


Lacking Effects of Envelope Transcranial Alternating Current Stimulation Indicate the Need to Revise Envelope Transcranial Alternating Current Stimulation Methods

Neuroscience Insights
Volume 15: 1–11
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2633105520936623



Jules Erkens¹ , Michael Schulte², Matthias Vormann²
and Christoph S Herrmann^{1,3}

¹Experimental Psychology Lab, Department of Psychology, Cluster of Excellence 'Hearing4All', European Medical School, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany.

²Hörzentrum Oldenburg GmbH, Oldenburg, Germany. ³Research Center Neurosensory Science, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany.

ABSTRACT: In recent years, several studies have reported beneficial effects of transcranial alternating current stimulation (tACS) in experiments regarding sound and speech perception. A new development in this field is envelope-tACS: The goal of this method is to improve cortical entrainment to the speech signal by stimulating with a waveform based on the speech envelope. One challenge of this stimulation method is timing; the electrical stimulation needs to be phase-aligned with the naturally occurring cortical entrainment to the auditory stimuli. Due to individual differences in anatomy and processing speed, the optimal time-lag between presentation of sound and applying envelope-tACS varies between participants. To better investigate the effects of envelope-tACS, we performed a speech comprehension task with a larger amount of time-lags than previous experiments, as well as an equal amount of sham conditions. No significant difference between optimal stimulation time-lag condition and best sham condition was found. Further investigation of the data revealed a significant difference between the positive and negative half-cycles of the stimulation conditions but not for sham. However, we also found a significant learning effect over the course of the experiment which was of comparable size to the effects of envelope-tACS found in previous auditory tACS studies. In this article, we discuss possible explanations for why our findings did not match up with those of previous studies and the issues that come with researching and developing envelope-tACS.

KEYWORDS: Cortical entrainment, speech perception, speech envelope, transcranial electric stimulation

RECEIVED: March 6, 2020. **ACCEPTED:** May 28, 2020.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was part of the mEEG4HStim project and funded by the BMBF grant (grant no. V51KM035).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C.S.H. has filed a patent for the method of envelope-tACS. C.S.H. received honoraria as editors from Elsevier Publishers, Amsterdam.

CORRESPONDING AUTHOR: Jules Erkens, Experimental Psychology Lab, Department of Psychology, Cluster of Excellence 'Hearing4All', European Medical School, Carl von Ossietzky University of Oldenburg, Ammerländer Heerstraße, 114-118, 26131 Oldenburg, Germany. Email: jules.erkens@uni-oldenburg.de

Introduction

Speech perception is the process of discerning an auditory stimulus as speech, and linking the combinations of sounds to their linguistic meaning.¹ Neural oscillations have been shown to play a crucial role in this process; natural speech consists of a band of multiple frequencies. Very important for the comprehension of speech is the frequency range of 1-10 Hz,^{1,2} where we can find the speech envelope or temporal envelope. When presented with a pseudo-rhythmic stimulus like speech, neural oscillations match up in phase and frequency of the stimulus with a process called cortical entrainment.³⁻⁶ It is believed this cortical entrainment to the envelope tracks acoustic properties of attended speech.^{7,8} Several studies have shown the relation between entrainment and speech processing, using electroencephalography (EEG),^{9,10} magnetoencephalography (MEG),¹¹⁻¹³ and electrocorticography (ECoG).¹⁴ Single-cell studies in animals have shown phase-locking to temporal envelopes of nonspeech sounds.¹⁵ In patients with auditory neuropathy, an affliction that weakens the transmission of temporal information in sounds that weakens entrainment, speech comprehension is reduced while recognition of other sounds is left mostly intact.¹⁶

Transcranial alternating current stimulation (tACS)^{17,18} has been useful in research regarding cortical entrainment. Using a sinusoidal current, tACS can enhance the naturally occurring oscillations of the cortex, decreasing or increasing neural firing depending on the polarity of the stimulation.¹⁷⁻¹⁹ In particular, the immediate effects and sustained after effects of tACS on alpha activity have been well established.²⁰⁻²⁴ In auditory research, tACS has been useful in making causal connections between brain activity and the hearing process; where brain recording methods can only infer correlation between neural entrainment and cognitive processes,²⁵ tACS makes it possible to infer causal links between the 2 by enhancing or disrupting entrainment to a certain frequency.^{26,27} Using these methods, evidence has been found that neural entrainment plays an active role in speech perception, instead of merely being a result of it.²⁸⁻³⁴ Using tACS, perception of auditory stimuli can be altered³⁵ (Neuling et al, 2012)²⁶ or improved^{28,29} depending on the phase of the stimulation. The effects tACS has on neural processing has potential to be used in the medical field; although the use of tACS for medical application is still very new, there have been results for tACS as treatment for auditory



hallucinations in schizophrenic patients^{36,37} and attention deficit hyperactivity disorder (ADHD).³⁸

A new method dubbed envelope-tACS^{28,29} has shown results in improving speech perception by electrically stimulating the envelope of a targeted speech stimulus. By subthreshold enhancing neural excitability in phase with the speech envelope, entrainment to the stimulus could potentially be strengthened. Significant results with these methods are of importance, as they reveal new possibilities for the usage of transcranial electrical stimulation (TES) methods; where previous methods used continuous stimulation patterns like alternating current (tACS)³⁹ or transcranial direct current stimulation (tDCS),⁴⁰ inducing entrainment with envelope-tACS involves more complex waveforms consisting of multiple frequencies with a concise beginning and end, as opposed to a continuous cyclical signal. Envelope-tACS could potentially be used as a hearing aid,^{41,42} as by directly influencing the neural processing of sound, it could alleviate hearing fatigue, a common complaint of conventional hearing aid users.^{30,34,43,44} Furthermore, hearing aid users commonly report that their hearing aid helps little or is even detrimental in difficult hearing situations, like social activities with multiple simultaneous speakers.⁴⁵ As conventional hearing aids can only support the processing of speech up to the cochlear level, degradation of processing beyond that point is not alleviated. This ‘cortical hearing loss’ is a well-established effect of natural aging, where cognitive decline reduces patients’ ability to compensate for acoustic degradation.⁴⁶⁻⁴⁹ These effects are most apparent when separating speech from background noise.⁵⁰⁻⁵² Finally, EEG studies show a change in cortical entrainment to auditory stimuli in the elderly.⁵³⁻⁵⁵ Using a brain-computer interface to measure the attended stream of sound using EEG, envelope-tACS could enhance entrainment to an attended speech stimulus by stimulating with the corresponding speech envelope.

For tACS to have a positive effect on perception, the phase of the electrical stimulation has to be temporally aligned with the targeted stimuli. Because of individual differences in anatomy and processing speed between participants,^{30,56,57} multiple experimental conditions using different latencies between stimulus presentation and electrical stimulation phase have to be used, to probe for which stimulus-stimulation latency (or time-lag) is optimal. In the case of sinusoidal stimulation, the goal is to stimulate in phase with the entrainment to a sound stimulus, enhancing entrainment. In the case of envelope-tACS,³⁰ entrainment is targeted to a specific critical frequency, the syllable rate (Figure 1).

