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Citation for published version (APA):

Riecke, L., Formisano, E., Herrmann, C. S., & Sack, A. T. (2015). 4-Hz Transcranial alternating current stimulation phase modulates hearing. *Brain stimulation*, 8(4), 777-783.
<https://doi.org/10.1016/j.brs.2015.04.004>

Document status and date:

Published: 25/04/2015

DOI:

[10.1016/j.brs.2015.04.004](https://doi.org/10.1016/j.brs.2015.04.004)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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4-Hz Transcranial Alternating Current Stimulation Phase Modulates Hearing

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ARTICLE INFO

Article history:

Received 20 January 2015

Received in revised form

10 March 2015

Accepted 16 April 2015

Available online 13 May 2015

Keywords:

tACS

Hearing

Oscillation

Entrainment

Auditory cortex

ABSTRACT

Background: Non-invasive brain stimulation with transcranial alternating currents (tACS) has been shown to entrain slow cortical oscillations and thereby influence various aspects of visual perception. Much less is known about its potential effects on auditory perception.

Objective: In the present study, we apply a novel variant that enables near-equivalent stimulation of both auditory cortices to investigate the causal role of the phase of 4-Hz cortical oscillations for auditory perception.

Methods: We measured detection performance for near-threshold auditory stimuli (4-Hz click trains) that were presented at various moments during ongoing tACS (two synchronous 4-Hz alternating currents applied transcranially to the two cerebral hemispheres).

Results: We found that changes in the relative timing of acoustic and electric stimulation cause corresponding perceptual changes that oscillate predominantly at the 4-Hz frequency of the electric stimulation, which is consistent with previous results based on 10-Hz tACS.

Conclusion: tACS at various frequencies can affect auditory perception. Together with converging previous results based on acoustic stimulation (rather than tACS), this finding implies that fundamental aspects of auditory cognition are mediated by the temporal coherence of sound-induced cortical activity with ongoing cortical oscillations at multiple time scales.

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Introduction

Periodic fluctuations between relatively depolarized and hyperpolarized neuronal states are ubiquitous throughout the brain and form the basis of neural oscillations [1,2]—a topic of ongoing interest in the cognitive neurosciences [3–6]. Several auditory studies found consistently that the phase of slow (0.5–12 Hz) spontaneous neural oscillations is coupled with neural excitability in the auditory cortex [7,8] as well as various auditory cognitive phenomena such as target detection [9–11], selective attention [12–17], and speech comprehension [18–20]. Complementary to

these correlational studies, few studies used a modulatory approach that allowed obtaining causal evidence for a functional role of the phase of slow cortical oscillations in auditory perception. Specifically three studies manipulated cortical oscillatory phase and tested the effects on auditory detection performance: Neuling et al. [21] applied transcranial alternating current stimulation (tACS) [22–24] at 10 Hz, and found that tone detection performance fluctuated along with the phase of the ongoing tACS. Henry et al. [25,26] applied auditory stimulation, not tACS, that was modulated periodically at 3 Hz or 5 Hz, and found consistently that gap detection performance fluctuated along with the phase of this ongoing auditory modulation. All three studies attributed the observed covariations between (electric or auditory) stimulation and perception to neural entrainment, i.e., phase alignment of cortical oscillations (at the frequency of the ongoing external stimulation) to the stimulation itself. In sum, the phase of cortical oscillations in the range of 3 Hz, 5 Hz, and 10 Hz seems to be crucial for auditory perception. It is still unclear whether such a causal link also holds for other frequencies.

This work was supported by Veni grant 451-11-014 to LR from the Netherlands Organization for Scientific Research. The authors declare no conflict of interest.

