural and the behavioral stimulation effect across participants. Accordingly, participants with a strong tACS-induced lateralization of alpha power were expected to display a stronger visuospatial attentional leftward bias and vice versa.

## 2. Results

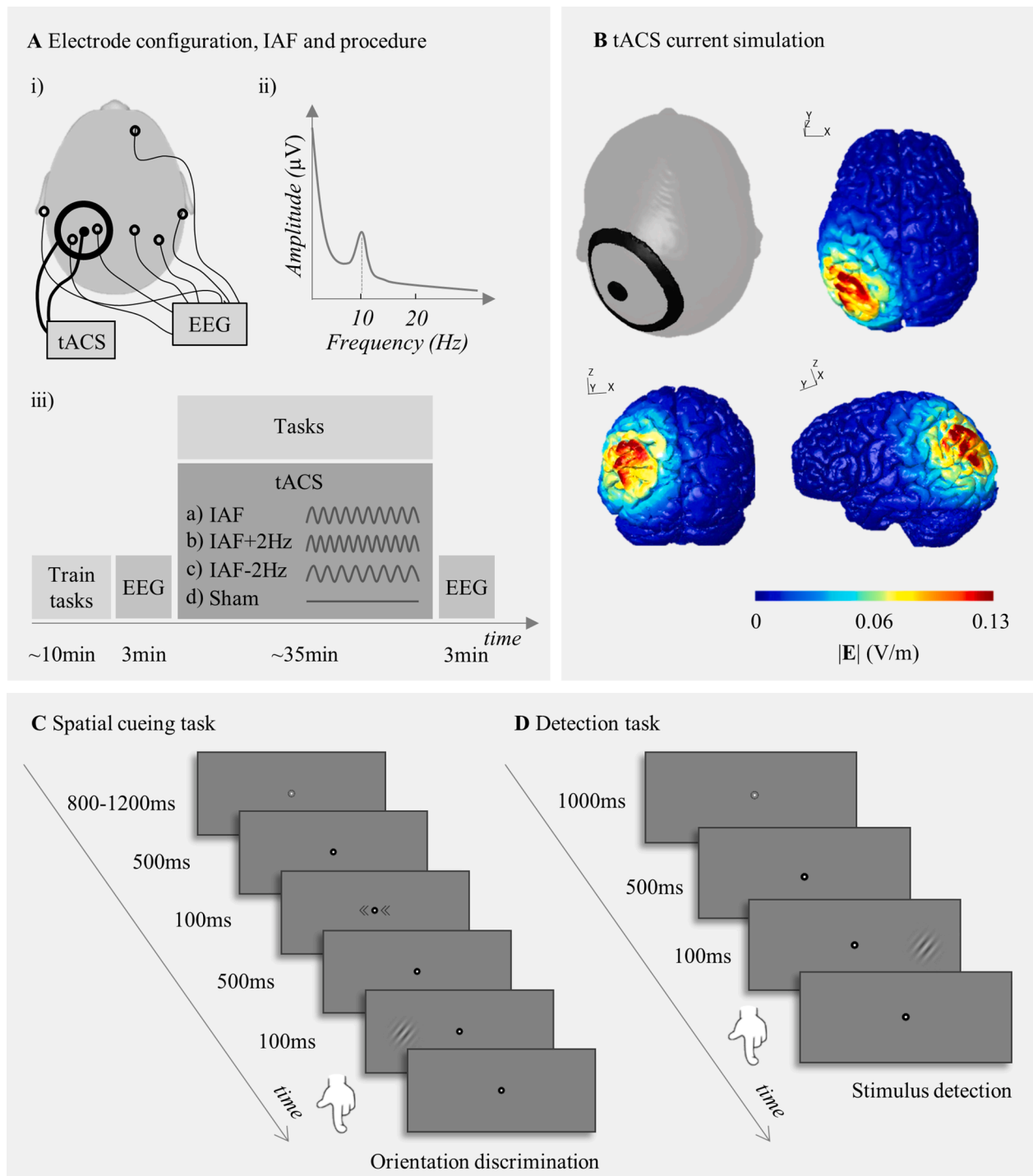
### 2.1. EEG data

#### 2.1.1. IAF is a stable trait marker and negatively correlates with age

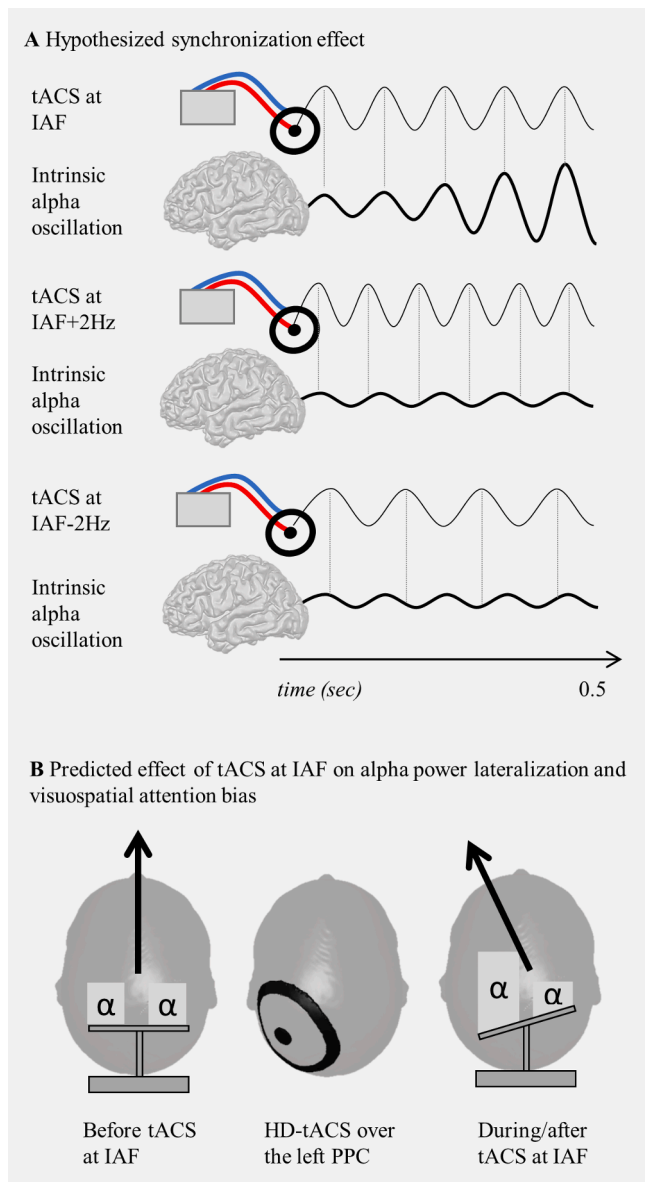
To verify the reliability of the IAF, we first examined its between-subject and within-subject variation. Our results show that the IAF spanned the 8 to 11.4 Hz range across participants and negatively correlated with age ( $r_{19} = -0.573$ ,  $p = .007$ ) (Fig S1). The test-retest reliability between the IAF estimates of the four sessions was very high as indicated by an average measure intraclass correlation coefficient (ICC) of 0.98 ( $F(20, 60) = 50.45$ ,  $p < .001$ ). This shows that the IAF is a stable trait marker, with minimal variation between sessions.

#### 2.2. tACS at IAF but not at IAF $\pm$ 2 Hz induces a leftward lateralization of alpha power

We hypothesized that tACS induces a leftward lateralization of alpha power during stimulation. However, the electrical stimulation artifact in the EEG during stimulation hampers the assessment of the online stimulation effect (Noury et al. 2016; Kasten and Herrmann 2019). For this reason, we measured offline EEG immediately before and after tACS to test whether there are alpha power lateralization effects that outlasts tACS. The effect of tACS on alpha power lateralization was quantified with the proportion increase in alpha power lateralization (PIAL) index, which indicates the proportion increase in alpha power (from the EEG measurement before to the EEG measurement after tACS) for the left relative to the right hemisphere. We hypothesized that only tACS at IAF, but not IAF $\pm$ 2 Hz, induces a leftward lateralization of alpha power, i. e., a greater PIAL score in the IAF as compared to the sham condition. To this end, we fitted a mixed model on the electrophysiological entrainment index PIAL using stimulation condition as a factor. We found a significant main effect of stimulation condition ( $F_{3,60} = 2.91$ ,  $p = .042$ ) and one-sided planned comparisons revealed a higher PIAL for the IAF ( $M = 8.16$ ,  $SE = 6.98$ ) as compared to the sham condition ( $M = -11.46$ ,



