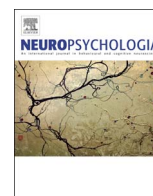




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Probing neural mechanisms underlying auditory stream segregation in humans by transcranial direct current stimulation (tDCS)



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ABSTRACT

One hypothesis concerning the neural underpinnings of auditory streaming states that frequency tuning of tonotopically organized neurons in primary auditory fields in combination with physiological forward suppression is necessary for the separation of representations of high-frequency A and low-frequency B tones. The extent of spatial overlap between the tonotopic activations of A and B tones is thought to underlie the perceptual organization of streaming sequences into one coherent or two separate streams. The present study attempts to interfere with these mechanisms by transcranial direct current stimulation (tDCS) and to probe behavioral outcomes reflecting the perception of ABAB streaming sequences. We hypothesized that tDCS by modulating cortical excitability causes a change in the separateness of the representations of A and B tones, which leads to a change in the proportions of one-stream and two-stream percepts. To test this, 22 subjects were presented with ambiguous ABAB sequences of three different frequency separations (ΔF) and had to decide on their current percept after receiving sham, anodal, or cathodal tDCS over the left auditory cortex. We could confirm our hypothesis at the most ambiguous ΔF condition of 6 semitones. For anodal compared with sham and cathodal stimulation, we found a significant decrease in the proportion of two-stream perception and an increase in the proportion of one-stream perception. The results demonstrate the feasibility of using tDCS to probe mechanisms underlying auditory streaming through the use of various behavioral measures. Moreover, this approach allows one to probe the functions of auditory regions and their interactions with other processing stages.

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1. Introduction

In laboratory experiments on auditory stream segregation, A and B tones are usually presented either in alternation (ABAB) or in a repeated pattern of ABA triplets (ABA_n, in which _n represents a pause) (van Noorden, 1975). Depending on the stimulation parameters, i.e., the frequency separation (ΔF) between the A and B tones and their temporal separation, three different perceptual domains can be distinguished. With small frequency separations, A and B tones are predominantly heard as single stream, whereas large frequency separations and high tone presentation rates generally lead to the percept of two segregated streams. With intermediate stimulus parameters, in the ambiguous domain, both of these percepts are possible. Notably, there are other factors than frequency separation and presentation rate that influence stream

segregation. Thus, depending on the experimental setting, perceptual switches in principle can occur over a broad range of frequencies and repetition rates (Denham et al., 2013).

One current hypothesis concerning the neural underpinnings of auditory stream segregation suggests that the frequency tuning of tonotopically organized neurons in primary fields of auditory cortex in combination with physiological forward suppression is necessary to separate representations of high-frequency A and low-frequency B tones (Bee and Klump, 2004, 2005; Fishman et al., 2004, 2001; Kanwal et al., 2003). When the presentation rate is increased, tonotopically overlapping neural responses in auditory cortex become suppressed, and when the frequency separation between A and B tones is increased, the spatial overlap between the tonotopic activations decreases. As a consequence, the A and B tones are represented by increasingly distinct neuron populations, which may serve as the neural correlate of perceptually segregated streams.

Such neural mechanisms, first suggested from animal electrophysiology data recorded in primary fields of auditory cortex to

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pure tone stimuli, have gained further support from human imaging studies using pure tones as well as amplitude modulated tones, harmonic tone complexes, or bandpass-filtered harmonic complex tones (Deike et al., 2004, 2010; Dollezal et al., 2014; Gutschalk et al., 2005, 2007; Snyder et al., 2006; Wilson et al., 2007). These studies showed larger summed activity in auditory cortex with stream segregation, which is consistent with there being less interaction between two distinct populations of active neurons when they are farther apart in their frequency tuning. However, even though these mechanisms offer a plausible explanation of auditory stream segregation, the data from previous studies do not provide direct evidence. The present study attempts to causally interfere with these mechanisms by transcranial direct current stimulation (tDCS), and probe behavioral outcomes in the perceptual organization of ambiguous ABAB streaming sequences.