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Advantages of the modulatory approach over the correlational approach are that it allows drawing stronger theoretical inferences and possibly offers some practical benefits due to its potential to influence perception via neural entrainment. In fact, without prior neural entrainment to periodic stimulation, oscillatory phase-dependent modulations in auditory perception seem to be more difficult to obtain in human listeners [27,28]. Compared with ongoing auditory stimulation, tACS is arguably the preferred modulatory approach for auditory studies as it can be applied both in silence and at selected scalp position, thereby allowing experimenters to bypass the peripheral auditory system and entrain local spontaneous cortical oscillations while reducing possible confounding by auditory-evoked spiking activity [29–33]. The only auditory tACS study so far [21] targeted electric stimulation on the auditory cortices in the two cerebral hemispheres using bilateral electrodes placed above the ears. Unfortunately, the alternating currents induced with this approach flow in opposite directions in the two cortical hemispheres (from medial to lateral in one hemisphere vs. from lateral to medial in the other hemisphere). This asymmetry introduces an inter-hemispheric phase shift of 180° in bilateral structures, which may be detrimental especially to auditory perception considering that sound processing in the auditory cortices is normally associated with bilateral synchronous neural phase-locking (see e.g., Ref. [34]), except perhaps for spatially specific stimuli and tasks.

In the present study, we investigated whether the phase of tACS in the delta/theta range can modulate auditory perception. Frequencies in this range may serve several aspects of auditory perception and cortical processing: Firstly, delta/theta amplitude fluctuations in speech signals are critical for speech comprehension [35] and can entrain auditory cortical oscillations in human cortex [15,16,18,19,36]. Secondly, these frequencies constitute dominant spectral components of auditory-evoked cortical potentials (e.g., Ref. [37]). Finally, sounds modulated at these frequencies are highly effective in exciting neurons in the middle superior temporal gyrus and lateral Heschl's gyrus in both cerebral hemispheres [38]—thus these bilateral auditory cortical regions were chosen as target regions in the present study. We specifically chose 4 Hz because it is well separated from and harmonically unrelated to the previously explored 10-Hz frequency in the alpha range [21].

To avoid inter-hemispheric phase shifts, we used a novel bilateral dual-channel variant of tACS that allows applying near-equivalent (in terms of both phase and intensity) electric stimulation to bilateral homolog structures. Using this approach, we sought to induce neural entrainment at matched 4-Hz oscillatory phases in the bilateral auditory cortical target regions and directly tested our hypothesis that the phase of experimentally-entrained delta/theta oscillations would modulate auditory perception. We assessed the effect of the oscillatory phase on auditory perception by measuring human listeners' detection performance for near-threshold auditory stimuli presented at various moments (phase angles) within the ongoing oscillatory tACS [21]. We expected that tACS would entrain neural oscillations in the target regions and hypothesized that this would influence auditory perception such that performance for auditory stimuli presented at phase angles within one tACS half-cycle would differ significantly from performance at phase angles spanning the opposite half-cycle. In line with this hypothesis, the results indeed show that performance varied significantly across tACS half-cycles. A spectral analysis corroborates the notion that this effect on perception takes the form of an oscillation predominantly at the applied 4-Hz tACS frequency.

Material and methods

Participants

Fourteen paid volunteers (seven females, ages: 22–38 years) participated in the study. They reported no history of neurological, psychiatric, or hearing disorders, were suited to undergo non-invasive brain stimulation as assessed by prior screening, and gave their written informed consent before taking part. They had normal hearing (defined as hearing thresholds of less than 25 dB HL at 250, 500, 750, 1000, 1500, 3000, and 4000 Hz), except for one participant who had mild hearing loss in the left ear for the two highest frequencies. Excluding the data of this participant from the analyses did not alter the conclusions of the study.

Acoustic stimulation

Auditory stimuli were comprised of repetitive acoustic pulses. When presented sufficiently loud, such click trains can evoke excitation patterns along the cochleotopic axis that are more widespread and possibly more strictly phase-locked than those evoked by tones, due to their broader spectra and more concise temporal structure, rendering them suitable for studying temporal processing in the auditory system in the absence of a clear pitch percept [39]. In the present study, a train of four clicks presented at the same rate as tACS (4 Hz, see next section) was used. While single clicks or tones might have been suitable as well, these repetitive clicks were deemed a more effective probe for phase-dependent auditory perception, because they may allow detecting the overall sound by perceptually tracking its amplitude envelope; i.e., based on *multiple* perceptual snapshots and the additional overall temporal pattern that may arise from these snapshots. The repetition rate of the clicks was chosen to match specifically the tACS frequency to ensure that acoustic and electric stimuli would share a common amplitude envelope; i.e., the putative snapshots would be sampled at the same phase angle on consecutive tACS cycles. To reduce the potential of individual clicks to evoke neural responses that could possibly reset the neural oscillatory phase, the sound level was set individually to a low value near click detection threshold (see below, *Procedure* section). The click train was generated by summing all harmonics of a 4-Hz fundamental frequency within the range from 112 to 3976 Hz. The starting phase and amplitude of the sinusoidal harmonics were fixed, thus the resulting sound waveform resembled a periodic sequence pulsating at the fundamental frequency of 4 Hz. The waveform was bandpass-filtered between 224 and 1988 Hz (3 dB cutoff frequencies, fourth-order Butterworth filter with zero phase shift). The portion between 125 and 1125 ms was extracted to obtain a train of four clicks centered on a 1-s interval. The auditory stimuli were presented diotically via a high-fidelity soundcard (Focusrite Forte) and insert earphones (EARTone 3A).

