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Modulation of Interhemispheric Auditory Communication by Transcranial Alternating Current Stimulation

Dissertation

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Table of Contents

1. Synopsis	5-28
1.1 Introduction	
1.1.1 Auditory Perception and Interhemispheric Connectivity.....	6-9
1.1.2 The Relevance of Altered Transcallosal Communication and High-Frequency Oscillations in Schizophrenia.....	9-11
1.1.3 Shaping of Cortical Oscillatory Network Activity by Non-Invasive Electric Brain Stimulation.....	11-13
1.1.4 Objectives and Hypotheses.....	13-14
1.2 General Methods and Material	
1.2.1 Participants.....	14-15
1.2.2 General Procedure.....	15-17
1.2.3 EEG Acquisition and tACS Parameters.....	17-18
1.2.4 Analysis of Behavior and Interhemispheric Auditory Connectivity.....	18-19
1.2.5 Statistics.....	19-20
1.3 Summary of Results	
1.3.1 Augmented Effective Connectivity in the Gamma-Band Mediates Conscious Auditory Perception.....	20-21
1.3.2 Anti-Phasic tACS at 40Hz Does Not Modulate the Right Ear Advantage at Group Level.....	21
1.3.3 Bidirectional Impact of 40Hz-tACS Revealed by Intrinsic Phase Asymmetries.....	21-22
1.4 Discussion	
1.4.1 Directional Oscillatory Coupling Mediates Conscious Auditory Perception.....	22-24
1.4.2 Oscillatory Phase Asymmetries as a Crucial Network Parameter in Stimulation Protocols.....	24-26
1.4.3 Confounds and Limitations.....	26-27
1.4.4 Conclusion and Future Prospects.....	27-28
2. List of Abbreviations	29-30

3. References	31-49
4. Publication 1: The Callosal Relay Model of Interhemispheric Communication: New Evidence from Effective Connectivity Analysis	
4.1 Publication.....	51-59
5. Publication 2: Intrinsic 40Hz-phase asymmetries predict tACS effects during conscious auditory perception	61-87
5.1 Publication.....	61-79
5.2 Supplementary Material.....	80-87
6. Summary	88-90
6.1 Summary (English).....	88
6.2 Zusammenfassung (German).....	89-90
7. Author Contribution Statement	90
8. Acknowledgements	91
9. Curriculum Vitae (entfällt aus datenschutzrechtlichen Gründen).....	92
10. Eidesstattliche Erklärung (Declaration of Academic Integrity).....	92

1. Synopsis

1.1 Introduction

Asymmetries are widely distributed across most biological systems in nature (Geschwind & Galaburda, 1985), ranging from normal deviations in lower animal species to highly-defined complex functional lateralization in humans. Lateralized functions are discussed to originate from evolutionary, hereditary, developmental and pathological variables (Toga & Thompson, 2003). In this regard, the evolutionary expansion of the left brain hemisphere represents a salient example of outstanding volume asymmetries in language-related cortical structures, such as the Planum temporale, Broca's area and other regions of speech perception and production. Specifically, the lateralization of language-related functions has been argued to be advantageous as the transfer of auditory information within the collection of focal regions in a single hemisphere might be efficient, and it elegantly avoids the competition between both hemispheres during the innervation of muscles during speech production (Toga & Thompson, 2003). Moreover, the development of unilateral network specialization might have been fostered by the temporal limitations during transcallosal information processing between hemispheres in large brains. Consequently, unilateral specializations of distinct brain functions can be regarded as adaptations to the level of complexity in the evolutionary cortical expansion of the human brain (Wang, Buckner, & Liu, 2014).

The combination of theoretical progress in language research and the substantial progress of high-resolution neuroimaging tools significantly improved our understanding of speech and language in terms of micro- and macrostructure and neurophysiology. While old concepts of language processing were based on deficit-lesion observations suggesting causal structure-function relations, recent evidence from multi-modal neuroimaging studies challenged the old concept by underlining the crucial role of the corpus callosum (CC) - the main white matter (WM) commissure connecting the right and left auditory cortices - for conscious auditory perception and speech comprehension (Friederici, von Cramon, & Kotz, 2007; Westerhausen & Hugdahl, 2008). Language-related hemispheric asymmetry can be experimentally investigated with the well-known dichotic listening (DL) paradigm, which had been introduced for the first time in 1954 (Broadbent, 1954) and implemented in the clinical context of neuropsychiatric conditions in temporal lobe dysfunctions seven years later (Kimura,

1961). When healthy and right-handed participants listen to different acoustic stimuli (e.g. words or syllables) presented to each ear simultaneously, they will most likely report the cues that stimulated the right ear (RE). Clearly, this right ear advantage (REA) for verbal material is the most consistent finding (Hugdahl, 2011), as it is linked to the supremacy of the transcallosal anatomic connection between the RE and the left hemisphere. However, the exact neurophysiological mechanisms of interhemispheric auditory communication remain largely unknown.

In this thesis, the interhemispheric coupling of auditory cortices during DL was investigated in two experimental studies exploiting novel electroencephalography (EEG)-analysis approaches and non-invasive brain stimulation. Hence, this thesis comprises two manuscripts providing novel insight into how conscious auditory perception is mediated by synchronized long-range oscillatory coupling in the gamma-band range, and how it could be modulated by transcranial alternating current stimulation (tACS). Accordingly, the introduction of this thesis will give a short overview on the current state of knowledge regarding interhemispheric auditory communication in the healthy human brain (1.1.1), leading to the clinical relevance of the underlying anatomic pathway (CC) and synchronized oscillatory coupling in the gamma-band range in Schizophrenia (SZ) (1.1.2). Next, the current state of research on how large-scale cortico-cortical network activity can be modulated by different non-invasive brain stimulation (NIBS)-techniques will be depicted (1.1.3). The introduction will be completed by the major objectives and hypotheses of this work (1.1.4).

1.1.1 Auditory Perception and Interhemispheric Connectivity

Auditory processing begins in the inner ear with afferent fibers of the bipolar neurons in the spiral ganglion projecting their potentials to the cochlear nuclei in the medulla oblongata. These potentials are subsequently transferred over three main pathways: The dorsal acoustic stria, the intermediate acoustic stria and the trapezoid body. In the superior olivary nucleus, first binaural interactions are processed with its medial and lateral divisions enabling the localization of sounds in space. The lateral lemniscus is formed by postsynaptic axons from the cochlear nuclei and the superior olivary nucleus, forth ascending to the midbrain, where the acoustic signal is transferred to the brachium in the left or right inferior colliculus. Therefrom the postsynaptic cells in the colliculi convey the information via axons to the corpus geniculatum mediale in the thalamus. Finally, the central auditory pathway beginning in the cochlea is termi-

nated by the geniculate axons reaching the primary auditory cortex (PAC) in the superior temporal gyrus (STG), also known as Heschl's gyrus (HG) or Brodmann area (BA) 41. Due to the tonotopic arrangement of neurons and fibers in frequency-specific architectural order, sound frequency and location can be differentiated in the HG with fibers decoding low frequencies terminating anterolaterally and high frequency fibers at its posteromedial part. While tones are perceived without any further interpretation in the HG, the neighboring secondary auditory cortex (SAC) - comprising BA42 and BA22 – translates the perception of complex sounds, such as phonemes, words or melodies (Kilian-Hutten, Valente, Vroomen, & Formisano, 2011). The functional importance of the corresponding posterior division of the superior temporal gyrus (STG) is demonstrated by clinical studies showing the impact of lesions in these subregions leading to highly-specific impairments in acoustic-phonetic processing (Boatman, 2004). Furthermore, the functions of the SAC depend on handedness and hemisphere: In the dominant hemisphere (i.e. left hemisphere in right-handed individuals), the cortical populations of BA42 and BA22 define the sensory speech centre, whereas the SAC in the non-dominant hemisphere encodes acoustic information of prosody and melody.

How does the human brain organize a cost-efficient long-range cortico-cortical communication across both auditory cortices? As the main WM commissure in the human brain containing more than 300 million fibers (out of which 70% are myelinated), the CC connects primarily homotopical cortical regions of the right and left hemisphere and thus enables inhibition, integration and transfer of sensory, cognitive, motor and emotional information (van der Knaap & van der Ham, 2011). The CC exhibits a topographical organization into five modality-specific areas, which can be divided from anterior to posterior as genu, rostrum, truncus, isthmus and splenium (Witelson, 1989). The interhemispheric auditory pathways project over the posterior third subregion of the CC (isthmus and splenium), which thus enables rapid bilateral interaction between both auditory cortices (e.g. for sound localization in space). The influence of lesions on the transcallosal interaction between the auditory cortices has been investigated with the DL paradigm, which demands the differentiation of two similar, but not identical auditory cues being presented synchronously to both ears. Interestingly, not all lesions in the CC lead to a left ear (LE) suppression during DL, which had often been reported in right-handed patients after surgical dissection of the cerebral

hemispheres (Milner, Taylor, & Sperry, 1968; Sparks & Geschwind, 1968; Springer & Gazzaniga, 1975): Patients with surgical sections in the splenium and the most posterior part of the trunk of the CC exhibited a strong LE suppression – they were unable to report a single auditory syllable through the LE, whereas no LE extinction was observed in patients with lesions from the anterior division (genu and rostrum) to the posterior 17-28% of the CC (Sugishita et al., 1995). These observations were explained by the fact that the information from the LE are transferred to the right hemisphere but cannot be processed to the functionally relevant left hemisphere. In contrast, perception through the RE benefits from the predominant transfer over contralateral auditory pathways and the inhibition of ipsilateral pathways (Brancucci et al., 2004). Collectively, the REA is a result of the supremacy of contralateral auditory pathways and the fact that conscious perception of acoustic stimuli through the LE necessitates additional interhemispheric processing across the CC, which is in accordance with the “structural model” (Kimura, 1967) and the “callosal relay model” (Zaidel, 1983).

The integrity of the auditory interhemispheric pathways has been investigated with diffusion tensor imaging (DTI), which revealed remarkable interindividual variability with respect to the exact location and shape of the pathways among healthy participants (Westerhausen, Grüner, Specht, & Hugdahl, 2009). While there was wide agreement that specific WM parameters, such as myelination, diameter or fiber density, can modulate interhemispheric processing in terms of speed (Schulte, Pfefferbaum, & Sullivan, 2004) or the quality of transfer (Hellige, Taylor, Lesmes, & Peterson, 1998), the functional relevance of the interindividual fiber tract variability remained largely unclear. In 2009, Westerhausen and colleagues demonstrated that this variability in midsagittal tract size was significantly positively correlated with the amount of LE reports, whereas a negative correlation for the RE reports was not observed. In accordance with this structure-function association, an EEG study performed by Steinmann and colleagues (2014) demonstrated that conscious perception of syllables through the LE was accompanied by increased undirected connectivity (lagged phase synchronization, LPS) in the gamma-band range between the left and right SAC, as compared to hearing syllables through the RE. Crucially, this effect was not found in lower frequency bands (0.1-30 Hz) and confined the left and right SAC, suggesting that synchronization in the gamma-frequency range plays a key role in

auditory information integration from distant cortical sites, and thereby enables conscious auditory perception and healthy speech processing and comprehension.

The next section will highlight the clinical importance of the interhemispheric auditory pathways and oscillatory gamma-band coupling in SZ.

1.1.2 The Relevance of Altered Transcallosal Communication and High-Frequency Oscillations in Schizophrenia

Oscillatory gamma-band activity (30-100 Hz) can be observed across species during both sleep and waking states in all sensory modalities, as well as involvement in the motoric system and for higher cognitive operations such as memory consolidation (Buzsáki & Draguhn, 2004; Buzsáki & Wang, 2012; Donner, Siegel, Fries, & Engel, 2009; Fries, 2015; Siegel, Donner, Oostenveld, Fries, & Engel, 2008). To date, a commonly accepted view of the gamma-related rhythmogenesis is that gamma oscillations depend on the time constant of gamma-aminobutyric acid (GABA)_A- and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptors (Johnston, D & Wu SM-S, 1994) and cortical pyramidal cells (Destexhe & Paré, 1999). Clearly, rhythmic gamma-band activity is inextricably linked with perisomatic inhibition (I) between parvalbumin-positive interneurons through GABAergic synapses, which is a mechanism that enhances neural synchronization (Lytton & Sejnowski, 1991). Consequently, gamma-band oscillations rely on the balanced interplay between pools of excitatory (E), glutamatergic pyramidal cells and GABAergic interneurons (I) (Brunel & Wang, 2003; Wilson & Cowan, 1972). In line with this concept, disturbances in the E-I dynamics were experimentally induced by a knock down of glutamatergic AMPA-receptors on fast-spiking interneurons, which resulted in significantly reduced gamma-band amplitudes (Fuchs et al., 2007). Importantly, post-mortem studies revealed reduced density of parvalbumin interneurons in frontal cortical regions in SZ-patients (especially in the dorsolateral prefrontal cortex; DLPFC), supporting the hypothesis of deficient GABAergic transmission and E-I-imbalance due to dysfunction of the N-methyl-D-aspartate receptor (NMDAR) in SZ (Kaar, Angelescu, Marques, & Howes, 2019; Lewis, Hashimoto, & Volk, 2005). In accordance with these histological findings, several EEG studies demonstrated altered gamma-band synchrony in first-episode SZ-patients (Symond, Harris, Gordon, & Williams, 2005), as well as reduced phase locking and power of the auditory evoked gamma band response (Leicht et al., 2011, 2010; Roach & Mathalon, 2008). Furthermore, positive correlations between

symptom severity regarding auditory verbal hallucinations (AVH) and phase synchronization in the gamma-band between the left and right auditory cortices has been reported in an increasing number of EEG and magnetoencephalography (MEG) studies (C. Mulert, Kirsch, Pascual-Marqui, McCarley, & Spencer, 2011; Spencer et al., 2004; Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009; Uhlhaas & Singer, 2010). In a recent EEG study (Steinmann, Leicht, Andreou, Polomac, & Mulert, 2017), non-linear gamma-band connectivity (LPS) was significantly increased during LE percept in patients with AVH compared to SZ-patients without AVH and healthy control subjects. Specifically, this AVH-related difference in interhemispheric connectivity was positively correlated with AVH symptom scores, all other SZ-related symptoms were not associated with this connectivity difference.

Consistent with this, stronger anatomical interhemispheric connectivity – measured with structural MRI and DTI-based tractography – between the left and right auditory cortices was positively correlated with the occurrence of AVH in young first-episode patients who had been ill for a short time period of 5 to 7 years (Hubl et al., 2004; C. Mulert et al., 2012). However, findings of increased interhemispheric auditory connectivity in hallucinating SZ-patients have not always been replicated, as the reverse pattern of decreased connectivity has been reported in studies using fMRI (Gavrilescu et al., 2010) and DTI: Chronic SZ-patients with longer periods of illness (11 to 17 years) exhibited decreased CC volume and fiber integrity, which was associated with more severe AVH (Knöchel et al., 2012; Wigand et al., 2015). These findings might reflect ongoing pathophysiological progression in SZ, as widespread decline of fiber tracts was often found to be correlated with illness duration and age (Friedman et al., 2008; Rotarska-Jagiela et al., 2009). Furthermore, the opposite findings in first episode and chronic patients highlight that the auditory interhemispheric connectivity depends on the phase of illness.

The above depicted alterations in interhemispheric processing in hallucinating SZ-patients are accompanied by an often replicated pattern observed when SZ-patients perform the DL task: Patients with current experience of AVH exhibit a significantly reduced REA compared to SZ-patients without AVH and HC (Bruder, G. et al., 1995; Green, MF, Hugdahl, K, & Mitchell, S, 1994; Hugdahl et al., 2008). Crucially, SZ-patients without AVH do not exhibit an augmented shift towards LE processing compared to HC. Furthermore, a diminished REA has even been recommended as a trait

marker for reduced left-hemispheric lateralization of language-related functions in AVH patients (Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013).

Collectively, the above summarized cellular, electrophysiological, anatomical, clinical and behavioral findings converge in the theory of interhemispheric miscommunication in hallucinating patients (Steinmann, Leicht, & Mulert, 2019), highlighting the possibility of novel pharmaceutical (NMDAR) or neurostimulation (tACS) interventions to modulate altered gamma-band synchronization in the targeted auditory network.

1.1.3 Shaping of Cortical Oscillatory Network Activity by Non-Invasive Electric Brain Stimulation

The application of electric currents to the human brain has a long history in medicine and science. This fascination dates back to the discussion on how electric stimulation might induce visual sensations such as phosphenes (von Helmholtz, 1867), or even brighter visual effects by increased intensity (Rohracher, 1935). All forms of transcranial electric stimulation (tES) rely on the general concept of applying an electric field on the scalp surface to evoke a membrane potential change in the targeted cortical region, which in turn should increase the probability of a neuron generating action potentials. In monkeys (Rush & Driscoll, 1968) and in humans (Dymond, Coger, & Serafetinides, 1975), approximately 50% of the externally applied current perforates through the skull. When electroconvulsive therapy was introduced in the 1930s to treat psychiatric conditions (particularly depression), scientists and physicians applied high current intensities up to 60 mA to induce generalized seizures. Other early efforts were electrically induced anesthesia with direct or alternating currents up to 40 mA and the induction of electrosleep at intensities between 3-10 mA (Brown, 1975). The ensuing decades of research and clinical practice have shown that intensities below 4 mA are sufficient to modulate cortical oscillatory activity and behavior without the participant being aware of the stimulation or perceiving side effects (Nitsche et al., 2008; Nitsche & Paulus, 2000). To date, the most established non-invasive stimulation techniques are transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and repetitive transcranial magnetic stimulation (rTMS). During TMS, a magnetic field penetrates the skull for a short duration (<1ms) to elicit very rapid changes in field strength with the coil being oriented parallel to the cortical neurons. In contrast to tES, action potentials are directly triggered by TMS, which can be applied with greater accuracy than tES-techniques (Barker & Shields,

2017). While tDCS was most often applied to modulate the cortical excitability with an excitatory effect in the region under the anodal electrode (Fertonani & Miniussi, 2017), tACS can be exploited to mimic intrinsic oscillatory cortical activity at a specific frequency with exogenously applied sinusoidal currents. A third form of tES is transcranial random noise stimulation (tRNS) where a normally distributed random level of current with a frequency range of 0.1-640 Hz with no overall DC offset is applied (typically sampled at 1280 Hz). The desired increase of cortical excitability in the targeted tissue has been shown to last at least one hour, which has been explained by mechanisms of long-term potentiation (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009) and stochastic resonance, as sub-threshold oscillatory activity could be elevated to a supra-threshold level due to the added noise (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008).

Importantly, brain stimulation has emerged as a tool to overcome the limitations of studies investigating brain lesions in patients, as the induction of electromagnetic currents offers the possibility to establish causal relations between brain regions and specific functions (Hallett, 2007). As each NIBS-technique bears special advantages, the rising interest in the application of these techniques in neuropsychiatric conditions has led to significantly improved stimulation protocols.

Specifically, the therapeutic potential of tDCS has been proven in patients suffering from chronic pain (Antal, Terney, Kühnl, & Paulus, 2010), dementia (Boggio et al., 2012; Boggio, Khoury, et al., 2009; Ferrucci et al., 2008), addiction (Boggio, Liguori, et al., 2009; Boggio et al., 2008, 2010), affective disorders (Brunoni et al., 2011; Nitsche et al., 2009; Palm et al., 2012), attention deficit hyperactivity disorder (Allenby et al., 2018; Soff, Sotnikova, Christiansen, Becker, & Siniatchkin, 2017) and SZ (Brunelin et al., 2012; Mondino et al., 2016).

While tDCS is a technique aimed at modifying spontaneous excitability by a tonic hyper- or depolarization of the resting membrane potential, tACS is better suited to manipulate neural oscillations at frequency bands that are linked to specific cognitive functions. Throughout the past years, it has been demonstrated that tACS can be successfully employed to modulate higher functions such as intelligence (Santarnecchi et al., 2013), memory (Marshall, Helgadóttir, Mölle, & Born, 2006; Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012) or creativity (Lustenberger, Boyle, Foulser, Mellin, & Fröhlich, 2015); as well as lower functions such as visual (Helfrich, Knepper, et al., 2014; Kanai, Chaieb, Antal, Walsh, & Paulus, 2008; Laczó, Antal,

Niebergall, Treue, & Paulus, 2012; Strüber, Rach, Trautmann-Lengsfeld, Engel, & Herrmann, 2014) and auditory perception (T. Neuling, Rach, Wagner, Wolters, & Herrmann, 2012; Rufener, Zaehle, Oechslin, & Meyer, 2016).