Having to measure multiple time-lags between sound presentation and stimulation set down technical and ethical limitations to experimental design; to find the optimal effects of envelope-tACS, the time-lag should be as close as possible to the time it takes for the signal to be processed in the brain. However, the amount of different time-lags that can be measured is limited by the maximum duration of stimulation a

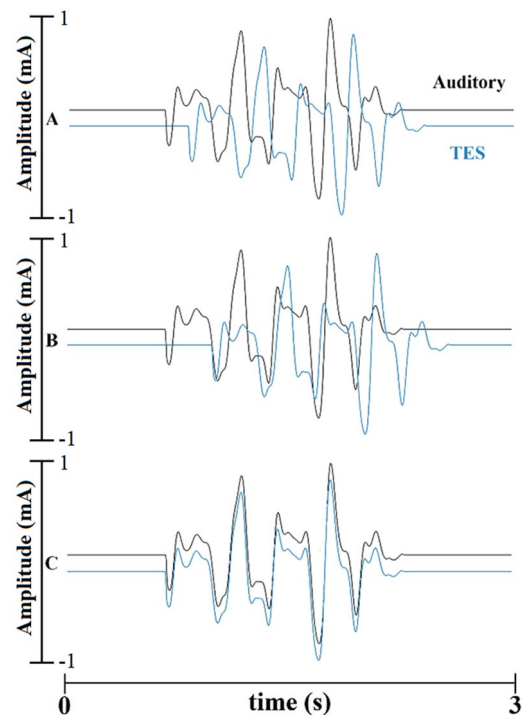


Figure 1. Synchronization of auditory signal and electrical stimulation on the cortex. (A) When electrical stimulation arrives out of phase with the cortical activity caused by the auditory stimulus, entrainment to the speech envelope is disrupted and performance should decrease. (B) When synchronization is off by a multiple of a full phase of the carrier frequency, excitation still coincides with the auditory signal, and performance should improve. However, entrainment to higher frequencies might not be optimal. (C) When envelope-tACS is temporally aligned with the cortical signal in its entirety, speech entrainment is fully enhanced and the performance enhancing effects of envelope-tACS should be at its strongest. tACS indicates transcranial alternating current stimulation; TES, transcranial electrical stimulation.

participant is allowed to receive per day. Furthermore, selecting the optimal time-lag based on a participants’ performance and then evaluating the effect of envelope-tACS based on that performance quickly turns into circular analysis or ‘double dipping’.⁵⁸ Previous envelope-tACS studies have circumvented these issues by investigating the phasic effects of envelope-tACS, showing the sinusoidal performance changes caused by envelope-tACS³² or comparing performance of the conditions that are close to the optimal time-lag to those that should be close to antiphase.^{28,29} Although these studies provide evidence that there is a beneficial effect of envelope-tACS, it is difficult to assess how large the effect of envelope-tACS actually can be, given an as-close-as-possible phase alignment between the stimulation waveform and the neural signal. In this study, we set out to discover more about the potentially positive effects of envelope-tACS, using a larger amount of time-lags with smaller intermediate steps to find a more close to optimal time-lag. Furthermore, an expansive control condition was used to be able to say more about the effects of envelope-tACS, without the issues of circular analysis.

Materials and Methods

Participants

Thirty-two participants (16 female, mean age 24, age range: 20–31) took part in the study. All participants were native German speakers, had normal hearing, and were right-handed according to the Edinburgh Handedness Scale.⁵⁹ Participants were given written explanation of the methods used during the tests, an informed consent form, and a questionnaire assessing exclusion criteria for electrical stimulation. At the end of the experiment, participants filled in a form regarding side-effects of the stimulation.^{60,61} and received monetary compensation. Out of 30 participants, 24 felt they had received electrical stimulation, whereas the remaining 6 claimed to have received no stimulation.

Procedure

The experiment was approved by the ethics committee of the University of Oldenburg. Participants were given a written explanation regarding the methods used in the experiment. They then filled out an informed consent form, as well as a questionnaire regarding exclusion criteria for TES. Electrodes were attached to the head as described by Baltus et al.⁶² Marks on the head were made at electrode locations FC5, FC6, P7, and P8 according to the international 10–20 system. These electrode locations were chosen to optimally stimulate the desired regions.^{62–64} On each of the 4 locations, 2.5-cm diameter round rubber TES electrodes were placed using Ten20 Conductive paste (Weaver and company Aurora, USA). Once the electrodes had been prepared, the participant was seated in a dimly lit, electrically shielded, and sound attenuated booth.

Oldenburg sentence task

After preparation of the electrodes, participants were instructed about the Oldenburg sentence task (OLSa).⁶⁵ They were presented with grammatically correct German sentences of 5 words, together with noise at different signal-to-noise ratios (SNRs). Participants had to orally repeat as many words as possible; the order in which they repeated the words did not have to match the presentation order, and they were encouraged to guess. Eighteen blocks of 20 sentences each were presented, starting with 2 practice blocks. Each block had a duration of approximately 5 minutes, for a total of 80 minutes. After every 6 blocks, there was a short break.

Sound stimuli were generated using a Fireface 802 sound-card (RME, Germany) at a sampling rate of 44100 Hz. All sound was played over a single speaker (JBL Control 1 Pro) standing upright in front of the participant, at a 95 cm distance from the centre of the head. An adaptive procedure was performed to adjust SNRs as described by Brand and Kollmeier.⁶⁶ The target sentences and background noise were both initially presented at 65 dB SPL (each block started at 65 dB SPL

regardless of performance in the previous block). Participants were scored during the task on a scale from 0 to 5 depending on how many words they repeated correctly; the volume of sequential sentences was altered depending on their score on the previous trial, while the volume of the background noise stayed constant. Using a staircase procedure, the task difficulty was modified in this manner to approach a 50% performance rate over the course of the block; the final SNR between the sentence and the background noise at the end of the block was then saved as the speech comprehension threshold (SCT). A lower SCT score meant participants could repeat approximately 50% of the target words at a worse SNR. Thus, the lower the SCT score, the better a participants' performance on that block. In total, one SCT was calculated for each of the 16 blocks (8 stimulation conditions and 8 sham conditions) using the performance of the last of the 20 trials of the staircase procedure. Sentence scoring for all participants was done double-blind by a native German speaker, that is, neither the participant nor the scorer knew whether a subject was in the stimulation or the sham condition. For more in-depth information on how the staircase procedure was performed and how the step sizes were calculated.⁶⁶

Transcranial electrical stimulation

While the participant performed the OLSa, envelope-tACS was applied using a multichannel stimulator with 2 channels, one for each hemisphere (DCSTIMULATOR MC, neurConn GmbH, Ilmenau, Germany). During the 2 training tasks, no stimulation was presented. Out of the 16 experimental blocks, 8 were accompanied with sham stimulation; each sentence was preceded by a short (250 ms) sinusoidal stimulation with an intensity of 1 mA peak to peak to imitate potential skin sensations as in the stimulation condition. Eight experimental blocks were accompanied by envelope-tACS: electrical stimulation shaped as the speech envelope of the accompanying sentence.^{30,32} To achieve this, the absolute values of the Hilbert transformation of the sentence were computed and low-pass filtered at 10 Hz (second-order Butterworth). The tACS signal was sampled at 44100 Hz, and peak-to-peak amplitude of the stimulation was set to not exceed 1 mA. Stimulation per trial was the same length as the duration of the spoken sentences (approximately 3 seconds), no tACS was applied other than during this brief window. Each of the 8 stimulation conditions had a different delay between the start of the auditory stimulus and envelope-tACS; this time-lag varied from 25 to 200 ms, in steps of 25 ms, resulting in 8 different tACS time-lag conditions. For example, a time-lag of 100 ms indicated that the onset of the audio preceded the start of the envelope-tACS stimulation by 100 ms. This range of latencies was chosen to encompass a 5 Hz cycle, as it was close to the 5.12 Hz sinusoidal fit for envelope-tACS found by Wilsch et al.³² Furthermore, measuring points were chosen to be

around 100 ms, as this has been found to be around the latency of the envelope in the brain signal.^{11,10,67,68} Steps of 25 ms were chosen to have an even distribution of time-lags over the time period of interest. Each tACS time-lag condition was paired with a sham condition. The order in which each participant performed each different time-lag block was counterbalanced, and sham and stimulation blocks were alternated (sham first for 16 participants, stimulation first for 16 participants). This was done as a control for effects caused by the length of the task (ie, fatigue and learning effects). With 8 envelope-tACS conditions consisting of 20 sentences with 3 seconds of envelope-tACS each, every participant received approximately 8 minutes of envelope-tACS.

Results

Effects of tACS

Statistical analysis was performed using SPSS software, version 26.0 (IBM, Armonk, NY) and Matlab r2016a (Mathworks, Natick, MA). Four participants were excluded from the analysis: 1 participant reported seeing phosphenes and was therefore excluded, 1 participant reported being very fatigued and was excluded as they performed exceedingly poorly (more than 2 standard deviations from the norm), and 2 participants had to be excluded due to technical issues during the task.