Electric stimulation

Figure 1 schematizes the applied tACS approach. Square rubber electrodes were attached to the scalp with conductive gel at positions defined by the International 10–20 system. The stimulation electrodes (size: 5×5 cm) were placed over the temporal cortices (centered on positions T7 and T8), whereas the return electrodes (size: 5×7 cm) were placed symmetrically to the left and right side of the midline (respectively) so that their long sides were centered on the vertex (position Cz) and bordering each other. This configuration was chosen to produce relatively strong currents in the target

Figure 1. Stimulation setup. Schematic of the dual-channel tACS approach. A 4-Hz sinusoid was generated digitally and transmitted through a digital-to-analog converter (DAC). The DAC output was split and fed into two coupled tACS systems. The two 5×5 cm stimulation electrodes were placed above the left and right temporal cortex at scalp position T7 and T8 respectively. The two 5×7 cm return electrodes were placed symmetrically to each so that their long sides were centered next to each other on scalp position Cz (white dot). The return electrodes were coupled to create two near-equivalent electric circuits. Analogously, audio and trigger signals were generated digitally and fed via the DAC into a stereo soundcard and a PC (used for visual stimulation and behavioral response collection) respectively.

auditory cortical regions (see [Introduction](#) section), as suggested by prior electric field simulations on a standard head model using the Matlab toolbox COMETS [40]. A sinusoidal current with fixed starting phase was applied to each circuit using two battery-operated stimulator systems (Neuroconn, Ilmenau, Germany), similar to previous two-channel approaches based on direct currents (e.g., Ref. [41]). The frequency of the current matched the rate of the clicks, i.e., 4 Hz, as explained in the previous section and the [Introduction](#) section. To create two approximately equivalent circuits, the stimulators were driven with identical waveforms (see next section), the return electrodes were coupled, and the skin was prepared so that the impedances of the left-lateralized and right-lateralized circuit were matched while keeping the net impedance below 10 k Ω . TACS intensity was set individually near detection threshold by reducing current peak amplitude simultaneously for both circuits in 0.1-mA steps from 1 mA to the point where participants reported feeling comfortable or uncertain about the presence of tACS under every electrode (on average 0.8 ± 0.1 mA, mean $\pm$ SD across participants). As a consequence, current density did not exceed 0.04 or 0.0286 mA/cm² for the stimulation electrodes and return electrodes respectively. In each repetition of the experiment (hereafter referred to as ‘run’), current amplitude was ramped up over the first 10 s of the run using raised-cosine ramps during which no trial was presented. For runs comprising sham stimulation (described below, see [Experimental Design and Task](#) section), this onset ramp was followed by an additional offset ramp lasting 60 s (or 30 s for the first four participants). Ramps at the end of the run were flipped, i.e., they followed the reverse trajectory.

Synchronization of acoustic and electric stimulation

Prior to the experiment, three waveforms were generated digitally and individually for each run (sampling rate: 16 kHz) to define the acoustic stimulation, the electric stimulation, and the onsets of experimental trials (trial triggers) within the entire run, respectively. During the experiment, each of these waveforms was continuously fed in chunks into a separate channel of a common digital-to-analog converter (National Instruments) operated by LabView software. The outputs of the two ‘stimulation channels’ were further split and fed into stimulation devices (stereo soundcard and two tACS systems; see previous two sections). The ‘trigger channel’ output was fed into a PC on which Presentation software was running to control visual stimulation and button response acquisition.

