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

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Introduction

Learning to speak and speaking require the continuous mapping of speech sounds onto articulatory motor plans (auditory-motor mapping). Previous studies using various techniques (histology, lesion mapping, diffusion tensor-imaging, and transcranial magnetic stimulation) have provided converging evidence for the relevance of a dorsal cortical processing stream, including auditory and motor areas, for auditory-motor mapping [1–4].

In the present study, we investigated the mechanism underlying the interaction (or ‘communication’) between auditory and motor cortex during auditory-motor mapping. We hypothesized that communication between the two regions is mediated by interregional synchronization of local theta (3–7Hz) oscillations. This idea is motivated by two recent studies that have investigated frontotemporal oscillatory coupling during passive story listening [5] and syllable processing [6].

We used transcranial alternating current stimulation (TACS) to disrupt or enhance the communication between auditory and motor cortices during auditory-motor mapping, by modulating the interregional phase-coupling of local theta oscillations in the two regions. Auditory-motor mapping was assessed using a behavioral task that required participants to listen to and verbally repeat nonwords. Nineteen healthy volunteers participated in the study (for details, see *Supplemental Material*). Electric currents were applied through two high-density (HD) electrode configurations each consisting of concentric conductive rubber electrodes [7]. The electrodes were centered over the speech motor areas (i.e., left inferior frontal cortex, between FT7 and FC5) and auditory speech areas (i.e., left superior temporal cortex, between and P7 and P5).

The experiment included three stimulation conditions: 1) *In-phase stimulation* was applied with a relative phase lag of 0° between the central electrodes placed over the motor and auditory areas to induce frontotemporal synchronization. 2) *Anti-phase stimulation* was applied with a relative phase lag of 180° to induce frontotemporal desynchronization. 3) Sham stimulation (placebo; for details, see *Supplemental Material*).

Verbal repetition performance was assessed while trained participants listened and repeated nonword stimuli. The stimuli were presented in noise at an individually tailored signal-to-noise ratio. They consisted of three syllables presented at a rate of 4Hz. The same frequency was used for the TACS current. To consider that the phase at which TACS exerts its strongest auditory effect (‘best lag’) may vary across individuals, the relative timing of TACS and nonword stimuli was varied across six phase lags spanning one TACS cycle [8] (Fig. 1A).

For data analysis, repetition performance was calculated in each condition as the percentage of correctly repeated trials. Afterwards, for each participant and each stimulation condition, the six phase-lag conditions were concatenated to build a time series and its maximum (best lag) was subsequently aligned across individuals to compensate for inter-individual variations.

TACS-induced modulation of interregional theta-phase coupling was assessed by comparing participants' repetition performance across the aligned time series in the different stimulation conditions. This was done using a two-way repeated measures ANOVA, including *Stimulation condition* (in-phase; anti-phase; sham) and *Phase lag* (−60°; 60°; 120°; 180°; 240°). Contrary to our predictions, this analysis revealed no significant interaction of *Stimulation condition* x *Phase lag* ($p > .57$), and no significant main effect of *Stimulation condition* ($p > .91$) (Fig. 1B).

These results provide no evidence that auditory-motor cortical theta synchronization mediates auditory-motor speech mapping. One potential interpretation is that auditory-motor mapping may rely on mechanisms different from auditory-motor theta phase coupling. For example, auditory-motor mapping might depend on oscillatory phase coupling, but in frequency bands outside the theta range that we investigated [5,9]. The latter idea is supported by two studies; for example, Schoffelen et al. [9] found that the direction of information flow between language-relevant brain areas depends on the contribution of distinct frequency bands. They found that rhythmic activity in the alpha frequency range (8–12Hz) propagates from temporal cortical areas to frontal cortical areas, whereas beta activity (15–30Hz) propagates in the opposite direction, when participants read sentences and word lists during MEG recording. Moreover, the results by Park and colleagues [5] indicate that top-down communication from the left inferior frontal gyrus to