In recent years, tDCS has become a promising tool for modulating cortical excitability and behavior in a noninvasive and painless manner in both clinical and neuroscientific research (for reviews, see Costa et al. (2015), Nitsche et al. (2008), Nitsche and Paulus (2011) and Priori (2003)). During tDCS stimulation, a weak constant electric current is applied to the cortical surface, with the current flowing from an active electrode to a reference electrode. Although part of the current is shunted through the scalp, an effective proportion is delivered to the brain tissue (Miranda et al., 2006). Depending on the polarity of the current, tDCS causes an increase or decrease in cortical excitability minutes to hours after stimulation (for a review of the physiological basis of tDCS, see Stagg and Nitsche (2011)). It has been suggested that anodal tDCS enhances, and cathodal tDCS diminishes, excitability in the cortical region affected by the current. During stimulation, the effects of both anodal and cathodal tDCS depend primarily on changes in membrane potential: Anodal tDCS causes depolarization and cathodal tDCS causes hyperpolarization of the resting membrane potential, the result being an increase and decrease in firing rate, respectively. Aftereffects are suggested to depend on the modulation of GABAergic and glutamatergic synapses in anodal tDCS and of glutamatergic synapses in cathodal tDCS.

In the present study, we examined the effect of tDCS on the perceptual organization of ambiguous ABAB streaming sequences. We applied anodal and cathodal tDCS over the left temporal cortex, this choice being motivated by our previous discovery that left auditory cortex is specifically involved in active segregation of A and B streams (Deike et al., 2004, 2010). We hypothesized that depending on the polarity, tDCS modulates the frequency selectivity and the degree of forward suppression in the neural populations activated by the successively presented tones A and B. With depolarizing anodal stimulation, tonotopic activation should be broadened and, therefore, suppression should be reduced. This should increase the overlap of the neuron populations activated by tones A and B. In contrast, hyperpolarizing cathodal stimulation should narrow the spatial activation in the auditory cortex and reduce overlapping activation. As a perceptual effect, tDCS should therefore modulate the proportion of one-stream and two-stream perception as a function of frequency separation. In particular, it is our hypothesis that anodal tDCS reduces two-stream and enhances one-stream perception, whereas cathodal tDCS enhances two-stream and reduces one-stream perception. Because tDCS effects are known to be moderate (Bestmann et al., 2015; Bikson and Rahman, 2013), we chose highly ambiguous sequences that we expect to be prone to be biased by tDCS, such that it manifests in a significant behavioral outcome. To demonstrate an influence of tDCS on behavior, i.e., a bias in perceptual organization, we used the most ambiguous stimulus sequences of a previous study (Deike et al., 2012), i.e., the Δf condition of 6 semitones. Deike et al. (2012) defined perceptual ambiguity on the basis of the probability of one- versus the probability of two-stream perception

during the presentation of a tone sequence, with equal probability of one- and two-stream percept indicating the maximum ambiguity. In a further study (Deike et al., 2015), the same authors introduced an ambiguity index that quantifies perceptual ambiguity based on probabilities of one- and two-stream perception. With this measure, the highest ambiguity among the tested Δf conditions was found at a Δf of 6 semitones. Additionally, as a parametric approach we tested the neighboring Δf conditions of 5 and 7 semitones that are still ambiguous, yet show a bias toward the one-stream and the two-stream percept, respectively. This gives the opportunity to find stimulus conditions susceptible to tDCS that might allow further insights into the topic of auditory streaming as well as testing the effect of tDCS on perception. Moreover, ambiguous sequences are characterized by the phenomena of decision uncertainty (Deike et al., 2015) and bistability (Denham et al., 2013; Pressnitzer and Hupé, 2006). Therefore, we assessed these phenomena through the behavioral measures of the *initial decision time*, the *mean switching rate per sequence*, and the *duration of first perceptual phase* to explore potential effects of tDCS.

2. Materials and methods

2.1. Subjects

Twenty-two listeners (11 male, 8 female), aged between 21 and 41 years, participated in the experiment. Having been explained about the risks of the research, the subjects gave their written, informed consent to the study and the procedure, which was approved by the Ethics Committee of the Otto-von-Guericke University of Magdeburg. All subjects were blind to the stimulation conditions and naïve to the experimental aims. The first author participated in the experiment but was also blind to the stimulation conditions, with the procedure being performed by a technical assistant. She was not informed about the stimulation conditions until testing was completed.