A 2-way repeated measures analysis of variance (ANOVA) using the 8 different stimulation time-lags as the factor 'offset' and stimulation and sham as a 2-level factor did not reveal a significant effect for offset: $F(7, 189) = .72, p = .66, \eta^2 = .026$, stimulation: $F(1, 27) = .080, p = .78, \eta^2 = .003$, or interaction: $F(7, 189) = .29, p = .96, \eta^2 = .011$. This was to be expected as previous studies using tACS have shown different optimal time-lags for participants. Therefore, to assess the effect of envelope-tACS, the best-scoring tACS time-lag condition of each participant was compared to that participant's best sham condition. A *t*-test comparing best stimulation ($M = -7.7, SD = .68$) versus best sham ($M = -7.7, SD = .67$) condition did not show any significant effect, $t(27) = -.56, p = .58, d = .060$.

Another method to investigate stimulation effect that has been used in previous papers using tACS, compares the performance of the 2 time-lags nearest to the best time-lag.^{30,69} First, for each participant, the best stimulation time-lag is chosen. Under the hypothesis that envelope-tACS enhances or disrupts entrainment depending on time lag, task performance should increase or decrease depending on the half-cycle of the critical frequency of the sound envelope. As Wilsch et al³² found that a frequency of 5.12 Hz best matched the modulation effect tACS had on intelligibility when using the OLSa, a critical frequency of 5 Hz was used. Since the performance of the best stimulation time-lag has to be used to define a participant's best time-lag, this condition can no longer be used to evaluate performance (as this would be circular). Therefore, the SCTs of the 2 conditions closest in phase to the optimal phase condition, that is, the excitatory half-cycle, were compared to

the SCTs of the 2 conditions adjacent to the opposite to best condition, that is, the inhibitory half-cycle. The creation of the phase conditions was done for stimulation and sham separately, independent of each other (Figure 2A and B). A paired samples *t*-test of the positive half-cycle ($M = -7.93, SD = .78$) compared to the negative half-cycle ($M = -7.73, SD = .69$) revealed a significant effect, $t(27) = -1.95, p = .031, d = .27$, one-tailed, for the stimulation condition (Figure 2C). When comparing the positive half-cycle ($M = -7.86, SD = .77$) to the negative half-cycle ($M = -7.89, SD = 0.66$), no significant effect was found, $t(27) = .16, p = .43, d = .040$, one-tailed, for the sham condition.

Learning effect

Although the OLSa is supposedly robust against learning effects⁶⁵ and the use of 2 training trials, a one-way repeated measures ANOVA using the 16 experimental OLSa lists as the factor 'order' revealed a significant effect of presentation order, $F(7.24, 195) = 6.6$ Greenhouse-Geisser corrected, $p < .001, \eta^2 = .20$, Figure 3A. This 1-way repeated measures ANOVA was then repeated for the stimulation and sham conditions separately, using the 8 OLSa lists as the factor 'order'. The learning effect was significant for both stimulation, $F(4.86, 131) = 6.9$ Greenhouse-Geisser corrected, $p < .001, \eta^2 = .20$, Figure 3B, and sham, $F(4.65, 125) = 6.8$ Greenhouse-Geisser corrected, $p < .001, \eta^2 = .20$, Figure 3B, separately. Tests of within-subjects contrasts using the 16 experimental OLSa lists as the factor 'order' revealed a significant linear effect of presentation order, $F(1, 27) = 23.0, p < .001, \eta^2 = .46$, as well as a quadratic effect of presentation order, $F(1, 27) = 22.0, p < .001, \eta^2 = .45$. When using the 8 experimental OLSa lists as the factor 'order' for stimulation and sham separately, the linear and quadratic effects of presentation order were also significant, stimulation linear effect: $F(1, 27) = 14.5, p = .001, \eta^2 = .35$, stimulation quadratic effect: $F(1, 27) = 12.4, p = .002, \eta^2 = .32$, sham linear effect: $F(1, 27) = 24.7, p < .001, \eta^2 = .48$, sham quadratic effect: $F(1, 27) = 5.18, p = .03, \eta^2 = .16$. Conditions were randomized to correct for a potential learning effect; however, as we are interested in the best-performing condition, this learning effect had to be accounted for.

Counterbalancing issue

To prevent learning effect issues over the different time-lag conditions, a Williams' design⁷⁰ was used. Over all participants, conditions were ordered using an 8-by-8 Latin square design that is balanced to prevent carry-over effects (Figure 4A). Eight pairs of conditions were made, that is, each time-lag condition with its matching sham measurement. For half of the participants, sham was always measured first for these condition-pairs, and for the other half the stimulation condition of the block-pair was always measured first. As we measured 32 participants in total, this meant the 8-by-8 Latin square condition order was repeated 4 times, twice with sham first and twice with stimulation first. In this way, each condition-pair occurred exactly 4 times at each

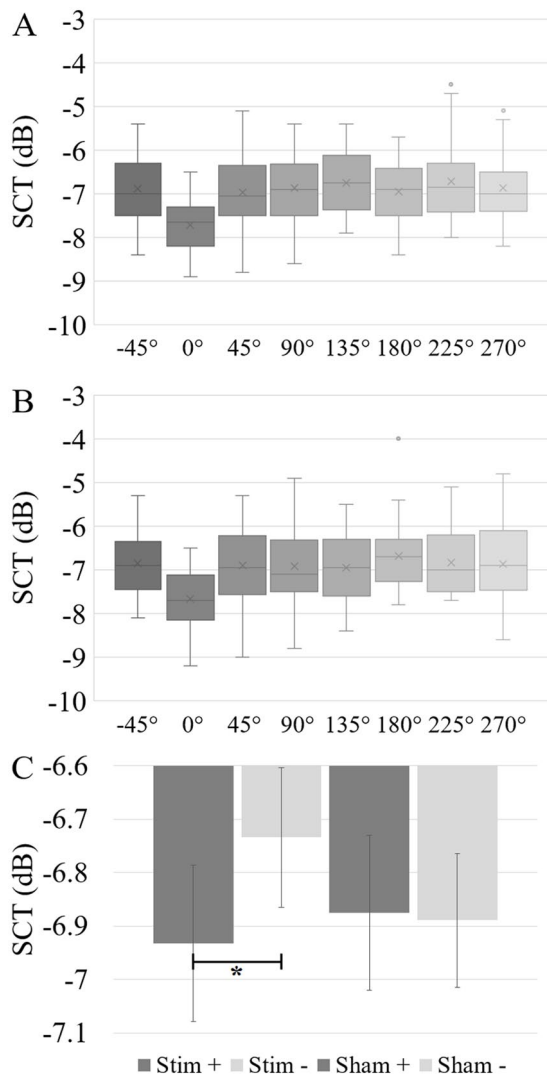


Figure 2. (A) Distribution of performance after aligning the best-performance conditions for stimulation. Note that a lower SCT indicates a better performance on the task. Participants' best-performing time-lag condition is set to 0°, and all other time-lag conditions are shifted accordingly. Performance on the -45° and 45° conditions are then averaged to calculate the excitatory (positive) half-cycle, and performance on the 135° and 225° conditions are averaged to calculate the inhibitory (negative) half-cycle. (B) Distribution of performance after aligning the best-performance conditions for sham. All sham conditions were identical and were instead assigned the time-lag of their paired stimulation condition. Sham conditions were then assigned their phase condition dependent on the best-performing sham condition (which was set as phase 0°), independent of the performance in the stimulation conditions. (C) Participants performed significantly better in the positive half-cycle stimulation conditions compared to the negative half-cycle stimulation conditions. This was not the case when comparing the positive and negative half-cycle conditions of sham. SCT indicates speech comprehension threshold.

point in the order of measurements. Furthermore, the Latin square was counterbalanced so that no condition-pair preceded or followed the same condition-pair more than once. Ergo, as the Latin square was repeated 4 times, each condition-pair preceded or followed the same condition-pair exactly 4 times over all participants. This way, counterbalancing was optimized so no single

time-lag was affected by any learning effect. However, due to the way the Latin squares of the Williams' design are generated, this caused an issue with the counterbalancing necessary for the half-cycle analysis (Figure 4B). For stimulation conditions, 35 of the positive half-cycle measurements were measured in the late half of the experiment (2 per participant) and 21 were measured in the early half. For sham conditions, 37 of the positive half-cycle measurements were measured in the late half of the experiment, and 19 were measured in the early half.

