

1 **Dual-site high-density 4Hz transcranial alternating current stimulation**
2 **applied over auditory and motor cortical speech areas does not**
3 **influence auditory-motor mapping**

4 Basil Preisig^{1,2}, Matthias J. Sjerps^{1,2}, Anne Kösem^{1,2,3}, & Lars Riecke⁴

5

6 ¹Donders Institute for Cognitive Neuroimaging, Radboud University, Kapittelweg 29, 6525 EN
7 Nijmegen, the Netherlands

8 ²Max Planck Institute for Psycholinguistics, Wundtlaan 1, 6525 XD Nijmegen, the Netherlands

9 ³Lyon Neuroscience Research Center (CRNL), Brain Dynamics and Cognition Team, INSERM
10 U1028, CNRS UMR5292, Université Claude Bernard Lyon 1, Lyon, France

11 ⁴Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht
12 University, 6229 EV Maastricht, the Netherlands

13

14

15 *Address for correspondence: Basil C. Preisig, PhD, basilpreisig@gmx.ch

16

1 **Abstract**

2 *Background:* Verbal repetition of auditory speech requires the mapping of a sensory acoustic
3 input onto articulatory motor plans (auditory-motor mapping). Recent evidence indicates that
4 auditory-motor mapping could rely on low frequency neural synchronization (i.e., theta
5 oscillatory phase coupling) between sensory and motor speech areas.

6 *Objective:* In the present study, we apply dual-site high-density (HD) Transcranial Alternating
7 Current Stimulation (TACS) above the auditory and motor cortex to induce, or disrupt, theta
8 phase coupling between the two areas. We predicted that functionally coupling the two areas
9 would strengthen auditory-motor mapping, compared with functionally decoupling them. We
10 assessed the strength of auditory-motor mapping using a verbal repetition task.

11 *Results:* We found no significant effect of TACS-induced theta phase coupling on auditory-
12 motor mapping as indexed by verbal repetition performance.

13 *Conclusion:* Auditory-motor mapping may rely on a different mechanism than we
14 hypothesized, for example, oscillatory phase-coupling outside the theta range. Alternatively,
15 modulation of interregional theta-phase coupling may require more effective stimulation
16 protocols, for example, TACS at higher intensities.

17

18 **Keywords:** tACS, speech, auditory cortex, motor cortex, verbal repetition, neural oscillations

19

1 **1 Introduction**

2 Speaking requires the mapping of speech sounds onto articulatory motor plans (auditory-motor
3 mapping). According to current speech processing models, the mapping of auditory speech
4 representations onto articulatory motor plans is accomplished by the dorsal processing stream.
5 This processing stream connects the posterior superior temporal lobe and the ventral premotor
6 cortex/posterior Broca's area via a sensorimotor interface in the Sylvian fissure at the boundary
7 between the parietal and temporal lobes (area SPT) [1–3]. There is substantial evidence for
8 dorsal stream involvement in auditory-motor mapping [4–8]. However, the neural bases of
9 auditory-motor mapping are only partially understood.

10 Previous research in healthy participants and in patients with brain lesion has provided causal
11 evidence for dorsal stream processing during auditory-motor mapping: For instance, it has been
12 shown that auditory-motor mapping, as measured by verbal repetition of auditory sentences,
13 pseudowords, or syllables, can be modulated in healthy participants by exciting or inhibiting
14 cortical regions belonging to the left dorsal stream with Transcranial Magnetic Stimulation
15 (TMS) [5,6]. Moreover, studies using various methods (histology, lesion mapping and diffusion
16 tensor-imaging) have provided converging evidence for the relevance of dorsal stream integrity
17 for auditory-motor mapping [4,7–9].

18 In the present study, we further investigated the mechanism underlying the interaction (or
19 ‘communication’) between auditory and motor cortex during auditory-motor mapping. We
20 hypothesized that the communication between the two regions is mediated by interregional
21 synchronization of local theta (3-7Hz) oscillations [10–12]. This idea is motivated by two recent
22 studies that have investigated frontotemporal oscillatory coupling during passive story listening
23 [13] and syllable processing [14]. Park and colleagues [13] found that the frontal and motor
24 cortices modulate the phase of speech-coupled low-frequency oscillations in the auditory
25 cortex. Moreover, Assaneo & Poeppel [14] reported that neural oscillatory synchronization of

1 auditory and motor cortex during syllable processing is restricted to the theta range, peaking at
2 ~4.5Hz, close to the natural syllable rate across languages [14]. More generally, the theta
3 frequency band is thought to play a functional role in auditory speech perception because it
4 overlaps with intelligibility-relevant temporal fluctuations in the acoustic speech signal (~1-
5 8Hz). Ongoing theta oscillations in auditory cortex can align to the amplitude envelope of an
6 acoustic speech signal, a phenomenon called speech-brain entrainment [15] that may contribute
7 to the linguistic/phonological analysis of speech signals (for a review see [16]).

8 Previous brain stimulation studies have shown that speech perception can be modulated with
9 4-Hz transcranial alternating current stimulation (TACS), suggesting a causal role of theta
10 speech-brain entrainment in speech comprehension [17]. Here, we used TACS to disrupt or
11 enhance the communication between auditory and motor areas during auditory-motor mapping,
12 by modulating interregional phase-coupling of local theta oscillations in auditory cortex and
13 motor cortex. We assessed the causal influence of TACS-induced interregional phase-coupling
14 on auditory-motor mapping using a behavioral task that required participants to listen to and
15 verbally repeat nonwords. Verbal repetition is a auditory-motor task commonly used to assess
16 dorsal stream processing, i.e., auditory-motor mapping [2,18]. To induce interregional theta
17 phase-coupling (synchronization) between auditory cortex and motor cortex, we applied theta
18 (4Hz) TACS simultaneously above each of the two regions (in-phase stimulation). Theta-TACS
19 is thought to entrain theta oscillatory phase in cortex ([19–22], but see also [23]). To decouple
20 (desynchronize) the two regions, we included a second TACS condition in which we reversed
21 the phase of TACS above one of the regions (anti-phase stimulation). We predicted that stronger
22 auditory-motor theta phase-coupling (in-phase stimulation vs. anti-phase stimulation) would
23 lead to an improvement in auditory-motor mapping that would be reflected by an improvement
24 in verbal repetition performance.