All subjects had normal audiograms, with absolute thresholds ≤ 20 dB hearing level in the range of 250 – 6000 Hz. All subjects were right-handed (Edinburgh Handedness Inventory; laterality quotient ≥ 60) and showed a language laterality toward the left hemisphere tested as described in Bethmann et al. (2007). One additional subject was excluded from the final analysis because he received two sham stimulations and missed one anodal stimulation by mistake.

2.2. Stimuli and procedure

The stimuli, which were digitally synthesized in *MATLAB* (The Mathworks, Natick Massachusetts, USA), were harmonic tone complexes consisting of the fundamental frequency, F_0 , and four partials with frequencies ranging from $2 \cdot F_0$ to $5 \cdot F_0$. All partials started and ended simultaneously and had equal amplitude. Each tone complex lasted 25 ms, including 3.8-ms cosine-squared onset and offset ramps. The tone complexes were presented in ABAB sequences of 30-s duration with a presentation rate of 6 Hz. A and B tone complexes were characterized by the F_0 ranges. In different conditions, three average frequency separations (ΔF) between the F_0 of A and B tone complexes were used (5, 6, and 7 semitones). These ΔF values were achieved by varying the F_0 of both the A and B tone complexes between conditions and relative to a F_0 center of 392 Hz. In this way, the subjects were prevented from becoming familiar with a specific frequency, which might have biased their percept toward the two-stream one. In addition, within each ΔF condition, individual exemplars of both A and B tone complexes varied in F_0 , differing from the geometric mean by 0, ± 1 , or ± 2

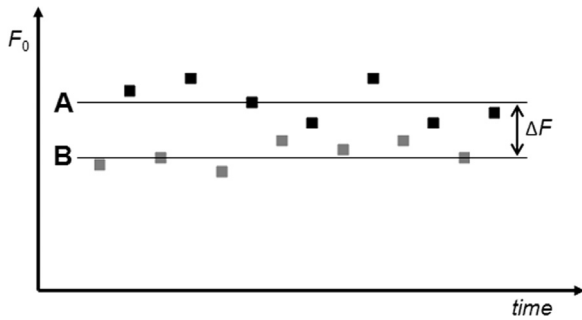


Fig. 1. Stimulus material. The schematic depiction shows, as an example, part of a sequence of the ΔF condition of 6 semitones. Squares represent the A (black) and B (gray) tone complexes. The geometric means of their F_0 (black lines) differ by 6 semitones. The F_0 of the individual exemplars of A and B tone complexes differ from their geometric means by 0, ± 1 , or ± 2 semitones.

semitones (F_0 variants) (for details, see Deike et al., 2012). Within each sequence, the different F_0 variants were presented randomly and with equal probability. The assigned ΔF values therefore represent the geometric mean F_0 separations between A and B tone complexes. For illustrative purpose, part of an example sequence (ΔF of 6 semitones) is schematically depicted in Fig. 1. For each of the three ΔF conditions, five different random sequences of A and B tone complexes were presented twice each, resulting in the presentation of 10 sequences per ΔF condition during the experiment. The different sequences were presented in pseudo-random order and alternated with silence of 10-s duration. The stimuli were presented binaurally through insert earphones (ER-3A, Etymotic, Elk Grove Village, Illinois, USA) at an individually adjusted, comfortable sound level, using *Presentation* (Neurobehavioral Systems, Berkeley, California, USA).

Prior to the psychophysical measurements, the subjects received written instructions and additional verbal clarifications if necessary. The subjects were asked to listen to the sound sequences and to indicate their current percept by pressing the left mouse button with their right index finger when they perceived the low- F_0 and high- F_0 tone complexes as one coherent stream, and the right mouse button with their right middle finger when they perceived them as two separate streams, i.e., when they heard a low- F_0 and a high- F_0 stream in parallel. The subjects were encouraged to indicate as promptly as possible after the onset of each sequence, whether they heard one stream or two streams, and to update their response every time the percept switched. To familiarize the subjects with the sound sequences and the task, they were exposed to sequence examples prior to the actual measurements.