Experimental design and task

Figure 2A illustrates the experimental design. The relative timing of acoustic and electric stimulation was manipulated in six conditions by varying the onset of the click train, together with the trial trigger, in six steps of 41.7 ms (30°) across one 4-Hz period of the ongoing tACS (i.e., relative to the current tACS phase angle). For simplicity we hereafter refer to this parameter as ‘phase’. **Figure 2B** illustrates the task, trial design, and stimulus protocols. Auditory perception was assessed based on click detection performance in a two-interval two-alternative forced choice task. This task was chosen because it is less prone to induce fluctuations in perceivers’ strategies (i.e., response bias) than more criterion-dependent yes/no tasks used in the related previous modulatory studies (see [Introduction](#) section). Two gray digits (1 and 2) were shown continuously on the screen. Each digit occupied a visual angle of approximately 1° that was slightly enlarged for 1 s to indicate one of two consecutive observation intervals. To reduce the likelihood that this visual change would reset neural oscillatory phase, it was chosen to be small (approximately 0.2°) while still being sufficiently detectable. The click train was presented in one of these intervals (selected at random with equal probability), whereas the other interval contained only silence. The participant’s task was to indicate which of the two intervals contained the clicks by pressing one of two buttons during the response interval, which was indicated after the second observation interval by the digits changing color to white for 1.5 s. Upon button press, feedback on response correctness was provided by green or red color for the remainder of the trial, whereas upon no button press, pink color was presented for 0.5 s. Trials were separated by rest intervals lasting on average 1.5 s; due to the phase manipulation, the exact duration depended on which phase condition was presented on the subsequent trial. To ensure that visual stimuli (i.e., size and color changes) were not predictive for click onset timing, their timing relative to the click

Figure 2. Experimental design. Panel A sketches the experimental conditions. Each trial contained four clicks (see four black bars within each row) presented during and at the same frequency as tACS (gray waves). Six phase conditions (corresponding to the six rows) were created by varying the timing of the clicks relative to the tACS phase angle. Panel B illustrates two consecutive trials of the two-interval two-alternative forced choice task. The first three rows sketch visual (screen), electric (tACS), and auditory (clicks) stimulation respectively, and the fourth row exemplifies listeners’ behavior (correct response on first trial, incorrect response on second trial). Blue vertical lines indicate trial onsets/triggers. Inter-trial interval duration and onset of visual stimulation were jittered across trials (not shown in Figure; see main text). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

train was jittered across trials. This was achieved by shifting collectively all visual stimuli within the trial by a delay drawn randomly without replacement from a uniform $[-118.1; 118.1]$ ms distribution; thus each trial from a given condition within a run was associated with a slightly different timing of the visual stimuli relative to the trial trigger/click train. In each run of the experiment, 18 trials per condition were presented in random order (total duration: approx. 9.9 min). In total, four tACS runs and one run comprising sham stimulation were presented (for details, see next section), thus 72 trials were obtained for each of the six tACS phase conditions. Subjects were blinded for stimulation conditions (tACS phase, sham). Runs comprising sham stimulation were identical to tACS runs, except that they involved no electric stimulation beyond the on/off ramps (see above, *Electric Stimulation* section). The sham stimulation runs served to provide a control measure of auditory performance (baseline).

Procedure

The experimental procedures were approved by the local ethics committee of the Faculty of Psychology and Neuroscience of Maastricht University (*Ethische Commissie Psychologie*) and involved the following steps: First, the participant was seated in a comfortable chair in a sound-attenuating booth. Second, pure tone audiometry was conducted. Third, electrodes were attached to the participant's head (see above, *Electric Stimulation* section) and task instructions were provided. Fourth, click detection thresholds were measured with an adaptive staircase procedure [42] and used for the subsequent training and experiment. Fifth, task training was conducted for approximately 10 min until the participant felt confident that s/he could perform the task well; these steps were conducted without tACS. Sixth, tACS threshold was estimated (see above, *Electric Stimulation* section) and used for the subsequent experiment. Seventh, five runs of the experiment, including a randomly positioned sham run, were conducted with short breaks in between runs. Finally, during debriefing, participants were asked to provide a percentage for each run quantifying their confidence that they received no tACS.

