Selective modulation of interhemispheric connectivity by transcranial alternating current stimulation influences binaural integration

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Brain connectivity plays a major role in the encoding, transfer, and integration of sensory information. Interregional synchronization of neural oscillations in the γ-frequency band has been suggested as a key mechanism underlying perceptual integration. In a recent study, we found evidence for this hypothesis showing that the modulation of interhemispheric oscillatory synchrony by means of bihemispheric high-density transcranial alternating current stimulation (HD-TACS) affects binaural integration of dichotic acoustic features. Here, we aimed to establish a direct link between oscillatory synchrony, effective brain connectivity, and binaural integration. We experimentally manipulated oscillatory synchrony (using bihemispheric γ-TACS with different interhemispheric phase lags) and assessed the effect on effective brain connectivity and binaural integration (as measured with functional MRI and a dichotic listening task, respectively). We found that TACS reduced intrahemispheric connectivity within the auditory cortices and antiphase (interhemispheric phase lag 180°) TACS modulated connectivity between the two auditory cortices. Importantly, the changes in intra- and interhemispheric connectivity induced by TACS were correlated with changes in perceptual integration. Our results indicate that γ-band synchronization between the two auditory cortices plays a functional role in binaural integration, supporting the proposed role of interregional oscillatory synchrony in perceptual integration.

Significance

Sensory processing depends upon the integration of widely distributed neural assemblies. During every day listening, our ears receive different information (due to interaural time and amplitude differences) and it is known that both hemispheres extract different acoustic features. Nonetheless, acoustic features belonging to the same source become integrated. It has been suggested that the brain overcomes this “binding problem” by synchronization of oscillatory activity across the relevant regions. Here we probe interhemispheric oscillatory synchronization as a mechanism for acoustic feature binding using bihemispheric transcranial alternating current stimulation. Concurrent functional MRI reveals that antiphase stimulation of auditory areas changes effective connectivity between these areas, and that this change in connectivity predicts perceptual integration of dichotic stimuli.

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Interhemispheric integration relies on commissural fibers linking homotopic sensory cortices in both hemispheres (26). Seminal work in the mammalian visual system demonstrated that a complete section of the corpus callosum blocks the information transfer from one to the other brain hemisphere (27-29). In the human auditory system, cross-hemispheric integration relies on structural connections linking the auditory cortices within the posterior third (isthmus/splenium) of the corpus callosum (30, 31). The functional relevance of these pathways has been demonstrated in lesion studies (10, 32, 33) and dichotic listening studies (34, 35). Mechanistically, auditory integration across hemispheres may rely on oscillatory synchrony in the γ-frequency band (36). In a recent study, we found evidence for this hypothesis, showing that external modulation of oscillatory synchrony by means of high-density (HD) transcranial alternating current stimulation (TACS), a neuromodulatory technique allowing noninvasive modulation of phase synchronization between cortical regions (37-40), changes the propensity of auditory integration during dichotic listening (41).

However, the neurophysiological origin of the reported behavioral effect remains unclear. In the present study, we reasoned that TACS modulates the interhemispheric connectivity between the auditory cortices and this leads to changes in perceptual integration, but this assumption still needs to be verified with simultaneous physiological measures. To this end, we combined functional MRI (fMRI) with bihemispheric HD-TACS over the bilateral superior temporal lobe and we tested whether TACS-induced modulation of auditory integration (41) is mediated by changes in interhemispheric brain connectivity. Bilateral γ-TACS was applied in two conditions: In-phase TACS (0° interhemispheric phase lag) and antiphase TACS (180° interhemispheric phase lag) (Fig. 1). The effects of TACS were quantified by the comparison with a sham stimulation condition. We hypothesized that TACS induces phase lag-selective changes in interhemispheric connectivity that correlate with TACS-related changes in binaural integration.

To test the putative effect of TACS on interhemispheric auditory connectivity, we analyzed TACS-induced modulations of interhemispheric effective connectivity on the bilateral Heschl’s gyrus (HG) and posterior superior temporal sulcus (pSTS). Both areas showed strong auditory activation that was modulated by TACS. We quantified interhemispheric brain connectivity using fMRI and dynamic causal modeling (DCM), an established approach for directed effective connectivity analysis (42) (SI Appendix, Fig. S1).

We found that the integration of binaurally presented acoustic features is related to effective interhemispheric connectivity between the auditory cortices. Furthermore, our results show that γ-TACS induced a phase lag-selective modulation of interhemispheric connectivity between the auditory cortices: Bilateral TACS with an interhemispheric phase lag of 180° (TACS 180°), but not without such a lag (TACS 0°), reduced interhemispheric connectivity. Importantly, the TACS-induced changes in effective connectivity were correlated with TACS-induced behavioral changes of perceptual integration.