2.3. tDCS procedure

For tDCS, the subjects were seated comfortably in a recliner chair in front of a personal computer screen in an acoustically shielded chamber (Industrial Acoustic Chamber, Niederkrüchten, Germany). Direct current was delivered by a battery-driven, constant current stimulator (Eldith, NeuroConn GmbH, Germany) using a pair of rubber electrodes in a 5×7 cm saline-soaked synthetic sponge. For stimulation of the left auditory cortex, the active electrode (to which the term anodal/cathodal stimulation refers) was placed over the temporal (T7) location as defined by the International 10–20 system for electroencephalography electrode placement. The reference electrode was placed over the contralateral supra-orbital area. This electrode positioning has been shown to modulate excitability in temporal, i.e. auditory cortical regions (Fregni et al., 2006; Mathys et al., 2010; Tang and Hammond, 2013; Zaehle et al., 2011). A constant current of 1 mA intensity was delivered for 15 min before the task, with a linear

fade in/fade out of 8 s. Each participant performed three consecutive sessions at 1-week intervals to avoid interference effects. In two out of three sessions, participants were stimulated with anodal and cathodal direct current, respectively, and in one session subjects underwent a sham condition. For the sham condition, the same electrode montage was used as in the stimulation conditions, but the current was applied for 30 s and was ramped down without the subject's awareness. This procedure ensured that in all conditions subjects felt the initial itching that recedes over the first seconds of tDCS. Accordingly, none of the subjects was able to determine whether they received real or sham stimulation. The session order was counterbalanced across subjects.

Fifteen subjects reported a slight tingling sensation under the electrode during the first seconds of stimulation, three subjects had sensation of a short light flash when the electrodes were removed, and three subjects had a sensation of dizziness during stimulation. Two subjects reported a weak headache after stimulation.

2.4. Data analysis

To determine the influence of tDCS and its polarity on the perceptual organization of streaming sequences, we calculated for each subject, ΔF condition, and tDCS stimulation condition the *proportion of time* that the sound sequences were perceived as one stream or two streams (see Deike et al. (2012)). For the calculation of this proportion, all perceptual organizations (i.e., one-stream and two-stream percepts) following the first decision up to the end of the sequence were considered.

To explore the potential influence of tDCS on the decision and the bistability characteristics of ambiguous streaming sequences as used in this study, the *initial decision time*, the *mean switching rate per sequence*, and the *duration of first perceptual phase* were calculated (see Deike et al. (2015)). Taking the variability of the data into account (see also, Denham et al. (2014) and Pressnitzer and Hupé (2006)), a nonparametric statistical analysis was carried out. Pairwise comparisons were performed within each ΔF condition using Wilcoxon signed-rank tests to examine the influence of tDCS and its polarity on the given behavioral measures. All tests were two-tailed except those testing the proportions of perceptual organizations. In this study we used one-tailed tests, as we had directional hypotheses, as delineated in the introduction. Additionally, we calculated the Cohen's effect size d_z (dependent samples) for each test that reached a significance level of $p \leq 0.05$ using the software *G*Power* 3.1 (Faul et al., 2007).

3. Results

The main aim of the study was to test the hypothesis that the change in excitability of neurons in auditory cortex caused by tDCS will lead to a change in the way A and B tones are perceptually organized as streaming sequences. Specifically, we expected tDCS to change the relative proportions of time that the stimulation was perceived as either one stream or two separate streams. The *proportion of the two-stream percept* was significantly lower after anodal stimulation (44.87%, $\pm 3.68\%$) than after sham stimulation (49.40%, $\pm 3.50\%$; $p=0.004$, $d_z=0.70$) and cathodal stimulation (50.02%, $\pm 3.74\%$; $p=0.048$, $d_z=0.35$) at the ΔF condition of 6 semitones (see Fig. 2A). The *proportion of the one-stream percept* was higher with anodal stimulation (40.53%, $\pm 3.84\%$) than with sham stimulation (37.88%, $\pm 3.59\%$; $p=0.051$, $d_z=0.33$). There was also a trend for this proportion to be higher following anodal stimulation than following cathodal stimulation (37.35%, $\pm 3.87\%$; $p=0.075$) (see Fig. 2B).