In 2014, Helfrich and colleagues combined bilateral tACS at 40 Hz over the parieto-occipital cortex with concomitant EEG recordings to entrain gamma-band oscillations and probe their causal role in visual feature integration across both hemispheres. The utilized high density (HD)-stimulation protocol was successfully implemented to selectively up- and down-regulate interhemispheric coherence with ensuing perceptual correlates by driving both hemispheres at 40 Hz with either 0° or 180° phase lag. Since phase-dependent modulation of neural oscillations has been demonstrated numerous studies (Fehér, Nakataki, & Morishima, 2017; Gundlach, Müller, Nierhaus, Villringer, & Sehm, 2016; Helfrich, Knepper, et al., 2014; T. Neuling et al., 2012; Polanía, Moisa, Opitz, Grueschow, & Ruff, 2015; Schilberg et al., 2018), it is conceivable that tACS might be an ideal technique to investigate the causal impact of phase relationships in the gamma-band range on conscious auditory perception during a DL task.

1.1.4 Objectives and Hypotheses

The overall goal of this thesis was to confirm and extend the anatomical and neurophysiological framework of the callosal relay model during conscious auditory perception. So far, it had been confirmed that the midsagittal fibers interconnecting both auditory cortices exhibit considerable variation across individuals, and that strong fibers improve the interhemispheric transfer with an ensuing shift towards LE reports. Accordingly, elevated functional connectivity (FC) in the gamma-band between the left and right SAC was associated with the conscious perception of syllables through the LE, which suggests that synchronized gamma-band coupling might reflect a key mechanism for cortical integration of auditory information. Even though the callosal relay model held the assumption that the interhemispheric transfer entails a clear direction - from the right to the left hemisphere-, empirical evidence for this assumption has not yet been found. To address this issue, functional and effective connectivity (EC) in the gamma-band were investigated by means of exact low-resolution electromagnetic tomography (eLORETA) source estimation in the DL paradigm. Specifically, the aim of study 1 was to assess FC and EC between the left and right PAC and SAC for both directions during the perception of syllables through the left or right

ear. As previously reported by Steinmann and colleagues (2014), functional gamma-band connectivity was hypothesized to be significantly elevated during LE percept as compared to RE percept. Importantly, it was hypothesized that conscious auditory perception through the LE necessitates increased causal interhemispheric information flow in the gamma-band from the right to the left SAC. Moreover, this effect was not expected for the other direction (i.e. from the left to the right SAC) or the PACs.

The goal of study 2 was to modulate interhemispheric information processing during DL by spatially matched HD-tACS at 40 Hz with a phase shift of 180° between the right and left SAC. Since it has been demonstrated that the interhemispheric integration of alternating visual cues can be disrupted by driving both hemispheres at 40 Hz with a phase-lag of 180°, it was hypothesized that the interhemispheric auditory transfer could be selectively modulated by utilizing a similar stimulation protocol with a tailored multi-site electrode montage. Thus, 40 Hz-tACS with a phase-shift of 180° was hypothesized to disrupt auditory network synchrony and increase the laterality index (LI) compared to sham-tACS.

Another aim of study 2 was to support the concept of a delayed non-zero phase relationship during the interhemispheric auditory transfer. Since previously reported EEG metrics (LPS, Steinmann et al., 2014; iCoh - isolated effective coherence, Pascual-Marqui et al., 2014) do not characterize the phase relationship between the left and right SACs in degree notation, a source space analysis was carried out to assess the intrinsic phase lag between auditory cortices at 40 Hz. Furthermore, this exploratory control analysis was performed to investigate whether the behavioral effect of the anti-phasic 40Hz-stimulation might depend on the intrinsic auditory network asymmetry during the sham session.

1.2 General Material and Methods

1.2.1 Participants

All participants were recruited from the University Medical Center in Hamburg, Germany. The exclusion criteria for both studies were:

- Left-handedness
- Past or ongoing psychiatric or neurological conditions
- Hearing impairments

- Drug abuse or addiction
- Metal or electronic implants in the skull
- History of head trauma
- Current use of agents known to affect brain function

Normal hearing was verified by pure tone audiometry for frequencies between 125 and 8000 Hz (Esser Home Audiometer 2.0), and participants with interaural differences stronger than 15dB or auditory thresholds exceeding 25dB were excluded from the studies. Right-handedness was verified with the empirically validated Edinburgh Handedness Inventory (Oldfield, 1971).

The sample in study 1 consisted of $N = 33$ healthy participants (18 men, range: 19–57 years, $M = 31.4$ years, $SD = 9.1$ years), while the sample in study 2 finally comprised $N = 26$ healthy German native speakers (18 men, range: 18–49 years, $M = 28.5$ years, $SD = 7.9$ years) after the exclusion of two subjects with excessive error rates in task performance and one subject with insufficient data quality. Please note that 26 out of 33 subjects in study 1 participated in a previous study (Steinmann et al., 2014). Hence, these data were reanalyzed by exploiting the novel metric iCoh (Pascual-Marqui et al., 2014) to account for causal directionality during the interhemispheric auditory communication.

Both studies were approved by the ethical committee of Medical Association Hamburg and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent and were paid for participation.

1.2.2 General Procedure

Both experiments were run in the Psychiatry Neuroimaging Department of the University Medical Center Hamburg in an electrically shielded and sound-attenuated cabin. Auditory stimulation was applied through closed system headphones (Sennheiser, HAD 200) at 75dB while all subjects were seated 60cm in front of a BenQ XL2420T screen (1920 x 1080, 120 Hz). The presentation of stimuli and collection of behavioral responses were controlled utilising the software Presentation® (Neurobehavioral Systems, Albany, CA).

Paradigm

Interhemispheric auditory communication was investigated with the DL task – a well validated experimental paradigm for bistable auditory perception which necessitates the transcallosal processing of information between the left and right auditory cortex. In both study 1 and 2, six consonant-vocal (CV) syllables were paired and presented simultaneously via closed headphones at 75 dB to each ear. Importantly, effects of syllable voicing were controlled by combining only syllables with the same voice onset time (VOT), which yielded 12 dichotic CV-pairs (short VOT: /ba/da/ga/; long VOT: /pa/ka/ta/). Each trial was introduced by the appearance of a fixation cross which the subjects were instructed to fixate on. After 1s of fixation, the syllable-combination was presented under temporal alignment to ensure synchronous onset of the initial consonants. The mean duration of the syllable presentation varied between 400-500 ms depending on the VOT. Subsequently, the subjects navigated through the six syllables in a circular formation by clicking the left mouse button and confirmed their response by clicking the right mouse button. At the end of each trial, a constant inter-stimulus interval of 1 s was applied between visual presentation offset and the onset of the next auditory stimulus.

Procedure in Study 1

The aim of study 1 was to investigate the gamma-related interhemispheric auditory transfer during DL regarding a causal sender-receiver relationship by means of functional and effective directional connectivity. For this purpose, we obtained neurophysiological (EEG) and behavioral (DLT) data in one recording session from each participant, which lasted approximately 1,5 hours on average.

After performing the audiometry test, filling out a sociodemographic questionnaire and the Edinburgh Handedness Inventory, the participants provided written informed consent and were prepared for the ensuing EEG recording. All participants were familiarized with the auditory stimuli by performing 6 practice trials prior to the main experiment, which comprised 240 trials in two even blocks. Moreover, the participants were not informed that each trial entailed two different syllables after being instructed to select the syllable they understood most clearly. After performing the auditory task during concomitant 64-channel EEG recording, the subjects were debriefed and paid for participation.

Procedure in Study 2

The effect of bilateral anti-phase stimulation at 40 Hz on conscious auditory perception was investigated in a within-subject design with each participant taking part in two single-blinded tACS-sessions on two different days. The order of sham- and verum-sessions was counterbalanced across participants.

As in study 1, the participants performed pure tone audiometry, filled out all questionnaires and provided informed consent before the EEG and tACS electrodes were mounted. After performing 6 practise trials, EEG was recorded during all ensuing conditions (Resting State 1, Sham/Verum, Resting State 2). Importantly, the stimulation was well tolerated, mainly noticeable for all participants during the ramp-in phase and did not induce phosphenes or painful skin sensations. At the end of the second recording session, participants were debriefed, asked to assign the tACS-conditions to the sessions and received expense allowance.

1.2.3 EEG Acquisition and tACS Parameters

Study 1

EEG was recorded using 60 Ag/AgCl electrodes mounted on an ActiCAP using the Brain Vision Recorder 1.10 (Brain Products, Munich, Germany) at a sampling rate of 1000 Hz, corresponding to the 10/20 system. Eye movements were recorded with four additional channels at the outer canthi bilaterally and infra-orbitally on the left and right. All EEG-channels were referenced to FCz with impedances kept below 5 k Ω .

Study 2

Concomitant EEG recording during tACS was implemented by mounting EEG and tACS Ag/AgCl electrodes in a custom-made cap for 104 electrodes (Easycap). The EEG recording was obtained at a rate of 5000 Hz using slightly abrasive electrolyte gel (Abralyt 2000, Easycap) from 60 electrodes (10/20 system) with impedances below 15 k Ω and no amplitude clipping during stimulation. As in study 1, electrooculography was recorded with four additional channels as depicted above.

Based on 40 possible electrode positions, an optimized current flow for tACS configurations with four electrodes to each hemisphere had been modelled to mimic the bipolar electromagnetic field of oscillatory activity in the SAC/BA42. TES was employed by a battery-driven stimulator (DC-Stimulator Plus, NeuroConn) through 8 AgCl elec-

trodes using Signa electrolyte gel (Parker Laboratories Inc.). The total impedance of the stimulation electrodes was kept below 5 k Ω , monitored by the NeuroConn stimulator. During each DL-session, an alternating sinusoidal current was applied at 40 Hz for 20 minutes with a ramp-up phase over 10 seconds to 1000 μ A (peak-to-peak), which discontinued in the sham session.

1.2.4 Analysis of Behavior and Interhemispheric Auditory Connectivity

The magnitude of the ear effect was assessed as a behavioral laterality index (LI; range: -100, +100) according to the formula:

$$LI = 100 * \frac{(\text{correct RE reports} - \text{correct LE reports})}{(\text{correct LE reports} + \text{correct RE reports})}$$

with positive values indicating a bias towards RE responses and negative values towards LE responses. In both studies, LI values were computed for each session comprising 240 trials, while the tACS-related behavioral modulation in study 2 was computed as

$$LI_{mod} = LI_{verum} - LI_{sham}$$

EEG Analysis - Study 1

The preprocessing of EEG data was carried out using Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany). After downsampling to 256Hz, bandpass filtering from 20 to 120 Hz and re-referencing all sensors to common average, the data were visually inspected and cleaned from muscle artifacts and noise. Horizontal eye movements and blinks, electrocardiographic and saccadic spike potential artifacts were identified and discarded based on time courses, frequency distributions and topographies using independent component analysis (ICA). Finally, all correct and artifact-free responses were segmented into 2048ms epochs, starting 200ms before the auditory stimulus appeared, and exported for functional and EC analyses. To prevent a sample size bias, the number of trials was balanced between conditions in a randomizing subsampling procedure.

Oscillatory source space activity in the left and right PACs and SACs was reconstructed by exploiting eLORETA based on a transformation matrix for 60 electrodes with the above named regions of interest according to the Talairach-Atlas (Lancaster et al., 2000).

Interhemispheric FC was assessed by calculating lagged phase synchronization (LPS), which represents non-linear connectivity between two oscillatory signals after removing all zero-lag contributions, and thereby suppresses confounding influences of volume conduction (Nolte et al., 2004).

EC was calculated as iCoh (Pascual-Marqui et al., 2014) to estimate the causal directionality between the targeted cortical oscillators in the gamma-band range (30-100 Hz). Since FC between the right and left SAC was reported to exhibit peak synchrony during LE processing from 500ms to 700ms after stimulus onset (Steinmann et al., 2014), LPS- and iCoh-values were re-epoched and averaged for this post-stimulus onset interval.

EEG Analysis - Study 2

The EEG was analyzed using Matlab R2017a, the EEGLab (Delorme & Makeig, 2004) and CircStat (Berens, 2009) toolboxes, as well as the LORETA KEY software package (<http://www.uzh.ch/keyinst/loreta.htm>).

Throughout the process of data collection in this project, Noury and colleagues demonstrated that hitherto applied artifact removal approaches do not reliably reconstruct EEG phase information due to the non-linear properties of physiological parameters and the tACS-artifact itself (Noury, Hipp, & Siegel, 2016; Noury & Siegel, 2017). Therefore, the EEG analysis in study 2 was restricted to the sham session to investigate if the tACS-related behavioral modulation was associated with the interhemispheric phase asymmetries between the left and right auditory cortices.

Prior to projection into source space, a preprocessing pipeline including downsampling to 250 Hz, bandpass filtering from 1-100 Hz, manual and ICA-guided artifact- and noise-removal was employed using the EEGLab-toolbox. After segmenting the data into 400ms-epochs that started 200ms before syllable presentation, the number of exported trials was matched across subjects and conditions to avoid a sample size bias. Finally, the intrinsic phase asymmetries at 40 Hz were computed in degree notation and compared with respect to perceptual outcome (left of right ear) after extracting the tangential auditory dipole activities in the centroid voxels of the left and right BA42 with eLORETA.

1.2.5 Statistics

The significance level was set to $\alpha=0.05$ for all tests in both experiments.

Study 1

The data were checked for sphericity using Mauchly's test and for normal distribution with the Kolmogorov-Smirnoff-test. With *percept* (left or right ear report) as within-subjects variable and *gender* as between-subjects variable, a 2x2 repeated measures analysis of variance (RM-ANOVA) was carried out to (1) confirm the REA (Kimura, 1967), and (2) to investigate the influence of gender on the LI.

FC differences in the gamma-band range (30-100 Hz) between left and right ear percept were assessed for BA41 and BA42 separately with Wilcoxon signed rank tests. EC data were analyzed with respect to the within-subjects variables *percept* (left or right ear) and *direction* (right to left vs. left to right) in a 2x2 RM-ANOVA for the PACs and SACs, respectively. Wilcoxon-signed ranks tests were performed and corrected for multiple comparisons according to Bonferroni-Holm for all significant main effects, with effect sizes quantified as η^2 -partial (RM-ANOVA) or r (Wilcoxon tests).

Study 2

The impact of anti-phase stimulation on the LI was assessed with a two-sided t-test for paired samples, and the LI values during both tACS-sessions were checked for normality with Lilliefors test. Furthermore, effect sizes were quantified with Cohen's d . Differences between the intrinsic phase asymmetries during left and right ear percept were assessed with a non-parametric permutation test for paired conditions, which crucially does not depend on a priori assumptions about the data distribution. Finally, the circular-linear correlation between the interhemispheric phase asymmetry during LE percept and the tACS-related behavioral modulation (LI_{mod}) was assessed using the CircStat-toolbox.

1.3 Summary of Results

1.3.1 Augmented Effective Connectivity in the Gamma-Band Mediates Conscious Auditory Perception

The DL task represents one of the best-suited paradigms to evaluate the interhemispheric communication via transcallosal fibers between the left and right auditory cortices, and hence to proof the concept of the callosal relay model (Zaidel, 1983). In both studies of this thesis, we replicated the characteristic finding of REA in right-handed and healthy individuals, which was unaffected by gender. In line with Stein-

mann et al. (2014), the interhemispheric lagged phase synchronization of gamma-band oscillations between the left and right SAC was significantly increased during LE percept as compared to RE percept, underlining the importance of synchronous high-frequency oscillations during conscious auditory perception. The following key finding of study 1 expands this concept by introducing the hitherto unknown role of the dimension *direction* in this model: When participants consciously perceived a syllable through the LE, EC from the right to the left SAC was significantly elevated compared to the other direction (left to right SAC). In line with this, the effective gamma-band connectivity from the right to the left SAC was significantly increased during LE percept compared to RE percept. Crucially, the EC in the other direction (left to right SAC) yielded no significant difference between right and left ear percept. Importantly, this causal information flow was not found between the left and right PAC.

1.3.2 Anti-Phasic tACS at 40Hz Does Not Modulate the Right Ear Advantage at Group Level

The main purpose of study 2 was to selectively cause a behavioral shift towards RE reports (i.e., increase the REA) by transcranially inducing a bilateral anti-phasic (180°) electromagnetic field at 40 Hz targeted at the underlying neuronal oscillators in the left and right SAC. Clearly, the LI was not increased during tACS as compared to the sham session, indicating that tACS in the applied configuration did not affect DL performance at group level. Since the gamma-stimulation had been applied with the same phase lag across all participants, we hypothesized that the individual perceptual outcome during stimulation might be mediated by the interindividual differences in oscillatory phase asymmetries at 40 Hz.

1.3.3 Bidirectional Impact of 40Hz-tACS Revealed by Intrinsic Phase Asymmetries

The novel analysis of EEG phase dynamics revealed that conscious perception of a complex syllable sound through the LE does not only depend on elevated effective and functional coupling between the left and right SAC in the gamma-band range, but that its underlying mean coupling direction at 40 Hz differs significantly from hearing through the RE during the post-stimulus onset interval from 36 to 56ms: In this time window, the grand average phase asymmetry between the left and right SAC was

significantly elevated during LE percept as compared to RE percept. Furthermore, the intrinsic phase asymmetries were characterized as a robust oscillatory network trend with low intra- and high interindividual variation across the sample, ranging from 24° to 117°. Crucially, a control analysis demonstrated that the asymmetry values yielded high test-retest reliability scores, suggesting that the asymmetric phase dynamics at 40 Hz were stable across days.

As no behavioral tACS-effect on the REA had been found, a correlation analysis between the intrinsic phase asymmetry during LE percept (sham session) and the tACS-related differences in LI values ($LI_{\text{Verum}} - LI_{\text{Sham}}$) was carried out to establish a link between behavior and underlying physiology. Importantly, the behavioral outcome of the stimulation with a fixed lag of 180° between hemispheres depended on the individual asymmetry values: The REA was amplified when the asymmetry values approximated 0°, whereas participants with stronger phase asymmetry (closer to 180°) were associated with a perceptual shift to LE processing. In this study, the bidirectional impact of the alternating current stimulation was further confirmed by a subgroup division at the median phase angle of 82.11°: The behavioral tACS-modulation of the LI was significantly augmented in subjects with high phase asymmetry above the median angle compared to subjects with low asymmetries.

Collectively, study 2 revealed different temporal profiles of a novel oscillatory phase parameter in the high frequency spectrum during bistable auditory perception, and that individual differences in these spectral asymmetries predicted the behavioral outcome of our electric stimulation.

1.4 Discussion

1.4.1 Directional Oscillatory Coupling Mediates Conscious Auditory Perception

Synchronized activity of cortical high-frequency oscillations is suggested to play a key role in multisensory feature integration, thus facilitating sensory processing and the emergence of conscious perception. Recently, it has been demonstrated that the strength of interhemispheric gamma-band coupling, which is suggested to be mediated by cortico-cortical callosal fibers (Genç, Bergmann, Singer, & Kohler, 2011), directly influenced conscious visual perception (Rose, 2005), and that the individual perceptual outcome could be selectively altered by tACS (Helfrich, Knepper, et al., 2014; Strüber et al., 2014). The goal of this thesis was to extend these findings into

the auditory domain. Previous correlative findings indicated that the same mechanism might enable conscious auditory perception, as LE reports were associated with augmented undirected interhemispheric connectivity compared with RE reports (Steinmann et al., 2014).