25 To allow for a manipulation check, we further varied the phase relationship between the
26 auditory syllables and the 4-Hz TACS. We reasoned that the observation of a cyclic modulation

1 of verbal repetition performance would validate our a priori assumption that TACS entrained
2 theta oscillatory phase, which is difficult to verify with simultaneously obtained
3 electrophysiological measures [24]. Our results reveal no significant effect of our theta-phase
4 coupling manipulation on auditory-motor mapping.

5 **2 Material & Methods**

6 **2.1 Participants**

7 19 right-handed healthy volunteers (13 female, age: $M = 22$, $SD = 2.33$) participated in the
8 study. All participants had normal or corrected-to-normal visual acuity. The participants
9 reported no history of neurological, psychiatric, or hearing disorders. They had normal hearing
10 (defined as hearing thresholds of less than 25 dB HL at 250, 500, 750, 1000, 1500, 3000, and
11 4000Hz), according to a pure tone audiometry screening. All participants fulfilled the inclusion
12 criteria for noninvasive brain stimulation as assessed by a prior screening and gave written
13 informed consent prior to the experiment. Ethical approval to conduct this study was provided
14 by the local ethics committee (CMO region Arnhem-Nijmegen). The present study was
15 conducted in accordance with the principles of the latest version of the Declaration of Helsinki.

16 **2.2 Stimuli**

17 Trisyllabic nonword stimuli were created out of a sequence of three Dutch consonant vowel
18 (CV) syllables. CVs were composed of the voiceless consonants, /k/, /p/, and /t/, and the vowels
19 /y:/, /u:/, and /ʏ/ (“uu”, “oe” and “uh”). This led to a total of 9 combinations that were recorded
20 from a female Dutch speaker. The vowel part of the recorded CVs was time-compressed using
21 Praat [25] to obtain natural sounding syllables, but with equal durations (125ms). Syllables
22 were interleaved with 125-ms silent gaps, resulting in a syllable rate of 4Hz within each
23 nonword stimulus. The nonwords were built based on all CV combinations that contained three
24 different consonants and three different vowels, which led to a set of 36 unique stimuli. A
25 random subset of 18 stimuli was used for training and main experiment in the first session, and

1 the other half in the second session. All nonword stimuli were presented in stationary noise that
2 was matched to the average spectrum of the speech.

3 **2.3 Electric stimulation**

4 Electric currents were applied through two HD electrode configurations each consisting of
5 concentric conductive rubber electrodes [26]: a central round electrode, radius = 1.0 cm, and a
6 surrounding ring electrode (inner radius = 3.5 cm, outer radius = 4.0 cm). The central electrodes
7 were placed according to the international 10-20 system, in between FT7 and FC5 (frontal
8 configuration), and P7 and P5 (temporal configuration). These configurations were chosen to
9 produce relatively strong currents in the target regions, which were the speech motor areas (i.e.,
10 left inferior frontal cortex) and auditory speech areas (i.e., left superior temporal cortex), as
11 suggested by prior electric field simulations on a standard head model using the simnibs toolbox
12 [27].

13 Sinusoidal current stimulation was applied through two battery-driven transcranial current
14 stimulators (Neuroconn, Ilmenau, Germany). The frequency of the TACS current matched the
15 syllable rate of the nonword stimuli, i.e., 4Hz. TACS intensity was set to 1mA peak-to-peak
16 and kept constant across participants. The current density was 0.4 mA/cm² at the center and 0.1
17 mA/cm² at the concentric ring electrode. Impedance was kept below 10 kΩ. Before starting the
18 actual experiment, we assured that all participants well tolerated stimulation intensity.
19 Stimulation was ramped over the first and the last 10 s of each experimental block using raised-
20 cosine ramps.

21 The timing of the electric and auditory stimuli was controlled using a multichannel D/A
22 converter (National Instruments, sampling rate: 16kHz) and Datastreamer software [28]. Visual
23 stimulation and response recording were controlled using Presentation® software (Version
24 18.0, Neurobehavioral Systems, Inc., Berkeley, CA).