In summary, with respect to anodal stimulation, our hypothesis

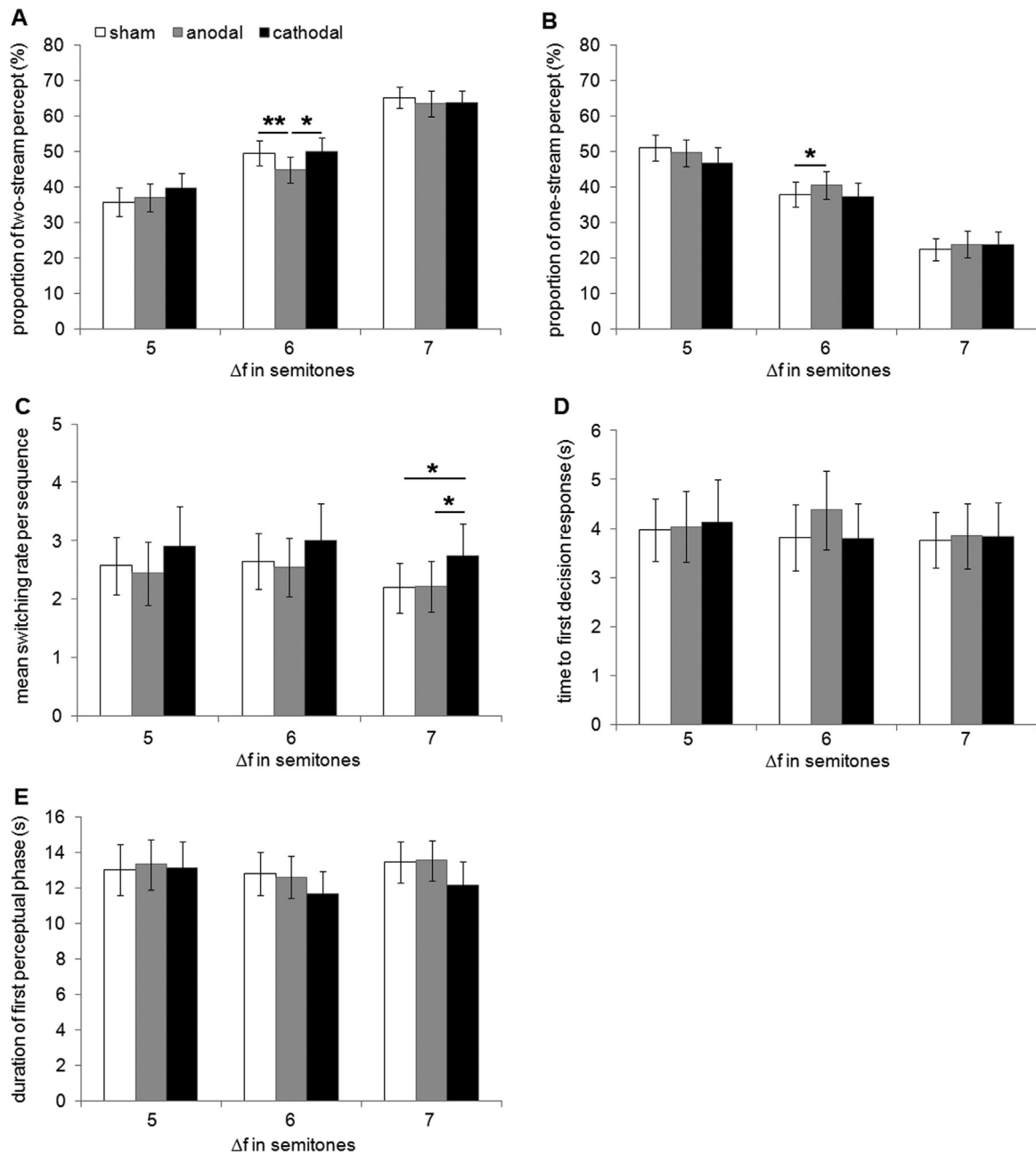


Fig. 2. Effects of tDCS stimulation on behavioral measures. The panels show the proportions of time that the subjects perceived the sequences as two streams (A) and as one stream (B), the mean switching rate per sequence (C), the time that the subjects needed to make a first decision on the perceptual organization of the ABAB sound sequences (D), and the duration of the first perceptual phase (E) at the different ΔF conditions and tDCS stimulations. Symbols and error bars represent the mean and SEM. In the ΔF condition of 6 semitones, the anodal stimulation significantly reduced the proportion of the two-stream percept (A) and increased the proportion of the one-stream percept (B). Additionally, the same ΔF condition showed a slightly longer initial decision time for anodal than for sham and cathodal tDCS stimulation (D). Cathodal tDCS stimulation led to higher mean switching rates than the other stimulation conditions, reaching significance in the ΔF condition of 7 semitones (C).

was confirmed in the ΔF condition of 6 semitones. Even though the effect of tDCS was restricted to a specific combination of one stimulation polarity and one ΔF condition, the results of the statistical tests appear reliable, showing medium effect sizes of 0.4–0.7. Moreover, the percept probabilities of the 6-semitone ΔF condition during sham stimulation was most ambiguous and differed significantly from that of the neighboring ΔF conditions (two-tailed Wilcoxon signed-rank tests $p < 0.001$).