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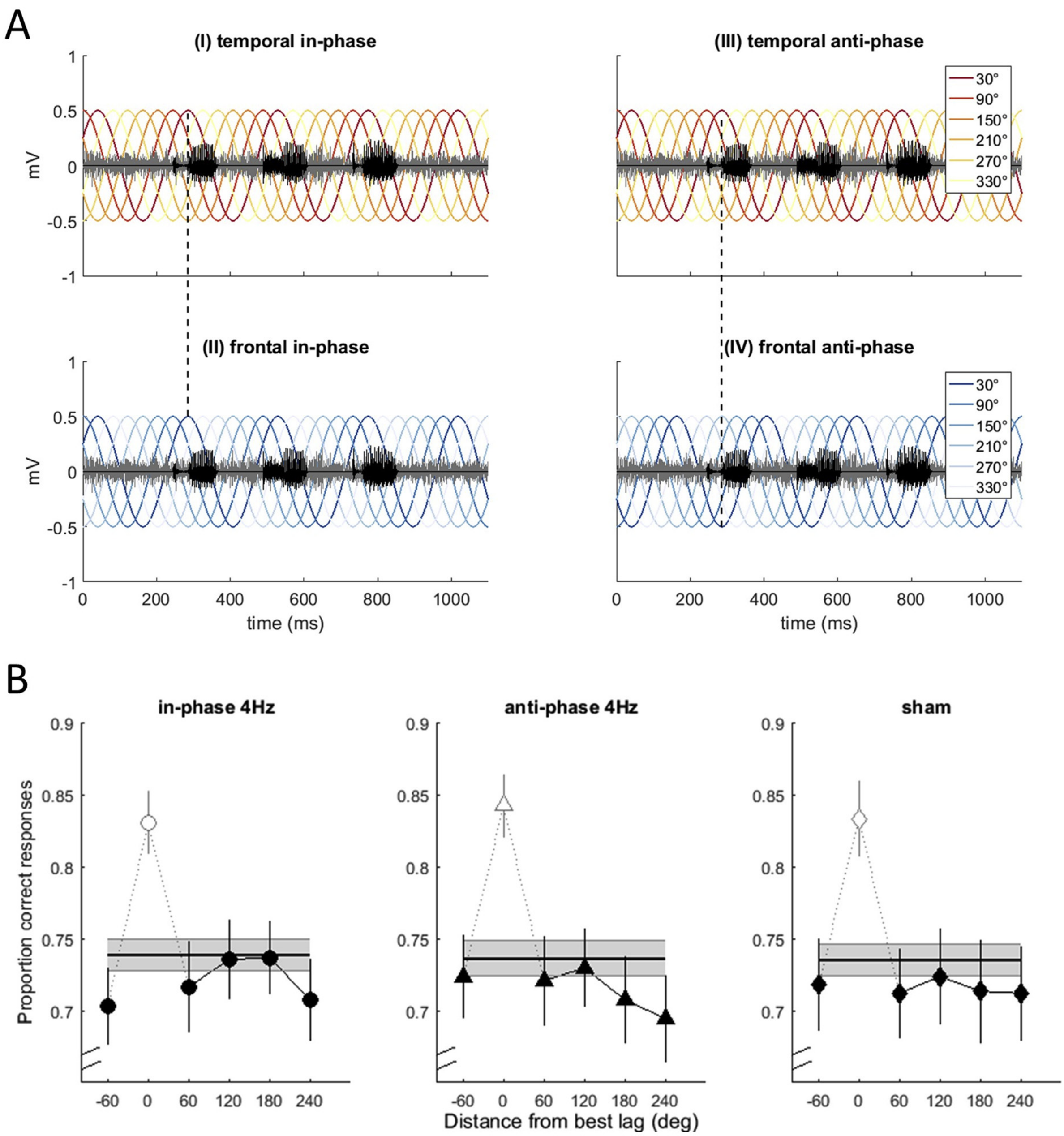

Figure 1. (A) Synchronization of electric and auditory stimulation, and synchronization/desynchronization of temporal and frontal cortex. This is an illustration of the timing between the sinusoidal electric currents (chromatic colors), the sound pressure curve of the stimulus (black) and the frequency matched noise (grey). Sinusoids with different chromatic colors represent the six phase lag conditions. In-phase stimulation (I + II) was applied with a relative phase lag of 0° (dotted line) between the temporal (I) and the frontal cortex (I + II), i.e., frontotemporal synchronization. Anti-phase stimulation (III + IV) was applied with a relative phase lag of 180° (dotted line) between the temporal (III) relative to the frontal cortex (IV), i.e., frontotemporal desynchronization.
(B) Participants' average performance (mean ± SEM across participants) as a function of phase lag condition is shown for each stimulation condition (in-phase 4Hz; anti-phase 4Hz, and sham) after alignment to the individual best lag. The peak performance at 0° is trivial and was excluded from the analysis. The horizontal line represents average performance per stimulation condition (mean ± SEM across participants). Contrary to our predictions, performance (pooled across phase-lag conditions) did not differ significantly across the three stimulation conditions.

the left auditory cortex during speech perception may be stronger in the delta frequency band than the theta frequency band.

A second possibility is that auditory-motor mapping relies on auditory-motor theta phase-coupling as we have hypothesized, but we failed to observe this because our theta-TACS protocol was not effective enough to modulate the strength of auditory-motor mapping. This interpretation, which is supported by supplemental results on TACS-induced theta phase entrainment (see supplemental Figure S1), could be related to electrode placement and stimulation intensity. Conventional electrode configurations usually include larger electrodes (standard size 5 × 7 cm) placed over bilateral homologue stimulation sites, which leads to an extended electric field spanning the area between the two stimulation electrodes in both cerebral hemispheres. In contrast, unilateral HD configurations, like our configuration, usually induce focal electric fields that are more restricted to the region of interest and surrounding brain tissue. The improved focality comes at the cost of a lower current quantity penetrating the brain; because of the smaller distance between the electrodes, more current is shunted through the skull or the cerebrospinal fluid [10].

Concerning stimulation intensity, it must be noted that the stimulation intensity in the present study (1mA peak-to-peak) was lower than the average stimulation intensity in another study of theta-TACS speech comprehension ($1.8mA \pm 0.1$ peak-to-peak) [10]. The reason for the lower stimulation intensity was that participants' sensation threshold tends to be lower with the HD-configuration due to the relatively high current density related to the smaller electrodes.

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

Conflict/Declaration of interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.01.007.

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