This thesis provided the first state-of-the-art directional connectivity analysis to decipher the causal information transfer between the left and right auditory cortices during DL. By exploiting eLORETA source estimation and EC analyses, study 1 demonstrated that the causal interhemispheric transfer during DL runs from the right to the left SAC with increased effective gamma-band connectivity and ensuing phoneme perception through the LE. Crucially, this connectivity effect was not found during the perception of RE syllables or between the PACs, which emphasizes the functional relevance of the SAC for the perception of complex sounds and phonemes (Binder et al., 2000; Kilian-Hutten et al., 2011). Here, EC analyses expanded the neurophysiological understanding of the interhemispheric auditory network by revealing a clear asymmetry during the underlying causal information flow in LE processing, which is mediated by synchronized gamma-band oscillations. This result confirms the callosal relay model, which postulated that additional transcallosal processing from the right auditory cortex via the CC to the left hemisphere is only required during LE, but not during RE perception (Zaidel, 1983). A recent study (Steinmann et al., 2018) combined DTI-based tractography and EEG-based non-linear connectivity (LPS) to investigate the relationship between interhemispheric gamma-band synchrony between the right and left SACs and the microstructure of the individual callosal fibers during DL. Interestingly, the authors did not observe a significant correlation between undirected functional gamma-band coupling and white-matter microstructure (fractional anisotropy, FA), whereas both metrics were significantly related to reduced leftward-asymmetry for language. In light of the EC analyses in this thesis, it might be conceivable that an EC metric such as iCoh, which is well suited to assess the causal directionality between neural oscillators under multivariate autoregressive modelling, might be related to the FA-values of the callosal fibers interconnecting the posterior STGs and explain variance in multiple regression to predict the behavioral LI.

As the CC exhibits homotopic and heterotopic connections (Virgilio & Clarke, 1997), the causal information flow across the auditory pathways might also reflect the combined input from both homotopic and heterotopic callosal fibers. Importantly, a control analysis for heterotopic connections (i.e. from the right SAC to the left PAC and vice

versa) demonstrated that increased directional gamma-band coupling was confined to the homotopic connection between the SACs, while this effect was not observed between heterotopic connections. This is in line with the observation of strong and stable homotopic interhemispheric FC in macaques and humans, and that the underlying direct anatomical projections between homotopic cortical areas were more resistant to change and exhibited stronger temporal stability across time compared to FC in intrahemispheric and heterotopic connections (Shen et al., 2015).

In sum, this thesis expanded the understanding of interhemispheric auditory connectivity during DL by revealing a causal, asymmetric relationship between the left- and right-hemispheric oscillators in the human auditory system. Furthermore, the results in study 1 emphasize the functional importance of the SACs in phoneme perception, and that conscious auditory perception of verbal material through the LE necessitates the right SAC driving the left SAC across homotopic callosal fibers through gamma-band oscillations.

1.4.2 Oscillatory Phase Asymmetries as a Crucial Network Parameter in Stimulation Protocols

TACS can be exploited as a non-invasive technique to probe the causal role of neural oscillations in sensory processing and higher cognitive functions, and it has been successfully employed to entrain targeted neural oscillators in cortical networks (Ali, Sellers, & Fröhlich, 2013; Helfrich, Schneider, et al., 2014; Ozen et al., 2010; Stonkus, Braun, Kerlin, Volberg, & Hanslmayr, 2016; Witkowski et al., 2016). In this thesis, a multi-site HD-electrode montage was derived from a current flow modelling to target the left and right auditory cortex and to selectively inhibit the transcallosal information flow from the right to the left SAC, which should increase the REA by decoupling both hemispheres at 40 Hz with a lag of 180°. Clearly, this hypothesis was not confirmed as the participants responded differently to the fixed stimulation protocol, and there was no behavioral effect of tACS at the group level. Hitherto, the interhemispheric oscillatory coupling between the left and right auditory cortices has not yet been characterized by means of a concrete phase lag in degree notation, and previous studies have demonstrated that interhemispheric coupling in the visual cortex can be inhibited at 40 Hz with a phase lag of 180° (Helfrich, Knepper, et al., 2014; Strüber et al., 2014). In light of the strong interindividual microstructural variability in size and shape of the underlying callosal pathway (Westerhausen et al., 2009), it is

conceivable that such interindividual variability could be observed in EEG-based phase asymmetries, which might explain the absence of a significant stimulation effect at group level. In line with this idea, the intrinsic phase asymmetry was characterized as a robust oscillatory network trend with considerable interindividual variation across the sample. Crucially, the anti-phasic gamma-stimulation influenced the auditory network activity bidirectionally in dependence of the phase-related intrinsic network disposition: The interhemispheric network was prone to excitation, as indicated by a shift to LE reports, when the intrinsic phase lag was close to the exogenously induced lag of 180° , whereas network inhibition and the ensuing shift to RE reports was facilitated when the intrinsic phase asymmetry differed heavily from the tACS-induced lag. In the past, it has been shown that the efficacy of tACS strongly depends on a wide range of parameters, such as the electrode montage (Helfrich, Knepper, et al., 2014; Strüber et al., 2014), stimulation intensity (Moliadze, Atalay, Antal, & Paulus, 2012), waveform and envelope (Dowsett & Herrmann, 2016) and the intrinsic cortical network state (Alagapan et al., 2016; Toralf Neuling, Rach, & Herrmann, 2013). Furthermore, Helfrich and colleagues (2014) argued that tACS-related effects on perception could be contorted by frequency-related interindividual variability, as stronger interhemispheric coherence modulations during 40 Hz stimulation were positively correlated with intrinsic coherence peaks close to 40 Hz in their study. In accordance with that, this thesis underlines the need for tailored and spatio-temporally matched tACS protocols to carefully include crucial oscillatory network parameters such as the intrinsic phase asymmetry. Given that these asymmetry values exhibited an excellent test-retest reliability score, it appears likely that the phase-related interindividual variability might be related to the strong variation of size and shape of the transcallosal pathways, and that the interaction of the cortical auditory oscillators and the external rhythmic source was mediated by the variance of interhemispheric asymmetries.

However, the key finding of elevated phase asymmetry (closer to 180°) in the gamma-band during LE percept contradicts the initial hypothesis of anti-phasic stimulation causing a shift towards RE processing. According to the initial communication through coherence (CTC) hypothesis (Fries, 2005), a tACS-induced shift to LE processing would be expected by a stimulation protocol with 0° between hemispheres, since the initial CTC-hypothesis proposed zero-phase synchronization in the gamma-band range as the key mechanism for bidirectional coupling between neuronal cell

assemblies. Importantly, more recent studies have proven that oscillatory phase synchronization between neuron populations does not occur at zero phase in the gamma-band range (Bastos et al., 2015; Bosman et al., 2012). In line with this, the EEG-based increase of FC during LE percept (Steinmann et al., 2014) reflects a shift away from 0° , as the reported metric (LPS) suppresses zero-lag contributions (Nolte et al., 2004). Moreover, the findings of elevated EC in study 1 and increased phase asymmetry in study 2 complement each other, since Granger-causal influences reflect non-zero lag synchronization between oscillatory signals. Collectively, both studies in this thesis demonstrate that the emergence of conscious auditory perception is enabled by long-range synchrony between the right and left SAC in the gamma-band range, and that the oscillatory coupling occurs with a clear delay (non-zero phase-lag).

1.4.3 Confounds and Limitations

Several limitations impede the analysis of encephalographic activity in the gamma-band range, with volume conduction, muscle activity and low spatial resolution being the most relevant issues to address. Therefore, all EEG data in this thesis were analyzed at the source space level by utilizing eLORETA and state-of-the-art ICA to minimize the impact of these artifacts (Hipp & Siegel, 2013). Importantly, concomitant fMRI and EEG recordings have demonstrated sufficient validity of LORETA-based source estimations (Mulert et al., 2005), and non-physiological influences are further suppressed by the reported connectivity metrics (LPS) in study 1 (Nolte et al., 2004). Another issue is the application of an multivariate autoregressive (MVAR)-model on EEG data, as the approach generally holds the assumption of stationarity between the neural oscillators as a linear and time-invariant system (Greenblatt, Pflieger, & Ossadtchi, 2012). However, the MVAR-model was exploited as a tool to reveal causal relationships under consideration of linear and non-linear domains of the interhemispheric auditory network, and offers a more realistic frequency resolution compared to the often reported metric partial directed coherence (PDC, Pascual-Marqui et al., 2014). Moreover, iCoh represents a reliable EC metric which has been shown to be unaffected by noise covariances (Pascual-Marqui et al., 2014), and the intrinsic phase asymmetry was characterized as a metric with high test-retest reliability in study 2 in this thesis.

One of the most obvious limitations of study 2 is the missing EEG analysis and characterization of the intrinsic phase signature *during* stimulation, as the EEG was recorded during all conditions. The decision not to analyze the EEG during electric stimulation was reasoned with the observation that no previously employed artifact removal approach, such as artifact template subtraction (Helfrich, Schneider, et al., 2014), notch filtering (Helfrich, Knepper, et al., 2014) or beamforming (Toralf Neuling et al., 2015), has been proven to reliably reconstruct true physiological oscillatory activity during tACS (Noury et al., 2016; Noury & Siegel, 2017). In light of the reliable neural framework based on decades of multimodal neuroimaging research dedicated to the interhemispheric transfer during DL (Hugdahl, 2011; Steinmann et al., 2019; Westerhausen et al., 2009), the results of this thesis entirely support the callosal relay model and suggest that the external driving force interacted with the intrinsic phase relationship between the left- and right-hemispheric oscillators.

1.4.4 Conclusion and Future Prospects

Taken together, this thesis provides novel insight into the role of gamma-band oscillations in the interhemispheric auditory transfer by revealing a causal sender-receiver relationship and oscillatory phase signature at 40 Hz between the left and right SAC. Furthermore, both studies highlight that long-range auditory network communication through synchronized gamma-band oscillations is characterized by a clear non-zero phase relationship, which is visible in EC and the intrinsic phase asymmetry. Specifically, the results demonstrate that such oscillatory phase asymmetries are stable across days, which offers the possibility to implement this network parameter into future stimulation protocols. Moreover, this thesis clarifies the need for systematic exploration of the parameter space of tACS and for individually tailored stimulation protocols based on intersubject variability and cortical state.

The results suggest that spatiotemporally-matched multi-site tACS might be an ideal tool for novel therapeutic interventions in neuropsychiatric conditions that are associated with cortical rhythmic disturbances, such as Parkinson's disease (Brittain, Probert-Smith, Aziz, & Brown, 2013), autism spectrum disorders and SZ (Ćurčić-Blake et al., 2017; Steinmann et al., 2017; Uhlhaas & Singer, 2012). Since DTI-based tractography revealed significant associations between the occurrence of AVH in SZ and the size and shape of the interhemispheric auditory fiber tracts (Hubl et al., 2004; Mulert et al., 2012; Wigand et al., 2015), the characterization of the intrinsic phase asymme-

tries in hallucinating patients might be a relevant subject to address in future studies. In this regard, the application of multimodal imaging techniques, such as DTI and EEG during DL to investigate the relationship between the intrinsic phase asymmetries and anatomical connectivity of the interhemispheric pathways, might be a promising next step to extend our understanding of oscillatory phase asymmetries in the human brain.

2. List of Abbreviations

AMPA	α -Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
AVH	Auditory Verbal Hallucinations
BA	Brodmann Area
CC	Corpus Callosum
CTC	Communication through Coherence (-Hypothesis)
CV	Consonant-Vocal (Syllable Combination)
DL	Dichotic Listening
DLPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
EC	Effective Connectivity
EEG	Electroencephalography
E-I	Excitation-Inhibition
eLORETA	Exact Low-Resolution Brain Electromagnetic Tomography
FA	Fractional Anisotropy
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
HC	Healthy Control (Subjects)
HD	High Density
HG	Heschl's Gyrus
ICA	Independent Component Analysis
iCoh	Isolated Effective Coherence
LE	Left Ear
LI	Laterality Index
LPS	Lagged Phase Synchronization
MEG	Magnetoencephalography
MVAR	Multivariate Autoregressive (Model)
NIBS	Non-Invasive Brain Stimulation
NMDA(R)	N-Methyl-D-Aspartate (Receptor)
PAC	Primary Auditory Cortex (Heschl's Gyrus)
PDC	Partial Directed Coherence
RE	Right Ear

REA	Right Ear Advantage
RM-ANOVA	Repeated-Measures Analysis of Variance
rTMS	Repetitive Transcranial Magnetic Stimulation
SAC	Secondary Auditory Cortex
STG	Superior Temporal Gyrus
SZ	Schizophrenia
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
tES	Transcranial Electric Stimulation
tRNS	Transcranial Random Noise Stimulation
VOT	Voice Onset Time
WM	White Matter

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4. Publication 1

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The Callosal Relay Model of Interhemispheric Communication: New Evidence from Effective Connectivity Analysis

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Abstract Interhemispheric auditory connectivity via the corpus callosum has been demonstrated to be important for normal speech processing. According to the callosal relay model, directed information flow from the right to the left auditory cortex has been suggested, but this has not yet been proven. For this purpose, 33 healthy participants were investigated with 64-channel EEG while performing the dichotic listening task in which two different consonant–vowel syllables were presented simultaneously to the left (LE) and right ear (RE). eLORETA source estimation was used to investigate the functional (lagged phase synchronization/LPS) and effective (isolated effective coherence/ICoh) connectivity between right and left primary (PAC) and secondary auditory cortices (SAC) in the gamma-band (30–100 Hz) during right and left ear reports. The major finding was a significantly increased effective connectivity in the gamma-band from the right to the left SAC during conscious perception of LE stimuli. In addition, effective and functional connectivity was significantly enhanced during LE as compared to RE reports.

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These findings give novel insight into transcallosal information transfer during auditory perception by showing that LE performance requires causal interhemispheric inputs from the right to the left auditory cortices, and that this interaction is mediated by synchronized gamma-band oscillations.

Keywords Auditory cortex · Dichotic listening task · Effective interhemispheric connectivity · EEG · Gamma-band oscillations

Introduction

Interhemispheric auditory connectivity via the corpus callosum has been shown to be responsible for the timely interplay of right and left speech-relevant brain regions recruited for normal speech comprehension (Friederici et al. 2007). However, it remains largely unknown how the auditory systems dynamically interact with one another and in particular in which direction the interhemispheric communication is realized. According to the callosal relay and the left-hemispheric specialization for language and speech processing, the directed flow of information from the right to the left-dominant hemisphere during certain language tasks has been suggested, but not yet proven (Hugdahl and Westerhausen 2016). Effective connectivity (EC) analysis provides the next step concerning the understanding of callosal dynamics underlying auditory processing by examining causal information flow at the spectral nature of oscillatory activity between distinct predefined brain regions (Pascual-Marqui et al. 2014). With EC analysis, it is possible to create and test realistic models of interacting neuronal systems to investigate explicitly the directed influence of one region on another (Friston 2011). In particular, Granger causality analysis of electrophysiological (EEG) data offers the important

advantage of high temporal resolution and the detailed investigation of specific frequency bands (Seth et al. 2015).

One of the most popular paradigms to investigate interhemispheric connectivity and hemispheric specialization of language and speech is the dichotic listening task. The term “dichotic listening” describes a paradigm in which two slightly different verbal stimuli (such as consonant–vowel syllables) are simultaneously presented, one to each ear, with the participants’ instruction to report the stimulus which was understood most clearly. Typically, the majority of healthy participants show the well-known right ear advantage (REA), that is, they report more often the right (RE) than the left ear (LE) stimuli (Hugdahl 2011). According to the “structural model” (Kimura 1967, 2011) or “callosal relay model” (Zaidel 1983), this REA is explained by the anatomy of the ascending auditory pathways and the left-hemispheric lateralization of language and speech processing (Hugdahl and Westerhausen 2016). Although the verbal stimuli can reach the auditory cortex via both contralateral and ipsilateral projections, it is assumed that under dichotic conditions the ipsilateral pathways are inhibited, while the contralateral pathways are more preponderant (Brancucci et al. 2004; Fujiki et al. 2002). Thus, only the right ear stimuli are directly transmitted to the relevant left-hemispheric processing areas, whereas the left ear stimuli—initially projected to the right hemisphere—require additional interhemispheric transfer across the corpus callosum in order to be finally processed in the speech-dominant left hemisphere. Accordingly, a “hardwired” bottom-up phenomenon seems to play a crucial role for the emergence of the REA. However, the magnitude of the REA also has been found to be associated with the structural and functional interhemispheric auditory connectivity: Using DTI-based tractography, it has been shown that there are remarkable shape differences among healthy individuals, with stronger fibers improving interhemispheric transfer so that participants reported more syllables presented to the left ear (Westerhausen et al. 2009). Moreover, using EEG recordings, evidence of our own group indicated that the functional connectivity (FC) between right and left secondary auditory cortices is mediated by synchronous gamma-band oscillations (GBO) (Steinmann et al. 2014a). Here, conscious perception of left ear syllables was significantly related to an increased interhemispheric gamma-band coupling, suggesting that GBO are a functional key mechanism in the transcallosal auditory transfer. However, the direction of information transfer during dichotic listening has not been investigated so far, although the callosal relay model suggests a clear direction.

Accordingly, it was the aim of this EEG study to investigate the relationship between functional and effective interhemispheric connectivity in the gamma-band (30–100 Hz) and lateralized auditory perception during dichotic listening. To address this question, eLORETA source estimation

was used to determine (1) the FC using lagged phase synchronization (LPS), and (2) the EC using isolated effective coherence (ICoh) between right and left (and vice versa) primary (PAC) and secondary auditory cortices (SAC) in the gamma-band during conscious perception of either right or left ear syllables. Specifically, we hypothesized that the effective connectivity analysis proves that perception of left ear stimuli requires interhemispheric causal transfer in the gamma-band from the right to the left secondary auditory cortices, a finding that would be in accordance with the callosal relay model of dichotic listening.

Methods

Participants

The sample consists of 33 healthy right-handed German native speakers (18 male, 15 female). The participants’ handedness was verified with the empirically validated Edinburgh Handedness Inventory (Oldfield 1971). Exclusion criteria were left-handedness or a history of hearing, psychiatric or neurological disorders. To ensure normal hearing in both ears, all participants were screened with pure tone audiometry for frequencies between 125 and 8000 Hz (Esser Home Audiometer 2.0). Participants with an auditory threshold higher than 25 dB, or an interaural difference larger than 15 dB in any of the frequencies were excluded from the study. All participants had normal IQ as tested with a vocabulary test (Herzfeld 1994). The group of participants partly overlapped with the sample of our previous study (Steinmann et al. 2014a). This study was approved by the ethics commission of the Medical Association Hamburg (Reference number: PV3485). All applied methods were in accordance with all relevant guidelines and regulations. After participants received a complete description of the experimental procedures, written informed consent according to the Declaration of Helsinki was obtained. Demographic data for all participants are presented in Table 1.

Paradigm

The subjects had to perform a dichotic listening task that was also used in our previous study (Steinmann et al. 2014a). In brief, six different consonant–vowel syllables (/ba/, /da/, /ka/, /ga/, /pa/, /ta/) were paired and presented simultaneously with one syllable to each ear. In order to control effects of syllable voicing, only syllables with the same voice onset time (VOT) were combined, resulting in 12 possible dichotic pairs. VOT describes the length of time between the release of a consonant and the onset of voicing, defined by the vibration of the vocal folds. Three of the syllables were voiced (/ba/, /da/, /ga/) and had a short voice onset time (VOT)

Table 1 Demographic characteristics of the sample: mean, standard deviation (SD) and range are given for each variable

Variable	Demographic data of participants (n = 33)		
	Mean	SD	Range
Age (years)	31.36	9.11	19–57
Gender (male/female)	18/15	n.a.	n.a.
Handedness	87.74	16.27	40–100
Educational level	1.36	0.60	1 (high)–3 (low)
Verbal IQ	111.27	10.00	86–129
Laterality index (LI)	24.65	22.42	–16.84 to 67.00
Right ear reports	134.81 (56.17%)	30.64	79–192
Left ear reports	80.00 (33.33%)	21.72	37–123
Error reports	25.69 (10.70%)	17.18	5–66

between 17 and 32 ms, and three were unvoiced (/pa/, /ta/, /ka/) with a long VOT in the range of 75–80 ms. Each syllable combination was temporally aligned to achieve simultaneous onset of the initial consonants. The mean duration was between 400 and 500 ms depending on the different VOT. After filling out the questionnaires and performing the hearing test, participants were asked to perform practice trials of 6 syllable pairs in order to get familiarized with stimulus material and experimental procedure. The main experiment consisted of 240 trials, which were presented in two blocks of 120 trials. Both blocks were presented to participants with the instruction to report the syllable they understood most clearly (non-forced condition), while they were not informed that each presentation consisted of two different syllables.