Additionally, in the 6-semitone ΔF condition, the *initial decision time* for anodal stimulation (4.38 s, ± 0.80 s) was longer than that for cathodal stimulation (3.79 ms, ± 0.71 s) as a trend ($p=0.095$). There was almost a trend for it to be longer than the initial decision time for sham stimulation (3.82 s, ± 0.67 s; $p=0.101$) (see

Fig. 2D).

In none of the three ΔF conditions was there a significant difference in the *duration of the first perceptual phase* between the stimulation conditions ($p \geq 0.140$) (see Fig. 2E).

The *mean switching rate per sequence* was higher during cathodal (2.75, ± 0.54) than during sham stimulation in the ΔF condition of 7 semitones (2.20, ± 0.43 ; $p=0.031$, $d_z=0.42$). It was higher during cathodal stimulation (3.01, ± 0.63) than during anodal stimulation in the ΔF condition of 6 semitones (2.55, ± 0.50 ; $p=0.067$) and 7 semitones (2.22, ± 0.44 ; $p=0.042$, $d_z=0.41$) (see Fig. 2C).

4. Discussion

The present study examined the effects of tDCS on the perceptual organization of ambiguous ABAB streaming sequences. We hypothesized on the basis of the Fishman model (Fishman et al., 2004, 2001) that tDCS, by modulating cortical excitability, causes a change in the separateness of the representations of A and B tones. Specifically, we expected that anodal tDCS causes a broadening of the representation of the A and B tones, whereas cathodal tDCS leads to a sharpening of the representation of the A and B tones. As a consequence, anodal tDCS should lead to less two-stream and more one-stream perception, whereas cathodal tDCS should lead to the opposite effects. With respect to anodal stimulation, this hypothesis was confirmed in the ΔF condition of 6 semitones: We found a significant decrease in the proportion of two-stream perception and an increase in the proportion of one-stream perception as compared with sham and cathodal stimulation. This finding supports the idea that anodal tDCS leads to a broadening of the representation of A and B tone frequencies in auditory cortical areas and is consistent with the results of Tang and Hammond (2013), who found a significantly broadened frequency selectivity for a 2-kHz tone during anodal tDCS, as quantified by equivalent rectangular bandwidth (ERB) measures.

The effect of anodal tDCS was restricted to the most ambiguous ΔF condition of 6 semitones. In the less ambiguous ΔF conditions of 5 and 7 semitones, we found no significant effect of tDCS on behavior. Hence, for the streaming stimuli as used in this study, an almost maximal ambiguity is necessary to achieve a behavioral outcome by means of tDCS. In the less ambiguous conditions, the bias toward either the one-stream (5 semitones) or the two-stream percept (7 semitones) might have been too strong to be modified by tDCS. Such a strong dependence of tDCS outcomes on stimulus parameters is consistent with previous reports and, more generally, with accumulating evidences on requirements that must be met so that tDCS becomes effective (Bikson and Rahman, 2013).

Our hypothesis on the effect of cathodal stimulation was not confirmed. This suggests that anodal and cathodal stimulation do not have opposite effects on stream segregation. The basis for this may lie in differences in the physiological effects of tDCS with different current polarities. In the present study, subjects performed the psychophysical task after receiving tDCS stimulation. Hence, the observed behavioral effects were the result of after-effects of tDCS in the stimulated area. In their review, Stagg and Nitsche (2011) pointed to converging evidence that the aftereffects of tDCS are the result of synaptic modulation. Anodal aftereffects appear to depend on the modulation of both GABAergic and glutamatergic transmission, whereas cathodal aftereffects are caused primarily by altered glutamatergic transmission. On the level of auditory cortex, frequency tuning and stream segregation have been shown to rely on the interaction of excitation and inhibition (for reviews see, Ojima (2011), Oswald et al. (2006) and Reyes (2011)). By enhancing glutamatergic and diminishing GABAergic transmission, anodal tDCS might increase tonotopic overlap. This would impede stream segregation. By reducing glutamatergic transmission without major effects on GABAergic inhibition, cathodal tDCS might not affect the balance between excitation and inhibition in auditory cortex to a degree that disturbs stream segregation. One might speculate that GABAergic transmission follows the reduction in glutamatergic transmission to counteract the glutamatergic effects of tDCS.