**Results**

**Auditory Integration.** To behaviorally evaluate interhemispheric auditory integration, we used a dichotic listening task. This task exploits the phenomenon that the dichotic presentation of an ambiguous speech sound (intermediate between the syllables /da/ and /ga/) and a spectral acoustic feature (third formant, F3), supporting either a /ga/ interpretation (low F3 ~2.5 kHz) or a /da/ interpretation (high F3 ~2.9 kHz), can lead to an integrated syllable percept (Fig. 2). Binaural acoustic feature integration can occur independently of the ear to which the feature is presented. Previously, we found a slight response time advantage for the left ear (LE) (43). Hence, the acoustic feature was presented to the LE and the ambiguous speech sound to the right ear (RE).

Twenty-eight participants heard ambiguous syllables whose perceived identity depends upon auditory integration of the spectral acoustic feature (binaural integration). Occasionally, clear stimuli that could be readily interpreted based on monaural input were presented as catch-up to monitor task adherence (for details, see Materials and Methods). Participants were asked to indicate by button press with the index finger of their left hand, whether they heard the syllables /da/ or /ga/. Behavioral analyses indicated that participants could successfully integrate the spectral acoustic feature: The proportion of integrated trials (trials on which the participant’s response matched with acoustic feature presented to the LE, while an ambiguous syllable was presented to the RE) was significantly above chance [72.08% ± 3.10%, mean ± SEM, one-sample t test against chance (50%): t(27) = 10.57, P < 0.001].

![Fig. 1.](https://example.com/fig1.png)

**Fig. 1.** (Top) Stimulation electrodes were centered over CP6 (right hemisphere) and CP5 (left hemisphere) (41). (Middle) The interhemispheric phase synchrony was manipulated using 40 Hz TACS with an interhemispheric phase lag of 0° (TACS 0°) or 180° (dotted line, TACS 180°). The colors represent the polarity (positive = red; negative = blue) of the current for the time stamp highlighted by the dotted line. (Bottom) Simulation of the electric field strength induced by bihemispheric TACS in a template brain. LH: Left hemisphere; RH: Right hemisphere.
Stimulus discrimination ($d'$) was significantly better for catch-up control trials than in the binaural integration condition [control: $1.66 \pm 0.13$, binaural integration: $0.88 \pm 0.10$, mean $\pm$ SEM; paired $t$ test: $t(27) = 8.58, P < 0.001$, effect size: $d = 1.21$]. Furthermore, response times were longer in the binaural integration condition [control: $639.22 \text{ ms} \pm 10.77$, binaural integration: $665.52 \text{ ms} \pm 10.17$, paired $t$ test: $t(27) = 5.42, P < 0.001$]. This difference likely reflects the increased time participants needed to integrate the stimuli in the binaural integration condition.

In contrast to our previous report (41), we found no significant main effect of TACS stimulation [sham: $0.93 \pm 0.11$, TACS 0°: $0.81 \pm 0.09$, and TACS 180°: $0.87 \pm 0.10$; repeated-measures ANOVA $F(2, 54) = 1.57, P = 0.217$, effect size: $\eta^2 = 0.008$]. Based on previous findings (41), we hypothesized that binaural integration would be weaker during TACS 0° as compared to sham. Although we replicated this effect (planned pairwise comparison TACS 0°: $0.81 \pm 0.09$, sham: $0.93 \pm 0.11$, paired $t$ test, $P = 0.036$, one-tailed, effect size: $d = 0.21$), it is much smaller than previously reported ($d = 0.37$) and did not reach statistical significance after correction for multiple comparisons using a false-discovery rate (FDR) correction (44) ($P = 0.107, n$ corrections = 3). Interestingly, we found that not all participants show the same behavioral susceptibility for TACS 0°. Participants with higher binaural integration scores during sham stimulation showed a larger reduction in binaural integration in response to TACS 0°, whereas participants with low binaural integration increased binaural integration under TACS stimulation [$\beta = -0.26, t(27) = -3.15, P = 0.008, R^2 = 0.26$]. A qualitatively similar, but not significant, relationship was observed for TACS 180° [$\beta = -0.20, t(27) = -1.70, P = 0.102, R^2 = 0.07$] (SI Appendix, Fig. S2).

The Influence of TACS on Local Brain Activity. We first examined the mean auditory blood-oxygen level-dependent (BOLD) response and TACS-induced BOLD-response modulations relative to sham stimulation. Whole-brain analysis revealed a significant hemodynamic response in the supratemporal plane during auditory syllable perception (showing multiple activation foci, including the HG), either with or without TACS stimulation (Fig. 3A and SI Appendix, Fig. S3). Previous studies have found that TACS can modulate the magnitude of local brain activity relative to sham stimulation (45, 46). In line with these findings, we found that the BOLD modulation induced by TACS 180° ($\Delta$ TACS – sham) was significantly larger than the modulation induced by TACS 0° ($\Delta$ TACS – sham) in the right pSTS. This area is located beneath the center of the annular TACS electrode (Fig. 3B). To test the relevance of the pSTS for binaural integration, we correlated binaural integration during sham stimulation with the magnitude of bilateral pSTS activation. Our results show that participants with higher mean BOLD responses in bilateral pSTSs showed higher binaural integration scores [$\beta = 0.14, t(27) = 2.14, P = 0.042, R^2 = 0.13$]. This suggests a functional role of the pSTS in binaural integration.