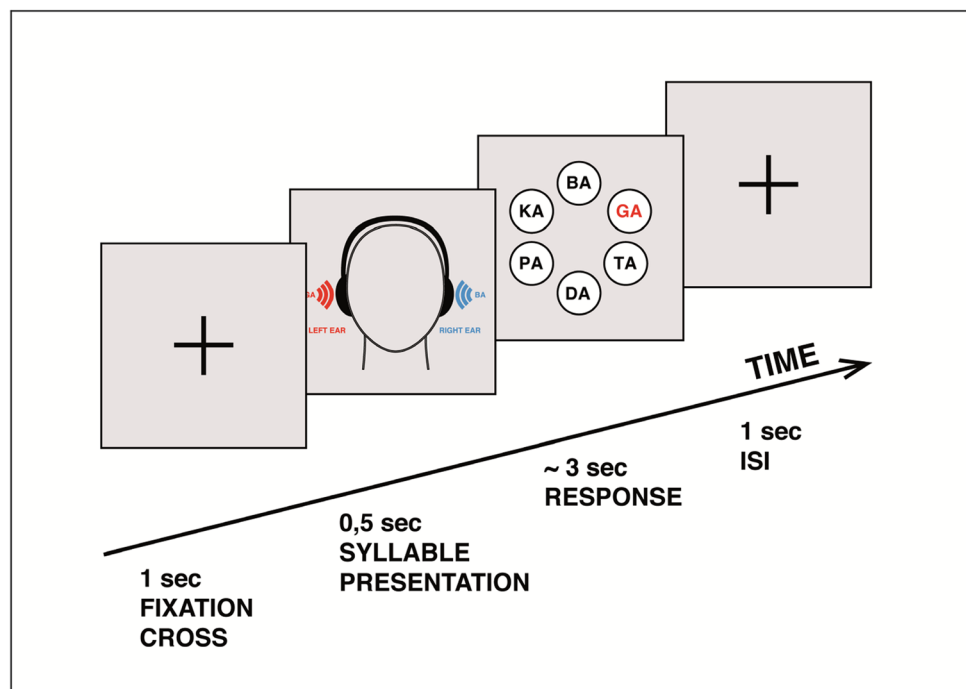
Participants were encouraged to relax, reduce eye and head movement, fixate on the cross, and avoid jaw muscle contraction. Responses were made by button press using the dominant (right) hand. The stimulus administration and response collection were controlled using Presentation® software (Neurobehavioral Systems, Albany, CA). After the recording, the percentage of correctly reported syllables was calculated separately for left and right ear stimuli. In order to assess the magnitude of the ear effect, a behavioral laterality index (LI) was calculated for every subject according to the formula: $LI = 100 \times (RE - LE) / (RE + LE)$; where RE = number of correct right ear reports and LE = number of correct left ear reports. The scale varies between –100 and +100, with negative values indicating a LEA and positive values a REA (Fig. 1).

EEG Recording

The recording took place in a sound-proof and electrically shielded cabin, while participants listened through closed system headphones (Sennheiser, HAD 200) to the randomly presented 240 syllable pairs at approximately 75 dB. The EEG recordings were conducted at a sampling rate of 1000 Hz with 64 Ag/AgCl electrodes mounted on an elastic cap (ActiCaps, Brain Products, Munich, Germany) using the Brain Vision Recorder 1.10 (Brain Products, Munich, Germany). Eye movements were recorded using four EOG channels. Impedances were kept below 5 K Ω .

Offline processing was carried out using Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany). The data

Fig. 1 Dichotic listening task. The beginning of each trial was indicated by the appearance of a fixation cross in the centre of the screen. Subjects were instructed to fixate their eyes on the cross. The response was given via a response screen which appeared immediately after hearing the syllable pair. The screen showed all six syllables presented in a circular formation. By clicking with the *right* (dominant) hand the *left* mouse button it was possible to navigate through the six answer alternatives and with the right mouse button the selection was confirmed. Between the offset of the visual presentation and the onset of the next auditory stimulus a stable interstimulus interval (ISI) of 1 s was applied



was bandpass filtered from 20 to 120 Hz and down-sampled to 256 Hz. All channels were re-referenced to common average and FCz (reference during recording) was recovered as a regular channel. Epochs with muscle artifacts in any channel were identified by visual inspection and rejected from further analysis. Independent component analysis (ICA) was applied to identify and remove blink, horizontal eye movement, electrocardiographic, and saccadic spike potential (SP) artifacts based on their characteristic topographies, time-courses, and frequency distributions (Carl et al. 2012). In order to improve the identification of SP artifact components in the gamma-band frequency range (Yuval-Greenberg et al. 2008) an additional “radial electro-oculogram channel” (REOG, defined as the average of all EOG channels: $REOG = (HEOGR + HEOGL + VEOGS + VEOGI)/4 - Pz.$) was used following the procedure described by Keren et al. (2010). The SP artifact components appeared in the REOG channel consistently as a sharp biphasic deflection. Subsequently, the artifact-free data was segmented in epochs of 2048 ms starting 200 ms prior to stimulus onset. Correct-response epochs were exported for connectivity analysis and balanced between the number of right and left reports trials for each subject, ending up in a mean number of 82 trials for both conditions.

Interhemispheric Auditory Connectivity Analysis

All further analyses were executed using the LORETA KEY software package as provided by Roberto Pascual-Marqui (The KEY Institute for Brain-Mind Research University Hospital Psychiatry, Zurich) at <http://www.uzh.ch/keyinst/LORETA.html>.

For analysis of FC, the lagged phase synchronization (LPS) between auditory cortices was calculated, as done previously (Steinmann et al. 2014a). LPS measures the similarity between signals in the frequency domain based on normalized (unit module) Fourier transforms; thus it is related to nonlinear functional connectivity (Pascual-Marqui et al. 2011). The LPS measure represents the connectivity between two signals after the instantaneous, zero-lag contribution has been excluded. Such a correction is necessary when using scalp EEG signals or estimated intracranial signals, because zero-lag connectivity in a given frequency band is often due to non-physiological effects or intrinsic physical artifacts, in particular volume conduction (Nolte et al. 2004; Stam et al. 2007). Thus, this measure removes this confounding factor considerably and is thought to contain only physiological connectivity information. The LPS formula is defined as:

$$\varphi_{xzy}^2(t, \omega) = \frac{\{\text{Im} [f_{x,y}(t, \omega)]\}^2}{1 - \{\text{Re} [f_{x,y}(t, \omega)]\}^2} \quad (1)$$

where t denotes the time domain and ω denotes the frequency domain of the respective imaginary and real part from the complex coherency.

In order to account for the causal directionality at the spectral nature of oscillatory activity during dichotic listening, EC was computed as isolated effective coherence (iCoh) (Pascual-Marqui et al. 2014), where iCoh from region-of-interest (ROI) j to ROI i at a discrete frequency ω is defined as:

$$\kappa_{i \leftarrow j}(\omega) = \frac{[S_\varepsilon]_{ii}^{-1} \left| \left[\tilde{A}(\omega) \right]_{ij} \right|^2}{[S_\varepsilon]_{ii}^{-1} \left| \left[\tilde{A}(\omega) \right]_{ij} \right|^2 + [S_\varepsilon]_{jj}^{-1} \left| \left[\tilde{A}(\omega) \right]_{jj} \right|^2} \quad (2)$$

where $S(\varepsilon)^{-1}$ denotes the matrix inversion of the spectral density matrix (i.e., Hermitian covariance), and A denotes the autoregressive coefficients at a given frequency ω , while resulting coherence values satisfy

$$0 \leq \kappa_i \leftarrow j(\omega) \leq 1. \quad (3)$$

Contrary to the LPS analysis, this method provides the opportunity to assess the direct nature of neuronal connections under multivariate autoregressive (MVAR) modeling of partial directed coherence (Baccala and Sameshima 2001). Importantly, causal directionality between a priori defined ROI can only be estimated by setting the effects of all other possible neuronal connections to zero, which is a necessary condition in the assessment of Granger-causal influences (Granger 1969). In the present study, right and left primary auditory cortices (PACs/BA41), known to support any type of sound processing (Johnsrude et al. 2002), and right and left secondary auditory cortices (SACs/BA42), known to be involved in the processing of complex sounds and speech sounds (Binder et al. 2000; Zaehle et al. 2004), were defined as ROIs using the anatomical definitions provided by the eLORETA software based on the Talairach Daemon. Previously, we have reported LPS differences between right and left reports in two gamma sub-bands (slow gamma: 30–50 Hz, mid gamma: 50–90 Hz), but not in any other frequency band (delta, theta, alpha, beta). Therefore, LPS and iCoh analysis were focussed on the gamma-band range (30–100 Hz). In order to get high frequency resolution for the iCoh analysis, we decided for an AR-order of 8 (high order-concatenation), because the frequency resolution in linear AR modelling mainly depends on its order (Ding et al. 2000). Because MVAR modelling presupposes the issue of stationarity, we guaranteed synchronized trial data by epoching the exported segments to a shorter time window of 200 ms with an onset at 500 ms post-stimulus. The choice of this window was based on the fact that the

syllable presentation ends around 500 ms, and importantly that non-directional connectivity between left and right SACs was found to reach highest synchrony during left ear report in this time window (Steinmann et al. 2014a). Thus, LPS and iCoh were calculated in a time frame from 500 to 700 ms to syllable presentation onset for right and left ear reports, respectively, and for iCoh in both directions (left to right hemisphere and vice versa, respectively). Under consideration of all randomized and re-epoched trials, one mean iCoh-value (frequency resolution: 1 Hz) was calculated for each subject and each direction. Finally, iCoh values in the gamma-band range were averaged from 30 to 100 Hz.

Statistics

SPSS version 22 was used for the statistical analysis of behavioral and demographic characteristics (<http://www.spss.com>). For all analyses the significance level was set to $\alpha=0.05$. All data were tested for normality using the Kolmogorov–Smirnov-test and for Sphericity using Mauchly's test. In case of violation of the sphericity assumption, Greenhouse–Geisser-corrected p -values and degrees of freedom were reported. Effect sizes for significant results were quantified as η^2 -partial (RM-ANOVA) or r (Wilcoxon tests). A 2×2 repeated measures analysis of variance (RM-ANOVA) with *Condition* (RE/LE-reports) as within-subjects factor and *Gender* as between-subjects factor was used to check for gender differences with respect to the LI. Wilcoxon signed rank test was used to investigate differences in FC (LPS) in the gamma-band between *LE* and *RE Percepts* (for PAC and SAC respectively). For EC data (iCoh) we used two (for PAC and SAC respectively) 2×2 RM-ANOVAs with *Condition* (RE/LE-report) and *Direction* (Right to Left/Left to Right) as within-subjects factors. Significant main effects were further explored using Wilcoxon-signed ranks post-hoc tests which were corrected for multiple comparison with Bonferroni-holm.

Results

Task Performance

Participants reported significantly more syllables presented to the RE (135 ± 5.3) than to the LE (80 ± 3.8) as indicated by a main effect of *Condition* [$F_{1,32} = 40.93$; $p < .001$, $\eta^2_{\text{partial}} = 0.57$], reflecting the typical REA (LI: $M = 24.65 \pm 22.42$). There was no significant main effect of *Gender* ($p = .23$) and no significant *Condition* \times *Gender* interaction ($p = .23$). The LI's were normally distributed (one-sample Kolmogorov–Smirnov test, $p = .74$). 28 out of 33 participants showed a positive

LI, whereas 4 participants had a negative LI and one subject showed no ear advantage (LI = zero).

Interhemispheric Functional Connectivity (FC) Between Auditory Cortices

The Wilcoxon signed rank test revealed a significant increase of LPS between right and left SAC during *LE Percept* ($Md = 0.0561$) compared to *RE Percept* ($Md = 0.0453$) [$Z = 3.181$, $p < .001$, $r = 0.55$, Fig. 2]. There was no significant difference for PAC.

Interhemispheric Effective Connectivity (EC) Between Auditory Cortices

In accordance to our hypothesis, there was a significant interaction effect of *Condition* \times *Direction* [$F_{1,32} = 6.666$, $p = .014$, $\eta^2_{\text{partial}} = 0.17$] for the whole gamma-band range. Bonferroni-holm corrected post-hoc tests revealed that the perception of syllables presented to the LE was accompanied by a significantly increased interhemispheric iCoh from the right to the left SAC compared to the other direction ($Z = 2.00$, $p = .025$, $r = 0.35$; Fig. 3). Moreover, the iCoh from the right to the left SAC was significantly increased during perception of LE syllables compared to RE syllables ($Z = 2.69$, $p = .016$, $r = 0.34$), whereas the iCoh from the left to the right SAC showed no significant difference between LE and RE Percept. Perception of RE syllables was not accompanied by any significant difference between the two directions. There were no further significant main effects or an interaction effects, nor for any of the analyses for PAC (Fig. 4).

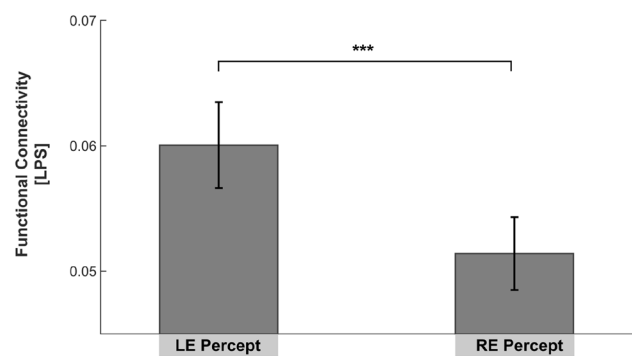


Fig. 2 LPS between *right* and *left* SAC in the gamma-band frequency range (30–100 Hz) calculated for a time-window from 500 to 700 ms after stimulus onset. Significantly increased LPS was found during left ear (LE) compared to right ear (RE) Percept. Significant findings are highlighted with an *asterisk*

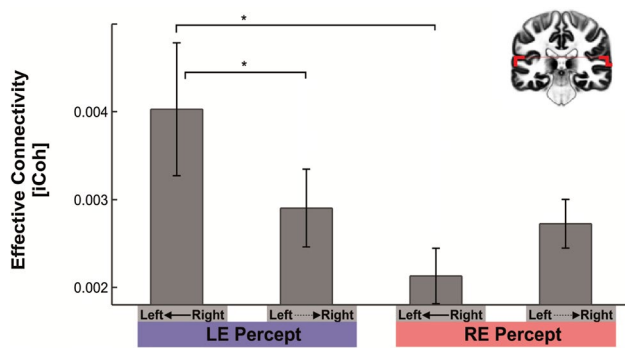


Fig. 3 Means of iCoh of the four potential directions during left (LE) and right ear (RE) Percepts in the gamma-band frequency range (30–100 Hz): Significantly increased iCoh was found during LE Percepts (blue) from right to left SAC compared to the other direction (i.e., left to right). Moreover, significantly increased ICoh was found during LE Percepts (blue) compared to RE Percepts (red) for ICoh from right to left SAC. Shaded error bars represent 95% CI. Significant findings are highlighted with an asterisk. (Color figure online)

Discussion

The aim of this study was to determine the degree and the direction of the interhemispheric auditory connectivity in the gamma-band by means of LPS and iCoh during dichotic listening and to further proof the concept of the callosal relay model. For this purpose, the dichotic listening is a well-suited paradigm, as it is one of the most frequently applied tasks for assessing language lateralization and interhemispheric interaction with a good understanding of the underlying structural substrate (Westerhausen and Hugdahl 2008).

The characteristic finding is the REA, which we were able to replicate in this study. In accordance with our hypothesis, the major finding was a significantly increased EC in the gamma-band from the right to the left SAC during conscious perception of left ear stimuli. In addition, this causal information flow as well as the gamma-band phase synchrony was significantly enhanced during LE as compared to RE reports. There was no significant difference between directions during conscious perception of RE syllables, indicating that this pathway is redundant. These results are fully consistent with the callosal relay model, suggesting that only left ear perception requires additional interhemispheric transfer from the right auditory cortex via the corpus callosum to the language-processing areas of the left hemisphere (Zaidel 1983). DTI-based tractography studies have shown that the splenium bordering the isthmus (both located at the posterior third of the corpus callosum) contains the interhemispheric pathways that interconnect primary and secondary auditory cortices (Hofer and Frahm 2006; Huang et al. 2005). This callosal region is characterized by large number of fast-conducting, highly myelinated auditory

pathways of more than 3 μm in diameter (Aboitiz and Montiel 2003; Fabri and Polonara 2013). Thus, these fibers are the thickest among the callosal fibers suggested to promote synchronous activation across distant brain regions with high transmission velocity (Singer 1999). The understanding of hemispheric differences and interhemispheric interaction during dichotic listening was considerably improved through studies of split-brain patients (Springer and Gazzaniga 1975; Sugishita et al. 1995) and patients with splenial lesions (Pollmann et al. 2002) as well as patients with multiple sclerosis (Gadea et al. 2002, 2009; Pelletier et al. 2001). Such studies demonstrated that atrophy or disruptions of the splenial commissures lead to enhanced REA or even a complete left ear extinction. All these data indicate that callosal disruptions impair the interhemispheric information transfer and alter the behavioural laterality index. Furthermore, in healthy participants a strong relationship between naturally occurring interindividual variability in midsagittal callosal area and the dichotic listening performance has been observed (Westerhausen et al. 2009; Yazgan et al. 1995). Here, a stronger interhemispheric connectivity resulted in a reduced REA, which is most likely caused by a better processing of the left ear stimuli. Thus, several pieces of evidence support the notion that conscious perception of left ear syllable requires interhemispheric interaction. Besides, the corpus callosum consists not only of homotopic but also heterotopic connections (Di Virgilio and Clarke 1997) and it might be speculated that the interhemispheric transfer from right to left could result from combined inputs of homotopic and heterotopic callosal fibers. In order to clarify this point, such EC analysis (i.e., from right PAC to left SAC and vice versa) were performed with no significant findings (all $p > 0.5$). This is in accordance with the literature suggesting that homotopic connections are more numerous (Jarbo et al. 2012) and exceptionally strong compared to heterotopic pathways (Shen et al. 2015).