As this learning effect might have affected our results, we investigated to how much of the difference in performance between the positive and negative half cycle could be accounted for by the difference in presentation order between the 2 conditions. To quantify this difference, for each participant and for stimulation and sham separately, we added the presentation order of the 2 positive half-cycle conditions and then subtracted the presentation order of the 2 negative half-cycle conditions from this. This value expressed for a given participant how large the difference between the 2 conditions were; a positive value indicated their positive half-cycle conditions were presented after their negative half-cycle conditions, whereas a negative value indicated the reverse. We then used these values as a covariate for a 2-way repeated measures ANOVA comparing the positive and negative half-cycles. For both stimulation and sham, there was no significant effect of half-cycle after correcting for presentation order, stimulation: $F(1, 26) = 1.2, p = .28, \eta^2 = .044$, sham: $F(1, 26) = 3.3, p = .082, \eta^2 = .11$, as well as a significant interaction effect between half-cycle and presentation order, stimulation: $F(1, 26) = 5.2, p = 0.031, \eta^2 = .17$, sham: $F(1, 26) = 18.7, p < .001, \eta^2 = .42$.

To correct for the learning effect, OLSa lists were sorted by presentation order and then averaged over all participants per presentation number, regardless of condition. Then, the average of each presentation order was subtracted from each measurement of that presentation order (Figure 5A and B). Using this demeaned data, a repeated measures ANOVA using the 8 different time-lags as factors did not reveal any significant results, $F(7, 189) = .74, p = .64, \eta^2 = .027$. Notably, demeaning the data changed the best stimulation time-lag of 8 participants and the best sham condition of 9 participants (Figure 5C and D). A t -test comparing best stimulation ($M = -.66, SD = .67$) versus best sham ($M = -.64, SD = .63$) condition did not show any significant effect of stimulation, $t(27) = -.23, p = .82, d = .03$. A paired samples t -test between standard deviation of stimulation time-lags ($M = .47, SD = .15$) versus standard deviation of sham time-lags ($M = .45, SD = .18$) revealed no significant difference, $t(27) = .49, p = .62, d = .121$. A paired samples t -test of the average of the adjacent to best time-lags ($M = .059, SD = .67$) compared to the average of the 2 opposite time-lags ($M = .16, SD = .77$) revealed no significant effect of phase, $t(27) = -1.2, p = .25, d = .14$, for the stimulation condition. When comparing the average of the adjacent to best sham time-lags ($M = .18, SD = .71$) to the opposite sham time-lags ($M = .074, SD = .65$), no significant effect was found, $t(27) = 1.2, p = .11, d = .17$.

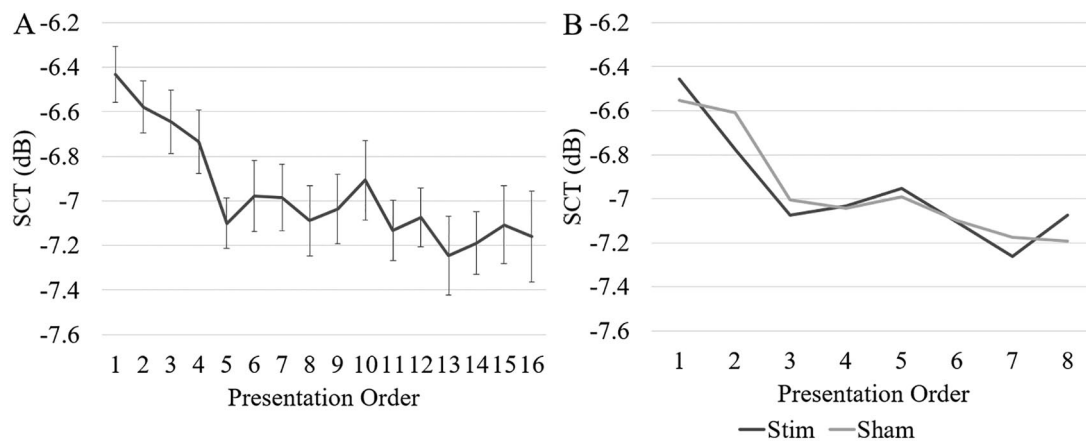


Figure 3. (A) Mean speech comprehension threshold of all participants per OLSa list in presentation order. Bars depict the standard error of the mean. (B) Speech comprehension threshold of the stimulation (dark) and sham (light) over the 8 pairs of stimulation and sham blocks. OLSa indicates Oldenburg sentence task.

A							
25	50	200	75	175	100	150	125
50	75	25	100	200	125	175	150
75	100	50	125	25	150	200	175
100	125	75	150	50	175	25	200
125	150	100	175	75	200	50	25
150	175	125	200	100	25	75	50
175	200	150	25	125	50	100	75
200	25	175	50	150	75	125	100

B							
0°	45°	315°	90°	270°	135°	225°	180°
315°	0°	270°	45°	225°	90°	180°	135°
45°	90°	0°	135°	315°	180°	270°	225°
270°	315°	225°	0°	180°	45°	135°	90°
90°	135°	45°	180°	0°	225°	315°	270°
225°	270°	180°	315°	135°	0°	90°	45°
135°	180°	90°	225°	45°	270°	0°	315°
180°	225°	135°	270°	90°	315°	45°	0°

Figure 4. (A) Latin square counterbalancing using Williams' design. Each row represents 1 possible presentation order a participant could have been given. In total, each row was used for 4 different participants, of which 2 received the order stimulation – sham conditions and the other 2 participants received the order sham – stimulation conditions. In this manner, each time-lag condition is counterbalanced over all participants to prevent learning and fatigue from affecting one time-lag condition more than another. Each time-lag condition also precedes and follows each other time-lag condition only once, in this way, counterbalancing for carry-over effect. (B) Possible presentation orders of the time-lag conditions after phase shifting. After measuring the time-lag conditions, participants' best performing time-lag is assigned to the 0 phase shift condition. Due to the learning effect in our data, best-performing time-lags were more common to be late in the presentation order. As the best-performing time-lag is not used in the phase-shift, analysis this would not be an issue; however, due to how the Latin square used in Williams' design is generated, the presentation order of the positive half-cycle conditions (highlighted in grey) is not statistically independent of the presentation order of the best time-lag. Because of this, the positive half-cycle conditions were more likely to be measured in the latter half of the data recording session than in the first half, regardless of what presentation order of (A) was used.

Discussion

The purpose of this study was to expand upon previous studies on the effects of envelope-tACS. Using 8 different time-lags for stimulation as well as an expansive within-subject sham measurement, we tried to achieve a better approximation of a given participant's optimal time-lag to achieve the highest

possible potential gain from envelope-tACS. Next to this, we assigned a separate sham condition to each stimulation time-lag condition instead of using only a single sham condition, to be able to better evaluate the optimal time-lag condition. No significant effect of stimulation was found; there was no difference in performance between the best-performing stimulation