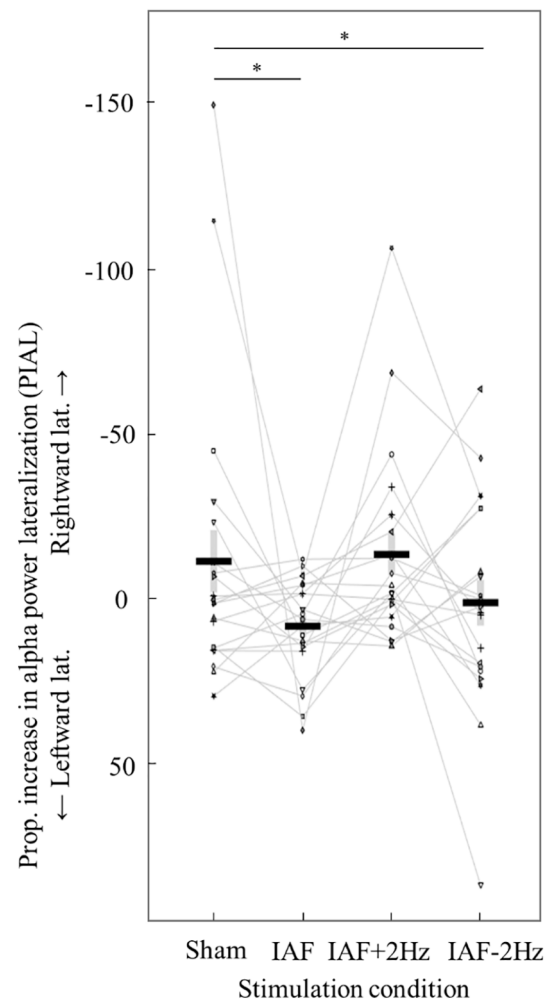
**Fig. 1.** Electrode setup per stimulation condition, procedure and example trial of the endogenous and exogenous attention tasks. (A) tACS and EEG electrode configuration. The small tACS disk electrode was placed on the i) left parietal ii) left temporoparietal cortex iii) right parietal or iv) right temporoparietal cortex and the large ring electrode was centered on it. By mounting the tACS electrodes over the parietal or temporoparietal cortex, we targeted the intraparietal sulcus (IPS) of the dorsal attention network (DAN) or the temporoparietal junction (TPJ) of the ventral attention network (VAN) respectively. In between the disk and the ring electrode, we mounted one single EEG electrodes and mirrored to it also one single EEG electrodes in the contralateral hemisphere. (B) Procedure. At the beginning of each session, we measured resting state EEG data. Then, participants completed a shortened practice version of the attention tasks while receiving tACS of increasing intensity in order to adapt to the skin sensation. Subsequently, we applied alpha-tACS (or sham tACS) to one of the target sites while the participants performed both attention tasks in two alternating blocks. Here, the initial task (and thereby also the logically following task blocks) was randomized between participants. As soon as the participant completed all task blocks, the tACS device was switched off and resting state EEG data were measured again. Each participant underwent all five stimulation conditions in separate sessions and randomized order. (C) Example trial of the endogenous and exogenous attention task. In both tasks, a given trial started with a fixation period followed by an endogenous (in the endogenous attention task) or an exogenous cue (in the exogenous attention task). The endogenous cue consisted of central arrow heads pointing to the left, right or both sides whereas the exogenous cue consisted of four laterally placed dots, which surrounded the potential target location. This was followed by a fixation interval and subsequently a sinusoidal grating rotated by 45° either clock- or counterclockwise, was presented either in the left or right hemifield. The participants were instructed to discriminate the grating's orientation as fast and accurately as possible (valid trial in this example).



**Fig. 2.** Rationale and hypotheses. (A) *Hypothesized effect of tACS at IAF, IAF + 2 Hz and IAF-2 Hz on the intrinsic alpha power during stimulation in the theoretical framework of the synchronization theory.* Depicted are the alternating currents of tACS at IAF, IAF + 2 Hz and IAF-2 Hz respectively as well as the expected effect of the alternating current on intrinsic alpha power over time. The dashed lines indicate the phase of the tACS current relative to the phase of the intrinsic alpha oscillation. The theory of synchronization predicts that tACS at IAF boosts intrinsic alpha power by consistently stimulating in phase. In contrast, tACS at IAF+/-2Hz are not synchronized to the intrinsic alpha oscillation and therefore do not induce the same increase in alpha power (see Thut and colleagues (2011) for a more detailed explanation of the synchronization theory). Note that we did not assess the alpha power increase during tACS (online) in this experiment but only measured the after-effects of tACS on oscillatory power (offline). (B) *Predicted effect of tACS at IAF on offline alpha power lateralization and visuospatial attention bias.* We hypothesized that before tACS at IAF, alpha power is equal in both hemispheres, accompanied by an unbiased visuospatial attentional locus. During and potentially also after tACS at IAF over the left posterior parietal cortex (PPC), alpha power lateralizes to the left hemisphere, which results in a visuospatial attentional leftward bias.

SE = 6.98)( $t_{60} = 2.29$ ,  $p = .013$ ), indicating a leftward lateralization of alpha power induced by left hemispheric tACS at IAF. In contrast, the two control frequency stimulation conditions did not differ from sham (IAF + 2 Hz vs sham:  $t_{60} = -0.24$ ,  $p = .406$ ; IAF-2 Hz vs sham:  $t_{60} = 1.46$ ,

$p = .075$ ) (Fig. 3). Furthermore, the IAF stimulation condition differed from the IAF + 2 Hz ( $t(60) = -2.53$ ,  $p = .007$ ) but not from the IAF-2 Hz stimulation condition ( $t(60) = -0.83$ ,  $p = .205$ ). Hence, only tACS at IAF but not at IAF+/-2Hz induced a leftward lateralization of alpha power relative to sham, indicating a frequency specific stimulation effect. A visualization of the stimulation effect per participant can be found in Fig. 3-figure supplement 1). However, the IAF condition did not differ from the IAF-2 Hz condition, which suggests that tACS at IAF-2 Hz might have a slight effect on alpha power lateralization. Note that this analysis focused on the first minute of the post-measurement to maximise entrainment effects (see Fig. 3-figure supplement 2 for a visualization of the PIAL effect in the first, second and third minute of the post-measurement). An analysis of the full three minutes of EEG data led to a similar pattern of results but no significant effects (Fig. 3-figure supplement 3A). Further analyses of hemisphere-specific alpha power changes revealed that the IAF condition did not differ from the sham condition for either hemisphere (Fig. 3-figure supplement 4). It is therefore unclear whether the lateralization effect is driven by left- or right-hemispheric alpha power changes. The [supplementary material](#) includes the outcomes of additional post-hoc analyses on the tACS effect



**Fig. 3.** Electrophysiological stimulation effect: Proportion increase in alpha power lateralization (PIAL) per stimulation condition (N = 21). A positive value of PIAL indicates a greater %-increase in alpha power (from the pre- to the post-measurement) in the stimulated left relative to the non-stimulated right hemisphere. The marker symbols and grey lines visualize the data of individual participants respectively. The bold horizontal black lines depict the mean across participants and the vertical grey lines visualize the respective standard error of the mean across participants.



on alpha power lateralization (see Fig. 3-figure supplement 5 and Fig. 3-figure supplement 6) and power spectrum plots of the power increase from the pre- to the post-measurement for the frequencies  $-7\text{ Hz}$  to  $+7\text{ Hz}$  relative to the IAF per stimulation condition (Fig. 3-figure supplement 7).

To conclude, an analysis of the change in alpha power lateralization from the pre- to the first minute of the post-measurement revealed that only tACS at IAF but not at IAF $\pm 2\text{ Hz}$  induced a leftward lateralization of alpha power relative to sham. Interestingly, tACS at IAF differed from IAF  $+2\text{ Hz}$  but not IAF-2 Hz, which might suggest that tACS at a lower frequency than the IAF might have similar, yet weaker effects as compared to stimulation at IAF.

### 2.3. Effects of tACS on power at and around the stimulation frequency and intrinsic IAF

We also assessed the effects of tACS on the proportion increase in power lateralization at and around the stimulation frequency (PIPL) to find out whether tACS at IAF-2 Hz and IAF  $+2\text{ Hz}$  modulated lower and upper alpha power respectively. For this, we directly compared tACS at IAF $\pm 2\text{ Hz}$  to tACS at IAF and sham by fitting a mixed model on PIPL with stimulation condition (all four conditions) as factor. We found a main effect of condition ( $F_{3,60} = 3.01$ ,  $p = .037$ ), driven by a significant higher PIPL score in the IAF ( $M = 8.16$ ,  $SE = 6.22$ ) as compared to the sham condition ( $M = -11.46$ ,  $SE = 6.22$ ) ( $t_{60} = 2.44$ ,  $p = .034$ ). In contrast, the IAF  $+2\text{ Hz}$  ( $M = -11.25$ ,  $SE = 6.22$ ) ( $t_{60} = 0.03$ ,  $p = .490$ ) and the IAF-2 Hz condition ( $M = 2.17$ ,  $SE = 6.22$ ) ( $t_{60} = 1.70$ ,  $p = .095$ ) did not differ from sham (Fig. 3-figure supplement 8). Further tests revealed that the IAF condition differed from the IAF  $+2\text{ Hz}$  ( $t_{60} = 2.42$ ,  $p = .029$ ) but not from the IAF-2 Hz condition ( $t_{60} = 0.75$ ,  $p = .230$ ).

In another control analysis, we tested whether tACS at the flanking control frequencies IAF $\pm 2\text{ Hz}$  shifted the IAF towards the stimulation frequency. To this end, we analysed the change in IAF from the pre- to the post-measurement and fitted a mixed model on the IAF change score with stimulation condition as factor. There was no significant effect ( $F_{3,60} = 0.48$ ,  $p = .699$ ) (IAF:  $M = -0.17$ ,  $SE = 0.07$ ; IAF  $+2\text{ Hz}$ :  $M = -0.11$ ,  $SE = 0.07$ ; IAF-2 Hz:  $M = -0.22$ ,  $SE = 0.07$ ; sham:  $M = -0.19$ ,  $SE = 0.07$ ) indicating that tACS had no effect on the intrinsic IAF (Fig S2).

To conclude, we found an effect of tACS at IAF on alpha power lateralization but no effect of tACS at IAF $\pm 2\text{ Hz}$  on alpha power, power at and around the stimulation frequency or intrinsic IAF. This underlines the frequency-specificity of the electrophysiological stimulation effect.