1 **2.4 Experimental design and task**

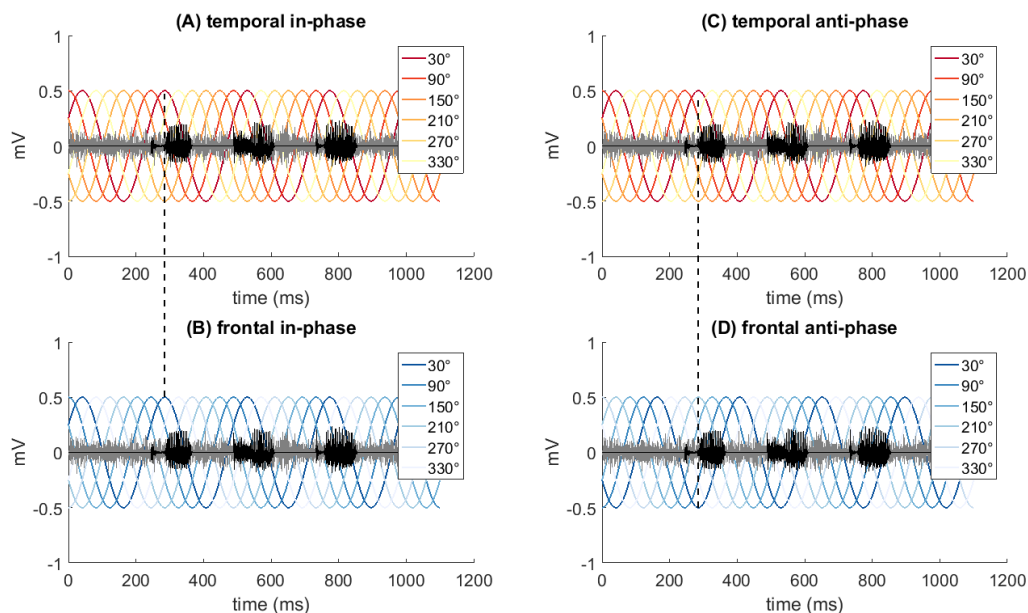
2 Verbal repetition performance was assessed using a verbal repetition task that required
3 participants to listen to each nonword and to verbally repeat it as accurately and as quickly as
4 possible. The verbal response intervals were defined by inter-stimulus interval (ISI) of
5 approximately 6 seconds. The exact ISI depended on the phase lag condition of two consecutive
6 trials. The experimental procedure included two sessions that were conducted within 5 to 10
7 days. Participants were seated in a sound-attenuated booth and first familiarized with the verbal
8 repetition task in a stepwise procedure: First, they listened to and repeated all CV syllables three
9 times. The noise in this phase of the experiment was set to a moderate level (SNR: +10 dB).
10 Second, nonword repetition was practiced audiovisually (i.e., with the addition that written
11 nonwords were presented on the screen) at the same noise level. Third, nonword repetition was
12 practiced again without visual presentation. Finally, to avoid potential range effects, an adaptive
13 staircase procedure [29] was used that identified the individual noise level (SNR, $M = -0.64$ SD
14 = 3.04) yielding an intermediate performance level of 70%.

15 Each session of the experiment consisted of three experimental blocks each representing a
16 different stimulation condition: *in-phase*, *anti-phase*, or *sham stimulation*. 1) *In-phase*
17 *stimulation* was applied with relative phase lag of 0° between the central electrodes placed over
18 the motor (i.e., left inferior frontal) and sensory speech areas (i.e., left superior temporal lobe),
19 i.e., frontotemporal synchronization. 2) *Anti-phase stimulation* was applied with a relative
20 phase lag of 180° between the central frontal electrode relative to the central temporal electrode,
21 i.e., frontotemporal desynchronization. 3.) During *sham stimulation* (placebo) the onset ramp
22 was followed immediately by an offset ramp, i.e., no stimulation was applied during the actual
23 experiment. The ramp was repeated at the end of the block. The order of stimulation conditions
24 was reversed across consecutive sessions and counterbalanced across participants.

25 Following the procedure of previous studies [17,20,21], the relative timing of TACS and
26 nonword stimuli was manipulated across six different phase-lag conditions by varying the onset

1 of the nonword stimuli in steps of 30° (41.7ms) across the 4Hz TACS cycle. For a visual
2 illustration of the different experimental conditions see Figure 1.

3



4

5 Figure 1. Synchronization of electric and auditory stimulation, and synchronization/desynchronization
6 of temporal and frontal cortex. This is an illustration of the timing between the sinusoidal electric
7 currents (chromatic colors), the sound pressure curve of the stimulus (black) and the frequency matched
8 noise (grey). Sinusoids with different chromatic colors represent the six phase lag conditions. In-phase
9 stimulation (A+B) was applied with a relative phase lag of 0° (dotted line) between the temporal (A)
10 and the frontal cortex (B), i.e., frontotemporal synchronization. Anti-phase stimulation (C+D) was
11 applied with a relative phase lag of 180° (dotted line) between the temporal (C) relative to the frontal
12 cortex (D), i.e., frontotemporal desynchronization.

13

14 2.5 Data analysis

15 The behavioral data, i.e., recorded participant responses, were analyzed as follows: First, a
16 blinded research assistant scored the recordings from all trials offline. Afterwards, author BCP,
17 who was also blinded, scored one randomly selected block per participant. Interrater agreement
18 was high (raw agreement: 97% and Cohen's kappa: 0.85). Second, repetition performance was
19 calculated in each condition as the percentage of correctly repeated trials. Third, for each
20 participant and each stimulation condition, the six phase-lag conditions were concatenated to

1 build a time series that enabled assessing periodic variations in repetition performance across
2 the TACS cycle.

3 The phase lag that leads to the best performance (best lag) may vary across participants because
4 of anatomical differences, i.e., the relative orientation of the current flow to the stimulated
5 neural tissue. To compensate for such potential inter-individual differences, the phase-lag series
6 was realigned to the best lag (defined here as 0°) under the assumption that TACS modulated
7 performance at the critical 4Hz frequency. Importantly, to avoid non-independency the best lag
8 was excluded from subsequent analyses, as it necessarily represents the maximum of the time
9 series due to the best-phase alignment.