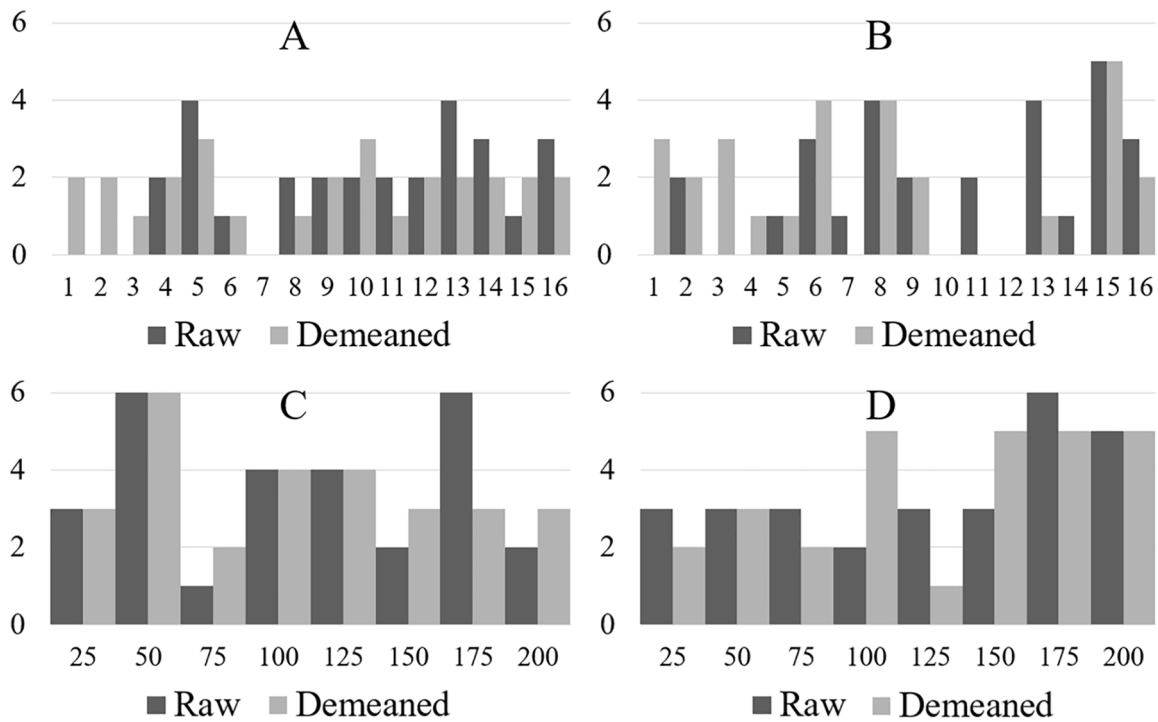


Figure 5. Distribution of high-performance measurement per presentation order for stimulation (A) and sham (B). Dark grey shows the distribution of best performances before correcting for the learning effect, light grey shows the distribution after subtracting the mean of all participants per presentation order condition. Distribution of high-performance time-lag condition for stimulation (C) and sham (D). Dark grey shows the distribution of best performances before correcting for the learning effect, light grey shows the distribution after subtracting the mean of all participants per presentation order condition.

condition compared to the best-performing sham condition. Furthermore, there was no single stimulation offset at which participants on average performed better at. Comparing the difference in performance between the supposed half-cycles of the stimulation conditions was the one test that pointed to a possible effect of envelope-tACS. Participants performed better in the positive half cycle conditions compared to negative half-cycle conditions for stimulation, but not for sham. However, after correction for the learning effect, this effect was removed. Although it seems correct to dismiss this finding, we believe it is important to discuss this in light of previous envelope-tACS studies. This comparison between half-cycles to investigate the supposed phasic nature of the stimulation is one that has previously shown results.^{30,32} In general, the effects found of envelope-tACS on auditory task performance are small; Riecke et al³⁰ report a 4.7% increase in speech performance between participants' best- and worst-performing time-lag for envelope-tACS. Wilsch et al³² reported a performance increase of -7 dB between the best stimulation condition and sham. In our study, the average difference in performance of the best performing stimulation condition compared to the other stimulation conditions was $.8$ dB, that is, $.3$ dB larger than the gain between the best-performing sham condition compared to the other sham conditions. Regardless of statistical significance, the small sizes of these effects make experimental designs using envelope-tACS very susceptible to covariates; despite the use of 2 training rounds and the robustness of the OLSa for learning effect, there was still a learning effect in our

data. Although this effect was strongly significant and has a large effect size ($P < .001$, $\eta^2 = .200$), the absolute difference between the highest and lowest performing presentation order condition was only $.8$ dB; within the 1 dB margin of error of the OLSa.⁶⁵ The OLSa might have not been a precise-enough measurement to find an effect of envelope-tACS in the manner we intended, that is, the absolute change in SCT. It should be noted that although Wilsch et al³² used the OLSa as well, they investigated the phasic nature of the performance change, regardless of the absolute change in SCT.

Differences with previous studies

As our results were not in line with previous studies on envelope-tACS, it is important to consider the differences in experimental procedure. Wilsch et al³² used the OLSa as well, and used the same methods for the creation of the stimulation waveform. They used a wider range of time-lags, (0-250 ms in steps of 50 ms compared to our 25-200 ms in steps of 25 ms) but had larger interval steps, having only 6 time-lag measurements compared to our 8. Furthermore, they varied stimulation intensity per participant depending on the sensitivity threshold of that participant, varying from $.4$ to 1.5 mA, whereas we stimulated all participants at 1 mA. Riecke et al³⁰ used a different, Dutch speech task and created the stimulation waveform in a comparable manner; the most notable difference being that our stimulation waveform was low-pass filtered at 10 Hz, whereas theirs was at 16 Hz. They used a much wider range of

time-lags, varying between 205 ms before sound onset until 570 ms after sound onset. They only measured 6 time-lags; however, making 195 ms steps between time-lags. Like Wilsch et al³² and Riecke et al³⁰ used individual stimulation intensities per participant, quoting a mean of .9 mA stimulation intensity.

The first difference that stands out between these studies and ours is that both studies had individual stimulation intensities. For our study, we opted to stimulate all participants at 1 mA peak-to-peak for several reasons. First, we wanted to assure all participants would receive stimulation at a high-enough intensity that there would be an effect. Second, during piloting, it became apparent that most participants were comfortable at around 1 mA stimulation regardless of using individual stimulation thresholds; this was also the case for Riecke et al,³⁰ who mention only having a .1 mA standard deviation to their mean .9 mA stimulation intensity. Third, time limitations in the experimental design made using individual intensities troublesome; due to our expansive control condition, our experiment was already fairly long and taxing on the participants. Testing for individual stimulation intensities would have made the experiment even more taxing on the participant. Not using individual stimulation intensities might have been a factor in our experiment not finding a significant effect of stimulation, as individual differences between participants when using tACS has been shown to influence stimulation effectiveness.^{56,71} However, as individual stimulation intensities would only be dependent on the self-reported skin sensation of the participants, we believed individual measurements would not mediate the issues of individual differences enough to justify the extra measurement time.

The second difference in experimental design between our study and the studies of Riecke et al³⁰ and Wilsch et al³² is the distribution of time-lags that were chosen to test at. For our study, we intentionally chose to use a larger number of smaller intervals between time-lags to find a more exact approximation of participants' individual optimal time-lag. The range of 25 to 200 ms was chosen based on results by Wilsch et al,³² and we measured around 100 ms based on studies on the latency of the envelope in the brain signal.^{10,11,18,68} The trade-off of this more exact measurement however, was a less wide range of time-lags; the measurement window of Wilsch et al³² was comparable (0-250 ms), yet Riecke et al³⁰ used a much larger measurement window, each interval between time-lags being larger than the difference between our earliest and latest time-lag (195 ms compared to 175 ms). Because of this, it is possible that some participants' optimal time-lag was out of our measurement window. Finally, although the latencies of the event related potentials (ERP) have been hypothesized to be an estimate of the optimal stimulation time-lag, Riecke et al³⁰ found that, on average, participants performed best when stimulation preceded sound presentation.

Future research

Transcranial electric stimulation methods have shown promising results as a noninvasive research method. As interest in the

method has grown, more intricate experimental designs have been developed. Speech envelope-shaped stimulation is a natural step in the development TES methods by inducing more complex stimulation waveforms instead of signals consisting of single frequencies but does come at the price of requiring more specific approximation of the optimal stimulation time-lag. Meta-analysis⁷² has shown that tACS can affect perception and cognitive performance; however, the found effects are generally small to moderate. Furthermore, there is still a large difference in stimulation parameters to account for, as well as an incomplete understanding of the neural mechanisms that tACS actually affects. Finally, individual differences in anatomy appear to influence the effectiveness of tACS;^{73,74} there is an ongoing debate regarding the minimum stimulation intensity required to guarantee enough current reaches the desired areas.⁷⁵⁻⁷⁹ A study by Asamoah et al⁸⁰ found that for studies involving tACS applied to the motor cortex, at least part of the found effects could be explained by rhythmic stimulation of peripheral nerves inducing entrainment of direct entrainment in the cortex. Whether this effect applies to stimulation of other brain areas like the auditory cortex requires further research.