In addition to the whole-brain analysis, we conducted a region-of-interest (ROI) analysis, including the bilateral HG and bilateral pSTS. The ROIs were defined functionally (for details, see Materials and Methods). The mean difference in the BOLD signal between TACS (TACS 0°; TACS 180°) and sham stimulation was extracted from the bilateral HG and pSTS. We then tested whether the TACS effect ($\Delta$ TACS – sham [mean $T$ value]) in these areas differed as a function of TACS (TACS 0°; TACS 180°).

Across all ROIs, we found a statistical trend for a main effect of TACS stimulation [TACS 0°: $-0.09 \pm 0.14$; TACS 180°: $0.33 \pm 0.17$, mean $\pm$ SEM, repeated-measures ANOVA, $F(1, 26) = 3.89, P = 0.059$, effect size: $\eta^2 = 0.13$], indicating that the BOLD signal modulation during TACS 180° ($\Delta$ TACS – sham) was significantly larger than the modulation induced by TACS 0° ($\Delta$ TACS – sham), but no interaction of TACS x ROI was observed [$F(3, 26) = 0.83, P = 0.481$, effect size: $\eta^2 = 0.01$] (Fig. 3C). Bayesian repeated-measures ANOVA revealed that the model including the main effect TACS (Bayes factor [BF]$_{10}$ = 185.940) was more likely under the alternative hypothesis than under the null hypothesis. Although, the “frequentist” repeated-measures ANOVA suggests only a statistical trend, the BF provides strong evidence (47) for the presence of the TACS effect.

Our results indicate that TACS modulates local brain activity in areas that are associated with binaural hearing (48) and phoneme perception (49). In a next step, we tested at the network level for each of the ROIs, whether the phase of bilateral TACS modulates interhemispheric effective connectivity.
Inter- and Intrahemispheric Connectivity Correlates with Binaural Integration during Sham Stimulation. DCM allows the assessment of the effective interaction of brain regions, and how their interaction changes across different experimental conditions. The strength and direction of regional interactions are computed by comparing observed BOLD responses in a given ROI with BOLD responses that are predicted by a neurobiologically plausible model (42, 50). This model describes how activity in, and interactions between, regional neuronal populations are modulated by external inputs (in our case, TACS and auditory stimuli), and how the ensuing neural dynamics translate into a measured BOLD signal. We used DCM to quantify effective connectivity between auditory cortical areas and to compare this connectivity across our experimental conditions to test the role of interhemispheric connectivity in binaural integration.

First, we report intra- and interhemispheric connectivity between our ROIs (left HG, right HG, left pSTS, and right pSTS) during sham stimulation (connections with a posterior probability, \( P_{p} > 0.95 \) are reported) and its correlation with binaural integration (Fig. 4). The \( P \) values from the regression of DCM coupling parameters on this connection were positively correlated with binaural integration scores. Furthermore, the model revealed a negative unidirectional interhemispheric connection from right to left pSTS (right \( \rightarrow \) left pSTS: \( -0.77 \) Hz, \( P_{p} > 0.99 \)). This means that an activation increase in the right pSTS was causing a decrease in activation in the left pSTS. Individual coupling parameter for this connection were negatively correlated with binaural integration (right \( \rightarrow \) left pSTS: \( \beta = -0.73 \), \( t(27) = -4.55, P < 0.001, R^2 = 0.46 \)), suggesting a stronger negative influence from the right onto the left pSTS was associated with higher binaural integration scores.