To date, our knowledge of interhemispheric interaction during speech perception relies on the source space analysis of undirected statistical dependencies between ROIs (i.e., PAC and SAC) using LPS analysis as a tool of FC with high temporal resolution, emphasizing a crucial role of GBO for transcallosal functional coupling. The EC analysis provides now the next methodological step concerning the understanding of underlying causal mechanism of callosal transfer by indicating that this is mediated from right to left SAC. In contrast to FC, EC analysis offers the great advantage of permitting statements about directed statistical dependencies in a predefined neuronal system, comparing how well a defined model explains the observed data by performing a linear AR fitting in a specific order (Seth et al. 2015). Furthermore, EC is defined in both time and frequency domain and holds the potential to uncover the spectral characteristics of the measured interactions. In the present study, the

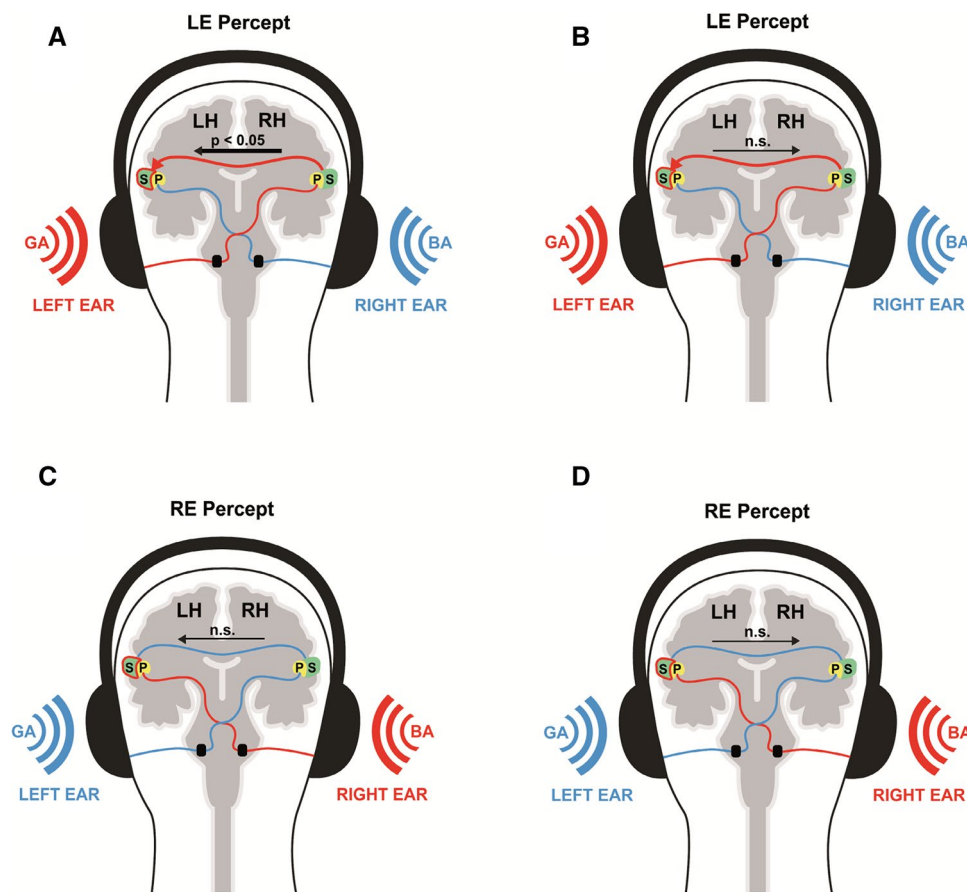


Fig. 4 **A, B** Schematic illustration that displays the processing pathway underlying conscious perception of left ear (LE) syllables. The *thin red line* indicates the contralateral pathway transmitting the LE stimulus from the left ear directly to the non-dominant right hemisphere. The subsequent transfer from the right to the left SAC—which is assumed to be responsible for syllable analysis—is illustrated by the *thick red line*. ICoh analysis demonstrated that conscious perception of LE syllables is associated with increased infor-

mation flow from the right to the left SAC (**A**), but not the other way round (**B**). **C, D** Schematic illustration that displays the contralateral processing pathway underlying conscious perception of right ear (RE) syllables, which does not require interhemispheric interaction. Conscious perception of RE syllables was not associated with a significant increased interhemispheric ICoh in any of the two directions. *LH* left hemisphere, *RH* right hemisphere, *P* primary auditory cortex, *S* secondary auditory cortex, *n.s.* not significant. (Color figure online)

main results suggest GBO to be the mechanism that coordinates the interhemispheric information flow from the right to the left SAC that subserve coherent auditory perception. This is of special interest, since a growing body of evidence already has indicated GBO and their synchronization as a fundamental mechanism that coordinates widely distributed neurons into dynamically formed functional networks that subserve coherent perception and cognition (Engel et al. 2001; Giraud and Poeppel 2012; Hipp et al. 2011). Interestingly, the structural and functional transcallosal connectivity has also been suggested to play a crucial role for the pathophysiology of auditory phantom percepts, such as auditory verbal hallucinations (AVH) in schizophrenia (Steinmann et al. 2014b). Here, disturbances of the interhemispheric auditory phase synchrony has been found again in the gamma-band frequency range (Mulert et al. 2011). Moreover, altered interhemispheric pathways (Mulert et al.

2012) as well as reduced language lateralization have been related to the emergence of AVH (Ocklenburg et al. 2013). Thus, to uncover the dynamical mechanism underlying the typical REA may not only be important for basic science on hemispheric lateralization and auditory perception, but may also have important implications for the understanding of clinical disturbances in such a network, as it can be observed in schizophrenia.

Concerning limitations and strengths of the present study that warrant discussion, the relatively low spatial accuracy has to be mentioned (Pascual-Marqui et al. 1994), although cross validation studies using simultaneous EEG and fMRI have suggested sufficient validity of the LORETA approach in general (Mulert et al. 2005, 2004). It has been shown that the Euclidean distance between EEG- and fMRI-based localizations typically ranges between 1 and 2 cm. However, our finding of increased LPS and iCoh between bilateral

SACs is consistent with our previous EEG study that has evidenced the SAC to be the main contributor to the left ear report probability. At first sight, the application of an MVAR-model on times series of EEG signals may appear contradictory since this approach technically presumes the observed data as the outcome of a linear time-invariant system (Greenblatt et al. 2012), while the brain can clearly be considered as a non-linear system. Nevertheless, AR-modelling is a powerful tool to identify causal relationships in linear and non-linear domains of a predefined neural network, under careful consideration of issues like stationarity, temporal filtering and volume conduction (Nunez 1981). Furthermore, EC measures have to be regarded as complementary rather than competitive to other measures, such as FC, which provide even better frequency resolution. One promising methodological next step to elucidate the relation between functional, effective and structural connectivity might be the investigation with multimodal imaging, including the combination of EEG und fMRI (Mulert et al. 2010) or EEG and DTI (Lei et al. 2015) during dichotic listening. This study was not designed to clarify top-down attentional influences, which have been suggested to contribute to the emergence of the REA during dichotic listening tasks (Kinsbourne 1970; Kinsbourne and McMurray 1975). Here, further studies using EC analysis including conditions with attentional focus on either the left or the right ear would be helpful.

In sum, the EC findings give novel insight into transcallosal information transfer during auditory perception supporting the assumption that left ear performance requires causal interhemispheric transfer from the right to the left auditory cortices and that this interaction is mediated by synchronized GBO.

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Author Contributions SS, CM, GL, JM designed the study; SS collected and analysed data; JM analysed data and wrote codes; GN gave methodological support. GL, CM, AE supervised the project; SS, JM, GL, CM wrote the paper; all authors discussed the results and commented on the manuscript at all stages.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflicts of interest.

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5.1 Publication 2

Meier J, Nolte G, Schneider TR, Engel AK, Leicht G, et al. (2019) Intrinsic 40Hz-phase asymmetries predict tACS effects during conscious auditory perception. *PLoS ONE* 14(4): e0213996. <https://doi.org/10.1371/journal.pone.0213996>

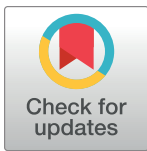
RESEARCH ARTICLE

Intrinsic 40Hz-phase asymmetries predict tACS effects during conscious auditory perception

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Abstract

Synchronized oscillatory gamma-band activity (30-100Hz) has been suggested to constitute a key mechanism to dynamically orchestrate sensory information integration across multiple spatio-temporal scales. We here tested whether interhemispheric functional connectivity and ensuing auditory perception can selectively be modulated by high-density transcranial alternating current stimulation (HD-tACS). For this purpose, we applied multi-site HD-tACS at 40Hz bilaterally with a phase lag of 180° and recorded a 64-channel EEG to study the oscillatory phase dynamics at the source-space level during a dichotic listening (DL) task in twenty-six healthy participants. In this study, we revealed an oscillatory phase signature at 40Hz which reflects different temporal profiles of the phase asymmetries during left and right ear percept. Here we report that 180°-tACS did not affect the right ear advantage during DL at group level. However, a follow-up analysis revealed that the intrinsic phase asymmetries during sham-tACS determined the directionality of the behavioral modulations: While a shift to left ear percept was associated with augmented interhemispheric asymmetry (closer to 180°), a shift to right ear processing was elicited in subjects with lower asymmetry (closer to 0°). Crucially, the modulation of the interhemispheric network dynamics depended on the deviation of the tACS-induced phase-lag from the intrinsic phase asymmetry. Our characterization of the oscillatory network trends is giving rise to the importance of phase-specific gamma-band coupling during ambiguous auditory perception, and emphasizes the necessity to address the inter-individual variability of phase asymmetries in future studies by tailored stimulation protocols.

Introduction

Synchronized neuronal activity across widely distributed cortical regions is encoded in unique spectral signatures and thought to reflect a key mechanism for cortical information integration and conscious perception in humans [1]. In particular, synchronization in the gamma-

decision to publish, or preparation of the manuscript.

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frequency range (30–100 Hz) has been associated with feature integration from distant cortical sites [2] and might efficiently route cortical information flow to task-relevant cortical regions [3]. While most of the previous work was done in the visual domain [1–3], recent findings indicated that a similar mechanism might underlie conscious auditory perception [4,5], where information from both ears is integrated across both auditory cortices during a dichotic listening (DL) task (Fig 1A) [6]. In this paradigm, healthy participants typically exhibit the well-known right ear advantage during DL; they report more often the syllable presented to the right than to the left ear [7], which is best explained by the supremacy of contralateral pathways from the speech-dominant left hemisphere [8]. Furthermore, left ear percept is associated with increased functional [4] and effective [5] gamma-band connectivity, which might be mediated by cortico-cortical callosal fibers [6].

Even though most of this evidence is correlative in nature, causal links between oscillatory key signatures during auditory processing and structural connections could be investigated with novel non-invasive brain stimulation techniques such as transcranial alternating current stimulation (tACS), which enable frequency-specific modulation of cortical oscillations [9]. In the past, tACS has been suggested to entrain cortical oscillations in a frequency-specific manner [10–15] and phase-dependent effects have been demonstrated in human [16–22] and animal studies [10,12], making it an ideal tool to probe the causal influence of phase relationships on conscious auditory perception [23,24]. Importantly, highly selective stimulation at different cortical sites can now be implemented by optimized stimulation protocols derived from computational models [14,18,19].

In this study, we tested whether the interhemispheric information flow during a dichotic listening (Fig 1A) can be modulated by spatially-matched multi-site 40Hz with a phase-lag of 180° between the left and right auditory cortex (BA42). Since it has been shown that the interhemispheric integration of alternating visual tokens into coherent motion percept can reliably be inhibited by 40Hz-tACS with a phase-lag of 180° between hemispheres [18,25], it is conceivable that interhemispheric auditory processing could be selectively altered using a similar stimulation protocol with a tailored high density (HD)-electrode montage derived from current flow modeling (Fig 2). We thus hypothesized that 40Hz-tACS with a phase-lag of 180° between hemispheres should inhibit network synchrony and thereby increase the laterality index.

Whilst previous studies support the concept that inter-areal gamma-band synchronization entails a delayed non-zero phase relationship [4,5,26], the associated metrics (lagged phase synchronization [27], isolated effective coherence [28]) however do not permit the deduction of a specific phase asymmetry between the left and right auditory cortices in degree notation.

To address this issue, we employed an exploratory control analysis to establish a link between the behavioral outcome of the anti-phase stimulation and the individual phase asymmetry during the sham session, recorded with 64-channel electroencephalography (EEG). Hence we investigated whether the time courses of the intrinsic phase asymmetry at 40Hz differed between left and right ear percept, and specifically assessed the circular-linear correlation between the intrinsic phase asymmetry and the behavioral tACS-related modulation.

Materials and methods

Participants

Twenty-nine healthy participants were recruited from the University Medical Center in Hamburg, Germany. All subjects were right-handed according to the Edinburgh handedness-scale [29], reported no history of neurological or psychiatric disease, filled out a sociodemographic questionnaire and further provided written informed consent and were paid for participation.

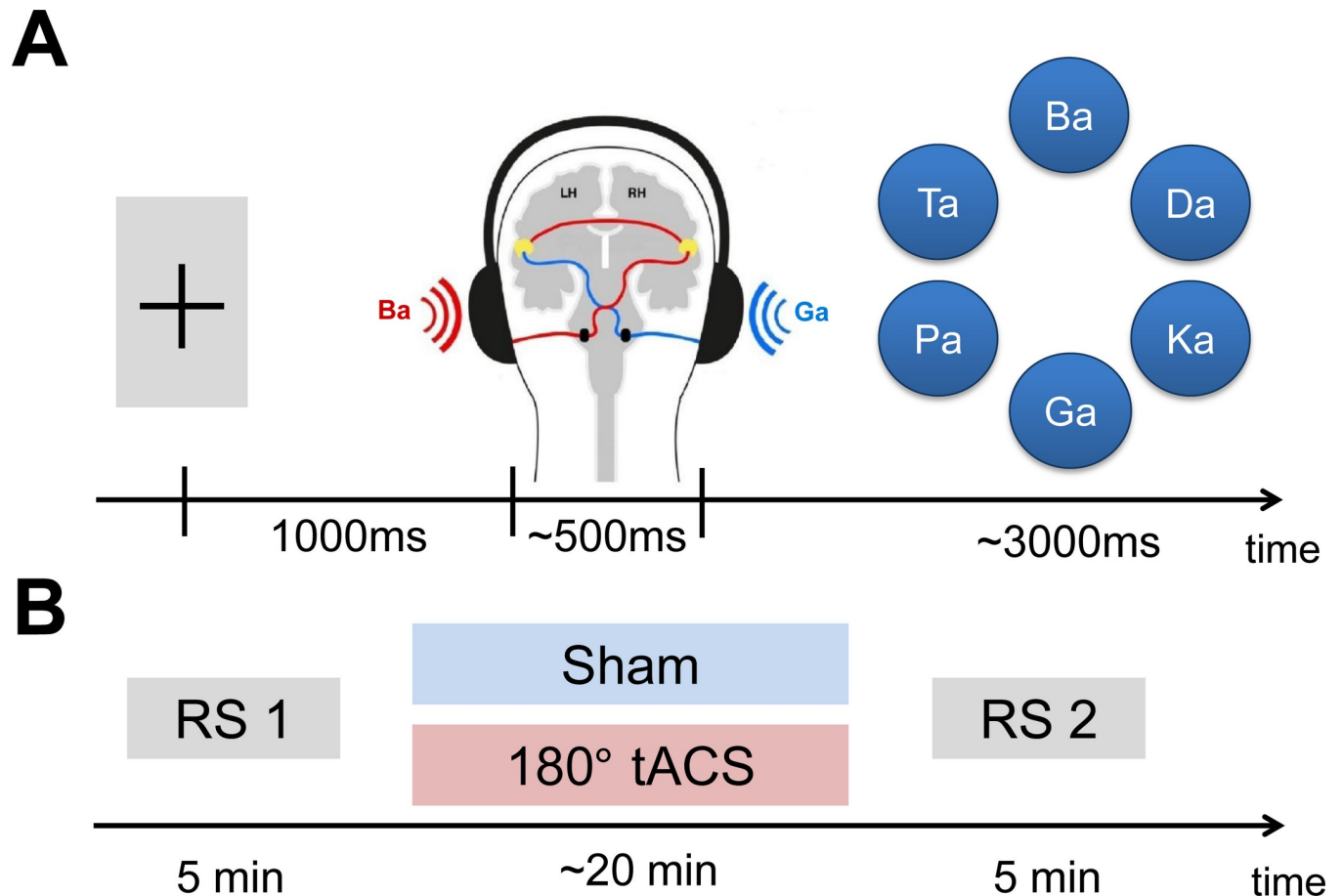


Fig 1. Dichotic listening task and procedure. (A) Exemplary single trial. After 1sec of central fixation, two syllables were presented simultaneously to both ears. After a delay, participants chose the syllable that they perceived out of six alternatives. (B) Procedure. Every subject participated in two sessions (sham and anti-phase tACS) on two different days. The order of sessions was randomized across participants. Every session started with a resting state (RS) EEG, followed by either sham or anti phase stimulation at 40Hz and another resting state EEG.

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Please note that we assessed sociodemographic data as a standard procedure to allow for potential comparisons of healthy control samples with clinical samples. Since no association between sociodemographic factors and early auditory perception in healthy participants had previously been found, we did not further report these data in this manuscript.

Normal hearing was validated by pure tone audiometry for frequencies between 125 and 8000Hz (Esser Home Audiometer 2.0). No participant exhibited interaural differences larger than 9 dB or an auditory threshold above 25 dB. The study was approved by the ethical committee of Medical Association Hamburg (Reference Number: PV4911) and conducted in accordance with the Declaration of Helsinki. One subject with insufficient data quality and two subjects with excessive error rates in task performance (>2 SDs over the mean in a session) were excluded. The remaining 26 subjects (18 men, range: 18–49 yrs, $M = 28.5$ yrs, $SD = 7.9$ yrs) were included in the final analysis.

Stimuli and procedure

We utilized the Bergen dichotic listening task [4,30], where six consonant-vocal (CV) syllables were coupled and presented simultaneously to each ear via closed headphones (Sennheiser, HAD 200) at 75 dB. We ruled out effects of syllable voicing by combining only syllables with

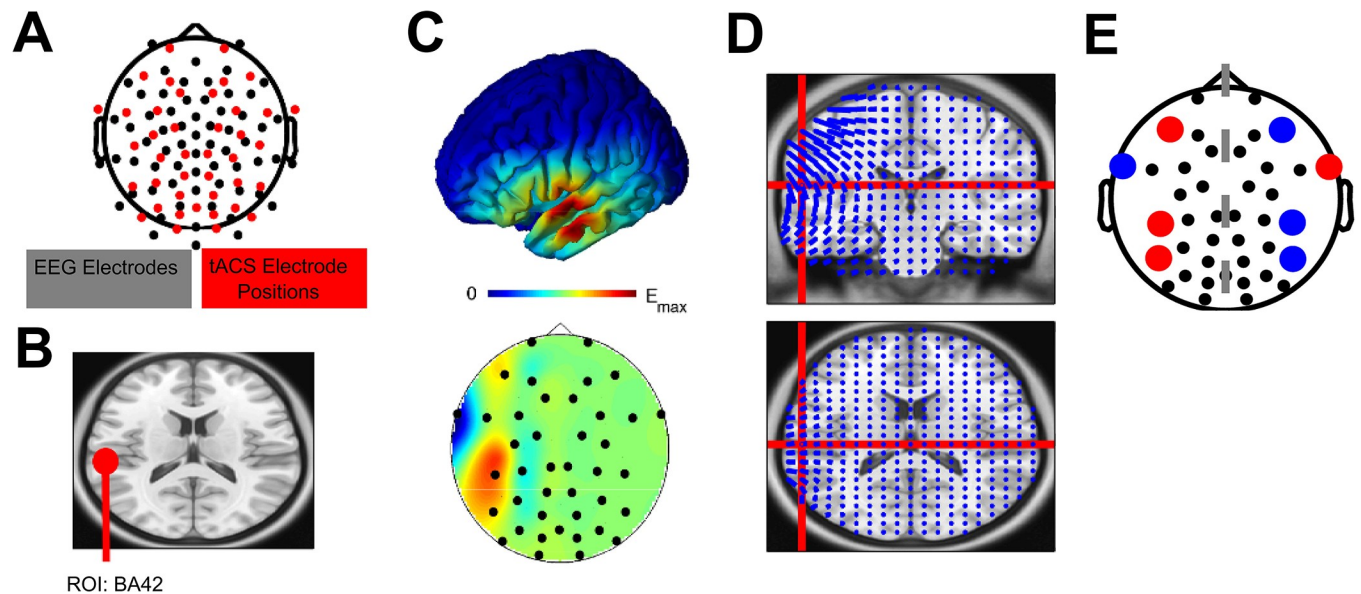


Fig 2. Spatiotemporally-matched tACS. (A) Electrode layout. Black dots indicate the 64 EEG electrodes, while all the red dots indicate the potential positions for tACS electrode placement. (B) Targeted region of interest: area 42. (C) Result of the electric field simulation to target the left BA42. Upper: Resulting electric field on an MNI brain. Lower: 2D topography that highlights which positions should be utilized for stimulation electrode placement. Here, we constrained the electrode placement to the 4 electrodes with the highest contribution. (D) Directionality of the electric field. Note, we modeled the electric field in a way that the field lines were parallel to the assumed tangential dipole orientation in BA42. (E) Resulting asymmetric tACS electrode placement relative to other potential tACS electrode positions (black). Red and blue dots indicate opposite polarities.

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the same voice onset time, which yielded 12 dichotic CV pairs. Voice onset time is characterized by the length of time between the release of a consonant and the onset of voicing. Three syllables (/ba/, /da/, /ga/) were voiced and had a short voice onset time (17–32ms), the other three syllables (/pa/, /ta/, /ka/) were unvoiced with a long voice onset time (75–80 ms). Stimulus onset was temporally aligned and lasted for 400–500ms.