Development of more complex waveform stimulation like envelope-tACS enhances these difficulties further. Previous envelope-tACS studies^{28,30,32} show that assuming there is an effect, behavioural changes are small, requiring intricate and time-consuming experimental designs with multiple measurements per participant. This makes it difficult to draw conclusions about how to optimize the stimulation method. For eventual application, the question becomes whether the optimal results of envelope-tACS are strong enough to become usable in the medical field. In the case of improving speech perception through envelope-tACS, if the optimal effect turns out to be not to be much higher than a gain of about 1 dB SPL, there will be very little practical use for the method. Furthermore, although potential application between sinusoidal tACS and envelope-tACS could differ, envelope-tACS should not only show a significant improvement to sham but also show better results than conventional sinusoidal tACS to be worth the more complex design and challenges of the method. As of now, there is little evidence that studies showing significant effects of envelope-tACS^{28-30,32} are more successful than sinusoidal tACS^{31,33,81,82}; differences in methods make this comparison difficult, however, and a more thorough meta-analysis is needed.

For the foreseeable future, the main goal in the development of envelope-tACS should be to gain a better understanding of how it affects speech processing and to optimize its effects. Using brain imaging methods in conjunction with tACS has produced results but has to work around the large stimulation artefact tACS causes when used together with EEG or MEG.^{83,84} Progress has been made in filtering the tACS artefact out of EEG recordings, yet it is difficult to assess whether the artefact is completely filtered out as a residual artefact looks similar to the expected effects of tACS,^{85,86} as well as additional

artefacts induced by hardware limitations.⁸⁶ In the case of sinusoidal tACS, the artefact in recording can be avoided by stimulating and recording interleaved,⁷³ but this is not an option when investigating the immediate effects of envelope-tACS.


Conclusion

The development of envelope-tACS struggles with the almost circular problem of having to find an optimal method of stimulation to find the strongest possible effects of the method, while needing strong enough effects to find the optimal method of stimulation. For the field to progress, methods need to be developed to better approximate the optimal stimulation time-lag, as well as a clearer understanding of what part of the auditory process is affected by the stimulation. Major progress has already been made in understanding how tACS travels through the brain,^{62,87} and brain imaging methods continues to expand our understanding speech processing.^{88–93} Keeping the results of previous auditory tACS studies in mind, we believe our results do not disprove an effect of envelope-tACS as much as they highlight the difficulties with the development of the method. Further research should aim to optimize the beneficial effects of tACS, after which the final question would be whether these effects are strong enough to have real-world applications.

Author Contributions

JE designed experiment, analysed data and wrote the manuscript. MS designed experiment and analysed data. MV planned and designed experiment. CSH designed experiment and wrote the manuscript.

ORCID iD

Jules Erkens  <https://orcid.org/0000-0001-5994-5795>

REFERENCES

- Ding N, Simon JZ. Cortical entrainment to continuous speech: functional roles and interpretations. *Front Hum Neurosci*. 2014;8:311. doi:10.3389/fnhum.2014.00311.
- Peelle JE, Gross J, Davis MH. Phase-locked responses to speech in human auditory cortex are enhanced during comprehension. *Cereb Cortex*. 2013;23:1378–1387. doi:10.1093/cercor/bhs118.
- Abrams DA, Nicol T, Zecker S, Kraus N. Right-hemisphere auditory cortex is dominant for coding syllable patterns in speech. *J Neurosci*. 2008;28:3958–3965. doi:10.1523/JNEUROSCI.0187-08.2008.
- Giraud A-L, Poeppel D. Cortical oscillations and speech processing: emerging computational principles and operations. *Nat Neurosci*. 2012;15:511–517. doi:10.1038/nn.3063.
- Hertrich I, Dietrich S, Trouvain J, Moos A, Ackermann H. Magnetic brain activity phase-locked to the envelope, the syllable onsets, and the fundamental frequency of a perceived speech signal. *Psychophysiology*. 2012;49:322–334. doi:10.1111/j.1469-8986.2011.01314.x.
- Thut G, Schyns PG, Gross J. Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Front Psychol*. 2011;2:170. doi:10.3389/fpsyg.2011.00170.
- Millman RE, Johnson SR, Prendergast G. The role of phase-locking to the temporal envelope of speech in auditory perception and speech intelligibility. *J Cogn Neurosci*. 2015;27:533–545. doi:10.1162/jocn_a_00719.
- Steinschneider M, Nourski KV, Fishman YI. Representation of speech in human auditory cortex: is it special? *Hear Res*. 2013;305:57–73. doi:10.1016/j.heares.2013.05.013.
- Aiken SJ, Picton TW. Human cortical responses to the speech envelope. *Ear Hear*. 2008;29:139–157. doi:10.1097/AUD.0b013e31816453dc.
- Baltzell LS, Horton C, Shen Y, Richards VM, D'Zmura M, Srinivasan R. Attention selectively modulates cortical entrainment in different regions of the speech spectrum. *Brain Res*. 2017;1644:203–212. doi:10.1016/j.brainres.2016.05.029.
- Ding N, Simon JZ. Emergence of neural encoding of auditory objects while listening to competing speakers. *Proc Natl Acad Sci USA*. 2012;109:11854–11859. doi:10.1073/pnas.1205381109.
- Ding N, Simon JZ. Neural coding of continuous speech in auditory cortex during monaural and dichotic listening. *J Neurophysiol*. 2012;107:78–89. doi:10.1152/jn.00297.2011.
- Luo H, Poeppel D. Phase patterns of neuronal responses reliably discriminate speech in human auditory cortex. *Neuron*. 2007;54:1001–1010. doi:10.1016/j.neuron.2007.06.004.
- Kubaneck J, Brunner P, Gunduz A, Poeppel D, Schalk G. The tracking of speech envelope in the human cortex. *PLoS ONE*. 2013;8:e53398. doi:10.1371/journal.pone.0053398.
- Wang X, Lu T, Liang L. Cortical processing of temporal modulations. *Speech Commun*. 2003;41:107–121. doi:10.1016/S0167-6393(02)00097-3.
- Zeng F-G, Oba S, Garde S, Sininger Y, Starr A. Temporal and speech processing deficits in auditory neuropathy. *NeuroReport*. 1999;10:3429–3435. doi:10.1097/00001756-199911080-00031.
- Antal A, Paulus W. Transcranial alternating current stimulation (tACS). *Front Hum Neurosci*. 2013;7:317. doi:10.3389/fnhum.2013.00317.
- Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci*. 2013;7:279. doi:10.3389/fnhum.2013.00279.
- Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. *Neuron*. 2010;67:129–143. doi:10.1016/j.neuron.2010.06.005.
- Dowsett J, Herrmann CS. Transcranial alternating current stimulation with sawtooth waves: simultaneous stimulation and EEG recording. *Front Hum Neurosci*. 2016;10:135. doi:10.3389/fnhum.2016.00135.
- Kasten FH, Dowsett J, Herrmann CS. Sustained aftereffect of α -tACS lasts up to 70 min after stimulation. *Front Hum Neurosci*. 2016;10:245. doi:10.3389/fnhum.2016.00245.
- Moliadze V, Sierau L, Lyzhko E, et al. After-effects of 10 Hz tACS over the prefrontal cortex on phonological word decisions. *Brain Stimul*. 2019;12:1464–1474. doi:10.1016/j.brs.2019.06.021.
- Nakazono H, Ogata K, Takeda A, Yamada E, Kimura T, Tobimatsu S. Transcranial alternating current stimulation of α but not β frequency sharpens multiple visual functions. *Brain Stimul*. 2020;13:343–352. doi:10.1016/j.brs.2019.10.022.
- Stecher HI, Pollok TM, Strüber D, Sobotka F, Herrmann CS. Ten minutes of α -tACS and ambient illumination independently modulate EEG α -power. *Front Hum Neurosci*. 2017;11:257. doi:10.3389/fnhum.2017.00257.
- Sejnowski TJ. Network oscillations: emerging computational principles. *J Neurosci*. 2006;26:1673–1676. doi:10.1523/JNEUROSCI.3737-05d.2006.
- Neuling T, Rach S, Wagner S, Wolters CH, Herrmann CS. Good vibrations: oscillatory phase shapes perception. *NeuroImage*. 2012;63:771–778. doi:10.1016/j.neuroimage.2012.07.024.
- Vosskuhl J, Strüber D, Herrmann CS. Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. *Front Hum Neurosci*. 2018;12:211. doi:10.3389/fnhum.2018.00211.
- Kadir S, Kaza C, Weissbart H, Reichenbach T. Modulation of speech-in-noise comprehension through transcranial current stimulation with the phase-shifted speech envelope. *IEEE Trans Neural Syst Rehabil Eng*. 2020;28:23–31. doi:10.1109/TNSRE.2019.2939671.
- Keshavarzi M, Kegler M, Kadir S, Reichenbach T. Transcranial alternating current stimulation in the theta band but not in the delta band modulates the comprehension of naturalistic speech in noise. *NeuroImage*. 2020;210:116557. doi:10.1016/j.neuroimage.2020.116557.
- Riecke L, Formisano E, Sorger B, Başkent D, Gaudrain E. Neural entrainment to speech modulates speech intelligibility. *Curr Biol*. 2018;28:161.e5–169.e5. doi:10.1016/j.cub.2017.11.033.
- Rufener KS, Zaehle T, Oechslin MS, Meyer M. 40 Hz-transcranial alternating current stimulation (tACS) selectively modulates speech perception. *Int J Psychophysiol*. 2016;101:18–24. doi:10.1016/j.ijpsycho.2016.01.002.
- Wilsch A, Neuling T, Obleser J, Herrmann CS. Transcranial alternating current stimulation with speech envelopes modulates speech comprehension. *NeuroImage*. 2018;172:766–774. doi:10.1016/j.neuroimage.2018.01.038.
- Zoefel B, Allard I, Anil M, Davis MH. Perception of rhythmic speech is modulated by focal bilateral transcranial alternating current stimulation. *J Cogn Neurosci*. 2019;32:226–240. doi:10.1162/jocn_a_01490.
- Zoefel B, Archer-Boyd A, Davis MH. Phase entrainment of brain oscillations causally modulates neural responses to intelligible speech. *Curr Biol*. 2018;28:401.e5–408.e5. doi:10.1016/j.cub.2017.11.071.
- Riecke L, Formisano E, Herrmann CS, Sack AT. 4-Hz transcranial alternating current stimulation phase modulates hearing. *Brain Stimul*. 2015;8:777–783. doi:10.1016/j.brs.2015.04.004.
- Ahn S, Mellin JM, Alagapan S, et al. Targeting reduced neural oscillations in patients with schizophrenia by transcranial alternating current stimulation. *NeuroImage*. 2019;186:126–136. doi:10.1016/j.neuroimage.2018.10.056.