Furthermore, the model revealed positive bilateral connections from lower (HG) to higher cortical areas (pSTS) (feedback connections, HG\(_{left} \rightarrow\) pSTS\(_{right} \): 1.10 Hz, \( P_{p} > 0.99 \); HG\(_{right} \rightarrow\) pSTS\(_{left} \): 0.51 Hz, \( P_{p} > 0.99 \)). In the left hemisphere, individual coupling parameters on this connection were positively correlated with participants’ binaural integration scores (left HG\(_{left} \rightarrow\) pSTS\(_{right} \): \( \beta = 0.63 \), \( t(27) = 2.93, P = 0.013, R^2 = 0.25 \)). Interestingly, we observed negative bilateral connections from higher (pSTS) to lower cortical areas (HG) (feedback connections, pSTS\(_{left} \rightarrow\) HG\(_{left} \): \( -0.80 \) Hz, \( P_{p} > 0.99 \); pSTS\(_{left} \rightarrow\) HG\(_{right} \): \( -0.76 \) Hz, \( P_{p} > 0.99 \)). Furthermore, we found a negative correlation on these connections between individual coupling parameters and binaural integration (left pSTS\(_{left} \rightarrow\) right HG: \( \beta = -1.05 \), \( t(27) = -3.13, P = 0.013, R^2 = 0.26 \); right pSTS\(_{left} \rightarrow\) right HG: \( \beta = -0.70 \), \( t(27) = -2.46, P = 0.028, R^2 = 0.17 \)). This indicates that stronger suppression of HG through activation in pSTS was associated with higher binaural integration scores. In this sense, stronger top-down inhibition from pSTS onto HG might be beneficial for binaural integration.
Fig. 4. In the center: ROIs and their connectivity estimates during sham stimulation. The numbers on the arrows represent average coupling parameters in Hertz (positive values are shown in green, negative values are shown in red). For a given connection, $x_1 \rightarrow x_2$, these rate constants express the activation change in $x_2$ per unit time as a function of the current activity in $x_1$. For example, a coupling strength of 0.10 Hz reflects an increase in activity in $x_2$ corresponding to the 10% of the current activity in $x_1$. The arrows with attached square represent the driving inputs, ambiguous speech sound (white), and F3 cue (gray) (Fig. 2). In the periphery: The relationship between the individual coupling parameters on a given connection and the binaural integration score. Note that participants with stronger positive interhemispheric connections for HG show higher binaural integration scores. The $P$ values from individual regression analyses are corrected for multiple comparison using FDR correction (44).
Antiphase TACS Modulates Interhemispheric Connectivity. Next, we analyzed how TACS stimulation modulates network connectivity relative to sham stimulation. Both TACS conditions had a negative modulatory influence on intrahemispheric network connectivity as compared to sham stimulation, but only TACS 180° significantly reduced interhemispheric connectivity between the bilateral HG and pSTS. The Bayesian contrast between all modulatory influences of TACS 0° and TACS 180° on interhemispheric connections witnessed a probability of 99% that the perturbation during TACS 180° is larger than during TACS 0°.

Below, we report TACS-induced modulation of intra- and interhemispheric connectivity and its correlation with TACS-induced changes in binaural integration (Fig. 5). The P values from individual regression analyses are corrected for multiple comparison using a FDR correction (44).

TACS 180° significantly reduced bidirectional interhemispheric connectivity at the level of HG (TACS 180° left → right HG: -1.08 Hz, Pp > 0.99; TACS 180° right → left HG: -0.89 Hz, Pp > 0.99). Importantly, the strength of the TACS-induced connectivity modulation was significantly correlated with TACS-induced changes in binaural integration across participants [TACS 180° right → left HG: β = 2.05, t(27) = 2.73, P = 0.017, R² = 0.20]: The stronger the induced interhemispheric connectivity reduction, the stronger the reduction in binaural integration (Fig. 5). Furthermore, both TACS conditions had a negative modulatory influence on the interhemispheric connection from the left to the right pSTS (TACS 0° left → right pSTS: -0.47 Hz, Pp > 0.99; TACS 180° left → right pSTS: -0.55 Hz, Pp > 0.99). On this connection, the TACS-induced modulation was negatively correlated with binaural integration: The stronger the negative modulation, the higher the participants’ binaural integration score [TACS 0° left → right pSTS: β = -4.38, t(27) = -12.12, P < 0.001, R² = 0.85; TACS 180° left → right pSTS: β = -3.51, t(27) = -7.38, P < 0.001, R² = 0.67].

A negative modulatory influence of TACS was also found on bidirectional interhemispheric connections between the left HG and the left pSTS (TACS 0° left HG → pSTS: -0.88 Hz, Pp > 0.99; TACS 180° left HG → pSTS: -0.91 Hz, Pp > 0.99; TACS 0° right HG → pSTS: -0.76 Hz, Pp > 0.99; TACS 180° right HG → pSTS: -0.82 Hz, Pp > 0.99). In the left hemisphere, the negative modulation of feedforward connectivity from HG to pSTS correlated positively with binaural integration: The stronger the negative modulation induced by TACS 180° left HG → pSTS, the lower the participants binaural integration score (TACS 0° left HG → pSTS: β = 1.64, t(27) = 3.10, P = 0.009, R² = 0.26). In the right hemisphere, for the same feedforward connection, we found a similar relationship with binaural integration for both TACS conditions [TACS 0° right HG → pSTS: β = 2.31, t(27) = 2.93, P = 0.012, R² = 0.23; TACS 180° right HG → pSTS: β = 4.43, t(27) = 6.08, P < 0.001, R² = 0.58].