Exploratory analyses of the sham run data from participants 1–4 suggested that the performance level that was targeted by the

auditory threshold procedure (70.7%) could not be reproduced well in the context of the main experiment (average difference: 7.2%) [43]. Therefore, for participants 5–14, the fourth step was integrated with the fifth step: sound level was adjusted step-wise during task training to the point where the participant reported being uncertain about the presence of the clicks, which was then taken as threshold.

Data analysis

Trials containing no button response ($1.3 \pm 2.5\%$ of all trials, mean $\pm$ SD across participants) and trials presented during the tACS ramps in the sham run were discarded from the data analysis. Data from tACS runs were concatenated and then the proportion of correct responses was extracted for each phase condition (Fig. 2A). From the resulting accuracies, a time series (six phases spanning a 4-Hz cycle) was reconstructed. The phase for which auditory performance is best may vary across individuals due to individual differences in anatomy, i.e., in the relative orientations of stimulated tissue and current flow. To compensate for such possible inter-individual variations in best phase, the maximum of the reconstructed series was aligned to the 90°-point and the series was phase-wrapped [10,44]. Following this phase alignment—under our hypothesis that oscillatory phase modulates perception specifically at the applied 4 Hz-tACS frequency—phases 30°–150° should delimit the positive half-wave of a 4-Hz oscillation, whereas phases 210°–330° should delimit the negative half-wave. To test this prediction, accuracies were averaged across the hypothesized positive half-wave (phases 30° and 150°) and across the hypothesized negative half-wave (phases 210°, 270°, and 330°) (Fig. 3A, dark and light gray-filled circles), and then the two resulting averages were statistically compared. Importantly, to avoid non-independency in the data, the 90°-point was excluded from this analysis, as it necessarily represented the maximum of the time series due to the best-phase alignment.

To test whether the hypothesized phase effect oscillated specifically at 4 Hz, spectral density was computed from the time series using the Fast Fourier transform, and then the magnitudes of the individual frequency components were statistically compared. The 90°-point could be included in this spectral analysis without

Figure 3. Results. Panel A shows auditory detection performance (mean $\pm$ s.e.m. across 14 participants) as a function of phase, after aligning listeners' best performance to the 90°-point (unfilled circle). The obtained series (black curve) matched well the overall shape of the sinusoidal tACS (gray curve). The flat line indicates listeners' baseline performance obtained during sham stimulation. Panel B shows the same curves as panel A, but for the six most representative individuals. Panel C shows average performance (mean $\pm$ s.e.m. across 14 participants) for the positive (+) and negative (–) half-wave of the hypothesized 4-Hz oscillation (dark gray and middle gray bar respectively; see corresponding circle fillings in panel A for reference) and baseline (sham stimulation, light gray bar). Performance during the positive half-wave was significantly better than during the negative half-wave, whereas baseline performance was intermediate. Panel D shows in black the magnitude spectrum (mean $\pm$ s.e.m. across 14 participants) obtained from frequency analysis of the individual series (see black curves in panel B, for examples). Overall, magnitude differed significantly across the frequency components, and the component corresponding to the tACS frequency exhibited the maximum. For reference, the light gray curve shows the magnitude spectrum of the group average series (black curve in panel A). Asterisks indicate P -values below 0.02.

inducing non-independency in the data, as the magnitude spectrum is unaffected by phase wrapping. In general, the frequencies of the oscillatory components that can be resolved with this analysis and their spacing are limited by the sampling rate and the number of data points respectively. The present data contained six points spanning a cycle of a 4-Hz fundamental, which corresponds to a sampling rate of 24 Hz and allows resolving the first three harmonics (4 Hz, 8 Hz, and 12 Hz).

Baseline performance was defined as the overall accuracy during the sham run, i.e., the average of all sham phase conditions. Participants' ability to identify sham stimulation was assessed by comparing their maximum confidence rating of the tACS runs with their rating of the actual sham run.

All measures described above were obtained from each subject and then submitted to second-level (random-effects) group analyses using parametric statistical tests (ANOVA and paired *t*-test). Distributions of the aforementioned measures did not differ significantly from normality as verified with Kolmogorov–Smirnov tests (all $P > 0.51$). A significance criterion $\alpha = 0.05$ was used and type-I error probabilities inflated by multiple comparisons were corrected by controlling the false-discovery rate [45].