37. Mellin JM, Alagapan S, Lustenberger C, et al. Randomized trial of transcranial alternating current stimulation for treatment of auditory hallucinations in schizophrenia. *Eur Psychiatry*. 2018;51:25-33. doi:10.1016/j.eurpsy.2018.01.004.
38. Dallmer-Zerbe I, Popp F, Lam AP, Philippen A, Herrmann CS. Transcranial alternating current stimulation (tACS) as a tool to modulate P300 amplitude in attention deficit hyperactivity disorder (ADHD): preliminary findings. *Brain Topogr*. 2020;33:191-207. doi:10.1007/s10548-020-00752-x.
39. Herrmann CS, Strüber D, Helfrich RF, Engel AK. EEG oscillations: from correlation to causality. *Int J Psychophysiol*. 2016;103:12-21. doi:10.1016/j.ijpsycho.2015.02.003.
40. Priori A, Brunoni AR, Fregni F, Boggio PS, Ferrucci R. *The Frontiers of Clinical Research on Transcranial Direct Current Stimulation (TDCS) in Neuropsychiatry*. Lausanne, Switzerland: Frontiers; 2015. doi:10.3389/978-2-88919-287-8.
41. Riecke L, Zoefel B. Conveying temporal information to the auditory system via transcranial current stimulation. *Acta Acust United Acust*. 2018;104:883-886. doi:10.3813/AAA.919235.
42. Ten Oever S, de Graaf TA, Bonnemayer C, Ronner J, Sack AT, Riecke L. Stimulus presentation at specific neuronal oscillatory phases experimentally controlled with tACS: implementation and applications. *Front Cell Neurosci*. 2016;10:240. doi:10.3389/fncel.2016.00240.
43. Hornsby BWY, Hornsby BWY. The effects of hearing aid use on listening effort and mental fatigue associated with sustained speech processing demands. *Ear Hear*. 2016;34:523-534. doi:10.1097/AUD.0b013e31828003d8.
44. Sarampalis A, Kalluri S, Edwards B, Hafter E. Objective measures of listening effort: effects of background noise and noise reduction. *J Speech Lang Hear Res*. 2009;52:1230-1240. doi:10.1044/1092-4388(2009/08-0111).
45. Kochkin S. MarkeTrak V: 'why my hearing aids are in the drawer': the consumers' perspective. *Hear J*. 2000;53:34-41. doi:10.1097/00025572-200002000-00004.
46. Borch Petersen E, Lunner T, Vestergaard MD, Sundewall Thorén E. Danish reading span data from 283 hearing-aid users, including a sub-group analysis of their relationship to speech-in-noise performance. *Int J Audiol*. 2016;55:254-261. doi:10.3109/14992027.2015.1125533.
47. Fitzgibbons PJ, Gordon-Salant S. Aging and temporal discrimination in auditory sequences. *J Acoust Soc Am*. 2001;109:2955-2963. doi:10.1121/1.1371760.
48. Gordon-Salant S, Yeni-Komshian GH, Fitzgibbons PJ, Barrett J. Age-related differences in identification and discrimination of temporal cues in speech segments. *J Acoust Soc Am*. 2006;119:2455-2466. doi:10.1121/1.2171527.
49. Schneider BA, Daneman M, Murphy DR. Speech comprehension difficulties in older adults: cognitive slowing or age-related changes in hearing? *Psychol Aging*. 2005;20:261-271. doi:10.1037/0882-7974.20.2.261.
50. Besle J, Schevon CA, Mehta AD, et al. Tuning of the human neocortex to the temporal dynamics of attended events. *J Neurosci*. 2011;31:3176-3185. doi:10.1523/JNEUROSCI.4518-10.2011.
51. Peelle JE, Troiani V, Wingfield A, Grossman M. Neural processing during older adults' comprehension of spoken sentences: age differences in resource allocation and connectivity. *Cereb Cortex*. 2010;20:773-782. doi:10.1093/cercor/bhp142.
52. Schneider BA, Daneman M, Pichora-Fuller MK. Listening in aging adults: from discourse comprehension to psychoacoustics. *Can J Exp Psychol/Rev Can Psychol Exp*. 2002;56:139-152.
53. Henry MJ, Herrmann B, Kunke D, Obleser J. Aging affects the balance of neural entrainment and top-down neural modulation in the listening brain. *Nat Commun*. 2017;8:15801. doi:10.1038/ncomms15801.
54. McAuley JD, Jones MR, Holub S, Johnston HM, Miller NS. The time of our lives: life span development of timing and event tracking. *J Exp Psychol Gen*. 2006;135:348-367. doi:10.1037/0096-3445.135.3.348.
55. Petersen EB, Wöstmann M, Obleser J, Lunner T. Neural tracking of attended versus ignored speech is differentially affected by hearing loss. *J Neurophysiol*. 2017;117:18-27. doi:10.1152/jn.00527.2016.
56. Krause B, Cohen Kadosh R. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. *Front Syst Neurosci*. 2014;8:25. doi:10.3389/fnsys.2014.00025.
57. Tavakoli AV, Yun K. Transcranial alternating current stimulation (tACS) mechanisms and protocols. *Front Cell Neurosci*. 2017;11:214. doi:10.3389/fncel.2017.00214.
58. Asamoah B, Khatoun A, Mc Laughlin M. Analytical bias accounts for some of the reported effects of tACS on auditory perception. *Brain Stimul*. 2019;12:1001-1009. doi:10.1016/j.brs.2019.03.011.
59. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9:97-113. doi:10.1016/0028-3932(71)90067-4.
60. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol*. 2011;14:1133-1145. doi:10.1017/S1461145710001690.
61. Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front Hum Neurosci*. 2013;7:161. doi:10.3389/fnhum.2013.00161.
62. Baltus A, Wagner S, Wolters CH, Herrmann CS. Optimized auditory transcranial alternating current stimulation improves individual auditory temporal resolution. *Brain Stimul*. 2018;11:118-124. doi:10.1016/j.brs.2017.10.008.
63. Wagner S, Burger M, Wolters CH. An optimization approach for well-targeted transcranial direct current stimulation. *SIAM J Appl Math*. 2015;76:2154-2174. doi:10.1137/15M1026481.
64. Wagner S, Rampersad SM, Aydin Ü, et al. Investigation of tDCS volume conduction effects in a highly realistic head model. *J Neural Eng*. 2014;11:016002. doi:10.1088/1741-2560/11/1/016002.
65. Wagner K, Kühnel V, Kollmeier B. Entwicklung und Evaluation eines Satztests für die deutsche Sprache, Teil 1: Design des Oldenburger Satztests. *Zeitschrift Audiol*. 2001;1:4-15.
66. Brand T, Kollmeier B. Efficient adaptive procedures for threshold and concurrent slope estimates for psychophysics and speech intelligibility tests. *J Acoust Soc Am*. 2002;111:2801-2810. doi:10.1121/1.1479152.
67. Herrmann B, Henry MJ, Obleser J. Frequency-specific adaptation in human auditory cortex depends on the spectral variance in the acoustic stimulation. *J Neurophysiol*. 2013;109:2086-2096. doi:10.1152/jn.00907.2012.
68. Naatanen R, Winkler I. The concept of auditory stimulus representation in neuroscience. *Psychol Bull*. 1999;125:826-859.
69. Riecke L, Sack AT, Schroeder CE. Endogenous delta/theta sound-brain phase entrainment accelerates the buildup of auditory streaming. *Curr Biol*. 2015;25:3196-3201. doi:10.1016/j.cub.2015.10.045.
70. Williams E. Experimental designs balanced for the estimation of residual effects of treatments. *Aust J Chem*. 1949;2:149-168. doi:10.1071/CH9490149.
71. Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Front Psychiatry*. 2012;3:91. doi:10.3389/fpsy.2012.00091.
72. Schutter DJLG, Wischniewski M. A meta-analytic study of exogenous oscillatory electric potentials in neuroenhancement. *Neuropsychologia*. 2016;86:110-118. doi:10.1016/j.neuropsychologia.2016.04.011.
73. Kasten FH, Duecker K, Maack MC, Meiser A, Herrmann CS. Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. *Nat Commun*. 2019;10:1-11. doi:10.1038/s41467-019-13417-6.
74. Stecher HI, Herrmann CS. Absence of alpha-tACS aftereffects in darkness reveals importance of taking derivations of stimulation frequency and individual alpha variability into account. *Front Psychol*. 2018;9:1-9. doi:10.3389/fpsyg.2018.00984.
75. Herrmann CS, Strüber D. What can transcranial alternating current stimulation tell us about brain oscillations? *Curr Behav Neurosci Rep*. 2017;4:128-137. doi:10.1007/s40473-017-0114-9.
76. Lafon B, Henin S, Huang Y, et al. Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nat Commun*. 2017;8:1-14. doi:10.1038/s41467-017-01045-x.
77. Liu A, Vöröslakos M, Kronberg G, et al. Immediate neurophysiological effects of transcranial electrical stimulation. *Nat Commun*. 2018;9:5092. doi:10.1038/s41467-018-07233-7.
78. Ruhnau P, Rufener KS, Heinze HJ, Zaehle T. Sailing in a sea of disbelief: in vivo measurements of transcranial electric stimulation in human subcortical structures. *Brain Stimul*. 2018;11:241-243. doi:10.1016/j.brs.2017.09.015.
79. Vöröslakos M, Takeuchi Y, Brinyiczki K, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nat Commun*. 2018;9:483. doi:10.1038/s41467-018-02928-3.
80. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nat Commun*. 2019;10:266. doi:10.1038/s41467-018-08183-w.
81. Heimrath K, Fiene M, Rufener KS, Zaehle T. Modulating human auditory processing by transcranial electrical stimulation. *Front Cell Neurosci*. 2016;10:53. doi:10.3389/fncel.2016.00053.
82. Wöstmann M, Vosskuhl J, Obleser J, Herrmann CS. Opposite effects of lateralised transcranial alpha versus gamma stimulation on auditory spatial attention. *Brain Stimul*. 2018;11:752-758. doi:10.1016/j.brs.2018.04.006.
83. Neuling T, Ruhnau P, Weisz N, Herrmann CS, Demarchi G. Faith and oscillations recovered: on analyzing EEG/MEG signals during tACS. *NeuroImage*. 2017;147:960-963. doi:10.1016/j.neuroimage.2016.11.022.
84. Witkowski M, Garcia-Cossio E, Chander BS, et al. Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS). *NeuroImage*. 2016;140:89-98. doi:10.1016/j.neuroimage.2015.10.024.
85. Kasten FH, Herrmann CS. Recovering brain dynamics during concurrent tACS-M/EEG: an overview of analysis approaches and their methodological and interpretational pitfalls. *Brain Topogr*. 2019;32:1013-1019. doi:10.1007/s10548-019-00727-7.
86. Kasten FH, Negahbani E, Fröhlich F, Herrmann CS. Non-linear transfer characteristics of stimulation and recording hardware account for spurious low-frequency artifacts during amplitude modulated transcranial alternating