For the intrahemispheric feedback connection from the left pSTS to left HG, TACS-induced negative modulations were related to increased binaural integration scores [TACS 0° left pSTS → HG: β = -2.87, t(27) = -6.55, P < 0.001, R² = 0.62; TACS 180° left pSTS → HG: β = -1.38, t(27) = -14.23, P < 0.001, R² = 0.89].

There were several other modulations that were not significantly related to differences in binaural integration across participants (Fig. 5).

Discussion

In the present study, we show that binaural integration is related to effective connectivity between the auditory cortices and we present evidence for the putative role of γ-band oscillatory activity in interhemispheric perceptual integration. Our results show that in-phase TACS (phase lag 0°) and antiphase TACS (phase lag 180°) reduce intrahemispheric connectivity, but only antiphase TACS modulates interhemispheric connectivity between the auditory cortices. Importantly, we found that TACS induced changes in intra- and interhemispheric connectivity are correlated with changes in binaural integration.

We would like to emphasize the phase selectivity of the γ-TACS effect: Antiphase, but not in-phase TACS reduced interhemispheric connectivity. We propose that the interhemispheric phase difference in the antiphase condition induced a lag in the relative phase of the underlying cortical areas, which is responsible for the reported change in interhemispheric connectivity. The induced lag underlies the observed changes in binaural integration and is potentially maladaptive for information transfer, consistent with the idea that neuronal groups, which do not undergo coherent excitability fluctuations, communicate less efficiently (14, 15). Our findings are in line with previous results from electrocorticographic recordings from the human auditory system (53), suggesting γ-band phase synchronization as a brain mechanism for interregional information transfer. However, while we emphasize that this is a plausible interpretation of the results, we acknowledge that two pieces of evidence are missing for this to be incontestable. First, without electrophysiological data we cannot confidently infer that the synthesis of respective cortical areas was affected. Second, our neurophysiological measure of effective brain connectivity does not allow us to state that the effect was frequency specific and confined to the γ-frequency band.

In line with our previous findings (41), our results suggest that TACS 0° is not beneficial but detrimental for binaural integration. The present connectivity results suggest that this is because TACS 0° reduces the intrahemispheric coupling of feedforward connectivity from the HG to pSTS. This is supported by the observation that a stronger perturbation of this connection goes along with a greater reduction of binaural integration. We observed a similar down-modulation of interhemispheric connectivity from the HG to pSTS by TACS 180°, but here only right hemispheric connectivity changes were related to changes in binaural integration.

We also found that not all participants show the same behavioral susceptibility for TACS stimulation. Participants with higher binaural integration scores were more likely to show a reduction in binaural integration in response to TACS 0°, whereas participants with lower binaural integration were more likely to show increased binaural integration in response to TACS 0°. Likewise, Rufener et al. (54) showed that in young participants with good performance, γ-TACS perturbed speech perception, whereas in elderly participants with lower performance in speech perception, γ-TACS enhanced speech perception. The authors proposed that the behavioral effect of γ-TACS on auditory speech perception may follow an inverted U-shaped relationship. Therefore, the impact of TACS may be positive or negative, depending upon a participant’s baseline performance. In participants with good performance, who show an optimal level of γ-band oscillatory activity, reflecting a high neural signal-to-noise ratio, TACS may add noise that makes performance worse. However, in participants with lower baseline performance, TACS might either reduce noise by inducing synchrony—and thereby boost performance—or increase noise, thereby making the stimulus-induced brain signal detectable through stochastic resonance (55, 56).

In the visual domain, γ-band phase synchronization has been suggested as a mechanism to bind and integrate different object features, such as shape and color, processed by distal cortical loci (8, 9). Recently, we have shown that γ-band phase synchronization contributes to the interhemispheric binding of acoustic features, indicating that this is also the case in the auditory modality (41). Here, our results show that interhemispheric
Fig. 5. In the center: ROIs and the average modulation (in Hertz) of their connections by TACS (red: TACS 0°; blue: TACS 180°). The numbers on the arrows represent average coupling parameters in Hertz. The arrows with attached square represent the driving inputs, ambiguous speech sound (white) and F3 cue (gray) (Fig. 2). In the periphery, the regression of significant TACS-induced connectivity modulations with TACS-induced changes in binaural integration. Inset figures depict the Bayesian model average (BMA) of the TACS-induced modulation, error bars show the variance of the estimated modulation. Bilateral γ-TACS with a phase lag of 180° (TACS 180°), but not TACS 0° reduced interhemispheric coupling between bilateral HG. Importantly, the strength of this modulation on the connection right → left HG is significantly correlated with TACS-induced modulation of the binaural integration score, the stronger the coupling reduction due to TACS 180°, the stronger the reduction of binaural integration. The P values from individual regression analyses are corrected for multiple comparison using FDR correction (44).