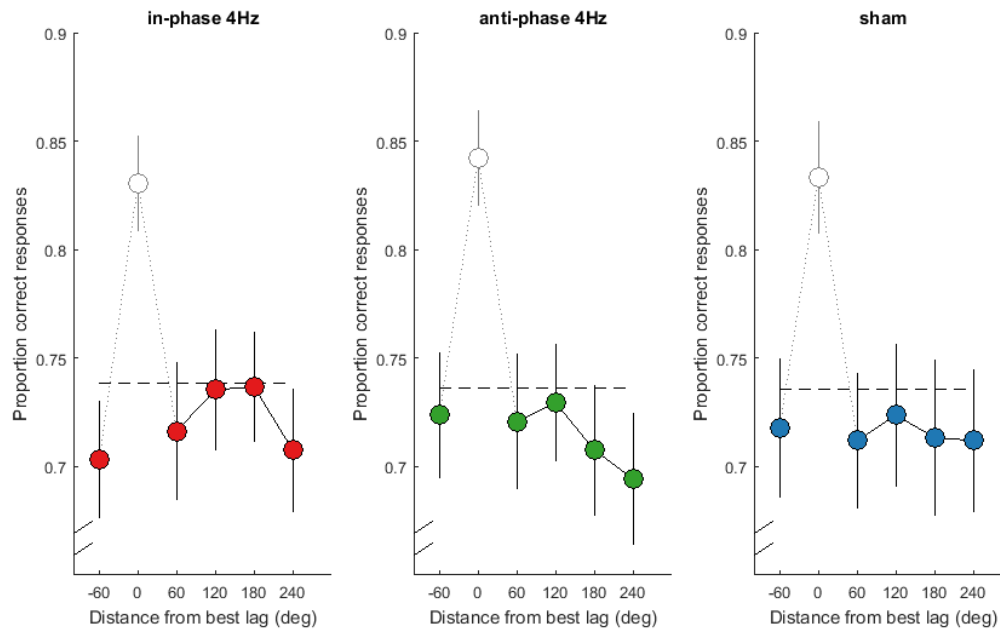
10 We tested whether interregional theta-phase coupling modulated behavioral performance by
11 comparing the aligned time series in the in-phase condition with the aligned time series in the
12 anti-phase condition. We further verified whether theta oscillatory phase indeed entrained to
13 our 4Hz TACS by comparing phase lags near the best lag (distance from best lag: 60° ; -60°),
14 which are supposed to delimit an ‘excitatory’ 4Hz half-cycle associated with relatively good
15 behavioral performance, with more distant lags (distance from best lag: 120° ; -240°) supposed
16 to delimit the opposite, i.e., an ‘inhibitory’ half-cycle associated with poorer performance. As
17 an additional test, we calculated the spectral density of the behavioral time series by applying
18 the Fast Fourier transformation and compared the power of the resulting different frequency
19 components within and across the different stimulation conditions (in-phase; anti-phase; sham).
20 If 4Hz TACS effects were caused by entrainment of theta oscillations, we expected behavior to
21 modulate in the theta range, and hence to observe maximum power at the 4Hz component.

22 Statistical testing was done using parametric tests for repeated measures. ANOVAs were used
23 to test for stimulation effect, session effect, phase (or frequency) effect, and interactions. Post
24 hoc comparisons were done using paired t-tests.

1 3 Results

2 Participants correctly responded on average $73.67\% \pm 3.5\%$ (mean \pm SEM) of the trials. The
3 average best lag across participants and stimulation conditions was $99^\circ \pm 23^\circ$ (mean \pm SEM),
4 which is equivalent to an audio lag of $69.05\text{ms} \pm 10.61\text{ms}$ (mean \pm SEM). The distribution of
5 the participants' best lags pooled across TACS conditions (in-phase and anti-phase) did not
6 deviate significantly from uniformity ($z = 1.789$, $p = 0.168$), suggesting that best lag varied
7 across participants. Moreover, best lag did not correlate significantly between sessions or
8 stimulation conditions ($ps >.70$). Therefore, participants' data were aligned to the best lag
9 separately for each session and stimulation condition.

10 To test our main hypothesis regarding interregional phase coupling, we analyzed the impact of
11 Stimulation condition across phase lags and sessions. A three-way repeated measures ANOVA,
12 including the within subject-factors *Stimulation condition* (in-phase; anti-phase; sham), *Phase*
13 *lag condition* after alignment (-60° ; 60° ; 120° ; 180° ; 240°), and *Session* (1; 2) was conducted.
14 The analysis did not reveal a main effect of *Session* ($p >.11$), nor an interaction *Stimulation*
15 *condition* x *Phase lag* x *Session* ($p >.39$). Therefore, the data were pooled across sessions and a
16 two-way repeated measures ANOVA, including only *Stimulation condition* (in-phase; anti-
17 phase; sham) and *Phase lag* (-60° ; 60° ; 120° ; 180° ; 240°) as factors was conducted. Contrary
18 to our predictions, we found no interaction *Stimulation condition* x *Phase lag* ($p >.57$), and no
19 significant main effect of *Stimulation condition* ($p >.91$) (Figure 2).