- current stimulation (AM-tACS). *NeuroImage*. 2018;179:134-143. doi:10.1016/j.neuroimage.2018.05.068.
87. Neuling T, Wagner S, Wolters CH, Zaehle T, Herrmann CS. Finite-element model predicts current density distribution for clinical applications of tDCS and tACS. *Front Psychiatry*. 2012;3:83. doi:10.3389/fpsyt.2012.00083.
88. Di Liberto GM, Lalor EC. Indexing cortical entrainment to natural speech at the phonemic level: methodological considerations for applied research. *Hear Res*. 2017;348:70-77. doi:10.1016/j.heares.2017.02.015.
89. Power AJ, Foxe JJ, Forde EJ, Reilly RB, Lalor EC. At what time is the cocktail party? a late locus of selective attention to natural speech. *Eur J Neurosci*. 2012;35:1497-1503. doi:10.1111/j.1460-9568.2012.08060.x.
90. Salvari V, Paraskevopoulos E, Chalas N, et al. Auditory categorization of man-made sounds versus natural sounds by means of MEG functional brain connectivity. *Front Neurosci*. 2019;13:1052. doi:10.3389/fnins.2019.01052.
91. Stephens GJ, Honey CJ, Hasson U. A place for time: the spatiotemporal structure of neural dynamics during natural audition. *J Neurophysiol*. 2013;110:2019-2026. doi:10.1152/jn.00268.2013.
92. Wöstmann M, Fiedler L, Obleser J. Tracking the signal, cracking the code: speech and speech comprehension in non-invasive human electrophysiology. *Lang Cogn Neurosci*. 2017;32:855-869. doi:10.1080/23273798.2016.1262051.
93. Zoefel B, VanRullen R. EEG oscillations entrain their phase to high-level features of speech sound. *NeuroImage*. 2016;124:16-23. doi:10.1016/j.neuroimage.2015.08.054.