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phase of γ-TACS modulates interhemispheric effective connectivity. This effect may reflect the functional consequences of interhemispheric γ-phase (de)synchronization. There is accumulating evidence for different hemisphere specializations in speech perception (6, 7, 57, 58). The Asymmetric Sampling in Time theory [AST, Poeppel (58)] proposed that speech signals are processed asymmetrically in the time domain at rates tuned to fundamental speech units. While left auditory areas preferentially extract information from short temporal integration windows (20 to 40 ms; segments that correspond roughly to the length of phonemes), the right hemisphere homologs preferentially extract information from longer integration windows (150 to 250 ms), which makes them better suited for the processing of slower acoustic modulations (e.g., speech prosody and musical rhythms). Moreover, it has been shown that the binding of syntax, processed in the left hemisphere, and speech prosody, dominant in the right hemisphere, relies on the integrity of the corpus callosum (10). If neural phase synchronization contributes to feature binding in the visual and auditory domain, we speculate that it may also contribute to the binding of different speech features processed in both hemispheres, as has already been suggested for auditory features like location, timber, or pitch (59).

Furthermore, our findings may have clinical implications for the therapeutic application of TACS. Previous studies showed that disturbances of interhemispheric structural or functional connectivity are associated with auditory phantom perceptions, such as tinnitus and auditory verbal hallucinations (11, 12). Enhanced interhemispheric functional connectivity has been reported between homotopic areas in tinnitus, including the middle temporal gyrus (11). The same study found that enhanced interhemispheric connectivity in the transverse gyrius was associated with the experience of increased tinnitus distress. In patients with auditory verbal hallucinations, a recent study found a significantly stronger γ-band phase synchronization between bilateral auditory cortices during dichotic listening as compared to patients without hallucinations and healthy controls (60). The same study reported a positive correlation between auditory hallucination symptom score and the enhancement of γ-band phase synchronization. This suggests that bhemispheric γ-TACS presents a promising avenue for the development of therapeutic interventions for auditory phantom perceptions in the near future.

Not only cortico–cortical (61), but also cortico–thalamocortical (62) circuits may contribute to binaural integration. During sensory processing, high-frequency oscillations in the γ-band occur in the thalamus and in the cortical areas to which they project (63, 64). Thus, neural synchronization in cortico–thalamocortical circuits has also been associated with the binding of sensory features (16, 65, 66). Previous studies have shown that cortical transcranial electric stimulation can indeed modulate cortico–thalamocortical circuits in animals (67) and humans (68). Hence, it is legitimate to ask whether the connectivity effects reported in the present study rely also on cortico–thalamocortical circuits. The present study was designed to test cortico–cortical connectivity effects. In contrast, to others (68), our design included a focal HD electrode montage. Therefore, it is unlikely that the applied currents could reach subcortical structures, such as the thalamus at intensities substantial enough to affect them. Additional control analyses (SI Appendix; Fig. S4) suggest that TACS did not modulate the BOLD signal in the thalamus. Importantly, this does not rule out a potential role of the thalamus in binaural integration, but it suggests that the reported effects depend more strongly on the effect of TACS on cortico–cortical connectivity.

In sum, our study showed that binaural integration is related to interhemispheric connectivity between the auditory cortices. Furthermore, γ-band TACS modulated interhemispheric connectivity depending on the induced interhemispheric phase lag, and the induced modulation in brain connectivity predicted changes in binaural integration. This suggests that binaural integration is mediated by interhemispheric connectivity and supports the notion that oscillatory γ-band synchrony could underpin interhemispheric integration.

**Materials and Methods**

**Participants.** Twenty-eight right-handed volunteers (mean = 21.89 y, SD = 3.08; 9 male) participated in the study. All participants had normal or corrected-to-normal visual acuity. The participants reported no history of neurological, psychiatric, or hearing disorders. All participants had normal hearing (hearing thresholds of less than 25 dB HL at 250, 500, 750, 1,000, 1,500, 3,000, and 4,000 Hz, tested on each ear using pure-tone audiometry) and no threshold difference between the LE and the RE larger than 5 dB for any of the tested frequencies. All participants gave written informed consent prior to the experiment. Data for this study was collected at the Donders Center for Cognitive Neuroimaging, Nijmegen, The Netherlands. The study was approved by the local research ethics committee (CMO region Arnhem-Nijmegen) and was conducted in accordance with the principles of the latest Declaration of Helsinki.

**Stimuli.** The stimuli created for the present study were based on stimuli reported in Preiss and Sjørs (43). A stimulus continuum form /da/ to /ga/ was created by shifting the F3 in 17 equidistant steps from −2.9 to −2.5 kHz. This procedure was implemented using a source-filter separation algorithm in Praat software (69). The intermediate step at which each participant reported receiving the stimulus as /da/ or /ga/ in −50% of the trials was selected for generating the ambiguous stimuli for RE presentation. To generate F3 speech cues for LE presentation, the F3 was extracted from the endpoints of the continuum (from /da/ and /ga/) by applying a bandpass filter with frequencies between 2,100 and 3,300 Hz. For a schematic representation of the stimuli, see Fig. 2.