Results

Figure 3A and B shows listeners' detection performance as a function of phase, for the group average and the six most representative individuals, respectively. As shown also by Fig. 3C, average performance was above baseline during the hypothesized positive 4-Hz half-wave (30° , 150°), whereas it was below baseline during the hypothesized negative 4-Hz half-wave (210° – 330°). Furthermore, performance was similar at 30° and 150° , and at 210° and 330° respectively, i.e., it was approximately symmetric with respect to the phase for which performance was best (90°). Performance at the best phase (90°) was on average $7.8 \pm 4.3\%$ better than at the opposite phase (270°) and $7.5 \pm 7.6\%$ better than baseline (mean $\pm$ s.e.m. across participants). Although on average the best performance (90°) and worst performance (210° , see Fig. 3A) were not associated with exactly opposite phases—suggesting the contribution of higher harmonics (see next paragraph)—these observations match well the characteristics of the hypothesized 4-Hz sinusoidal oscillation. This notion was confirmed by statistical analysis revealing an effect of tACS polarity on performance (positive vs. negative half-wave: $t(13) = 2.48$, corrected $P = 0.042$); thus the phase of tACS modulated listeners' auditory perception. Comparison with baseline revealed no effect (positive half-wave vs. baseline: $t(13) = 0.72$, corrected $P = 0.37$; negative half-wave vs. baseline: $t(13) = -0.32$, corrected $P = 0.38$). As explained in Data Analysis section, the 90° -point was excluded from the aforementioned statistical analyses. Balancing the number of data points by excluding also the 270° -point did not alter qualitatively the results.

The magnitude spectrum of the time series is shown in Fig. 3D to emphasize that the phase effect took the form of an oscillation predominantly at the tACS frequency. Magnitude peaked at the component corresponding to the tACS frequency and decreased monotonically at higher frequencies. While the higher harmonics (8 and 12 Hz) could explain a significant proportion of the overall variance in the time series [31], the bulk of this variance was explained by a 4-Hz sinusoid. This observation was supported by a one-way ANOVA including frequency (4 Hz, 8 Hz, 12 Hz) as factor, which revealed a main effect of frequency on spectral magnitude ($F(2,26) = 3.93$, $P = 0.032$). Post hoc tests further showed that the 4-Hz component was significantly stronger than the 12-Hz component ($t(13) = 2.65$, corrected $P = 0.020$) but not the 8-Hz component ($t(13) = 0.70$, corrected $P = 0.25$).

For control, analogous analyses were applied to the sham run data, which did not replicate the relevant tACS results above: there was no effect of sham stimulation polarity on performance ($t(13) = -1.29$, $P = 0.89$), no spectral peak at 4 Hz, and no main effect of frequency on spectral magnitude ($F(2,26) = 1.64$, $P = 0.21$). A two-way ANOVA on performance, including stimulus type (tACS or sham) and stimulation polarity (positive or negative half-wave) as factors, revealed a significant type $\times$ polarity interaction ($F(1,13) = 5.58$, $P = 0.034$). In contrast, a two-way ANOVA on spectral magnitude, including stimulus type (tACS or sham) and frequency (4 Hz, 8 Hz, 12 Hz) as factors, revealed no significant type $\times$ frequency interaction ($F(2,26) = 1.02$, $P = 0.38$). With the cautionary remark that tACS trials outnumbered sham trials by a factor of four, these outcomes show that the observed phase effect was related indeed specifically to tACS, whereas the specificity of the observed frequency effect remains uncertain. They further suggest that tACS effects did not carry over to the sham run.

Analysis of subjective tACS ratings further revealed that participants considered a tACS run, rather than the sham run, as the most likely run to contain no tACS (confidence ratings: $43.6 \pm 8.9\%$ and $36.1 \pm 10.5\%$ respectively, mean $\pm$ s.e.m. across participants). Thus, participants were unable to discriminate reliably between the absence and presence of tACS.

Discussion

We obtained an effect of the phase of 4-Hz tACS on auditory perception for near-threshold auditory stimuli: detection performance was significantly better at phase angles during half of the 4-Hz cycle than at phase angles during the opposite half-cycle. Performance without tACS was intermediate, but did not differ reliably from performance during tACS. Importantly, the overall pattern of the oscillatory phase-induced effect paralleled an oscillation predominantly at the tACS frequency: although the effect was not strictly frequency-specific (i.e., it was not restricted to the tACS frequency alone), most of the tACS phase-induced variance could be explained by a 4-Hz sinusoid rather than by higher harmonics, whereas sham data revealed no such frequency effect. In sum, these results provide evidence for a causal effect of 4-Hz tACS phase on auditory perception.