All subjects took part in both (single-blinded) tACS sessions on two different days ($M = 2.65$ days; range: 1–12 days), while the session order was counterbalanced (Fig 1B). After performing the hearing test and filling out all questionnaires, the participants performed 6 practice trials on the day of the first session to get familiarized with experimental procedure and stimulus material. 240 trials were randomly presented in 2 blocks during each tACS session (sham and anti-phase). Every trial started with the participant fixating a central fixation cross for one second, then a syllable combination was played through the headphones and participants indicated their choice from a circular formation showing all six syllables. Participants navigated through the alternatives by left mouse button clicks and confirmed their choice with a right button click. A fixed inter-stimulus interval of 1s was applied between the offset of the visual presentation and the ensuing auditory stimulus. Hence, the trial duration varied between 3.5 and 6.5s in dependence of the individual reaction time. After a fixed delay of 1s, the next trial started. The participants were instructed to report the syllable that they understood most clearly between all 6 syllables, while they were not informed that each trial consisted of two different syllables. Furthermore, we encouraged them to fixate on the cross, relax, reduce head and eye movement and avoid jaw muscle contraction.

We ran the experiment in an electrically shielded and soundproof cabin, where participants were seated with a distance of 60cm in front of a BenQ XL2420T screen (1920 x 1080, 120 Hz). Stimulus presentation was controlled via Presentation software (Neurobehavioral Systems, Albany, CA).

EEG acquisition and tACS

EEG and tACS Ag/AgCl electrodes were mounted in a custom-made elastic cap for 104 electrodes (EasyCap). EEG recordings were obtained from 64 Ag/AgCl electrodes (no amplitude clipping, impedances <15 k Ω , referenced to FCz) using a slightly abrasive electrolyte gel (Abralyst 2000, EasyCap). EEG was recorded during all conditions (Resting State 1, Sham, Verum, Resting State 2) using BrainAmp amplifiers (Brain Products GmbH). Signals were sampled at 5 kHz, amplified in the range of ± 16.384 mV at a resolution of 0.5 μ V and stored for offline analyses.

Transcranial stimulation was applied via a battery-operated stimulator (DC-Stimulator Plus, NeuroConn) using eight Ag/AgCl electrodes (12 mm diameter, EasyCap). Electrode placement was based on a current flow model, which was optimized to target the auditory cortex based on 40 available electrode positions (Fig 2A). The combined impedance of all electrodes was kept below 5 k Ω , as measured by the NeuroConn stimulator, using Signa electrolyte gel (Parker Laboratories Inc.). A sinusoidally alternating current of 1,000 μ A (peak-to-peak) was applied at 40Hz continuously for 20 minutes during each session. During sham and real stimulation the current was ramped up over 10 seconds to 1,000 μ A, but discontinued during the sham condition. All subjects confirmed that stimulation was acceptable and mainly noticeable during the ramp-in phase. It did not induce painful skin sensations or phosphenes. On debriefing, 50% of the subjects were able to correctly guess which tACS-session was assigned to T1 and T2, which confirmed that single blinding was successful.

Data analyses

The data were analysed in Matlab R2017a using the EEGLab [31] and CircStat [32] toolboxes, custom-written scripts, and the LORETA KEY software package [33] (The KEY Institute for Brain-Mind Research, Dept. of Psychiatry, University Hospital Zurich, Switzerland, <http://www.uzh.ch/keyinst/loreta.htm>).

Behavioral data. We assessed the distribution between right ear and left ear reports by means of a laterality index (LI), ranging from -100 to 100 according to the following formula:

$$LI = \frac{100 * (\text{correct RE reports} - \text{correct LE reports})}{(\text{correct RE reports} + \text{correct LE reports})} \quad (1)$$

while behavioral modulation was computed as

$$LI_{mod} = LI_{Verum} - LI_{Sham} \quad (2)$$

As a result, positive LI-values indicate a bias towards right ear reports; negative LI-values indicate more left ear reports and a value of zero signals a perfectly balanced distribution between left and right ear reports.

EEG data preprocessing. Since no artifact removal approach that reliably reconstructs EEG phase properties is known so far [34,35], we focused all EEG analyses on the sham session.

First, we removed noisy channels, downsampled the data to 250Hz and filtered the signal in the range from 1–100 Hz using two-pass finite element impulse response (FIR) filters as implemented in EEGLab. Moreover, we filtered out line noise at 50 Hz and its harmonics. The filtered data were visually inspected using the raw signal as well as a Fast Fourier transformation (FFT) to ensure that all artifacts were successfully suppressed. Then, removed channels were interpolated by spherical spline interpolation. Epochs containing saccades, noise or excessive muscle artifacts were removed after visual inspection, and all channels were re-referenced to a common average. Subsequently, an independent component analysis (ICA) was employed to

identify blinks, eye movements, electrocardiographic and saccadic spike potential artifacts with regard to time courses, characteristic topographies and frequency distributions [36,37]. Finally, DL-data were segmented into 400ms-epochs, starting 200ms before stimulus onset ($F_s = 250\text{Hz}$, 100 time points), and separated by perceptual outcome (left or right ear percept). Out of 240 trials, an average of $M \pm SD = 76.15 \pm 22.02$ left ear trials (min: 38; max: 129) and $M \pm SD = 119.85 \pm 20.18$ right ear trials (min: 93; max: 155) remained for the analysis of the EEG phase signature.

Importantly, the sample size bias affects the comparison of averaged electrophysiological measures in sensor space [38,39], and even more heavily in source space analyses due to its additional influence on the applied spatial filters [40]. Since matching the trial numbers across conditions within each subject would not sufficiently control for a sample size bias with respect to the ensuing circular-linear correlation analysis, we decided to rule out confounding influences of unequal trial numbers on the individual phase asymmetries by randomizing across conditions *and* subjects.

Hence, we randomly subsampled 38 trials (lowest number across all subjects) out of each subject's datapool for the left and right ear condition, respectively: In this procedure, all trials of each participant were stored in a Matlab-array, which was subsequently randomly permuted using the function *shuffle.m*. The first 38 trials along each permuted trial dimension were selected for both ear conditions separately. All instances of the presented data analysis relate to the first randomly selected sample of trials. In total, an absolute number of 3120 trials was discarded throughout the subsampling procedure. Crucially, we repeated this subsampling procedure in a supplementary analysis to confirm that our results were not restricted to one trial selection (see S2 Text, S2 Fig and S2 Table).

Source space analyses. Next, the preprocessed data were projected into source space using the LORETA KEY software. We calculated a transformation matrix for all 60 electrodes using exact LORETA zero-error tomography. Based on previous findings [4,5], we decided to focus on the secondary auditory cortex (BA42) given its functional relevance in early auditory perception and syllable perception in particular [41,42]. The ROIs were defined according to the Talairach-Atlas [43] as implemented in the LORETA KEY software. Importantly, we exploited the tangential dipole activity (z-component of the current density vector) in the centroid voxel of BA42 because this dipole component corresponds best to the time window of interest (-200 to 200ms), hence to its underlying neural generators covering the Planum temporale [44–46]. Having extracted the tangential auditory dipole activity and at 40Hz, we computed the asymmetry $\Delta\varphi$ for each time point t by deriving the angle φ of the complex conjugate product of the Hilbert-transformed data with the following formula:

$$\Delta\varphi(t) = |\varphi(\text{hilbert}(x_{\text{left}}(t)) \times \text{conjugate}(x_{\text{right}}(t)))| \tag{3}$$

where

$$0 \leq \Delta\varphi(t) \leq \pi \tag{4}$$

and

$$-\pi \leq \varphi(\text{hilbert}(x_{\text{left}}(t)) \times \text{conjugate}(x_{\text{right}}(t))) \leq \pi \tag{5}$$

Finally, we calculated each participant's average time course of $\Delta\varphi$ across trials for each time point (*circ_mean.m* function).

Statistical analyses. Unless stated otherwise, the significance level was set to $\alpha = .05$ in all tests, and all mean values are reported with standard deviation values ($M \pm SD$). All circular data were processed using the CircStat toolbox. Correlations between behaviour and phase

dynamics were assessed as:

$$\rho = \sqrt{\frac{r_{xs}^2 + r_{xc}^2 - 2 \times r_{xs} \times r_{xc} \times r_{cs}}{1 - r_{cs}^2}} \tag{6}$$

where r_{xc} , r_{cs} and r_{xs} are defined as

$$r_{xc} = \text{corr}(x, \sin(\varphi)) \tag{7}$$

$$r_{xs} = \text{corr}(x, \cos(\varphi)) \tag{8}$$

$$r_{cs} = \text{corr}(\sin(\varphi), \cos(\varphi)) \tag{9}$$

with φ being the circular and x being the linear variable (*circ_corrcl.m* function).

In contrast to repeated measures analyses of variance (RM-ANOVA), permutation-based cluster statistics do not depend on assumptions about the data distribution due to their non-parametric nature [47]. Thus, we assessed differences in time courses of the phase asymmetries between left and right ear trials percept trials (100 time points, -200 to 200ms) with a non-parametric permutation test for paired conditions where a permutation distribution was computed by randomly switching the condition labels within participants in each of 10.000 iterations. To address the issue of multiple comparisons, we here report the p-values using the statistics of the maximum difference (maxstat-method, see [47]) after 10.000 permutations.

Since we expected a clear right ear advantage for syllable perception in right-handed individuals, we first conducted two separate t-tests (paired samples, Bonferroni-corrected) to prove that syllables were more often reported through the right ear than through the left ear during both sham- and verum-tACS.

The influence of tACS on the laterality index was assessed with a two-sided t-test for paired samples. Furthermore, the distributions of LI-values during both tACS-sessions were checked for normality with Lilliefors test. Effect sizes were quantified by means of Cohen’s d (t-test). We additionally calculated a Bayes factor expressed as *BF10* for the hypothesized effect of tACS on the laterality index with a default scale factor of $r = 0.707$.

Results

Behavioral performance during sham- and verum-tACS

The right ear advantage was present during both sham- ($LI_{\text{sham}}: M = 23.714 \pm 18.557$) and verum-tACS ($LI_{\text{verum}}: M = 24.756 \pm 21.535$) as participants perceived significantly more syllables presented to the right ear (sham: $M = 134 \pm 19.779$; verum: $M = 136 \pm 23.841$) than to the left ear (sham: $M = 83 \pm 22.258$; verum: $M = 82 \pm 24.661$), which was confirmed by two-sided t-tests for both tACS-sessions (sham: $t(25) = 6.480$; $p < .001$, $d = 2.43$; verum: $t(25) = 5.809$; $p < .001$, $d = 2.22$). Moreover, behavioral performance was normally distributed during both sham- ($p = .50$) and verum-tACS ($p = .50$).

Twenty-three out of 26 participants showed a positive LI during both sessions, whereas 3 participants had a negative LI. Across all participants, reporting a syllable that was not presented occurred in $9.311\% \pm 5.276\%$ of cases during sham-tACS and in $8.862\% \pm 4.489\%$ of cases during verum-tACS.

Intrinsic 40Hz phase asymmetries predict stimulation outcome

The main influence of tACS on behavioral performance was assessed in a two-sided t-test on the LI values during sham and verum-tACS. This did not confirm the hypothesized increase of

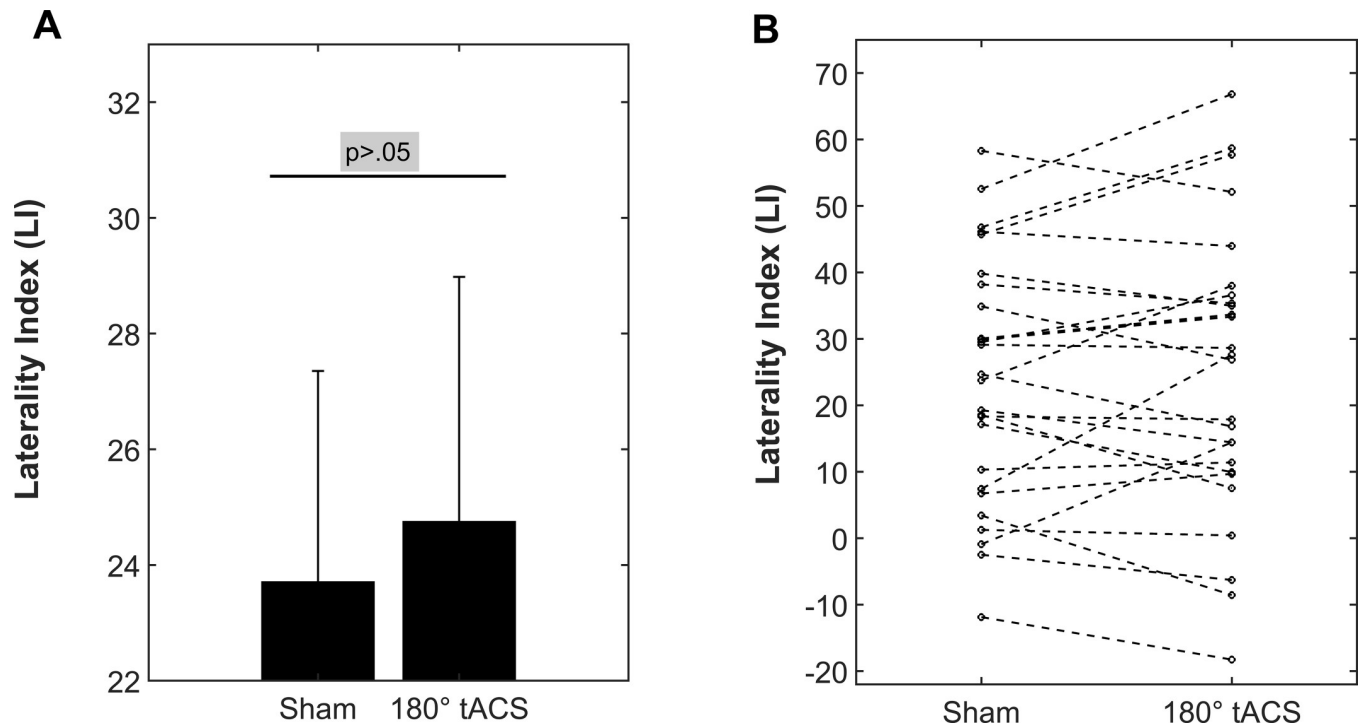


Fig 3. Behavioral results. Laterality Index (LI): Positive values indicate a bias towards right ear reports. (A) 180° tACS at 40Hz does not increase the LI (one-sided t-test for paired-samples, $t(25) = 0.597$, $p = .278$, $d = 0.05$). The error bars depict the standard error of the grand average behavioral performance (LI) during both conditions (mean \pm SEM). (B) The individual behavioral performances ($N = 26$) during both conditions. The dashed lines highlight the directionality of the individual modulations (up: increase of LI; down: decrease of LI).

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the LI (Fig 3A; $t(25) = 0.597$, $p = .556$, $d = 0.05$), which suggests that 40Hz-tACS applied in this electrode montage (Fig 2E) did not consistently amplify the right ear advantage.

The absence of a general tACS effect on behavioral performance, as indicated by a Bayes factor of $bf_{10} = 0.244$, raised the question whether the individual stimulation outcome might depend on the inter-individual differences in oscillatory phase dynamics between the left and right secondary auditory cortices (BA42) at 40Hz. Accordingly, if interhemispheric phase differences predicted a perceptual shift to the left or the right ear, this should be indicated by a circular-linear correlation between the intrinsic phase asymmetries between the left and right BA42 at 40Hz and the difference of LI-values during verum- and sham-tACS. Hence we calculated each participant's phase asymmetry at 40Hz during the sham session by extracting the angle of the complex conjugate product of the Hilbert-transformed source space data.

After dividing all trials into left or right ear responses, circular means were calculated across trials for each time point (-200ms to 200ms post-stimulus onset interval) in each subject. We applied a non-parametric paired sample permutation test to investigate whether the across participant phase asymmetry at 40Hz differed between left and right ear percept in a specific time period. The permutation test revealed that the phase asymmetries of the perceptual outcomes differed significantly in the post-stimulus onset interval from 36-56ms (Fig 4A; LE percept: $79.1^{\circ} \pm 20.8^{\circ}$; RE percept: $67.8^{\circ} \pm 18.1^{\circ}$; circular mean \pm SD; Permutation Test 't-max'-Method, multiple comparison corrected p -values are displayed in Table 1). Clearly, the grand average phase asymmetry at 40Hz between the left and right BA42 was augmented during left ear percept compared to right ear percept in this time window. As participants with a negative LI might exhibit an atypical organization of speech perception due to an altered interhemispheric communication between auditory cortices [6,48], we repeated the non-parametric

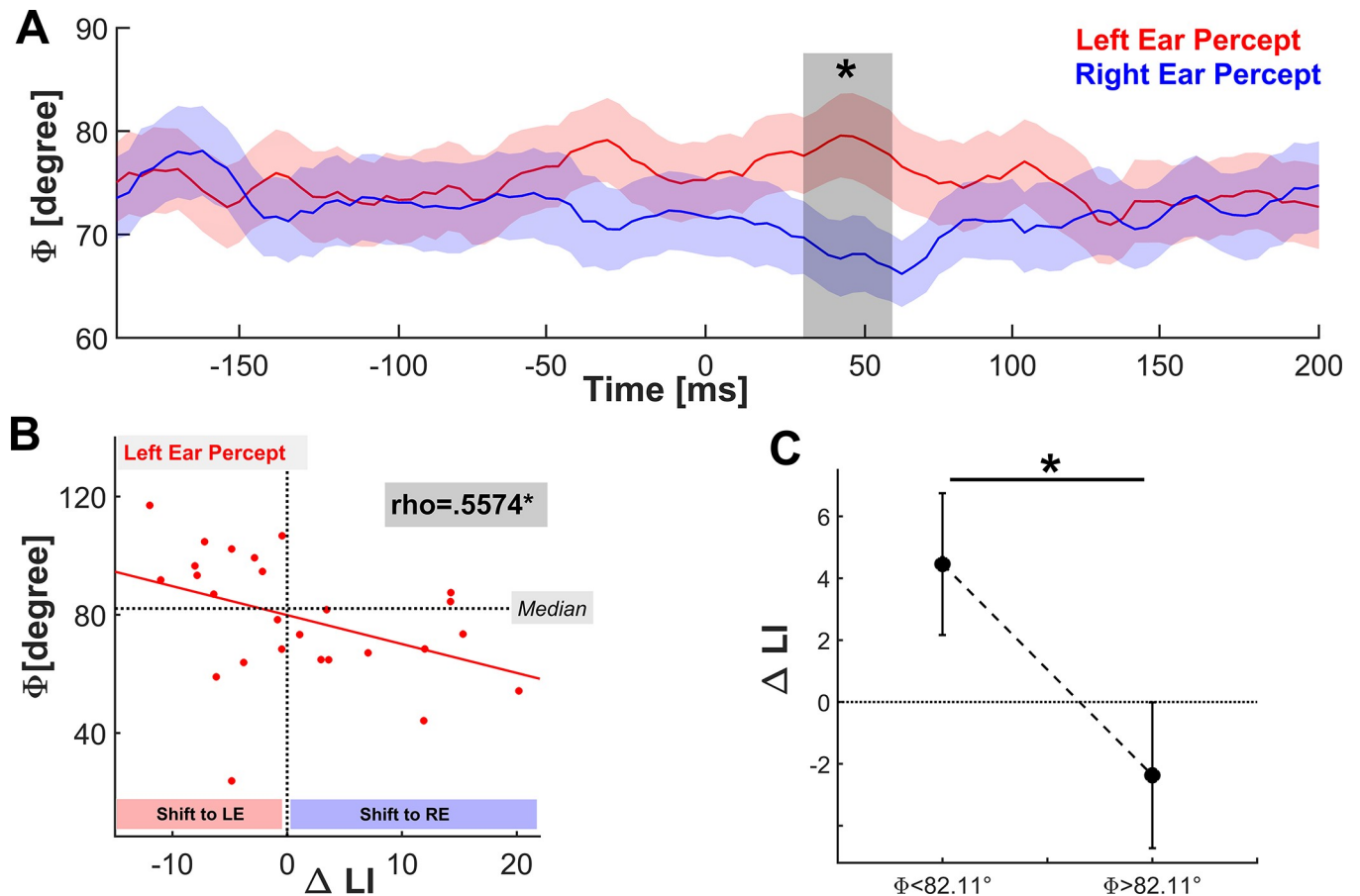


Fig 4. Oscillatory key signature of the interhemispheric phase lag. (A) Time course of the interhemispheric phase difference at 40Hz between the left and right BA42 averaged across all subjects ($M \pm SEM$) during sham-tACS. The shaded bar highlights the interval (36-56ms) where the phase shifts were statistically different between conditions (paired-sample permutation test with 10000 permutations, 'tmax'-method, $*p < .05$). (B) Circular-linear correlation between the individual phase shifts during auditory processing through the left ear in the cluster-corrected time window (36-56ms) and the behavioral outcome of the 180° stimulation at 40Hz ($\Delta LI = LI_{\text{verum}} - LI_{\text{sham}}$). The significant correlation ($\rho = .557, p = 0.0176$) indicates that tACS amplified the right ear advantage in subjects whose oscillatory asymmetry at 40Hz was smaller (closer to 0°) during conscious auditory processing. Contrary, augmented interhemispheric asymmetry (closer to 180°) was associated with a shift to left ear processing. (C) tACS-effect on behavioral performance after splitting the sample at the median angle ($\phi = 82.11^\circ$) into two equally sized subgroups ($N = 13$).