## 3. Behavioral data

### 3.1. Spatial cues modulate task performance

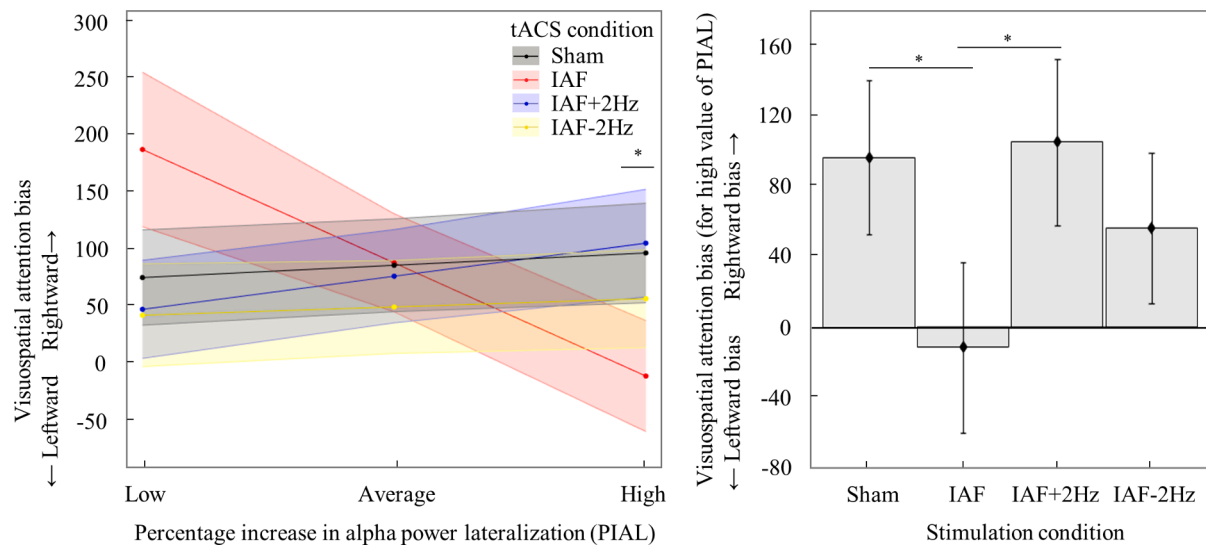
The average accuracy in the spatial cueing task was 90% and ranged between 61% and 100%. First, we assessed the cueing effect by looking into the differences in reaction time (RT) between the three different type of cue trials. We used the data of the sham condition for this analysis. We found a main effect of type of cue ( $F_{2, 38.01} = 9.47$ ,  $p < .001$ ). Accordingly, participants responded faster in valid ( $M = 593.67$ ,  $SEM = 40.39$ ) as compared to neutral ( $M = 612.83$ ,  $SEM = 40.41$ ) ( $t_{38.02} = -3.13$ ,  $p = .003$ ) and invalid trials ( $M = 619.31$ ,  $SEM = 40.41$ ) ( $t_{38.02} = -4.18$ ,  $p < .001$ ). The difference between invalid and neutral trials turned out to be not significant ( $t_{38.00} = 1.06$ ,  $p = .297$ ). This means that the valid but not the invalid cues modulated RTs. In the next sections, we investigated (for all three cue types) whether left tACS caused an attentional advantage for the processing of targets presented in the left hemifield.

### 3.2. For a high value of the alpha power lateralization effect, tACS at IAF, but not at IAF $\pm 2\text{ Hz}$ induces a visuospatial attentional leftward bias in the spatial cueing task

We subsequently tested whether tACS modulated the visuospatial attention bias, which was quantified with the inverse efficiency (RT/accuracy) for right minus left target trials. We hypothesized that tACS at IAF, but not at IAF $\pm 2\text{ Hz}$  condition, induces a greater visuospatial attention leftward bias as compared to sham. To this end, we fitted a mixed effect model on the visuospatial attention bias score (inverse efficiency<sub>left targets</sub> – inverse efficiency<sub>right targets</sub>) using stimulation condition and type of cue as factors and PIAL as covariate. There was a significant interaction effect between stimulation condition and PIAL ( $F_{3, 200.84} = 3.01$ ,  $p = .031$ ). All other main and interaction effects were not significant (stimulation condition:  $F_{3, 199.10} = 1.24$ ,  $p = .298$ ; type of cue:  $F_{2, 198.05} = 1.23$ ,  $p = .294$ ; PIAL:  $F_{1, 208.70} = 0.88$ ,  $p = .349$ ; stimulation condition  $\times$  type of cue:  $F_{6, 198.05} = 0.45$ ,  $p = .847$ ; type of cue  $\times$  PIAL:  $F_{2, 198.07} = 0.35$ ,  $p = .705$ ; stimulation condition  $\times$  type of cue  $\times$  PIAL:  $F_{6, 198.10} = 0.31$ ,  $p = .931$ ). This means that the effect of stimulation condition on the visuospatial attention bias depends on the electrophysiological stimulation effect PIAL. A simple slope analysis revealed a moderation effect: the stimulation condition effect was significant for a high ( $F_{3, 200.10} = 3.90$ ,  $p = .010$ ) but not for a low ( $F_{3, 200.05} = 2.45$ ,  $p = .065$ ) or average value ( $F_{3, 199.26} = 1.38$ ,  $p = .250$ ) of the covariate PIAL ( $\alpha_{\text{corrected}}: 0.025$ ) (see Fig. 4A for a moderation graph). Accordingly, there is an effect of stimulation condition on the visuospatial attention bias when the model assumes a high value but not a low or average value of the covariate PIAL. For the high value of the covariate PIAL, one-sided pairwise comparisons revealed that the IAF stimulation condition ( $M = -11.83$ ,  $SE = 48.77$ ) differed from sham ( $M = 96.42$ ,  $SE = 43.77$ ) ( $t_{200.51} = -3.05$ ,  $p = .003$ ), in line with an increased visuospatial attentional leftward bias. In contrast, tACS at the control frequency conditions did not differ from sham (IAF  $+2\text{ Hz}$  vs sham:  $t_{199.25} = 0.27$ ,  $p = .394$ ; IAF-2 Hz vs sham:  $t_{199.95} = -1.45$ ,  $p = .074$ ). Further one-sided pairwise comparisons revealed that the IAF condition differed from the IAF  $+2\text{ Hz}$  ( $t_{200.33} = 3.01$ ,  $p = .002$ ). However, the difference between the IAF as well as the IAF-2 Hz condition was only borderline significant ( $t_{200.21} = 1.95$ ,  $p = .026$ ) (Fig. 4B; see also Fig. 4-figure supplement 1 for the effect per cue type, Fig. 4-figure supplement 2 for a visualization of the behavioral stimulation effect per participant and Fig. 3-figure supplement 3B for the behavioral effect including PIAL with all three minutes of the EEG post-measurement as a covariate). Hence, at a high value of the covariate PIAL, tACS at IAF but not at IAF $\pm 2\text{ Hz}$  induced a significant leftward bias of visuospatial attention relative to the sham condition, which means that participants reacted faster and/or more accurately to target stimuli in the left relative to the right hemifield. The fact that the IAF but not the IAF $\pm 2\text{ Hz}$  stimulation condition differed from sham indicates a frequency specific stimulation effect. However, the IAF condition differed from the IAF  $+2\text{ Hz}$  but not from the IAF-2 Hz condition, which suggests that IAF-2 Hz might have a slight effect on the visuospatial attention bias. Further analyses per target location could not reveal whether the visuospatial attention bias effect was caused by performance changes in left or right target location trials (Fig. 4-figure supplement 3).

### 3.3. In the IAF stimulation condition, the electrophysiological stimulation effect correlates with the behavioral stimulation effect

We also analyzed the association between the electrophysiological and the behavioural stimulation effect in the spatial cueing task to further explore the significant interaction between stimulation condition and the covariate PIAL on the visuospatial attention bias score. To this end, we ran linear regression analyses between PIAL and the visuospatial attention bias score per stimulation condition. In the IAF stimulation condition, the electrophysiological stimulation effect PIAL was associated with the behavioural stimulation effect ( $b = -0.57$ ,  $p =$



**Fig. 4.** Behavioral stimulation effect in the endogenous attention task. Left: Moderation plot of the predicted visuospatial attention bias for a low, average, and high value of the covariate proportion increase in alpha power lateralization (PIAL) ( $N = 21$ ). The black, red, blue, and yellow dots and lines depict the average visuospatial attention bias for the sham, IAF, IAF + 2 Hz and IAF-2 Hz stimulation conditions respectively and the colored shaded areas visualize the respective standard error per condition. There was a significant interaction effect between the covariate PIAL and stimulation condition. Follow-up analyses on this interaction effect revealed a main effect of stimulation condition for a high but not for an average or low value of PIAL. Right: Visuospatial attention bias per stimulation condition for a high value of the covariate PIAL ( $N = 21$ ). A positive value of the visuospatial attention bias means that participants were less efficient in responding to target stimuli in the left relative to stimuli in the right hemifield. Note that the moderation and the bar graphs depict the results of a simple slope analysis, which predicts the stimulation effect for low, average or high values of the covariate PIAL. This comes down to an analysis of the visuospatial attention bias effect in subgroups of participants. However, instead of splitting up the sample, the simple slope analysis predicts the behavioral effect for this subgroup based on a regression equation that takes the data of all participants into account. In panel A, the lines and asterisks indicate significant main effects and in panel B they indicate significant pairwise comparisons on the estimated marginal means. The shaded error bars in panel A visualize the standard error of the mean and in panel B, the error bars depict the pooled standard error of the estimated marginal means across participants.

.014). For all the other stimulation conditions, there was no association between PIAL and the visuospatial attention bias (IAF + 2 Hz:  $b = 0.19$ ,  $p = .458$ ; IAF-2 Hz:  $b = -0.20$ ,  $p = .434$ ; sham:  $b = 0.25$ ,  $p = .289$ ). Note that also here, only the first minute of the post EEG measurement was included in the analysis. However, analyses of the full three minutes EEG data lead to the same pattern of results as well as similar statistics.

To conclude, only in the IAF but not in the IAF+/-2Hz condition did the electrophysiological and the behavioural effect correlate in magnitude, i.e., the greater tACS-induced leftward lateralization of alpha power, the greater the visuospatial attentional bias to the left (Fig. 5). This effect could also be found for the whole three minutes of the post-measurement (Fig. 5-figure supplement 1).