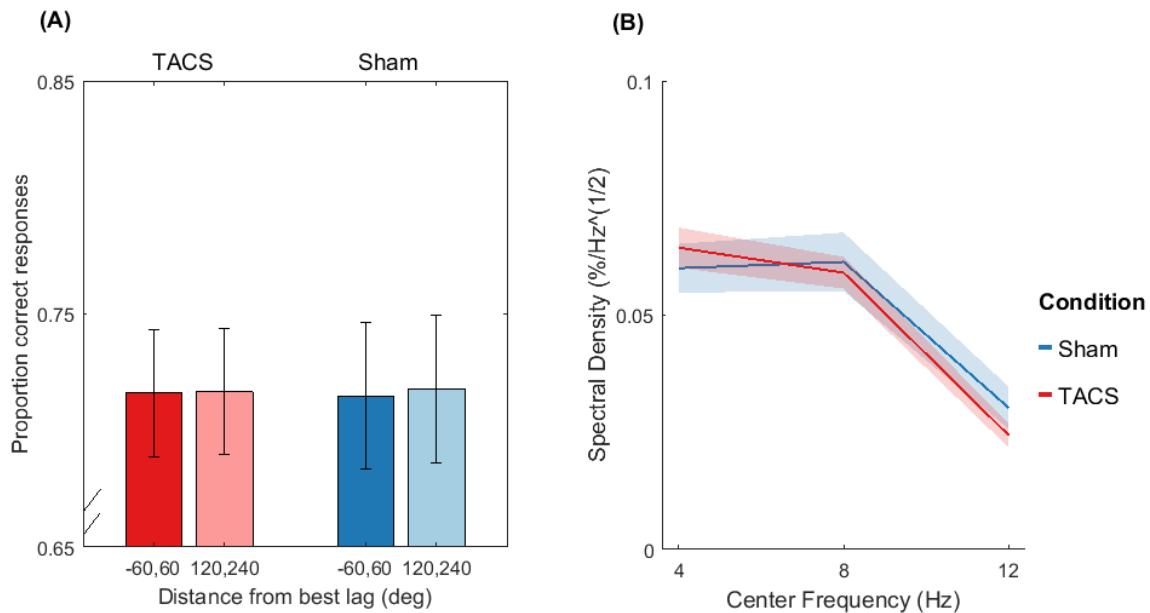
1

2 Figure 2. Participants' average performance (mean ± SEM across participants) as a function of phase
3 lag condition is shown for each stimulation condition (in-phase 4Hz; anti-phase 4Hz, and sham). The
4 peak performance at the best lag (0°) is trivial and was excluded from the analysis. The horizontal line
5 represents average performance per stimulation condition. Contrary to our predictions, performance
6 (pooled across phase-lag conditions) did not differ significantly across the three stimulation conditions.

7

8 To verify whether TACS entrained local theta oscillations independent of auditory-motor
9 mapping, we assessed whether performance was better at the presumed excitatory 4Hz half
10 cycle (-60°; 60°) vs. the presumed inhibitory half cycle (120°; 240°). A two-way repeated
11 measures ANOVA including the within-subject factors *TACS half cycle* (excitatory; inhibitory)
12 and *Stimulation Condition* (TACS; sham, the former was pooled across the in- and anti-phase
13 condition), revealed no significant interaction or main effect of *TACS half cycle* ($p > .69$) (Figure
14 3A). As an additional test of TACS phase, the spectral density of the behavioral time series was
15 analyzed. A two-way repeated measures ANOVA including the factors *Frequency* (4Hz; 8Hz;
16 12Hz) and *Stimulation condition* (TACS; sham) was conducted. The analysis revealed a
17 significant main effect of *Frequency* [$F(2,36) = 43.12, p < .01, \eta^2 = 0.388$], but no interaction
18 *Stimulation condition* × *Frequency* ($p > .32$), nor a main effect of *Stimulation condition* ($p > .70$).

1 Spectral power was significantly lower at 12Hz compared to 4Hz and 8Hz ($p_s < .01$, Holm-
2 Bonferroni-corrected) (Figure 3B).
3 In addition, we conducted exploratory analyses involving the application of the above analysis
4 to alternative measures (duration and latency of verbal productions). These analyses, which
5 were not in the focus of the study design, led to similar null results.



6
7 Figure 3. (A) The average performance (mean \pm SEM across participants) across the best-lag distances
8 presumed to resemble an excitatory half-cycle (-60, 60) and an inhibitory half-cycle (120, 240) did not
9 differ between TACS (pooled in-phase and anti-phase) and sham. (B) The power spectrum of the
10 behavioral times series (six phase lag conditions; see Figure 2) is shown for TACS vs sham. Our
11 prediction was that power peaks at the component corresponding to the TACS frequency and decreases
12 monotonically at higher frequencies. The analysis revealed indeed a main effect of frequency and
13 significantly lower power at 12Hz compared to 4Hz and 8Hz ($p_s < .01$, Holm-Bonferroni-corrected), but
14 these effects were not significantly stronger under TACS vs. sham.

15

1 **4 Discussion**

2 The aim of this study was to test whether inducing or disrupting the functional coupling between
3 auditory and motor speech areas in the theta range modulates auditory-motor mapping. We
4 hypothesized that theta phase coupling between the two areas would strengthen auditory-motor
5 speech mapping and that this would be observable as an improvement in listeners' ability to
6 verbally repeat nonwords. To test this, we applied theta-TACS simultaneously above listeners'
7 auditory cortex and motor cortex (either in-phase or anti-phase) to synchronize or
8 desynchronize the two areas and we measured the effect on verbal repetition performance. To
9 verify whether TACS successfully entrained theta oscillations, we varied the relative phase of
10 the auditory stimuli and TACS.

11 Our results show no significant effect of stimulation condition, i.e., no significant difference in
12 performance between in-phase compared to anti-phase stimulation, and no significant
13 difference between real stimulation compared to sham stimulation. In contrast to previous
14 studies on the auditory perception threshold [20,21,30] and speech comprehension [17,31], we
15 found no significant periodic variation in performance across TACS phases.

16 Our results indicate that auditory-motor mapping may rely on mechanisms different from
17 auditory-motor theta phase-coupling. Alternatively, it may rely on auditory-motor theta phase-
18 coupling as we have hypothesized, but we failed to observe this because of potential
19 methodological shortcomings. In the following paragraphs, we will discuss the two potential
20 interpretations in more detail.

21 First, auditory-motor mapping may rely on mechanisms different from auditory-motor theta
22 phase coupling. For example, auditory-motor mapping might depend on oscillatory phase
23 coupling, but in frequency bands outside the theta range that we investigated. The latter idea is
24 supported by two studies; for example, Schoffelen et al. [32] found that the direction of
25 information flow between language-relevant brain areas depends on the contribution of distinct

1 frequency bands while participants were visually presented with word lists and sentences. They
2 found that rhythmic activity in the alpha frequency range (8–12Hz) propagates from temporal
3 cortical areas to frontal cortical areas, whereas beta activity (15–30Hz) propagates in the
4 opposite direction, when participants read sentences and word lists during MEG recording.
5 Moreover, the results by Park and colleagues [13] indicate that top-down communication from
6 the left inferior frontal gyrus to the left auditory cortex during speech perception may be
7 stronger in the delta frequency band than the theta frequency band. Future studies may
8 investigate effects of phase-coupling in the delta, alpha, or beta range on auditory-motor
9 mapping using delta, alpha, or beta TACS respectively.

10 A second potential interpretation is that our verbal repetition task was not sensitive enough to
11 capture the presumed variations in auditory-motor mapping strength. However, Murakami and
12 colleagues [6] found TMS-induced modulations of auditory-motor mapping applying a similar
13 verbal repetition task. Their participants had to repeat single syllables and pseudowords
14 embedded in white noise. Furthermore, Restle et al [33] found TMS-induced effects while
15 participants had to repeat sentences in a foreign language. These previous findings thus indicate
16 that our behavioral measure (verbal repetition performance) is suited to capture effects of non-
17 invasive brain stimulation.

18 Third, in contrast to previously applied TMS protocols [6,33], perhaps our theta-TACS protocol
19 was not effective enough to modulate verbal auditory-motor mapping strength. This could be
20 related to two main parameters: electrode placement and stimulation intensity. For conventional
21 electrode configurations, larger electrodes (standard size 5 x 7 cm) are usually placed over
22 bilateral homologue stimulation sites, which leads to an extended electric field spanning the
23 area between the two stimulation electrodes in both cerebral hemispheres. In contrast, unilateral
24 HD configurations, like the concentric configuration applied in the current study, usually induce
25 more focal electric fields that are more restricted to the region of interest and surrounding brain
26 tissue in the hemisphere under the electrodes. The improved focality comes at the cost of a

1 lower current quantity penetrating the brain; because of the smaller distance between the
2 electrodes, more current is shunted through the skull or the cerebrospinal fluid [34]. Maybe this
3 disadvantage of unilateral HD-TACS outweighed the theoretical advantage of higher focality
4 [35] in the current study. Concerning stimulation intensity, it must be acknowledged that the
5 stimulation intensity in the present study (1mA peak-to-peak) was lower than the average
6 stimulation intensity in studies showing effects of theta-TACS on auditory perception (1.6mA
7 ± 0.1 peak-to-peak) and speech comprehension (1.8mA ± 0.1 peak-to-peak) [17,20,21]. The
8 reason for the lower stimulation intensity was that participants' sensation threshold tends to be
9 lower with the HD-configuration due to the relatively high current density related to the smaller
10 electrodes. In line with this potential limitation, it has been shown that transcranial direct current
11 stimulation is more effective in enhancing cortical excitability when applied at 2mA than at
12 1mA ([36], but see also [37]). Finally, there currently is controversy about whether theta-TACS
13 at its conventional intensity (1-2mA peak-to-peak) is powerful enough to entrain neural
14 oscillations. Lafon and colleagues [23] found no reliable effect of extracortical theta-TACS on
15 intracranial theta activity measured from implanted grid-electrodes in epilepsy patients.
16 Fourth, our TACS protocol may have been in fact effective (i.e., it entrained theta oscillatory
17 phase), but the motor act and/or the sound accompanying the utterance caused a reset of theta
18 phase that destroyed the TACS-induced phase entrainment. Indeed, a key difference to studies
19 that found theta-TACS-induced modulations of working memory [11,38–41] may be that our
20 participants had to perceive and verbally reproduce the presented nonwords. Moreover,
21 compared with TACS speech studies that used verbal repetition to test the recognition of
22 meaningful sentences [17,31], our speech stimuli were much shorter and thus provided less
23 opportunity for oscillations to recover from any articulation-induced phase reset.
24 Related to the previous point, it might be that in the previous TACS speech studies, successful
25 speech recognition required the participants to identify primarily the temporal structure of the
26 speech stimuli, thus facilitating the chunking and prediction of linguistic elements. In contrast,

1 successful verbal repetition of the artificial words in our study probably required more
2 articulatory cues. TACS may have provided temporal, not articulatory, cues that helped our
3 participants to identify the fixed temporal structure of our syllable sequences, not the identity
4 of the individual syllables. However, if articulation indeed disrupts endogenous and/or
5 exogenously induced theta entrainment, this would further question the functional role of theta-
6 phase coupling in auditory-motor mapping. This is an interesting question that should be
7 addressed in future studies. In this view, the role of theta oscillations is thus limited to the
8 temporal analysis of speech and auditory speech perception, but not speech
9 production/articulation.

10 In sum, based on these considerations the lack of an effect of theta phase coupling on auditory-
11 motor mapping may be ascribed to different physiologic mechanisms, i.e., phase coupling in a
12 different frequency band. Moreover, methodological limitation cannot be ruled out, specifically
13 insufficient TACS intensity. These interpretations could be further tested in future studies by
14 inducing interregional phase coupling within and across frequencies in the delta, alpha, or beta
15 range with dual-site HD TACS at higher intensity

16 **4.1 Conclusion**

17 In sum, our results do not conclusively advocate for a functional role of theta phase coupling in
18 auditory-motor mapping. Given the results of previous reports, neural phase coupling in other
19 bands, e.g., delta, alpha, or beta may play such a role. The results further highlight potential
20 limitations of unilateral dual-site HD TACS in interregional (de-) synchronization.

21 **5 Acknowledgments**

22 This work was supported by a grant awarded to B.C.P by the Swiss National Science
23 Foundation [P2BEP3_168728]. The authors would like to thank Birgit Knudsen, Iris Schmidt,
24 and Michel-Pierre Jansen for their assistance.

1 **6 Conflict / Declaration of Interest**

2 We wish to confirm that there are no known conflicts of interest associated with this publication
3 and there has been no significant financial support for this work that could have influenced its
4 outcome.

5

1 **7 References**

- 2 [1] Friederici AD. The brain basis of language processing: From structure to function. *Physiol Rev*
3 2011;91:1357–92. doi:10.1152/physrev.00006.2011.
- 4 [2] Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci*
5 2007;8:393–402. doi:doi.org/10.1038/nrn2113.
- 6 [3] Rauschecker JP, Scott SK. Maps and streams in the auditory cortex: nonhuman primates
7 illuminate human speech processing. *Nat Neurosci* 2009;12:718–24. doi:10.1038/nn.2331.
- 8 [4] Geschwind N. Disconnexion syndromes in animals and man II. *Brain* 1965;88:237–237.
- 9 [5] Restle J, Murakami T, Ziemann U. Facilitation of speech repetition accuracy by theta burst
10 stimulation of the left posterior inferior frontal gyms. *Neuropsychologia* 2012;50:2026–31.
11 doi:10.1016/j.neuropsychologia.2012.05.001.
- 12 [6] Murakami T, Kell CA, Restle J, Ugawa Y, Ziemann U. Left dorsal speech stream components
13 and their contribution to phonological processing. *J Neurosci* 2015;35:1411–22.
14 doi:10.1523/JNEUROSCI.0246-14.2015.
- 15 [7] Yourganov G, Smith KG, Fridriksson J, Rorden C. Predicting aphasia type from brain damage
16 measured with structural MRI. *Cortex* 2015;73:203–15. doi:10.1016/j.cortex.2015.09.005.
- 17 [8] Saur D, Kreher BW, Schnell S, Kümmerer D, Kellmeyer P, Vry M-S, et al. Ventral and dorsal
18 pathways for language. *Proc Natl Acad Sci* 2008;105:18035–40.
- 19 [9] Yourganov G, Fridriksson J, Rorden C, Gleichgerrcht E, Bonilha L. Multivariate connectome-
20 based symptom mapping in post-stroke patients: Networks supporting language and speech. *J*
21 *Neurosci* 2016;36:6668–79.
- 22 [10] Fell J, Axmacher N. The role of phase synchronization in memory processes. *Nat Rev Neurosci*
23 2011;12:105–18. doi:10.1038/nrn2979.
- 24 [11] Polania R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The Importance of Timing in
25 Segregated Theta Phase-Coupling for Cognitive Performance. *Curr Biol* 2012;22:1314–8.
26 doi:10.1016/j.cub.2012.05.021.
- 27 [12] Salazar RF, Dotson NM, Bressler SL, Gray CM. Content-specific fronto-parietal
28 synchronization during visual working memory. *Science* 2012:1224000.
29 doi:10.1126/science.1224000.

- 1 [13] Park H, Ince RAA, Schyns PG, Thut G, Gross J. Frontal top-down signals increase coupling of
2 auditory low-frequency oscillations to continuous speech in human listeners. *Curr Biol*
3 2015;25:1649–53. doi:10.1016/j.cub.2015.04.049.
- 4 [14] Assaneo MF, Poeppel D. The coupling between auditory and motor cortices is rate-restricted:
5 Evidence for an intrinsic speech-motor rhythm. *Sci Adv* 2018;4:eaao3842.
6 doi:10.1126/sciadv.aao3842.
- 7 [15] Zoefel B, VanRullen R. The role of high-level processes for oscillatory phase entrainment to
8 speech sound. *Front Hum Neurosci* 2015;9. doi:10.3389/fnhum.2015.00651.
- 9 [16] Kösem A, Wassenhove V van. Distinct contributions of low- and high-frequency neural
10 oscillations to speech comprehension. *Lang Cogn Neurosci* 2017;32:536–44.
11 doi:10.1080/23273798.2016.1238495.
- 12 [17] Riecke L, Formisano E, Sorger B, Başkent D, Gaudrain E. Neural entrainment to speech
13 modulates speech intelligibility. *Curr Biol* 2018;28:161–9. doi:10.1016/j.cub.2017.11.033.
- 14 [18] Hickok G, Poeppel D. Dorsal and ventral streams: A framework for understanding aspects of
15 the functional anatomy of language. *Cognition* 2004;92:67–99.
16 doi:10.1016/j.cognition.2003.10.011.
- 17 [19] Fehér KD, Nakataki M, Morishima Y. Phase-dependent modulation of signal transmission in
18 cortical networks through tACS-induced neural oscillations. *Front Hum Neurosci* 2017;11.
19 doi:10.3389/fnhum.2017.00471.
- 20 [20] Riecke L, Formisano E, Herrmann CS, Sack AT. 4-Hz transcranial alternating current
21 stimulation phase modulates hearing. *Brain Stimulat* 2015;8:777–83.
- 22 [21] Riecke L, Sack AT, Schroeder CE. Endogenous delta/theta sound-brain phase entrainment
23 accelerates the buildup of auditory streaming. *Curr Biol* 2015;25:3196–201.
- 24 [22] Zoefel B, Archer-Boyd A, Davis MH. Phase entrainment of brain oscillations causally
25 modulates neural responses to intelligible speech. *Curr Biol* 2018;28:401–408.e5.
26 doi:10.1016/j.cub.2017.11.071.
- 27 [23] Lafon B, Henin S, Huang Y, Friedman D, Melloni L, Thesen T, et al. Low frequency transcranial
28 electrical stimulation does not entrain sleep rhythms measured by human intracranial
29 recordings. *Nat Commun* 2017;8:1199. doi:10.1038/s41467-017-01045-x.