Although our data provide no direct measure of neural activity, there exists sufficient evidence from electrophysiology studies to imply that the obtained effect was mediated by slow cortical oscillations. Most likely, our 4-Hz tACS entrained slow auditory cortical oscillations [29–32], which then caused neural signals induced by the 4-Hz click train to arrive during relatively depolarized (or hyperpolarized) neuronal states so that these signals could trigger spike trains (or no spike trains) [7] and thereby produce click percepts (or no percept, respectively) [10,21,25,26]. According to this reasoning, our results indicate that 4-Hz tACS may entrain ongoing 4-Hz oscillations presumably in auditory cortex, and that the phase of these cortical oscillations may render sounds that are temporally coherent with the tACS more audible. This interpretation is in line with entrainment studies showing similar slow oscillatory phase-dependence in visual perception [46–49] and the more general view that slow neural oscillations facilitate perception to operate in a periodic manner (i.e., by sampling the environment as a sequence of perceptually relevant snapshots) rather than a continuous mode [3,27].

Together with previous 10-Hz tACS results [21], the present 4-Hz results indicate that tACS at frequencies within both the delta/theta range and alpha range can modulate the perception of near-threshold sounds. This converges with results from studies that used 3-Hz or 5-Hz auditory stimulation for neural entrainment and assessed auditory gap detection [25,26]. Noteworthy, we also

observed weaker significant perceptual modulations at higher harmonics of the tACS frequency. Based on modeling studies on network resonance dynamics [31], it is conceivable that the periodic electric force generated by tACS excites local cortical oscillations at multiple harmonics of the tACS frequency, with higher harmonics experiencing less reliable force (i.e., on a smaller proportion of cycles). However, such statements about harmonic neural entrainment and frequency-specificity remain uncertain in the present study due the inevitably limited frequency resolution of our spectral analysis. In sum, the existing findings constitute converging evidence that fundamental aspects of auditory cognition are mediated by the temporal coherence of sound-induced cortical activity with ongoing cortical oscillations at multiple time scales (delta, theta, and alpha bands). These neural oscillatory patterns could play a generic role for parsing temporal patterns in the auditory environment.

Compared with the previous auditory tACS study [21], the present study builds on more rigorous methods including homophasic bilateral tACS, a criterion-free task that does not encourage off-frequency listening [50], and an analysis of unfitted data from single tACS sessions. A direct comparison of effect sizes across the studies is hampered by several differences including the different measures of interest (present study: accuracy; [21]: detection threshold). Future studies may identify more systematically which stimulation setup and modality (single or dual channel; electric or acoustic) and which stimulation frequency (e.g., Ref. [26]: 3 Hz; Ref. [25]: 3.1 Hz and 5.075 Hz; Ref. [21]: 10 Hz; present study: 4 Hz) are most effective. Our novel tACS approach may prove useful for future studies of other cognitive phenomena that also depend on homophasic oscillatory activity in bilateral brain structures.

Our observation of improved hearing during opposite half-cycles of tACS suggests that tACS can essentially enhance the loudness of acoustic rhythms that are temporally coherent with it. This would have interesting implications for various auditory scene analysis problems that depend on the relative salience of concurrent sounds [51]; for example, when listening selectively to a particular instrument in an ensemble. While acoustically-induced neural entrainment relies on the intactness of the peripheral auditory system, it remains to be investigated whether tACS has potential to act as a non-invasive cortical hearing aid. Our data indicate a statistically non-significant trend toward a perceptual benefit of tACS compared with sham stimulation. As proposed above, this may encourage follow-up studies to optimize tACS parameters (frequency, electrode positions) on an individual basis (e.g., by identifying dominant ongoing EEG frequencies [31,52]) and obtaining a realistic anatomical head model a priori (e.g., Ref. [53]) in order to maximize this possible benefit.

Acknowledgments

We thank Charlie Bonnemayer and Sanne ten Oever for help with methods and Anne Bierbrauer for help with data acquisition.

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