Compared with sham and anodal stimulation, cathodal stimulation increased the number of perceptual switches across all ΔF conditions (significant at the 7-semitone ΔF). Diminished excitatory, glutamatergic transmission in stimulated auditory cortex might decrease its bottom-up influence on higher cortical regions involved in stream segregation such as the intraparietal sulcus

(Cusack, 2005) and the posterior medial frontal cortex (Dollezal et al., 2014). The intraparietal sulcus is thought to take part in the structuring of sensory information, and the posterior medial frontal cortex is associated with cognitive functions, monitoring response conflicts, and decision uncertainty (Ridderinkhof et al., 2004). Reduced impact of auditory cortex on the stream segregation network could increase perceptual uncertainty and strengthen top-down influences, which would explain the higher switching rates. Thus, the different effects of anodal and cathodal tDCS not only reflect the modulation of the processing in the stimulated cortical region under the electrode, but they also reveal more global network effects. This would be consistent with the results of several studies suggesting that tDCS affects cortico-cortical as well as cortico-subcortical excitability of neural networks distant from the stimulation site (Keeser et al., 2011; Lang et al., 2005; Polania et al., 2011; Polania et al., 2012). Such an influence of network activity on the current results might also be expected, because cortical frequency tuning arises through the convergence of feedforward thalamocortical and recurrent intracortical inputs (Bartlett, 2013; Happel et al., 2010; Liu et al., 2011; Metherate, 2011; Miller et al., 2001; Suga, 2012).

5. Limitations

The present study aimed at testing the effects of frequency tuning and forward suppression on stream segregation by manipulating the spatial separation of tonotopic activations through tDCS. To derive testable hypotheses, we employed the model by Fishman et al. (2001). Unlike in Fishman et al. (2001), the present study used harmonic tone complexes instead of pure tones. This might pose a problem, as it still remains unclear how the pitch of harmonic complexes is mapped in the brain (Bizley and Walker, 2010). To resolve this uncertainty, the present results have to be scrutinized by using pure tones.

Another limitation is the result of the tDCS technique itself. The method is highly controversial with respect to the spatial specificity as well as to the physiological and behavioral effects. Weak or restricted effects as also observed in this study might question the efficacy of the tDCS method. However, despite the methodological limitations, the current results give reason to further examine the observed tDCS effects while optimizing the stimulation paradigm. This refers to a refinement of the electrode positioning to the auditory cortex target region as described by Mathys et al. (2010), the individual adjustment of stimulus parameters to the subjects' most ambiguous ΔF condition, as well as to control for stimulation site by stimulating brain regions outside the auditory cortex.

Because of these general methodological limitations, one might further question whether the tDCS technique is able to evaluate current models of stream segregation. The present study focused on the Fishman model, as we assumed that tDCS results in changes of the frequency representation in the tonotopic map, which are comparable to those that are suggested to underlie the different perceptual organizations of streaming sequences. Even though our current results do not allow for unequivocal interpretation, the effect of anodal tDCS at the ΔF condition of 6 semitones supports our hypothesis and is thus compatible with the Fishman model. However, our results do not exclude the contribution of other mechanisms to stream segregation like neural coherence as in the model proposed by Elhilali et al. (2009). Thus, anodal tDCS might not only result in increased overlapping activation on the tonotopic map, but also in increased temporal coherence in neuronal responses across frequencies leading to enhanced one-stream perception. Further electrophysiological studies in animals are needed to examine the role of temporal coherence on stream segregation, and to explore how tDCS modulates the

representation of streaming stimuli on the mechanistic level.

6. Conclusions

Even though our current results do not allow for an unequivocal interpretation, they demonstrate the feasibility of using tDCS in combination with behavioral measures to probe the mechanisms underlying auditory stream segregation. Moreover, our results offer potential insight into the functions of the auditory regions and their interactions with other processing stages. Future studies should focus on these interactions, preferably using converging human and animal approaches.

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