**Experimental Design and Task.** The experiment comprised eight task-based fMRI runs (four TACS and four sham runs) presented in pseudorandom order. TACS was presented in two interhemispheric phase-synchronization conditions: In-phase TACS (0° interhemispheric phase lag) and antiphase TACS (180° interhemispheric phase lag) between the central electrodes placed over the left and the right auditory speech areas (i.e., bilateral superior temporal lobe) (39, 41) (Fig. 1). In addition, the phase relation between TACS current and the onset of the auditory stimulus was controlled across six predefined, equidistant TACS phases (TACS/yllable onset lag: 30°, 90°, 150°, 210°, 270°, 330°) (70, 71). In the sham condition, TACS was turned off after 12 s to evoke sensations associated with the initial onset of stimulation, but without stimulating in the remaining time of each fMRI run. Each sham run was presented in alternation with the respective TACS being followed by sham to reduce the risk of potential TACS after effects (72). The order of TACS (A = TACS 0°, B = TACS 180°, S = sham) was either A-S-B-S-A-S or B-S-A-S-A-S-B-S and counterbalanced across participants. Each fMRI run consisted of 128 trials, 88 of which included auditory stimulus presentation: 60 binaural integration trials for which the F3 frequency of the RE stimulus was set at the individual category boundary and 28 unambiguous control trials for which the F3 component of the RE stimulus supported a clear /da/ or /ga/ interpretation (Fig. 2). For binaural integration trials, the LE stimulus included the high F3 cue (on 30 trials) or the low F3 cue (on another 30 trials). For control trials, LE stimulus included a F3 cue with the same F3 frequency as the RE stimulus. Control trials did not require interhemispheric integration for disambiguation because participants could readily identify these stimuli based on monaural input alone (i.e., the unambiguous stimulus presented to the RE). For the fMRI analyses, all trials with auditory stimulus presentation were considered.

Each trial was 3 s long (equal to the repetition time of the fMRI sequence) and started with the acquisition of a single fMRI volume (TA = 930 ms). The auditory stimulus was presented 1,750 ms after trial onset plus an interval that depended on the phase relation between TACS and stimulus in the respective trial (between 4 and 24 ms, in steps of 4 ms). The presentation of the auditory stimulus lasted 250 ms. The participant’s response window corresponded to the interval from auditory stimulus onset to 70 ms before the onset of the next trial (1,154 to 1,176 ms).

In all of the 126 trials in each run, no speech sound was played. Four trials included the time required to ramp up and down TACS stimulation. The rest of the no-sound trials were included in order to take into account the hemodynamic delay and enable sampling long-lasting sound-evoked BOLD responses.
Transcranial Alternating Current Stimulation. We combined transcranial electric current stimulation with fMRI, which has previously been shown to be safe and result in minimal artifacts and loss of signal to noise in the MR signal (73–75). The timing of the electrical and auditory stimulation was controlled from the scanner control room using a multichannel D/A converter (National Instruments, sampling rate: 11 kHz) and Datastrem software (76).

Electric current was administered using two battery-driven transcranial current stimulators (Neuroconn) using a custom-built set-up. The stimulators were placed in a shielded box including radiofrequency filters inside the faraday cage of the MR scanner. A two-way converter (A/D and D/A, Lindy) was used to convey the input signals for electric stimulation via optic cables from the scanner control room to the current stimulators in the shielded box.

Electric currents were applied through two high-density electrode configurations each consisting of concentric rubber electrodes: A central circular electrode (radius = 1.25 cm) and a surrounding ring electrode (inner radius = 3.9 cm, outer radius = 5.0 cm). Electrodes were kept in place with adhesive, conductive Ten20 paste (Weaver and Company). Each pair of center-surround electrodes was connected to a separate current stimulator. The electrode configurations were centered according to the international 10-20 system over CPS (above the left cerebral hemisphere) and CP6 (above the right cerebral hemisphere). These scalp locations were chosen to produce relatively strong currents in the target regions over the auditory speech areas (i.e., left and right lateral superior temporal lobe), as suggested by prior electric field simulations on a standard head model (Montreal Neurological Institute) using FEKO software (77). Behavioral data (41) (Fig. 1). TACS was applied at a frequency in the low γ-frequency band (40 Hz). Before starting the experiment, we ensured that all participants tolerated the TACS well.

TACS intensity was adjusted individually to the point for which the participant reported feeling comfortable or uncertain about the presence of the current (1.48 mA ± 0.06 mA peak-to-peak, mean ± SD across participants). Impedance was kept below 10 kΩ with a current density at the concentric ring electrode. Stimulation was ramped up over the first and down over the final 6 s of each experimental block using raised-cosine ramps.