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permutation test after excluding three participants with an atypical LI to rule out potential confoundations (S2 Text). Importantly, the exclusion of these participants again yielded a significant difference between the perceptual responses of the phase asymmetries in the post-stimulus onset interval from 44-60ms (see S1 Table; Figure A in S1 Fig).

Having identified a specific time window that revealed a significant difference between conditions, we next tested our hypothesis that the individual auditory asymmetries predicted the behavioral modulation by tACS. Therefore, we computed one circular mean across all time points in this post-stimulus onset interval (36-56ms) across each subject's left ear trials during

Table 1. Corrected p-values for permutation statistics. Corrected p-values (Tmax-method) for the non-parametric paired sample permutation test (Fig 4A), which was applied to the intrinsic phase asymmetries at 40Hz during left ear and right ear processing. The permutation distribution was computed by randomly switching condition labels within participants in each of 10.000 iterations.

epoch	32-36ms	36-40ms	40-44ms	44-48ms	48-52ms	52-56ms	56-60ms
p-value	.1892	.0455	.0189	.0304	.0477	.0406	.0501

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sham-tACS and assessed the circular-linear correlation between these second order means of the intrinsic phase asymmetry and the individual tACS modulations (LI_{mod}). Interestingly, a significant correlation ($\rho = .557, p = 0.0176$) confirmed our assumption that the behavioral modulation depended on the temporal asymmetry: Stronger phase asymmetries (closer to 180°) were associated with a perceptual shift to left ear processing, whereas an amplification of the right ear advantage was associated with weaker phase asymmetries (closer to 0°). This was further supported by a subgroup analysis after performing a median split on phase asymmetries during left ear percept to divide into low ($\varphi < 82.11^\circ$) and high ($\varphi > 82.11^\circ$) asymmetry: The tACS-modulation was significantly elevated in subjects with phase asymmetries above 82.11° ($LI_{mod}: M = 4.455 \pm 8.257$) compared to subjects with asymmetries below 82.11° ($LI_{mod}: M = -2.371 \pm 8.485$) (Fig 4C; $t(24) = 2.079; p = .049; d = 0.815$). Please note that the median split analysis was performed for illustration purpose to highlight the bidirectional impact of the stimulation. Furthermore, the significant circular-linear correlation between tACS-related behavioral modulation and the intrinsic phase asymmetry ($\rho = .5932, p = 0.0175$) during left ear percept in the sham session was not affected by the exclusion of participants with an atypical LI during the sham session (Figure B in S1 Fig).

Since the participants performed the DL task during sham- and verum-tACS on two different days, this dataset could not yield information about the test-retest reliability of the intrinsic phase asymmetry. To determine this, we analyzed pilot data ($N = 18$) from another experiment where the DL task was performed during 64-channel EEG recording on two different days. Crucially, the phase asymmetry values at 40Hz exhibited a high test-retest reliability during left ear processing ($\rho = .8529; p = .0047$; see S3 Text, S3 Fig).

Collectively, the above findings reveal that high frequency phase asymmetries in the gamma-range exhibit different temporal profiles during ambiguous auditory perception, and that the individuality of these spectral asymmetries predicts the outcome of the electrical stimulation on a behavioral level.

Discussion

In this study, we tested whether (1) the transcallosal information flow between the left and right SAC can be modulated during conscious auditory perception with high-frequency tACS at 40Hz, and (2) to what extent the stimulation outcome was associated with the individual asymmetries of the spectral profiles.

Clearly, our bilateral HD-montage at a phase-lag of 180° failed to elicit a general effect throughout all subjects. Since the participants responded differently to our fixed stimulation protocol, we performed an exploratory source space analysis to derive an oscillatory key signature of the phase asymmetry at 40Hz during dichotic listening. Our EEG-analysis of the phase dynamics demonstrated that syllable perception through the left ear does not only depend on elevated functional [4] and effective [5] gamma-band coupling, but also that its mean coupling direction at 40Hz differs significantly from right ear processing. At first sight, the finding of increased phase asymmetry during left ear percept may contradict the idea that transcranially decoupling the left and right auditory cortex with a phase-lag of 180° causes a shift to right ear processing. Consequently, elevated interhemispheric coupling and ensuing shift to left ear percept would be expected by a stimulation with zero-lag between hemispheres. In accordance with that, the original communication through coherence hypothesis (CTC,[49]) initially proposed zero-phase synchronization in the gamma-frequency range as the key mechanism for bidirectional coupling between two neuronal groups, whereas phase synchronization in lower frequencies was suggested for enhanced delays in increasingly distant cortico-cortical communication. However, more recent studies evidenced that bidirectional coupling through

gamma-band coherence entails directedness with a systematic delay [26,50–52], and thus does not occur at zero phase. Importantly, this was further supported by EEG studies investigating dichotic listening: Increased functional connectivity during left ear percept should reflect a shift away from 0° , because the associated metric (lagged phase synchronization,[27]) suppresses zero phase-lag contributions [53]. In line with that, another study [5] exploiting source space effective connectivity analysis during dichotic listening revealed elevated isolated effective coherence (iCoh,[28]) for left ear percept from the right to the left BA42 compared to the other direction as well as compared to perception through the right ear. Delayed (non-zero) lag inter-areal gamma-band synchronization is visible in Granger-causal influences and iCoh specifically [28], because it signifies that variance in one oscillation explains unexplained variance in another oscillation several milliseconds later. Collectively, our characterization of the intrinsic phase asymmetry supports the above mentioned studies in that long-range auditory synchronization in the gamma-band range enables conscious auditory perception through the subdominant ear with a non-zero phase-lag.

Here, we characterized phase asymmetries as an oscillatory network trend which exhibited considerable inter-individual variation across our sample (range: 24° - 117° , see Fig 4B), and argue that the assessment of phase asymmetries might be a crucial network parameter to carefully consider, in order to optimize multi-site stimulation protocols with tailored phase-lags between the targeted oscillators. This is further supported by the fact that the asymmetry values showed a high test-retest reliability (see S3 Text, Figure B in S3 Fig), which suggests that phase asymmetries could indeed reflect a robust auditory network trend that exhibits low intra- and high inter-individual variability in a specific frequency range.

To date, tACS is debated as a highly-promising tool to non-invasively probe the causal influence of neuronal oscillations for a variety of cognitive functions [9,54], while its impact on large-scale networks heavily depends on a broad variety of parameters such as stimulation intensity [55], waveform and envelope [56,57], network state [58,59] or the electrode montage [18,25]. So far, it appeared to be the nature of non-invasive brain stimulation that its effects on physiology and behavior are often small [60], whilst the publication bias further impedes critical discussion on disadvantageous study protocols with regard to crucial stimulation parameters, such as intensity, montage frequency and phase-lag. In this study, our control analysis demonstrated that the behavioral outcome of the 180° -stimulation depended on the phase asymmetry: Elevated phase asymmetry was associated with a shift to left ear processing, while the right ear advantage was amplified when the asymmetry was closer to 0° (Fig 4B). Consequently, the subgroup division at the median angle of 82.11° revealed a bidirectional impact of our stimulation (Fig 4C), suggesting that the asymmetric nature of conscious auditory processing can selectively be modulated by spatiotemporally-matched tACS. Moreover, these findings support the concept that synchronized gamma-band activity not only mediates the integration of visual [18,25,61,62], but also auditory information from both hemispheres [63]. However, the circular-linear relationship raises the question how the external 40Hz driving force interacted with the intrinsic phase relationship of the neuronal oscillators in the left and right secondary auditory cortex. We argue that the selective modulation of conscious auditory perception might depend on the deviation of the exogenous from the endogenous phase lag: The interhemispheric network was prone to inhibition when the intrinsic lag differed strongly from the transcranially-induced 180° -lag, whereas a shift to left ear percept was facilitated when the deviation of the tACS-induced lag from the intrinsic lag was low. Hence, it is conceivable that long-range gamma-band synchronization can be efficiently amplified if the external driving force mimics an electrical field bilaterally with the intrinsic phase asymmetry. Accordingly, the cortical network dynamics should be most efficiently hampered if the deviation of the exogenous phase lag from the intrinsic lag approximates π .

Since schizophrenic patients with auditory-verbal hallucinations (AVH) exhibit increased interhemispheric gamma-band coupling during dichotic listening and thus a reduced right ear advantage [64–66], the current study was initially designed to increase the laterality index, which might offer a potential application of tACS in normalizing disturbed gamma-band connectivity underlying AVH in patients with schizophrenia. Our results suggest that the characterization of the intrinsic phase relationship in the gamma-band range might benefit tailored tACS protocols in future studies.

Importantly, the interindividual variability in shape and size of the targeted pathway was highlighted by a study that utilized Diffusion Tensor Imaging (DTI) of the CC with a focus on posterior subregions connecting the auditory cortices: Stronger anatomical connectivity between these areas was associated with augmented left ear processing [67]. Even though our data do not provide tractographic information about the CC, it is conceivable that the interindividual differences in angular asymmetries at 40Hz might relate to individual variation of structural features of the transcallosal auditory pathways, and that these phase oscillations reflect undulations of neuronal excitability [68]. Such phase-related interindividual differences in the gamma-band level out in the grand average across subjects, which may explain the absence of a general behavioral effect by 180°-tACS across all participants.

Several studies have pointed out the role of slow wave oscillatory dynamics for hearing [19,21], speech perception [24] and syllable perception in particular [69]. Here we provide evidence that high-frequency oscillations in the gamma-band range might not only shape auditory perception in terms of magnitude properties [70], but in terms of the individual interhemispheric phase signature. In our experiment, our effects are better explained by 40Hz-phase properties given that we applied the alternating currents at equal intensities to each hemisphere, while the phase asymmetry interacted with the [53]advanced protocols can selectively modulate long-range cortico-cortical signal transmission with phase-dependent effects in different modalities [16,18–20,71,72].

Confounds and limitations

A number of limitations hamper the analysis of gamma-band activity and long-range coupling in human EEG recordings, such as the effects of volume conduction in the cortical tissue, broadband muscle activity that might obscure physiologic gamma-band signatures or the low spatial resolution of EEG recordings. We addressed these issues by analyzing all data at the source space level using the eLORETA approach after carefully removing artifacts by means of an ICA [37]. In addition, we employed connectivity analyses which reduce the impact of volume spread and allow to estimate the directionality of these effects [53].

A further potential issue is the statistical validity of the grand average phase asymmetry time courses (Fig 4A), as each averaging and trial subsampling method has some limitations. To control for a sample size bias, we randomly selected a subsample of 38 trials for each participant and thus discarded event-related data from ensuing analyses. Importantly, this method was exploited in another EEG study investigating long-range connectivity estimates in source space [40] to avoid an additional sample size bias to spatial filters; and was further discussed as a valid method to compute grand average images across subjects and conditions [73]. Crucially, matching the trial numbers within subjects would not correct for a sample size bias with respect to circular-linear correlation analyses. Furthermore, our goal was to keep results comparable with our supplementary reliability analysis (see S3 Text, S3 Fig), as classical test theory demands an equal number of observations throughout all subjects for the assessment of reliability scores [38]. In this study, we accepted a minimum number of 38 trials since previous studies had demonstrated that an adequate reliability estimate of 0.8 can be obtained at a

minimum number of 21 trials in healthy control groups [74], as well as that averaging across 30 trials can yield sufficient test-retest reliabilities for early event-related potentials [75,76]. Importantly, our supplementary reliability analysis provided evidence that the respective metrics (laterality index, intrinsic phase asymmetry) are robust across days (see S3 Fig, S3 Text), as well as that other random trial selections yielded similar results (see S2 Fig, S2 Table).

To date, several studies have pointed out that the recovery of true oscillatory activity during electrical stimulation is not only hampered by linear, but non-linear components of the complex tACS artifact in particular [34,35,77], indicating that current approaches such as beamforming [78,79] or artifact template subtraction [11] fail to reliably reconstruct the EEG-signal. Since we did not attempt to disentangle the artifact from brain activity, our data—along with other studies employing current artifact removal techniques—do not provide evidence for the exact electrophysiological mechanisms acting *during* stimulation. While several studies suggested entrainment of neuronal oscillations as the key mechanism of the observed tACS effects [10–13,15], other reports interpreted the effects as plastic changes [80,81] or attenuated neuronal adaptation [82].

However, the interhemispheric network communication between the left and right auditory cortices during ambiguous syllable perception has been investigated over decades exploiting multimodal imaging methods [4–8,30,65,67,83], hence establishing a reliable neuronal framework for its behavioral measures. Collectively, we can argue that (1) the laterality index reflects hemispheric specialization for language, while its magnitude is related to inter-individual trait differences in transcallosal topography, mainly the posterior third of the CC connecting the auditory cortices [6,67], (2) the perception of syllables through the left ear is accompanied by elevated functional [4] and effective gamma-band coupling [5] between the left and right BA42, and that (3) oscillatory phase dynamics at 40Hz reveal different time courses between left and right ear percept in terms of interhemispheric asymmetry. Based on this evidence, it is plausible to assume that the external 40Hz driving force interacted with the intrinsic phase relationship of the neuronal oscillators in the left and right secondary auditory cortex. In this context, the employment of tailored HD-tACS protocols might be crucial to modulate cortico-cortical network communication by non-invasive brain stimulation.

Conclusions

In summary, our results support and expand the idea that interhemispheric gamma-band phase dynamics mediate conscious auditory perception [4,5] and demonstrate the potential of HD-tACS to selectively modulate frequency-specific large-scale cortical networks. However, the parameter space of tACS is not very well explored yet and it is unclear which stimulation parameters should be utilized to maximize its physiological efficacy [60,84]. Importantly, this study provides novel insights into how the intrinsic phase relationship can be exploited as a significant network parameter for the implementation of optimized stimulation protocols.

In the future, it might be possible to tailor therapeutic interventions by means of spatiotemporally-matched multi-site HD-tACS for certain neuropsychiatric diseases such as autism spectrum disorders [85], Parkinson's disease [86] or schizophrenia [66,87,88] that have previously been associated with impaired network synchronization [85,89]. In particular, auditory hallucinations in schizophrenia have been suggested to reflect an over-coupling between auditory and frontal areas [83,90]. The present findings underline the idea that tACS might be an ideal candidate for potential treatment of network disorders [91,92].

Supporting information

S1 Text. Electric field modeling.
(DOCX)

S2 Text. Supplementary control analyses.

(DOCX)

S3 Text. Test-retest reliability of the laterality index and the intrinsic phase asymmetry at 40Hz.

(DOCX)

S1 Fig. Oscillatory key signature of the interhemispheric phase lag after excluding participants with an atypical laterality index ($n = 23$).

(JPG)

S2 Fig. Sensitivity analysis of the 40Hz intrinsic phase asymmetry. Average time courses (solid lines) of the intrinsic phase asymmetry (related to Fig 4A in the manuscript) with standard errors of the circular means (dashed lines) for 10 different randomized trial selections ($M \pm SE$ over 38 trials during left (red lines) and right (black lines) ear percept, respectively). The turquoise-shaded bar highlights that the effect of increased phase asymmetry during left ear percept was present in the marked post-stimulus onset interval throughout all repetitions (*maxstat*-method; corrected p -values are displayed in S2 Table).

(JPG)

S3 Fig. Test-retest reliability of the laterality index and the intrinsic phase asymmetry at 40Hz during left ear percept.

(JPG)

S1 Table. Corrected p -values for supplementary permutation statistics (related to S1 Fig).

Corrected p -values (*tmax*-method) for the non-parametric paired sample permutation test (related to Figure A in S1 Fig), which was applied to the intrinsic phase asymmetries at 40Hz during left ear and right ear processing after excluding three participants with a negative LI ($n = 23$). The permutation distribution was computed by randomly switching condition labels within participants in each of 10.000 iterations.

(XLSX)

S2 Table. Corrected p -values (*tmax*-statistic) related to S2 Fig (Sensitivity analysis of the 40Hz intrinsic phase asymmetry). Each row indicates the corrected p -values of the non-parametric permutation test for a different randomized selection of 38 trials. For reasons of illustration, we here displayed p -values in the post-stimulus onset interval 32-64ms.

(XLSX)

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5.2 Publication 2: Supplementary Material

S1 Text. Electric field modeling

We here derive the formal expressions used to calculate an optimal stimulation of a given location and orientation inside the head. The electric field induced by inserting a unit current at some location (the stimulation electrode) and extracting it some other location (the reference) is well known to be equal to the electric lead field representing the sensitivity of an EEG sensor at that location (with that reference) to source activities. Hence, calculating electric field distributions during tACS stimulation is equivalent to solving the EEG forward problem, for which an analytic expansion of the electric lead field in spherical harmonics for a three-shell volume conductor of realistic shape was used (Nolte and Dassios, 2005). Within the volume inside the innermost shell a grid with neighboring grid-points having 5mm distance is defined, and EEG forward solutions are calculated for a fixed set of EEG electrodes.

We denote by $L(i,j,k)$ the electric potential at the i .th sensor, for the j .th grid-point, induced by a source of unit magnitude pointing into k .th direction with $k=1,\dots,3$. The electric field induced by a tACS stimulation of magnitude $\alpha(i)$ for the i .th sensor induces, apart from an irrelevant constant, an electric field at the j .th grid-point in the k .th direction equal to

$$E(j,k) = \sum_i L(i,j,k)\alpha(i) \quad (10)$$

The goal is to optimize the stimulation $\alpha(i)$ such that the induced electric field is fixed in a specified direction at a specified grid-point inside the head while simultaneously minimizing the stimulation of all other regions and directions. The latter can be defined in various ways, and we here chose to minimize the (square of the) 2-norm of the electric field leading to minimize the cost function

$$H = \sum_{j,k} E(j,k)^2 \quad (11)$$

under the constraint

$$\sum_i L_0(i)\alpha(i) = 1 \quad (12)$$

where $L_0(i)$ is the topography of an electric dipole at the specified location with specified orientation. It is possible (but not necessary) to choose the location at one of the grid-points, say the m .th. If the source direction is given by $u(k)$ with $k=1,\dots,3$ then

$$L_0(i) = \sum_k L(i,m,k)u(k) \quad (13)$$

Minimizing the cost function H under the constraint can be solved analytically and results in

$$\vec{\alpha} = \frac{1}{\lambda} K^{-1} \vec{L}_0 \quad (14)$$

with

$$K(p, q) = \sum_{j,k} L(p, j, k) L(q, j, k) \quad (15)$$

and

$$\lambda = \vec{L}_0^T K^{-1} \vec{L}_0 \quad (16)$$

The above formulation is only valid if K is invertible which is not the case if the reference electrode is included in the lead field tensor L or if, e.g., the topographies are referenced to common average reference. In such a case the inverse of K can be replaced by its pseudo-inverse. A more general, approach is to regularize K and make the replacement

$$K \rightarrow K + \beta id \quad (17)$$

where id is the identity matrix in the N -dimensional sensor space. Replacing the inverse of K with its pseudo-inverse corresponds to the limit $\beta \rightarrow 0$, while choosing a finite value for β leads to less total current inserted to the head compromising on the cost function. In this paper we have chosen a rather small regularization of

$$\beta = 10^{-4} \frac{\text{tr}(K)}{N} \quad (18)$$

S2 Text. Supplementary control analyses

Atypical laterality indexes during sham-tACS

Since the structural model of Kimura suggests that participants with a negative laterality index (LI) might exhibit an atypical organization of speech perception and thus an altered interhemispheric communication between auditory cortices [1], we carried out a supplementary analysis to assess if the main results (Fig 4A-B) are robust against potential confounding influences of participants with a negative LI. Therefore, we excluded three participants who scored a negative LI during sham-tACS (LI = -11.8; -2.5; -0.9) and repeated the non-parametric permutation test on the averaged time courses of the intrinsic phase asymmetries ($n=23$). Importantly, the exclusion of

these participants again yielded a significant difference between the perceptual outcomes of the phase asymmetries in the post-stimulus onset interval from 44-60ms (*tmax*-method, see S5 Table; Figure A in S4 Figure). Furthermore, the significant circular-linear correlation between tACS-related behavioral modulation and the intrinsic phase asymmetry ($\rho=.5932$, $p=0.0175$) during left ear percept in the sham session was not affected by the exclusion of these participants (Figure B in S4 Figure).