### 3.4. The stimulation effect does not depend on age or IAF

Subsequently, we tested whether age or IAF affected the behavioural stimulation effect by running linear regression models on the visuospatial attention bias score in the IAF stimulation condition. We found no effect of age ( $b = 0.42$ ,  $p = .057$ ) or IAF ( $b = 0.07$ ,  $p = .769$ ) on the visuospatial attention bias, which means that the behavioural stimulation effect is independent of those two factors. Furthermore, we tested whether age or the IAF had an influence on the association between PIAL and visuospatial attention bias in the IAF stimulation condition. According to log likelihood tests, adding age and IAF as predictors did not significantly improve the model (model<sub>PIAL</sub> vs model<sub>PIAL, IAF</sub>:  $X^2(1, N = 18) = 1.70$ ,  $p = .19$ ; model<sub>PIAL</sub> vs model<sub>PIAL, age</sub>:  $X^2(1, N = 18) = 0.00$ ,  $p = 1.00$ ; model<sub>PIAL</sub> vs model<sub>PIAL, IAF, age</sub>:  $X^2(2, N = 18) = 4.17$ ,  $p = .12$ ). This means that a model with only PIAL as predictor explains the data best.

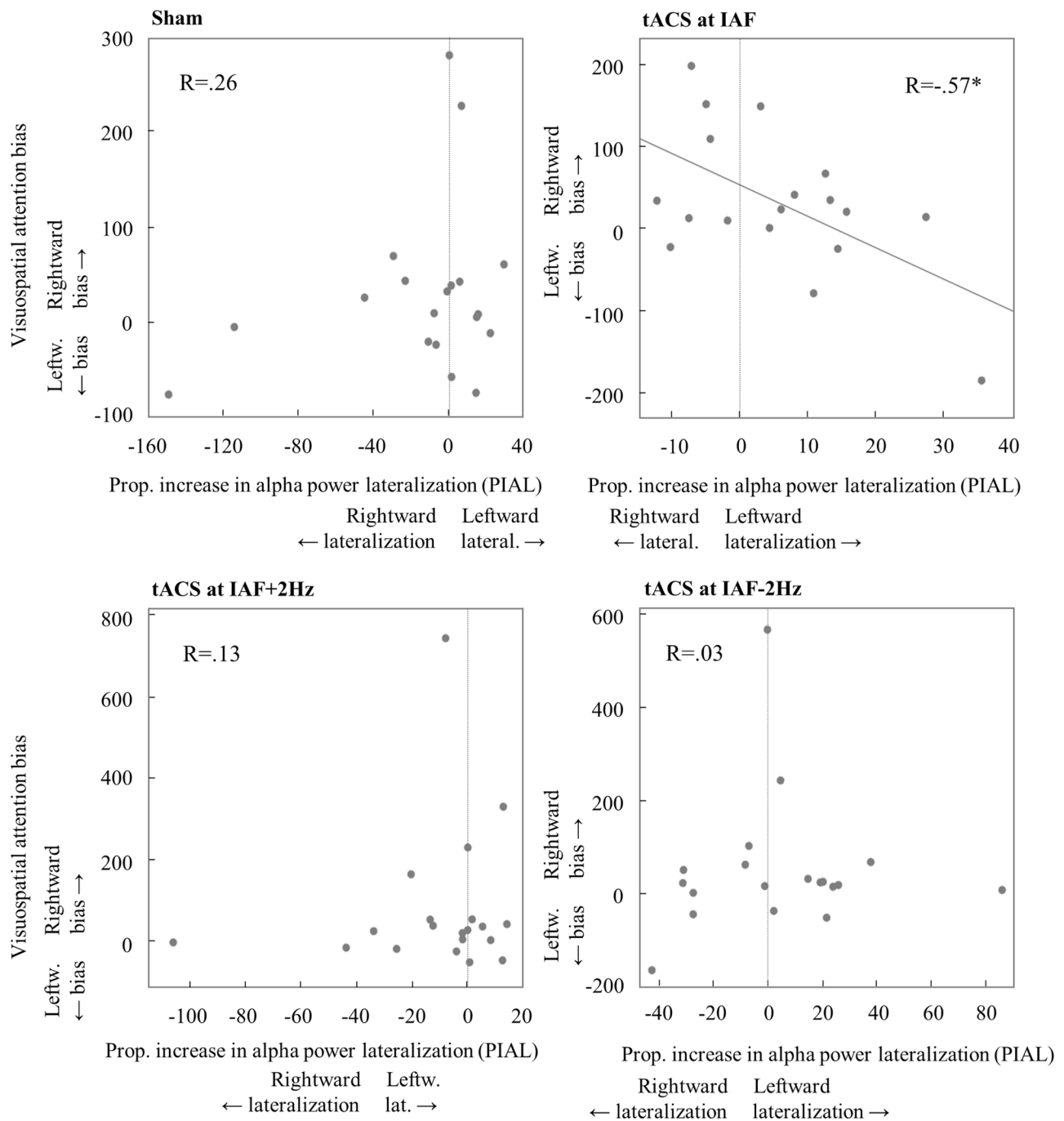
### 3.5. The effect of tACS on attention performance is task specific

To find out whether the tACS effects also influenced the low-level

visual processes, we performed a mixed model analysis on the contrast threshold bias score of the detection task using stimulation condition as factor and PIAL as covariate. There were no significant main (stimulation condition:  $F_{3, 51.41} = 0.41$ ,  $p = .746$ ; PIAL:  $F_{1, 60.81} = 1.11$ ,  $p = .297$ ) or interaction effects ( $F_{3, 54.73} = 0.14$ ,  $p = .934$ ) (Fig. 6). Additionally, we ran the same mixed model analysis using the bias in indicated target location score as dependent variable. Also here, the main (stimulation condition:  $F_{3, 50.05} = 1.77$ ,  $p = .166$ ; PIAL:  $F_{1, 55.19} = 0.27$ ,  $p = .607$ ) and interaction effects ( $F_{3, 51.71} = 0.13$ ,  $p = .944$ ) turned out to be not significant (Fig. 6-figure supplement 1). To verify whether the tACS effect is task specific, i.e., differentially affects performance in the endogenous attention task and the detection task, we compared the z-score transformed attentional bias scores of the two tasks in one analysis including task type (endogenous attention task, detection task) and stimulation condition (IAF, sham) as factors and PIAL as covariate. This was done separately for the two different dependent variables (threshold bias and the bias in indicated target location) of the detection task. We found a three-way interaction between task type, stimulation condition and PIAL comparing the visuospatial attention bias score of the endogenous attention task with the threshold bias scores of the detection task ( $F_{1, 113.80} = 6.45$ ,  $p = .012$ ). Similar results were found for the comparison between the visuospatial attention bias score of the endogenous attention task and the indicated target location score of the detection task ( $F_{1, 111.19} = 4$ ,  $p = .048$ ). Any follow-up analysis to these interaction effects is already reported in the manuscript and revealed an effect of tACS on attention performance for the endogenous attention task but not for either dependent variable of the detection task. Hence, our results indicate a differential effect of tACS on specifically attention performance in the endogenous attention task but not the detection task.

### 3.6. A post-questionnaire confirms that blinding was effective

Information about the experimental hypotheses and stimulation

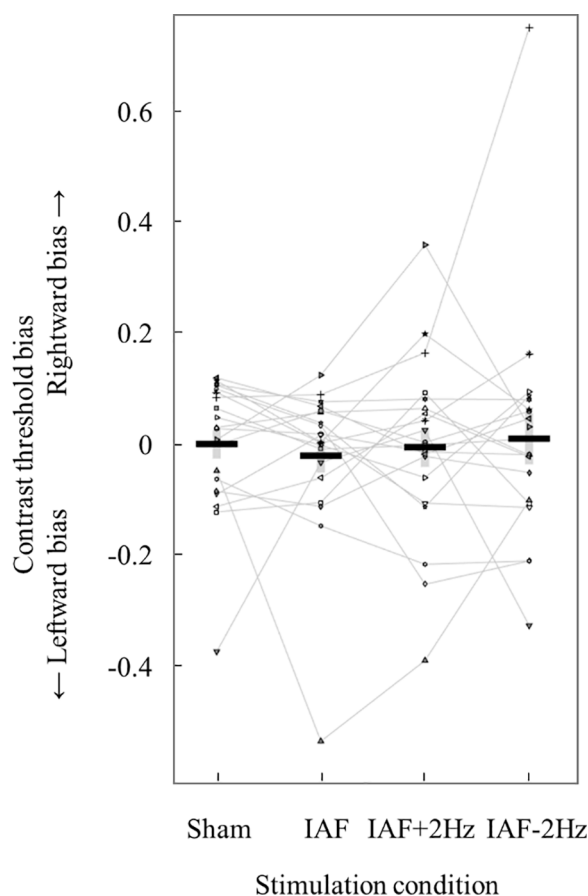


**Fig. 5.** Association between PIAL and visuospatial attention bias in the spatial cueing task per stimulation condition. A positive value of the proportion increase in alpha power lateralization (PIAL) indicates a greater increase in alpha power in the stimulated left relative to the non-stimulated right hemisphere from the pre- to the post-measurement. A positive value of the visuospatial attention bias score means that the participants were less efficient in responding to target stimuli in the left relative to stimuli in the right hemisphere. Per subplot, each point depicts the data of one participant. Linear regression analyses were performed to test whether the PIAL predicts the visuospatial attention bias. The asterisk marks effects with a p-values  $\leq 0.05$ . The R-value indicates the regression coefficient.

conditions were withheld from the participants until completion of the experiment. At the end of each session we administered a questionnaire, which prompted the participants to evaluate whether real or sham stimulation was applied. According to the Wald chi square, the actual stimulation condition did not affect the rated stimulation condition ( $\chi^2(3, N = 80) = 2.06, p = .56$ ), which means that participants could not differentiate between the active and sham stimulation conditions and blinding was therefore effective.

#### 4. Discussion

In this experiment, we measured the effects of individually tailored high-density alpha-tACS on offline occipitoparietal alpha power and visuospatial attention performance. We hypothesized that tACS at the individual alpha frequency (IAF) but not at flanking frequencies induces a leftward lateralization of alpha power and a leftward bias in visuospatial attention. In separate sessions and in a within-subject design, we applied HD-tACS at IAF, two control frequencies IAF + 2 Hz and IAF-2 Hz (1.5 mA) and sham for each 40 min to the left PPC. During



**Fig. 6.** Detection task: Contrast threshold bias per stimulation condition ( $N = 21$ ). A positive value means that participants were able to detect lower contrast stimuli in the right relative to the left hemifield (rightward bias). The marker symbols and grey lines visualize the data of individual participants and the connection between data points of individual participants respectively. The bold horizontal black lines and the vertical grey lines depict the mean and the standard error of the mean across participants respectively.

stimulation, we measured the visuospatial attention bias with a spatial cueing and a detection task and immediately before and after stimulation we acquired EEG data to assess the after-effects on alpha power. To have a great variation in IAF and to be able to generalize our findings to a wider target group, we tested participants of various age groups spanning from adolescence to mature adulthood. Our data show a leftward lateralization of alpha power in the IAF stimulation condition, which differed from sham in the first out of three minutes EEG recording after tACS. Only for the IAF stimulation condition we found a link between the electrophysiological and the behavioural stimulation effect across participants: the greater the leftward lateralization of alpha power, the greater the leftward bias in visuospatial attention in the spatial cueing task. We also showed a visuospatial attentional leftward bias in the IAF stimulation condition, which significantly differed from sham. However, in contrast to our previous alpha-tACS experiment (Schuhmann et al. 2019), this was a moderation effect, i.e., the tACS-induced visuospatial attention bias effect was only significant for a high value of the covariate, which coincides with a high value of electrophysiological tACS effect. This might be caused by additional variability in the data due to the cross-generational sample in this experiment. Note that there was a baseline attentional rightward bias in the control stimulation conditions, which was shifted towards the left during IAF tACS. This attentional bias at baseline has previously been reported in a similar paradigm (Schuhmann et al. 2019) and might be caused by a congruency effect, i.e., an attentional advantage if the

location of the stimulus matches the response hand (here: right hand) and vice versa (Aisenberg and Henik 2012). To conclude, our results indicate an effect of tACS at IAF on oscillatory alpha power and on visuospatial attention performance when taking the alpha power effect into account (moderation effect). There is also a link between the magnitude of the neural and the behavioural stimulation effect. This suggests that alpha oscillations play a functional role in the modulation of visuospatial attention and shows that tACS can be used to modulate it. The frequency specificity of the effects suggests that an individualization of the stimulation frequency might be necessary in heterogeneous target groups with a wide variation in IAF.

## 5. Frequency specific stimulation effect and personalized stimulation protocols

The synchronization theory proposes that the tACS effects are greatest if the stimulation frequency is tuned to the intrinsic frequency and the effects diminish with increasing deviation of the from the intrinsic frequency (Pikovsky et al. 2002; Thut et al. 2011). However, we are not aware of any experiment that compared the effect of tACS at the intrinsic frequency to tACS at close flanking control frequencies to verify this frequency-specificity. In line with the synchronization theory, we found a frequency-specific effect of tACS at IAF on alpha power lateralization and visuospatial attention bias as well as a direct link between those two dependent variables. In contrast, tACS at the flanking control frequencies IAF $\pm$ 2 Hz did not modulate alpha power lateralization or the visuospatial attention bias (as compared to sham). However, it should be noted that the visuospatial attention bias and alpha power lateralization effect in the IAF tACS condition differed from the IAF + 2 Hz but not from IAF-2 Hz condition, suggesting that tACS at frequencies < IAF may result in similar, yet weaker, stimulation effects as compared to tACS at IAF. As the IAF has previously been shown to decrease during time on task (Benwell et al. 2019), the seemingly differential effect of tACS at IAF + 2 Hz versus IAF-2 Hz could arise due to a gradual shift of the preferred stimulation frequency towards the latter.

The frequency-specificity of the stimulation effects in the present experiment is not only theoretically relevant but might also have practical implications for the use of tACS. Our results suggest that an individualization of the stimulation frequency might be necessary in heterogeneous samples with a wide variation in IAF. As the IAF negatively correlates with age in adults (Surwillo 1963; Köpruner et al. 1984) and is particularly low in patients with dementia (Moretti 2004; Cantero et al. 2009; Gawel et al. 2009), traumatic brain injury (Tebano et al. 1988; Nuwer et al. 2005) or stroke (Giaquinto et al. 1994; Juhász et al. 2009), an individualization of the stimulation frequency might be especially important for the application of alpha tACS in a sample covering a wide age range. Furthermore, tuning tACS to the IAF instead of stimulating at a fixed frequency of 10 Hz, might reduce variability (Vossen et al. 2015; Stecher and Herrmann 2018; Kasten et al. 2019) and therefore lead to more robust tACS effects even in homogenous samples of young, healthy participants.

### 5.1. Link between electrophysiological and behavioral stimulation effect

Our data reveal a link between the behavioral and electrophysiological stimulation effect in the IAF stimulation condition: participants with a high alpha power lateralization effect also displayed a marked visuospatial attentional leftward bias and vice versa. This suggests that alpha power plays a functional role in the modulation of visuospatial attention and shows that the magnitude of the electrophysiological tACS effect is a determinant for the magnitude of the behavioral tACS effect. We included the electrophysiological tACS effect as covariate in the analysis of the behavioral tACS effect to explain variability and to analyze the behavioral effect at different levels of the electrophysiological effect. As follow-up analysis on a significant interaction effect between the dependent variable and the continuous covariate, we



performed a simple slope analysis. This simple slope analysis comes down to an analysis of the behavioral tACS effect for responders versus non-responders where the increase in alpha power lateralization is used as an index of the tACS-responsiveness. As we found a visuospatial attention bias effect only for a high value of the electrophysiological effect, our data suggests that a leftward shift in attention is only observed if tACS successfully induced an (offline) leftward lateralization of alpha power. Note that this regression approach does not require a division into small subgroups. Instead, the regression equation takes the data of all participants into account and predicts the stimulation effect at different values of the covariate based on the regression equation.

### 5.2. Task specific tACS effect

Similarly to previous tACS and tDCS studies that targeted the left posterior parietal cortex, we found a behavioral stimulation effect in the spatial cueing but not in the detection task (Duecker et al. 2017; Schuhmann et al. 2019). This differential effect could be explained by fundamental differences between the two attention tasks. The spatial cueing task assesses higher-level attentional processes such as the ability to perform endogenous (top-down) attention shifts as well as the efficiency in discriminating the orientation of lateralized target stimuli. In contrast, the detection task measures low-level visual processing and the ability to perform exogenous attention shifts towards lateralized stimuli. Previous EEG studies that employed spatial cueing tasks found a lateralization of alpha power after presentation of a central, symbolic endogenous cue, but before a lateralized target stimulus was shown (Sauseng et al. 2005; Thut 2006; Gould et al. 2011; Händel et al. 2011). This suggests that alpha power changes are associated with endogenous attention shifts in a spatial cueing task. Furthermore, the HD-tACS ring electrode montage over the posterior parietal cortex is expected to overlap with the intraparietal sulcus (IPS) of the dorsal attention network (DAN), which is involved in endogenous shifts of attention. Moreover, an fMRI study showed that the posterior parietal cortex is involved in voluntary attention shifts while target detection is rather regulated by the temporoparietal junction (Corbetta et al. 2000). All of this might account for the stimulation effect in the spatial cueing task and the absence of effects on the contrast thresholds as measured with the detection task (however, see (Ergenoglu et al. 2004; Hanslmayr et al. 2007)).

### 5.3. High-definition electrode montage and stimulation site

The effect of unilateral HD-tACS at alpha frequency on visuospatial attention is in line with recent alpha tACS research on visuospatial (Schuhmann et al. 2019; Kasten et al. 2020) and auditory spatial attention (Wöstmann et al. 2018; Deng et al. 2019). However, other tACS experiments found no or inconsistent effects of lateralized alpha tACS on the visuospatial attention bias (Hopfinger et al. 2017; Veniero et al. 2017). These inconsistent results are surprising considering the quite established association between alpha power lateralization and visuospatial attention bias (Sauseng et al. 2005; Kelly et al. 2006; Thut 2006; Gould et al. 2011; Händel et al. 2011).

One aspect that distinguishes the experiments with an effect of tACS on the spatial attention bias (Wöstmann et al. 2018; Deng et al. 2019; Schuhmann et al. 2019) from experiments that report no or inconsistent effects (Hopfinger et al. 2017; Veniero et al. 2017), is the high-definition ring electrode montage (however, see (Kasten et al. 2020)). In contrast to traditional tACS montages, consisting of two rectangular or round tACS electrodes, the ring electrode montage creates a more focused electrical field between the large ring and the small disk electrode (Datta et al. 2008). This restricted current flow allows for a more precise anatomical targeting limited to one hemisphere, which is confirmed by a current simulation for the electrode montage in this experiment (Fig. 1B), which shows that the electrical field was confined to the left posterior parietal cortex.

An alternative explanation for the previous inconsistent and null results lies in the stimulation site. While left hemispheric stimulation tACS at alpha frequency modulated the visuospatial attention bias (Schuhmann et al. 2019; Kasten et al. 2020), no such effect could be found for right hemispheric stimulation (Hopfinger et al. 2017; Veniero et al. 2017; Kasten et al. 2020). In line with this, various EEG studies on auditory and visuospatial attention reported stronger alpha power dynamics over the left hemisphere (Sauseng et al. 2005; Okazaki et al. 2014; Wöstmann et al. 2016; Bagherzadeh et al. 2020). Furthermore, Meyer and colleagues (Meyer et al. 2018) showed that the task-related fMRI signal during a spatial cueing task is greater in the left as compared to the right frontoparietal attention network, especially after presentation of an invalid spatial cue. The left hemisphere also displayed a greater change in functional connectivity during a spatial cueing task as compared to the right hemisphere. In the right hemisphere, the functional connectivity was tonically higher during rest, while the left hemisphere was more specifically recruited during a condition of high attentional demands. This might explain why left but not right parietal tACS modulated visuospatial attention performance.

### 5.4. Alpha power lateralization effect and hemisphere-specific alpha power changes

Previous research has shown that medial tACS at alpha frequency enhances alpha power at the stimulation site (Zaehle et al. 2010; Neuling et al. 2013; Vossen et al. 2015). However, we are not aware of any prior experiment that has tested the effect of lateralized alpha tACS on electrophysiology. Our data show that tACS at IAF induces a leftward lateralization of alpha power relative to the sham, yet further analyses yielded ambiguous information about the hemisphere-specific alpha power changes. Based on the results of previous experiments employing medial tACS montages (Zaehle et al. 2010; Neuling et al. 2013; Vossen et al. 2015), we expected that left tACS at alpha frequency enhances alpha power in the stimulated left hemisphere. However, we found no difference in alpha power change between the stimulation conditions for either hemisphere and the pattern of results suggests that the leftward lateralization of alpha power in the IAF condition was rather driven (although not significantly) by a reduction of alpha power in the unstimulated right hemisphere. This effect could be explained by the interhemispheric inhibition theory, which claims that the two hemispheres mutually inhibit each other (Kinsbourne 1977, 1993; Cohen et al. 1994; Szczepanski et al. 2010). Accordingly, a deactivation of one hemisphere, due to brain damage or inhibitory brain stimulation protocols, leads to disinhibition and thus increased activation in the contralateral hemisphere (Seyal et al. 1995; Vuilleumier et al. 1996; Oliveri et al. 1999; Rushworth et al. 2001; Battelli et al. 2009; Szczepanski and Kastner 2013). Along these lines, a tACS-induced alpha power enhancement in the left PPC may have entailed the contralateral alpha power decrease causing the significant leftward lateralization of alpha power.

### 5.5. The functional role of alpha oscillations

It has previously been proposed that alpha oscillations serve as an active attentional inhibition mechanism, which enables the selective processing of relevant stimuli by suppressing distracting incoming sensory information (Jensen & Mazaheri, 2010; Kelly et al., 2006; Klimesch et al., 2007). A related theoretical framework suggests that high alpha power reflects sensory inhibition, while low alpha power represents enhanced processing of sensory stimuli (Adrian, 1944; Frey et al., 2014; Fu et al., 2001; Mazaheri et al., 2014). While these theories about the role of alpha oscillations are widely referred to, a recent review (Schneider et al., 2021) pointed out that most EEG paradigms have actually not directly test whether alpha oscillations are indeed associated with active distractor inhibition, target enhancement or both. The independent contributions of alpha oscillations to these two processes,

however, was recently probed by an auditory attention study that systematically and independently varied the distractor and stimulus parameters (Wöstmann et al., 2019). Their results provide evidence for a role of alpha oscillations in both target enhancement and distractor suppression, and interestingly they report that the alpha sources for these two processes were partially anatomically distinct. Here, we employed attention tasks with only target but no distractor stimuli. Our results show that tACS at IAF can induce a visuospatial attention bias, which underlines the functional role of alpha oscillations in attention performance. Yet, as we only included target stimuli, we measured the effect of alpha power modulation on target processing but not on distractor suppression and can therefore not infer whether left parietal tACS at IAF would also affect the latter. To disentangle the effect of left parietal IAF tACS on target enhancement versus distractor suppression, future tACS research should include target as well as distractor stimuli and independently covary the two parameters.

### 5.6. Neuronal mechanisms underlying the tACS effects

The neural mechanisms underlying the offline EEG effects are unclear. Possible explanations for the electrophysiological effect are entrainment echoes, tACS-induced plasticity or secondary electrophysiological effects related to outlasting modulations of visuospatial attention. It is plausible that tACS induced short-term plasticity, which involves changes of synaptic release of neurotransmitter, i.e., synaptic enhancement and synaptic depression. These short-term plasticity effects can range from seconds to minutes (Zucker and Regehr 2002), which matches the time scale of the tACS after-effect on offline alpha power. An alternative proposal would be long-term plasticity effects such as long-term potentiation (LTP) and long-term depression (LTD), which include lasting modifications in the synaptic efficacy (Gerrow and Triller 2010; Michmizos et al. 2011). tACS might have induced longer lasting changes (<1 min) in the stimulated area, which are however not measurable for the whole time-scale because they do not represent a natural default state and might therefore be counteracted. During the long period of rest in the post-measurement, participants might have adjusted the tACS-induced visuospatial attentional leftward bias and the associated alpha power lateralization by directing the spatial attention locus back to the midpoint. Alternatively, interhemispheric dynamical interactions, as proposed by the interhemispheric inhibition theory (Kinsbourne 1977, 1993; Cohen et al. 1994; Szczepanski et al. 2010), might have pulled the alpha power lateralization back into its original balanced state. An alternative account for the alpha power lateralization are secondary electrophysiological effects. tACS at IAF might have entrained alpha power in the left hemisphere during stimulation, which in turn induced the visuospatial attentional leftward bias. This attentional bias, which is naturally accompanied by a lateralization of alpha power, might have outlasted the stimulation causing the significant alpha power lateralization effect in the first minute of the post-measurement. One could also argue that the tACS after-effects reflect entrainment echoes, i.e., phase alignment to the preceding alternating current as well as synchronization to the exact stimulation frequency. Yet these entrainment echoes are usually observed at a much shorter time-scale of approximately 1.5 s after tACS (Hanslmayr et al. 2014). Future research should systematically assess whether this stimulation protocol leads to entrainment echoes by interleaving multiple short stimulation blocks with EEG recording blocks.

### 5.7. Limitations and ideas for future research

In line with our hypothesis, we demonstrated that unilateral alpha-tACS induces an offline alpha power lateralization. However, this effect could only be shown for the first minute of the post-measurement. An analysis of the full three-minute post-measurement data revealed no significant differences in alpha power lateralization between the IAF and sham stimulation condition. It is plausible that the longer-lasting

plasticity effects induced by lateralized alpha-tACS are reflected in dynamical alpha power modulations instead of resting state power modulations, e.g. the efficiency in upregulating alpha power in the left hemisphere during attentional shifts towards the left side or vice versa. Future research should therefore administer the endogenous attention task after tACS to assess the offline visuospatial attention bias as well as the offline alpha power dynamics during task performance. In any case it is important to note that the correlation between the alpha power lateralization effect and the visuospatial attention bias in the IAF stimulation condition was significant for all three minutes, which strengthens the fundamental effects on resting state alpha power as revealed for the first minute.

An often-ignored confounder in tACS experiments are the potential indirect stimulation effects caused by current spread to the eye (Rohracher 1935; Kanai et al. 2008). It has been proposed that these phosphores entrain neuronal assemblies in the visual cortex via the retinothalamic pathway (Karabanov et al. 2019). However, high-definition electrode montages, as used in this experiment, minimize the probability of retinal confounds (Karabanov et al. 2019) as the resulting focal and confined electric field implicates less volume conduction to remote structures (Datta et al. 2008, Datta et al., 2009; Dmochowski et al. 2011; Bortoletto et al. 2016). Moreover, a potential retinal stimulation does not account for the asymmetry of our effects as the left lateralized stimulation is expected to result in activity changes in the left as well as right optic tract of the left eye and therefore similar modulations in the left and right hemisphere. Another potential confounder are indirect stimulation effects caused by stimulation of peripheral sensory afferents (Asamoah et al., 2019a, Asamoah et al., 2019b; Vieira et al. 2020). Accordingly, tACS enhances the power of a certain oscillation in the sensory cortex and potentially also other cortical areas by rhythmically activating nerve fibers in the skin under the electrode or via attention that is drawn towards the sensation on the skin. Especially the latter is relevant in our experiment as the tACS montage and thereby also the skin sensation is lateralized to the left. It has recently been shown that tACS modulates single-unit activity in monkeys independently of whether the somatosensory input is blocked via topical anesthetic or not (Vieira et al. 2020). Most importantly, the stimulation effect in this experiment was frequency-specific. If lateralized skin sensations would have caused the visuospatial attention bias and alpha power lateralization effect, similar effects would be expected in the IAF, IAF + 2 Hz and IAF-2 Hz stimulation condition, assuming that they are accompanied by similar skin sensations. Nevertheless, future experiments should include a control stimulation site, such as a more lateralized or anterior montage, to directly control for cutaneous and retinal stimulation effects.

As it is still methodologically challenging to measure changes in alpha power during tACS (online) due to the electrical stimulation artifact, we only assessed the after-effects of the stimulation by calculating the proportion increase in alpha power lateralization from before to immediately after tACS. However, if possible, future experiments should investigate the effect of alpha-tACS during stimulation to directly verify entrainment echoes. The effects shown here should also be verified in a larger sample (Minarik et al. 2016).

## 6. Conclusion

Our results suggest that alpha oscillations play a functional role in the modulation of visuospatial attention and demonstrate that tACS can be used to modulate it. Future research should focus on increasing the effect size of the stimulation effect by e.g. repeatedly employing the same stimulation protocol in separate sessions, individualizing other stimulation parameters such as stimulation site or increasing the stimulation intensity. The frequency specificity of our findings might account for previous inconsistent or variable tACS effects and suggests that an individualization of the stimulation frequency is necessary in heterogeneous groups of participants with a wide variation in IAF.

## 7. Materials and methods

### 7.1. Participants

We tested 21 healthy, right-handed volunteers (8 female, mean age (SD) = 45.38 (17.10) years, age range = 19–72 years) with normal or correct to normal vision. Participants filled in an informed consent and a tACS safety screening form prior to each session. In the safety screening form we scanned for e.g. neurological disorders, skin diseases, medication and pregnancy, taking the recommended procedures of Antal and colleagues (Antal et al. 2017) into account. This study was performed in accordance to the Declaration of Helsinki and was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University (ERCPN number: 129). Participants received vouchers as compensation for their participation.

### 7.2. Procedure

Each participant received active tACS at IAF, IAF + 2 Hz and IAF-2 Hz as well as sham tACS on separate days and randomized order and the same procedure was followed in every session. To avoid carry-over effects, we scheduled sessions at least two days apart. Initially, participants performed a shortened practice version of the spatial cueing and the detection task. Then, we mounted recording EEG electrodes as well as stimulating tACS electrodes on the participant's head. Before stimulation, three minutes of resting state EEG data were collected while participants kept their eyes closed. This pre-measurement served as an estimation of alpha power before stimulation and was also used to determine the IAF. In order to account for potential day-to-day variations in the intrinsic frequency, the tACS stimulation frequency was always based on the IAF that was determined in the same session. Subsequently, tACS was applied at either IAF, IAF + 2 Hz, IAF-2 Hz or sham while participants performed a spatial cueing and a detection task. The order of the tasks was randomized order across participants. After completion of the tasks or after a maximum stimulation duration of 40 min, the tACS stimulator was switched off and three minutes of resting state EEG data were measured again (post-measurement) (Fig. 1A). During the spatial cueing task, we recorded eye movements with an eye tracker. These data were used for offline analysis of the behavioural performance. Information about the experimental hypotheses and the applied stimulation protocol were withheld from the participants until completion of the experiment. To verify whether blinding was maintained, we administered a questionnaire at the end of each session, which prompted the participants to evaluate the stimulation condition based on the subjective experience.

### 7.3. Eye tracker

An eye tracker (Eyelink1000, SR Research, Mississauga, Ontario, Canada) was used during the spatial cueing task. At the beginning of each session, we performed a 9-point calibration and validation procedure. Then, we assessed the participants' gaze position sample by sample point using monocular eye tracking at 1000 Hz. These data were used for the offline analysis. We did not record eye tracking data during the detection task because this task did not include an orienting or reorienting component.

### 7.4. tACS and electric field simulation

We mounted a high-definition ring electrode tACS montage (NeuroConn, Ilmenau, Germany) over the left posterior parietal cortex with a small circular electrode (Diameter: 2.1 cm; Thickness: 2 mm) positioned over P3 and a large ring electrode (Outer diameter: 11 cm; Inner diameter: 9 cm; Thickness: 2 mm) centered on it. The ring electrode montage around P3 was chosen to target the posterior parietal cortex, an area that has shown to be involved in the direction of attention towards

a location of interest (Corbetta et al. 2000; Yantis et al. 2002). We used the international 10–20 EEG system to determine the electrode position P3 on the participants' head. tACS was applied via an DC-stimulator plus (NeuroConn, Ilmenau, Germany) at a stimulation intensity of 1.5 mA peak to peak. In the active tACS conditions, the stimulation frequency was tuned to IAF, IAF + 2 Hz or IAF-2 Hz and the ramp up was set to 100 cycles. The tACS device was switched off as soon as the participant finished the task but never exceeded 40 min. Overall, the stimulation duration varied between 35 and 40 min. In the sham condition, we also applied tACS at IAF but ramped up and then immediately ramped down the stimulation with each 100 cycles. That way, we imitated the initial skin sensations of real tACS while minimizing neural and behavioral stimulation effects. Conductive gel (Ten20 paste, Weaver and Company, Aurora, CO, USA) was used to fasten the tACS electrodes on the skin and to keep impedances below 10k $\Omega$ .

For this experiment, we used a high-definition ring electrode tACS montage to enable spatially focal stimulation (Datta et al. 2008) of the left PPC. An electric current simulation was performed to visualize the stimulated regions using a custom-written MATLAB script (Heise et al. 2019) interfacing with the software SimNIBS (Saturnino et al., 2019a, Saturnino et al., 2019b) (Fig. 1B). For this simulation, we used a freely available individual head model of a healthy brain as an example participant (Boayue et al. 2018) and modelled the electrodes with a random connector location. The conductivity of the ten20 paste was set to 8 S/m, an estimation based on the concentration of Cl<sup>-</sup> in the gel (Saturnino et al. 2015).

### 7.5. EEG apparatus and data acquisition

First, we marked the electrode positions P5, PO3, P6 and PO4 on the participants' head according to the international 10–20 system. Then, single EEG electrodes were mounted at the marked spots using ten20 conductance paste (Weaver and Company). Spectral EEG was recorded via a BrainAmp MR Plus EEG amplifier (BrainProducts GmbH, Munich, Germany) and Ag-AgCl electrodes (BrainProducts GmbH, Munich, Germany). The recordings were online referenced to the left and offline re-referenced to both mastoids and the ground electrode was positioned over the right forehead. Impedances for all electrodes were kept below 5 k $\Omega$  and a sampling rate of 500 Hz and a bandpass filter of 0.1–200 Hz was used for online recording.

### 7.6. Task description

The spatial cueing task was a classical Posner task including endogenous cues and was used to assess the participants' speed and accuracy in discriminating the orientation of lateralized target stimuli in the left or right hemifield. Throughout the task, participants had to fixate on a central white fixation point, surrounded by a black or grey donut-shaped area, which was delimited by a black circle. A trial started with a jittered interval of 800–1200 ms, during which only the white fixation point, surrounded by a grey area was presented. Subsequently, the grey area turned black for 500 ms. Then, a central symbolic cue, which consisted of arrowheads pointing to the left ( $\llcorner\bullet\llcorner$ ), right ( $\gg\bullet\gg$ ) or both sides ( $\llcorner\bullet\gg$ ) flanking the central fixation point, was shown for 100 ms. The directional cues (left or right arrow heads) predicted the correct target location with 80% validity. The cue was followed by a cue-target interval of 500 ms during which only the central fixation point was presented. Then, the target stimulus was shown for 100 ms in either the left or right hemifield at 7° eccentricity from the fixation point. This target stimulus consisted of a sinusoidal grating with a Gaussian envelope (spatial frequency = 1.5 cycles per degree, envelope standard deviation = 0.75°) and was rotated clockwise or counter clockwise by 45°. Participants were instructed to differentiate the orientation of the stimulus as fast and accurately as possible, pressing the numerical button 1 or 2 for counter clockwise and clockwise rotated stimuli respectively (Fig. 1C). Trials with a very slow (greater than 1000 ms) or



anticipatory (<120 ms) response were repeated. The endogenous task took approximately 20 min and comprised 335 trials, of which 192 were valid, 48 invalid and 96 neutral cue trials.

The detection task measured the participants' ability to detect low-contrast target stimuli in the left, right or both hemifields. First, participants manually downregulated the contrast of bilaterally presented stimuli until they were barely visible. This contrast served as an initial value for the subsequent staircase procedure. A trial started with the presentation of a white fixation point, surrounded by a grey donut-shaped area, which was delimited by a black circle. After 1 s, the grey area turned black for 500 ms. Then, the target stimulus, a randomly oriented sinusoidal grating (spatial frequency = 1.5 cycles per degree, envelope standard deviation = 0.75°), was presented for 100 ms in the left, right or both hemifields at 14° eccentricity from the fixation point. Participants had to indicate the stimulus location, pressing the numerical button 1, 2 or 3 for left, bilateral and right target location respectively. In case no stimulus was perceived, the participants had to withhold the response (Fig. 1D). On a trial-by-trial basis, the contrast of the left, right and bilateral stimuli were independently adjusted according to the QUEST staircase algorithm (Watson and Pelli 1983) as implemented in the Psychophysics Toolbox (Brainard 1997) for MATLAB (prior standard deviation = 1, beta = 3.5, gamma = 0.01, delta = 0.01, aim performance = 50% detection rate). QUEST is a psychometric procedure which uses Bayesian statistics to predict the participant's contrast threshold based on the detection performance in the preceding trials. We used the function QuestQuantile to compute the trial-by-trial stimulus contrast based on the maximum likelihood estimate of the threshold. QuestMean was used to calculate the final detection threshold. As the contrast threshold of left, right and bilateral stimuli were independently determined, the detection task consisted of three interleaved staircase procedures of each 40 trials resulting in a total amount of 120 trials. The detection task took approximately 10 min.

Both tasks were presented on a gamma-corrected Iiyama ProLite monitor at 60 Hz. The background luminance and the video mode were set to 100 cd/m<sup>2</sup> and 1920x1080 respectively. Participants had to place their chin into a chin rest to assure a viewing distance of 57 cm as well as a central and stable position of the head. We used the software application Presentation (NeuroBehavioural Systems, Albany, CA) for the presentation of the stimuli and recording of the behavioural response. The behavioural responses were recorded via a standard USB-computer keyboard and the participant always pressed the response button with the right hand.

## 7.7. Preprocessing

### 7.7.1. Eeg

Resting state EEG measurements were analysed offline using the FieldTrip toolbox (Oostenveld et al. 2011) as implemented in MATLAB (MathWorks). We segmented the EEG data into 5-second epochs, resulting in a frequency resolution of 0.2 Hz. Trials with an amplitude over time variance deviating more than 2 standard deviation from the mean were rejected and excluded from the subsequent analyses. Then, we ran a Fourier analysis using Hanning tapers to calculate the power spectra between 1 and 100 Hz per channel and participant. The IAF was computed by averaging the power values over time and all four occipitoparietal channels and identifying the peak frequency in the power spectrum between 7 and 13 Hz.

The proportion increase in alpha power lateralization (PIAL) served as a measure of the neural stimulation effect and was determined by subtracting the proportion increase in alpha power (PIA) in the right hemisphere from PIA in the left hemisphere. PIA was defined as follows

$$PIA : \frac{(\alpha_{\text{PO}} - \alpha_{\text{PR}})}{\alpha_{\text{PR}}} \times 100$$

in which alpha reflects the average of the individual alpha power in the frequency interval IAF-1 Hz to IAF + 1 Hz, for the pre (PR) and the

post-measurement (PO) respectively. For the post-measurement, we only analysed the first minute of the post-measurement to maximize entrainment effects. The proportion increase in power (PIP) and the proportion increase in power lateralization (PIPL) were calculated in the same way as PIA and PIAL respectively with the only difference that the frequency window for the analysis was not centred on the individual alpha frequency band but on the stimulation frequency. For the IAF and sham stimulation conditions, this means that we analysed the alpha power in the frequency window spanning from IAF-1 Hz to IAF + 1 Hz. For the IAF + 2 Hz and IAF -2Hz condition, we derived the power for a lower (IAF-3 Hz to IAF-1 Hz) and higher (IAF + 1 Hz to IAF + 3 Hz) frequency band respectively.

### 7.7.2. Spatial cueing task

For the spatial cueing task, we removed trials containing eye blinks and eye movements within a window of 100 ms before cue onset until stimulus onset exceeding 2° of visual angle (7% of all trials). For the analysis of the reaction time scores (RT) we excluded trials with an incorrect or missing response (10% of all trials) and with deviating RT scores, falling outside the median +/-1.5\*interquartile range (IQR) per stimulation condition and trial type (2% of all trials). Subsequently, we calculated accuracy and RT scores per condition. As the distribution of RT scores have shown to be skewed (Bono et al. 2017), we used the median as an indicator of the central tendency (McHugh and Hudson-Barr, 2003). As dependent variable for the analysis of the tACS effect on the spatial cueing task, we used the visuospatial attention bias score. For this, we subtracted the inverse efficiency score (RT/accuracy) (Townsend and Ashby 1978; Snodgrass et al. 1985) of right from left target location trials per condition. As speed and accuracy were equally emphasized in the task instructions, the inverse efficiency score was chosen over RTs scores to account for the RTs-accuracy trade-off (Heitz 2014). Taking this trade-off into account by using a summary measure is especially relevant in this cross-generational experiment as elderly participants tend to place more emphasis on accuracy than younger participants (SALTHOUSE 1979).

### 7.7.3. Detection task

To investigate the effects of tACS on the detection task performance, we calculated two different bias scores. The contrast threshold bias score was calculated by subtracting the threshold for left from right targets. For the computation of the bias in indicated target location, we analysed the bilateral target trials in which an incorrect response was given. Here, we subtracted the number of trials in which the participant mistakenly indicated that the target appeared on the right side from the number of trials in which (s)he indicated that it appeared on the left side.

### 7.7.4. Statistical analysis

Mixed model regression analysis, an increasingly popular statistical approach (Krueger and Tian 2004; Cnaan et al. 2005; McCulloch and Neuhaus 2015; Boisgontier and Cheval 2016), was used to analyse the EEG and behavioural data in SPSS. We performed a fixed effect analysis using a compound symmetry covariance structure. Hence, given the chosen parameters, the mixed model analysis comes down to a Repeated Measures ANOVAs. However, in contrast to an ANOVA (as implemented in SPSS), this mixed model analysis allows for inclusion of a continuous covariate with several values per participant. This can be useful to explain variability and, as follow-up on significant interaction effects with the continuous covariate, enables an analysis of an effect at different levels of the covariate (simple slope analysis). Another advantage of mixed model analysis is that the omission of observations due to outlier removal does not lead to exclusion of data on a subject level. Instead, only single cells are omitted, while the rest of the data is still included in the calculation of the regression equation. As follow-up analysis on significant main effects of stimulation condition, we performed planned comparisons between the sham and the active stimulation conditions as well as between the IAF and the control frequency



stimulation conditions. Holm bonferroni correction was used throughout to correct for multiple comparisons. For all correlational analyses and analyses including continuous covariates, values with a Cook's distance higher than one were identified as influential cases and therefore excluded from further analyses.

#### 7.7.5. Eeg

First, we determined the IAF test-retest reliability by calculating the IAF for each session and running an intraclass correlation on the IAF estimates. A Pearson correlation analysis was used to analyse the association between age and the mean IAF over all sessions. Furthermore, we tested whether the IAF was shifted towards the stimulation frequency by fitting a mixed model on the IAF change score ( $IAF_{\text{post-measurement}} - IAF_{\text{pre-measurement}}$ ) with stimulation condition as factor. For the analysis of the neural stimulation effect, we fit a mixed effect model with stimulation condition as factor and PIAL as dependent variable. As follow-up analysis on the full model, we conducted several pairwise comparisons. To find out which hemisphere drives the alpha power lateralization effect, we ran an additional analysis on the proportion increase in alpha power per hemifield using stimulation condition as factor.

#### 7.7.6. Spatial cueing task

We first analysed the cueing effect in the spatial cueing task by fitting a mixed model on the median RT scores of the sham condition using Type of Cue as a factor. Then we analysed the tACS effect on the visuospatial attention bias score. The endogenous task was implemented as a 4 (stimulation condition: IAF, IAF + 2 Hz, IAF-2 Hz, sham)  $\times$  3 (type of cue: valid, neutral, invalid) within-subject design. Mixed effect models were fitted on the visuospatial attention bias scores including stimulation condition and type of cue as factors and the electrophysiological entrainment effect PIAL as a covariate. As follow-up analysis on significant interaction effects with the covariate, we conducted simple slope analyses (Preacher et al. 2004, 2006). This analysis is comparable to a follow-up analysis on a significant interaction between categorical variables. However, in contrast to a categorical variable, the continuous covariate does not have distinct levels at which the follow-up test could be conducted. The simple slope analysis enables an estimation of the categorical condition effect (the stimulation effect) at different levels of the continuous covariate (PIAL) by running several regression models on transformed versions of the covariate, which are shifted with respect to their intercept. As a regression model including an interaction effect estimates the main effect of stimulation at the intercept level of the covariate (PIAL), the intercept transformation allows for the estimation of the stimulation effect at different levels of the covariate. We first determined the mean and standard deviation of the original covariate variable and subsequently calculated three new covariate variables:  $\alpha_{\text{low}}$ ,  $\alpha_{\text{mean}}$  and  $\alpha_{\text{high}}$  (with a low, intermediate and high intercept respectively).  $\alpha_{\text{mean}}$  is the centred version of the original covariate and was computed by subtracting the precalculated mean from each individual score.  $\alpha_{\text{low}}$  and  $\alpha_{\text{high}}$  were determined by adding or subtracting one precalculated standard deviation from each individual score of the centred covariate respectively (Preacher et al. 2004, 2006). Subsequently, three mixed effect models, one per new covariate, were fitted, using stimulation condition and type of cue as factor and visuospatial attention bias as dependent variable. Per stimulation condition, we omitted estimates (averages per condition combination) with a particularly low accuracy score ( $<55\%$ ) and excluded estimates based on an insufficient number of trials ( $<10$ ) per condition. As a result, 1.2% and 2.8% of the total amount of observations were deleted respectively. Furthermore, we ran linear regression analyses per stimulation condition with PIAL as predictor and visuospatial attention bias as dependent variable. As control analysis, we subsequently tested whether a model including age or the IAF as additional predictors is superior to a model with only PIAL as predictor. To this end, we ran mixed model analyses on the visuospatial attention bias score with and without the additional predictors and compared the fit of the different

models using log likelihood tests. One influential case with a Cook's distance above 1 was excluded.

#### 7.7.7. Detection task

The detection task was implemented as a within subject design with one factor (stimulation condition: IAF, IAF + 2 Hz, IAF-2 Hz, sham). We ran two mixed model analyses score using stimulation condition as factor and PIAL as covariate. For the first analysis we used the threshold bias and for the second analysis the bias in indicated target location as dependent variable. Estimates based on an accuracy below 40% or above 60% were omitted to guarantee comparable contrast thresholds.

#### 7.7.8. Differential effect of tACS on the two attention tasks

To directly test directly whether tACS differentially affected performance in the endogenous attention and the detection task, we ran an additional analysis on the z-score transformed attention bias scores of both tasks. For this, we first calculated the mean and standard deviation over all conditions per participant and task and subsequently used these estimates for the calculation of the z-score (score - mean/standard deviation). For the detection task, this was done separately for the threshold bias and the bias in indicated target location scores. Then we ran a mixed model analysis including the z-scores of both tasks as dependent variable, PIAL as covariate and stimulation condition and task type (endogenous attention task, detection task) as factors. In order to reach convergence of the statistical model, only the IAF and the sham condition could be included as stimulation condition. Two separate analyses were run for the threshold bias and the bias in indicated target location scores of the detection task.

#### 7.7.9. Blinding success

At the end of each session, participants filled in a questionnaire, which prompted the participants to evaluate whether real or sham stimulation was applied. To statistically verify that blinding was maintained, we fitted generalized linear equations on the rated stimulation conditions using the actual stimulation condition (IAF, IAF + 2 Hz, IAF-2 Hz, sham) as factor. The rated stimulation condition was assessed on an ordinal scale with seven levels ranging from 'I definitely experienced placebo/sham stimulation' to 'I definitely experienced real stimulation'. A chi square analysis was used to test whether the actual stimulation condition affected the rated stimulation condition.

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### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brainres.2022.147834>.

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