Recently, concerns have been raised regarding the possibility of peripheral effects of electrical current stimulation induced through tactile sensation (78). In a previous study using the same TACS protocol, we found no association between sensation ratings on a visual analog scale (0 to 10 cm, no to strong sensation) and behavioral performance (41). This suggests that peripheral effects have caused the reported TACS effects.

MRI Data Acquisition and Processing. Anatomical and functional MRI data were acquired on a 3-Tesla Siemens Prisma scanner using a 64-channel head coil. A three-dimensional (3D) high-resolution T1-weighted anatomical volume was acquired using a 3D MPRA sequence with the following parameters: Rep/echo time (TR/TE) = 2300/1100/3 ms, 8° flip angle, field-of-view (FOV) = 256 x 216 x 176 and a 1 x 1 x 1 mm resolution. Parallel imaging (iPAT = GRAPPA) was used to accelerate the acquisition resulting in an acquisition time of 5 min and 21 s.

Functional images were acquired with sparse imaging to minimize the impact of echo-planar imaging (EPI) gradient noise during presentation of auditory stimuli (79). This was achieved by introducing a delay in the TR of impact of echo-planar imaging (EPI) gradient noise during presentation of auditory stimuli (79). This was achieved by introducing a delay in the TR of impact of echo-planar imaging (EPI) gradient noise during presentation of auditory stimuli (79). This was achieved by introducing a delay in the TR of impact of echo-planar imaging (EPI) gradient noise during presentation of auditory stimuli (79). This was achieved by introducing a delay in the TR of impact of echo-planar imaging (EPI) gradient noise during presentation of auditory stimuli (79).

Preprocessing included the following steps: 1) Functional realignment and movement-related effects and a constant term per functional imaging run were included in the model.

For each subject, parameter estimates from TACS runs were contrasted with sham runs. Since, the design included four sham runs, but only two TACS runs per condition per participant, the two TACS runs were contrasted with all 2 possible combinations of sham runs (in reflects all sham runs and k the two sham runs that were selected at a time to be contrasted with the two TACS runs per condition). The resulting six contrasts images per TACS condition were subsequently averaged into one contrast image per TACS condition that was later used for second-level, random-effects analyses to enable group-level statistical inference. Auditory stimuli evoked substantial bilateral auditory activation (Fig. 3A and SI Appendix, Fig. S3).
modulatory input (B-matrix) on all self-, inter-, and intrahemispheric connections in the model. Sham stimulation served as baseline (SI Appendix, Fig. S5).

**Group Level Inference.** To estimate the effective connectivity parameters at the group level (i.e., across participants), we used parametric empirical Bayes (PEB) (B8). The PEB approach assumes that all subjects have the same basic architecture: That is, they can be explained by the same DCM forward model, but they differ in terms of the strength of connections within that model.

PEB is a hierarchical model of connectivity parameters, with connectivity parameters from all subjects at the first level and a GLM at the second level, estimated using a variational scheme. Our first-level parameters of interest were connectivity during sham stimulation (intrinsic connectivity, A-matrix) and extrinsic modulations by TACS (B-matrix). Furthermore, we entered four between-subject covariates into the model: Binaural integration during sham stimulation, binaural integration \( \Delta \) TACS 0°, binaural integration \( \Delta \) TACS 180°, and gender.

Having estimated parameters of the full PEB model, we used Bayesian model reduction (BMR), to “prune” any GLM parameters that did not contribute to the model evidence. BMR compares the evidence for reduced models iteratively, discarding parameters that do not contribute to model evidence (84). The iterative procedure stops when discarding any parameter starts to weaken model evidence. A Bayesian model average (BMA) was started to weaken model evidence. A Bayesian model average (BMA) was

**Bayesian Analysis.** In case of a statistical trend, we complemented the inferential “frequentist” analyses with BF analyses. The use of BFs allows to evaluate evidence for the alternative hypotheses (H₁) relative to the null hypothesis (H₀), thus possibly dissociating the lack of a statistical effect from poor sensitivity to uncover an effect. BF₁₀ indicates the Bayes factor in favor of H₁ over H₀. For example, BF₁₀ = 5 means that the data are five times more likely under H₁ than under H₀ (85). BFs were computed by using JASP (86) with the default prior for fixed effects (r scale prior width = 0.5). According to the classification by Jeffreys (47), specific BF₁₀ can be considered “weak” (BF₁₀ 1–3), “moderate” (BF₁₀ 3–10), “strong evidence” (BF₁₀ >10) in favor of the alternative hypothesis.

**Data Availability.** Data have been deposited in di.dccn.DSC_3011204.02_657 (https://doi.org/10.34973/dt33-c34).

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86. JASP Team, JASP (Version 0.14.1, 2020).