- 1 [24] Noury N, Siegel M. Analyzing EEG and MEG signals recorded during tES, a reply. *NeuroImage*
2 2018;167:53–61. doi:10.1016/j.neuroimage.2017.11.023.
- 3 [25] Boersma P, Weenink D. Praat: doing phonetics by computer [Computer program]. n.d.
- 4 [26] Bortoletto M, Rodella C, Salvador R, Miranda PC, Miniussi C. Reduced current spread by
5 concentric electrodes in transcranial electrical stimulation (tES). *Brain Stimulat* 2016;9:525–8.
6 doi:10.1016/j.brs.2016.03.001.
- 7 [27] Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation:
8 a useful tool to understand the physiological effects of TMS? *Eng. Med. Biol. Soc. EMBC 2015*
9 37th Annu. Int. Conf. IEEE, IEEE; 2015, p. 222–225. doi:10.1109/EMBC.2015.7318340.
- 10 [28] ten Oever S, Graaf D, A T, Bonnemayer C, Ronner J, Sack AT, et al. Stimulus presentation at
11 specific neuronal oscillatory phases experimentally controlled with tACS: Implementation and
12 applications. *Front Cell Neurosci* 2016;10. doi:10.3389/fncel.2016.00240.
- 13 [29] Levitt H. Transformed up-down methods in psychoacoustics. *J Acoust Soc Am* 1971;49:467–
14 77. doi:10.1121/1.1912375.
- 15 [30] Neuling T, Rach S, Wagner S, Wolters CH, Herrmann CS. Good vibrations: Oscillatory phase
16 shapes perception. *NeuroImage* 2012;63:771–8. doi:10.1016/j.neuroimage.2012.07.024.
- 17 [31] Wilsch A, Neuling T, Obleser J, Herrmann CS. Transcranial alternating current stimulation with
18 speech envelopes modulates speech comprehension. *NeuroImage* 2018;172:766–74.
19 doi:10.1016/j.neuroimage.2018.01.038.
- 20 [32] Schoffelen J-M, Hultén A, Lam N, Marquand AF, Uddén J, Hagoort P. Frequency-specific
21 directed interactions in the human brain network for language. *Proc Natl Acad Sci*
22 2017;114:8083–8. doi:10.1073/pnas.1703155114.
- 23 [33] Restle J, Murakami T, Ziemann U. Facilitation of speech repetition accuracy by theta burst
24 stimulation of the left posterior inferior frontal gyrus. *Neuropsychologia* 2012;50:2026–31.
25 doi:10.1016/j.neuropsychologia.2012.05.001.
- 26 [34] Faria P, Hallett M, Miranda PC. A finite element analysis of the effect of electrode area and
27 inter-electrode distance on the spatial distribution of the current density in tDCS. *J Neural Eng*
28 2011;8:066017. doi:10.1088/1741-2560/8/6/066017.

- 1 [35] Kuo H-I, Bikson M, Datta A, Minhas P, Paulus W, Kuo M-F, et al. Comparing cortical plasticity
2 induced by conventional and high-definition 4×1 ring tDCS: A neurophysiological study. *Brain*
3 *Stimulat* 2013;6:644–8. doi:10.1016/j.brs.2012.09.010.
- 4 [36] Chew T, Ho K-A, Loo CK. Inter- and intra-individual variability in response to transcranial
5 direct current stimulation (tDCS) at varying current intensities. *Brain Stimulat* 2015;8:1130–7.
6 doi:10.1016/j.brs.2015.07.031.
- 7 [37] Batsikadze G, Moliadze V, Paulus W, Kuo M-F, Nitsche MA. Partially non-linear stimulation
8 intensity-dependent effects of direct current stimulation on motor cortex excitability in humans.
9 *J Physiol* 2013;591:1987–2000. doi:10.1113/jphysiol.2012.249730.
- 10 [38] Alekseichuk I, Pabel SC, Antal A, Paulus W. Intrahemispheric theta rhythm desynchronization
11 impairs working memory. *Restor Neurol Neurosci* 2017;35:147–58. doi:10.3233/RNN-160714.
- 12 [39] Jaušovec N, Jaušovec K. Increasing working memory capacity with theta transcranial
13 alternating current stimulation (tACS). *Biol Psychol* 2014;96:42–7.
14 doi:10.1016/j.biopsycho.2013.11.006.
- 15 [40] Vosskuhl J, Huster RJ, Herrmann CS. Increase in short-term memory capacity induced by
16 down-regulating individual theta frequency via transcranial alternating current stimulation.
17 *Front Hum Neurosci* 2015;9.
- 18 [41] Röhner F, Breitling C, Rufener KS, Heinze H-J, Hinrichs H, Krauel K, et al. Modulation of
19 working memory using transcranial electrical stimulation: A direct comparison between TACS
20 and TDCS. *Front Neurosci* 2018;12. doi:10.3389/fnins.2018.00761.

21