Sample size bias

The DL paradigm is characterized by a clear behavioral asymmetry as healthy right-handed participants report significantly more syllables perceived through the right ear, which complicates the statistical comparison of left and right ear trials in the form of a sample size bias. Since the statistical comparison of conditions in the EEG source space is additionally hampered as spatial filters, which are applied during LORETA, are biased by unmatched trial numbers [2], we decided to balance the trial numbers across subjects and conditions by randomly subsampling 38 trials out of each subject's datapool (see Methods, EEG data preprocessing). To confirm that our results were not confined to one specific trial selection, we repeated the trial subsampling procedure and the ensuing non-parametric permutation test 10 times as depicted in the Methods section. Throughout all repetitions, we observed increased intrinsic phase asymmetry during left ear percept compared to right ear percept in a similar time window (40-48ms post-stimulus onset; S6 Figure; p -values are displayed in S7 Table).

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S3 Text. Test-retest reliability of the laterality index and the intrinsic phase asymmetry at 40Hz

The circular-linear correlation analysis (Fig 4B) was performed on metrics (laterality index modulation, intrinsic phase asymmetry during sham-tACS) that were assessed on two different days. While previous studies revealed both low [1,2] as well as high [3–5] test-retest reliability values of the right ear advantage (REA) for verbal material during dichotic listening, the test-retest reliability of the intrinsic phase asymmetry at 40Hz has not yet been assessed.

To further discuss the test-retest reliabilities of the primary variables in this work (laterality index, intrinsic phase asymmetry), we took the opportunity to reanalyze unpublished pilot data where 18 right-handed healthy participants (9 female, mean age: 25.77 ± 3.95 years) performed the same dichotic listening task (240 syllables with CV-combinations) on two different days within two weeks during EEG-recording. The EEG recordings were obtained from 64 Ag/Cl electrodes (no amplitude clipping, impedances $<10\text{k}\Omega$), referenced to the nose tip) in an equidistant array using slightly abrasive electrolyte gel (Abralylt 2000, Easycap). EEG was sampled at 5000Hz using BrainAmp amplifiers (Brain Products GmbH), amplified in the range of ± 16.384 mV at a resolution of 0.5 μV and stored for offline analyses. Sensor space preprocessing and source space analysis (eLORETA; <http://www.uzh.ch/keyinst/loreta.htm>) were

kept identical to the analysis depicted in the Methods section, with a minor exception in that the pilot data ($n=18$) were resampled to 1000Hz instead of 250Hz.

Importantly, the assessment of reliability scores according to classical test theory demands that an equal number of observations is obtained throughout all individuals [6]. Consequently, we kept the randomizing trial subsampling procedure identical to the main experiment to prevent a sample size bias and calculated circular means across the same post-stimulus onset interval (36-56ms) over 35 trials (lowest number across both sessions and subjects) in the *left ear* condition. We hence computed the test-retest reliability by means of a circular-circular correlation (function: *circ_corrcc.m*, CircStat-toolbox [7]). Importantly, the asymmetry values exhibited a high test-retest reliability during left ear percept at 40Hz ($\rho=0.8529$, $p=.0047$; Figure B in S8 Figure).

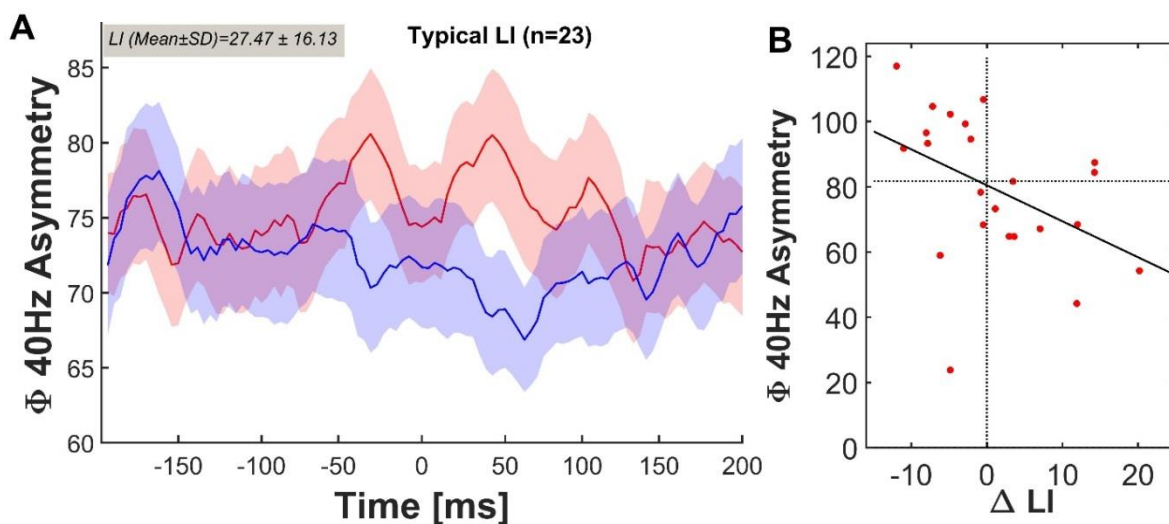
Furthermore, we assessed each participant's behavioral performance during both sessions (T1 and T2) by means of the laterality index and computed the test-retest reliability using the Matlab-function *cronbach.m* (written and provided by Alexandros Leontitsis, in accordance with [8]). Interestingly, this analysis revealed an excellent test-retest reliability of $\alpha=.9444$ (Figure A in S8 Figure), which is in line with the concept that the LI reflects individual trait differences in hemispheric integration via posterior parts of the corpus callosum.

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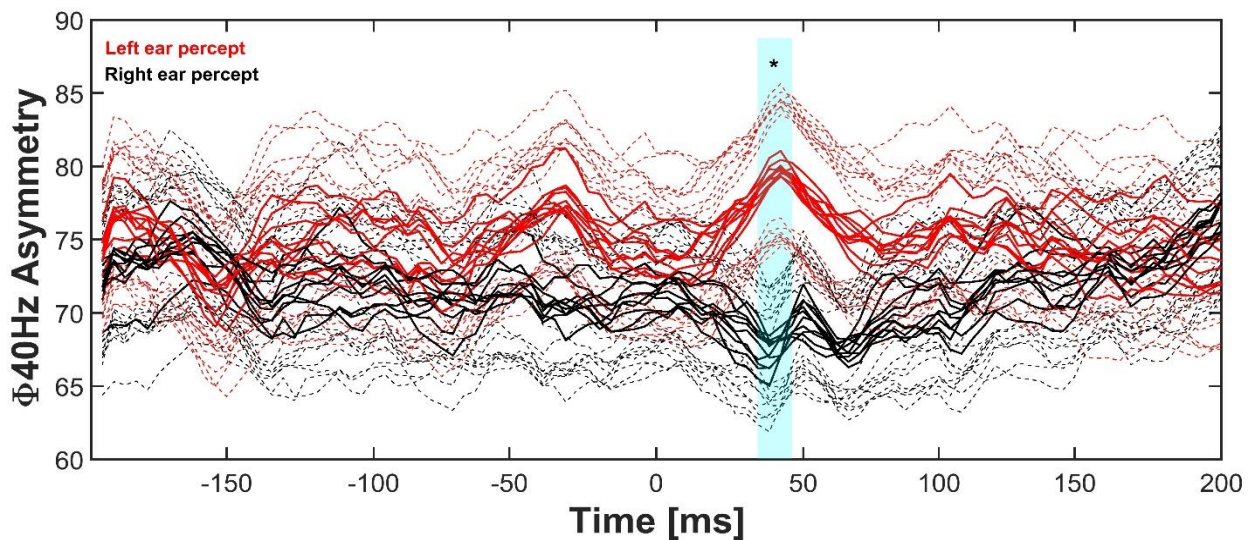
S4 Figure. Oscillatory key signature of the interhemispheric phase lag after excluding participants with an atypical laterality index ($n=23$).



S5 Table. Corrected p -values for supplementary permutation statistics (related to S4 Figure).

epoch	32-36ms	36-40ms	40-44ms	44-48ms	48-52ms	52-56ms	56-60ms
p -value	.4775	.1897	.0489	.0187	.0322	.0519	.0422

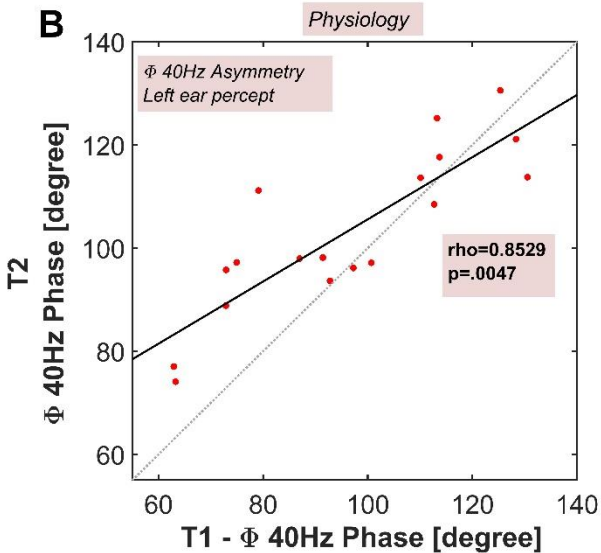
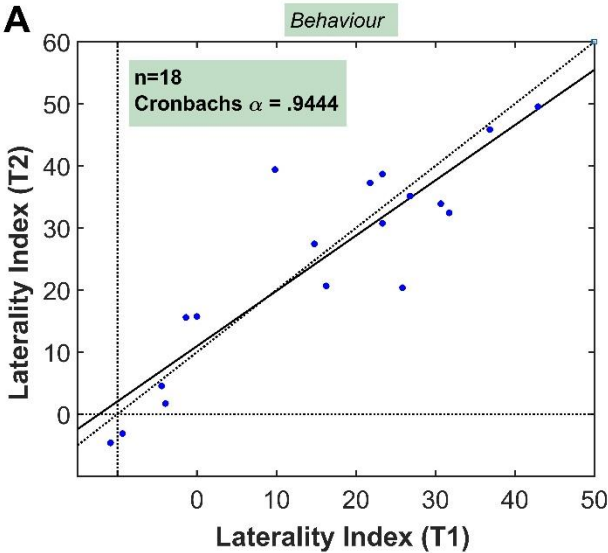
S6 Figure. Sensitivity analysis of the 40Hz intrinsic phase asymmetry. Average time courses (solid lines) of the intrinsic phase asymmetry (as shown in Fig 4A in the manuscript) with standard errors of the circular means (dashed lines) for 10 different randomized trial selections ($M \pm SE$ over 38 trials during left (red lines) and right (black lines) ear percept, respectively). The turquoise-shaded bar highlights that the effect of increased phase asymmetry during left ear percept was present in the marked post-stimulus interval throughout all repetitions (all $p < 0.05$, maxstat-method).



S7 Table. Corrected p -values (tmax-statistic) related to S6 Figure (Sensitivity analysis of the 40Hz intrinsic phase asymmetry)

Post-Stimulus Onset Interval	32ms	36ms	40ms	44ms	48ms	52ms	56ms	60ms	64ms
p -value (randomization 1)	0,5106	0,1412	0,0308	0,0151	0,086	0,3549	0,5482	0,6152	0,6643
p -value (randomization 2)	0,3497	0,0808	0,0291	0,0298	0,1595	0,2872	0,2873	0,4219	0,6806
p -value (randomization 3)	0,7878	0,1716	0,0493	0,0262	0,0726	0,1718	0,2218	0,1842	0,2432
p -value (randomization 4)	0,5139	0,2047	0,0549	0,0355	0,0535	0,1217	0,1411	0,2252	0,4216
p -value (randomization 5)	0,3363	0,1046	0,0444	0,0466	0,1108	0,4193	0,6482	0,5547	0,3348
p -value (randomization 6)	0,1145	0,0256	0,0061	0,0315	0,3477	0,9237	0,8098	0,5945	0,5196
p -value (randomization 7)	0,717	0,2643	0,0613	0,0833	0,377	0,7074	0,5889	0,489	0,4214
p -value (randomization 8)	0,2075	0,0728	0,0388	0,1066	0,4045	0,6489	0,5806	0,5437	0,4833
p -value (randomization 9)	0,4527	0,1176	0,0207	0,0243	0,1327	0,4898	0,6895	0,7086	0,4676
p -value (randomization 10)	0,862	0,3408	0,0286	0,0243	0,0652	0,3205	0,37	0,3017	0,3084

S8 Figure. Test-retest reliability of the laterality index and the intrinsic phase asymmetry at 40Hz during left ear percept.



6.1 Summary

Neural synchronization in the gamma-band range (30-100Hz) has been proposed to constitute a key mechanism to coordinate the information flow in large-scale cortical network interactions, thus enabling conscious perception and cognition in humans. Specifically, oscillatory gamma-band coupling has been suggested to mediate feature integration in the visual system, and recent evidence indicated that the same mechanism might enable conscious auditory perception and speech processing, where auditory cues from both ears are integrated across posterior transcallosal fibers between both auditory cortices. Hitherto, most of this evidence is correlative in nature, while only little is known about the directionality during the interhemispheric auditory transfer, and whether it can be modulated by means of transcranial alternating current stimulation (tACS). To address these questions, this thesis comprises two experiments exploiting electroencephalography (EEG) with effective connectivity (EC) analyses in the source space and spatiotemporally matched multi-site tACS at 40Hz during a dichotic listening (DL) task with syllables.

This thesis confirms the callosal relay model by providing electrophysiological evidence for the causal information transfer from the right to the left secondary auditory cortex (SAC) during left ear (LE) processing, which is mediated by elevated EC in the gamma-band range. Crucially, this directionality effect was not found during right ear (RE) percept or between the left and right Heschl's gyrus, highlighting the functional relevance of the SAC for the perception of complex sounds.

In the second experiment, anti-phase tACS at 40Hz did not cause the hypothesized increase of RE reports at group level. Importantly, a follow-up analysis revealed that bilateral gamma stimulation only disrupted the auditory interhemispheric integration in individuals with intrinsic 40Hz-phase asymmetries closer to 0° , whereas the auditory network was prone to excitation when the deviation of the intrinsic asymmetry from the tACS-induced lag was low. Moreover, the oscillatory phase asymmetries exhibited high interindividual variation across the sample and excellent test-retest reliability across days. Collectively, this thesis highlights that synchronized large-scale communication in the auditory system is mediated by directed gamma-band coupling from the right to the left SAC, and that this neurophysiological mechanism entails a clear non-zero phase lag. In future studies, the application of individually tailored stimulation protocols may improve therapeutic interventions to electrically modulate neuropsychiatric conditions with rhythmic disturbances, such as schizophrenia.

6.2 Zusammenfassung (Summary in German)

Synchronisierter oszillatorischer Aktivität im Gamma-Frequenzspektrum (GBO; 30-100 Hz) wird eine wichtige Funktion bei der Integration und Koordination sensorischer Inputs für bewusste Wahrnehmung und kognitive Funktionen zugeschrieben. Insbesondere bei der interhemisphärischen Verarbeitung visueller Informationen trägt die phasenspezifische Kopplung von GBO eine besondere Bedeutung, und neuere elektrophysiologische Befunde deuten darauf hin, dass dieser Mechanismus auch im auditorischen System bei Sprachwahrnehmung vorzufinden ist. In dieser Dissertation wurde die Modulierbarkeit interhemisphärischer Gamma-Band Kopplung zwischen dem linken und rechten sekundär auditorischen Cortex (SAC) mit bilateraler transkranialer Wechselstromstimulation (tACS) und Elektroenzephalographie (EEG) während der Bearbeitung einer dichotischen Höraufgabe mit Silben untersucht. Darüber hinaus wurde im EEG-Quellraum eine Analyse der effektiven Konnektivität zwischen den SACs durchgeführt, um neue Erkenntnisse über den kausalen transcallosalen Austausch akustischer Informationen im Rahmen eines Sender-Empfänger-Modells zu gewinnen.

Die Analyse der effektiven Konnektivität liefert Evidenz für den gerichteten Informationsfluss vom rechten zum linken SAC während der bewussten Wahrnehmung von Silben durch das linke Ohr, die durch erhöhte Kopplung von GBO ermöglicht wird. Wichtigerweise zeigte sich dieser Effekt nicht zwischen der linken und rechten primären Hörrinde oder bei der Wahrnehmung von Stimuli durch das rechte Ohr. Entgegen der Hypothese führte die antiphasische (180° -) Gamma-Stimulation nicht zur Desynchronisation und Erhöhung des behavioralen Rechtsohrvorteils. Entsprechenderweise zeigte eine Kontrollanalyse, dass die Wirkung der 40Hz-Stimulation phasenspezifisch durch den intrinsischen Phasenversatz zwischen den SACs moduliert wurde: Das interhemisphärische auditorische Netzwerk ließ sich durch 180° -Stimulation besser desynchronisieren bei Probanden, deren intrinsische Phasenasymmetrie im 40Hz-Spektrum näher an 0° lag, während es bei erhöhten intrinsischen Asymmetrien zu erhöhter Kopplung (reduziertem Rechtsohrvorteil) führte. Interessanterweise zeigten die Asymmetrie-Werte eine exzellente Test-Retest-Reliabilität sowie hohe interindividuelle Varianz innerhalb der Stichprobe. Zusammenfassend belegen die Ergebnisse, dass (i) der gerichtete transcallosale Informationsfluss zwischen den Hörrinden von rechts nach links durch synchrone GBO ermöglicht wird, dass (ii) diese Phasenkopplung zwischen weitflächigen kortikalen Oszillatoren eine

klare Verzögerung ($>0^\circ$) beinhaltet und dass (iii) beträchtliche interindividuelle Unterschiede dieser intrinsischen phasenbezogenen Asymmetrien zu berücksichtigen sind in künftigen Stimulationsprotokollen, welche eine hohe Relevanz für neue elektromagnetische Therapieansätze bei neuropsychiatrischen Erkrankungen (z. B. Schizophrenie) tragen.

7. Author Contribution to the Publications

1. *Conceptualization*

2. *Data Collection*

3. *Data Analysis*

4. *Writing – Original Draft*

5. *Writing – Review*

6. *Supervision*

Study 1: The Callosal Relay Model of Interhemispheric Communication: New Evidence from Effective Connectivity Analysis (Published in *Brain Topography*, 2017)

Steinmann, S.: 1,2,4

Meier, J.: 1,3,4

Nolte, G.: 5,6

Engel, A.K.: 5,6

Leicht, G.: 1,5,6

Mulert, C.: 1,5,6

Study 2: Intrinsic 40Hz-phase asymmetries predict tACS effects during conscious auditory perception (Published in *PLoS ONE*, 2019)

Meier, J.: 1,2,3,4

Nolte, G.: 1,4,5,6

Schneider, TR: 1,5,6

Engel, A.K.: 5,6

Leicht, G.: 1,5,6

Mulert, C.: 1,5,6

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9. Curriculum Vitae

[Left out for reasons of data protection]

[Entfällt aus datenschutzrechtlichen Gründen]

10. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: