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Investigating Auditory Perception in a Signal Detection Task during Transcranial Direct-Current Stimulation

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Abstract

Auditory verbal hallucinations (AVH) are not only reported by psychotic individuals but also by the general population. Research points to the involvement of the superior temporal gyrus (STG) in generating AVH; however, it is still unclear which role the STG plays in experiencing different types of auditory stimuli. The current study investigated this by employing a signal detection task during transcranial Direct-Current Stimulation (tDCS), in which participants were asked to either detect voice or tone stimuli. A non-clinical sample of 24 students and staff members from University of Groningen participated in a three-session study, each session consisting of tDCS over the STG, occipital cortex, or sham stimulation. It was expected that participants showed a biased form of responding to the auditory stimuli in the STG condition, namely that they were more willing to erroneously detect speech stimuli even though none were actually presented. Repeated measures analysis of variance could not find evidence for this response bias in the STG condition; however, a significantly reduced response bias was found for the stimulus type voice, pointing to distinctive mechanisms for perceiving auditory stimuli. Task sensitivity was investigated as secondary analysis, finding a reduced sensitivity for the stimulus type voice, regardless of stimulation condition. Additionally, subjective experiences during tDCS were inspected. Our results give rise to the question whether tDCS can be considered an efficacious tool to modulate auditory cortices. Limitations of the current study are discussed and recommendations for future research are presented, highlighting the importance of applying stricter stimulation protocols.

Keywords: auditory verbal hallucinations, AVH, transcranial Direct-Current stimulation, tDCS, signal detection task

Investigating Auditory Perception in a Signal Detection Task during Transcranial Direct-Current Stimulation

Auditory verbal hallucinations (AVH) are the experience of perceiving sounds in the absence of external stimuli (Larøi & Aleman, 2010; Shergill et al., 1998). AVH are commonly seen in patients with schizophrenia but also in a small proportion of the non-clinical population (Beavan et al., 2011), with an estimated prevalence rate of between 10-15% in the United States (Tien, 1991). It has been found that only a small proportion of these people also meet criteria for a diagnosis of psychosis (Johns et al., 2002), pointing to involvement of other factors distinct from the clinical psychopathology.

Research investigating neuronal underpinnings of experiencing AVH suggests the involvement of the superior temporal gyrus (STG), which comprises important areas responsible for auditory perception: the primary auditory cortex, and secondary auditory cortices, like the temporo-parietal junction, including Wernicke's area and the planum temporale. Hyperactivity in the STG was shown to relate to a higher incidence of AVH in schizophrenic patients (Homan et al., 2013). Similar activity patterns in the STG have been observed in non-clinical populations that are prone to experiencing AVH (Hugdahl, 2009).

Theoretical models into the origin of AVH propose an underlying failure of reality monitoring as one possible cause for experiencing AVH. Reality monitoring refers to the ability to discriminate correctly between internally generated events and external ones (Johnson, 1993). Hallucinating individuals show impairment in this process in that they misattribute internally generated stimuli as being produced by external sources. This has been shown in individuals experiencing AVH: they behave in a biased manner when presented with ambiguous stimuli and falsely attribute the origin of auditory stimuli to external sources (Aleman et al., 2003; Allen et al., 2004). In the literature, this biased way of responding has

been defined as ‘externalizing bias’, which describes the tendency to systematically misattribute internally generated events to an outside source (Brookwell et al., 2013).

To investigate this externalizing bias, signal detection tasks have been employed. Signal detection tasks are based on signal detection theory (SDT), which was developed to measure individuals’ ability to discriminate between two stimuli (Green & Swets, 1966). Research into AVH used this technique in that participants had to distinguish between signal present trials, incorporating a voice stimulus, and signal absent trials, incorporating only white noise (Brookwell et al., 2013). By employing SDT, parameters such as hit rate and false alarm rate can be calculated (Stanislav & Todorov, 1999). Based on these parameters, response bias can be derived, which represents the willingness of participants to detect auditory stimuli in ambiguous situations (such as in situations with a lot of noise presented). Response bias can be treated analogous to the externalizing bias reported in individuals with AVH.

Additional research utilizing SDT points to altered sensitivity in distinguishing between auditory stimuli and noise in individuals experiencing AVH. Li et al. (2002) employed signal detection tasks and have found reduced sensitivity in detecting and discriminating auditory stimuli in schizophrenic patients. However, Vercammen et al. (2008) demonstrated enhanced sensitivity in detecting speech stimuli in hallucinating individuals. Thus, findings about sensitivity in individuals experiencing AVH seem to be contradictory and further research is needed to shed light on how sensitivity to distinguishing between auditory stimuli and noise is altered in these individuals.

Signal detection tasks were furthermore used in combination with transcranial direct-current stimulation (tDCS) to investigate AVHs and the role of the STG. tDCS is a non-invasive method of electrical stimulation of the brain that utilizes electrodes on the scalp and aims to modify cortical excitability by applying weak electrical currents. The current

delivered by tDCS can either be ‘anodal’, thus delivering a positive current and thereby exerting an excitatory effect on the stimulated area, or ‘cathodal’, thus delivering a negative current and hence exerting an inhibitory effect on the stimulated area (Purpura & McMurtry, 1965).

It has been found that anodal stimulation of the left STG (Wernicke’s area) in healthy participants led to an increased number of false positives when engaging in signal detection tasks: participants more often falsely detected a voice embedded in white noise even though none was actually present (Barkus et al., 2007). Thus, increasing activity in the STG in healthy participants seems to influence their perception of auditory stimuli in line with the externalizing bias described above. Despite these findings, other tDCS studies could not replicate these effects in that they did not find a difference in applying tDCS compared to sham stimulation in experiencing AVH (Fitzgerald et al., 2014). More data has to be gathered in order to ensure efficacy of tDCS.

Additional research investigated tDCS as clinical treatment option for schizophrenic individuals, pointing to its’ promising potential in alleviating cognitive, negative and positive symptoms alike (Agarwal et al., 2013; Rabanea-Souza et al., 2019). Yet, research into clinical efficacy of tDCS for psychotic individuals is still in its infancy and further findings are needed to establish tDCS as treatment possibility for psychotic individuals.

Taken together, AVH is a phenomenon seen in both clinical and non-clinical populations, with STG activity playing a crucial role in its representation (Beavan et al., 2011; Hugdahl, 2009). It is however yet to be clarified how the STG is involved in perceiving different types of auditory stimuli, such as voice and non-voice stimuli, and whether tDCS functions as efficacious stimulation tool of this area.

Consequently, the current study aims to further explore the role of the STG in auditory perception by using a signal detection task and tDCS in a healthy sample. Specifically, it is

investigated how the response bias changes when anodal tDCS is applied over the STG when healthy participants are asked to detect different auditory stimuli, namely voice and tone stimuli. It is advantageous to recruit non-clinical sample due to ethical reasons but also as an explorative means to gain further insights into the role of STG and auditory perception.

The task at hand consisted of bursts of pink noise and participants were asked to either detect voice or tone stimuli embedded in noise. Further trials were included without any tone or voice stimulus present, but only pink noise. This is complementary to previous studies that only investigated voice perception in signal detection tasks but not non-voice stimuli (i.e., tones) (e.g., Barkus et al., 2007; Moseley et al., 2014; Moseley et al., 2016b). Thus, the current study adds to existing literature by accounting for possible differences in perception of varying auditory stimuli. Pink noise was chosen as it is thought to occur frequently in biological systems, such as in the heart rate of humans (Glass, 2001), and is often perceived softer as white noise due to less intense high frequencies (Boynton, 2020).

Transcranial direct-current stimulation was applied over different conditions: stimulation of the occipital cortex functions as an active control, sham stimulation as control condition, and anodal stimulation of the STG as experimental condition. The occipital cortex is thought not to interfere with speech perception and thus well-suited as active control site (e.g., Barkus et al., 2007). Sham stimulation is a useful method to ensure blinding integrity in imitating active stimulation. In that way, sham stimulation will contribute to adequately assess the expected efficacy of active stimulation and the role of the STG (Dissanayaka et al., 2018).

It is hypothesized that the participants show a lower response bias (corresponding to the externalizing bias) during STG stimulation concerning auditory stimuli, meaning participants are more willing to indicate the presence of a voice or tone stimulus in an ambiguous situation. Specifically, we expect a reduced response bias for voice stimuli since previous research has established that effect (e.g., Brookwell et al., 2013). Additionally,

interaction between stimulation condition (STG, occipital, and sham) and stimulation type (voice and tone) is examined.

If there is a significant effect of STG stimulation on response bias for voice stimuli only would imply that the effect is due to stimulating language specific areas in the STG. If the effect is significant for both voice and tone stimulus types, it would mean that stimulating the STG has significant effects on response bias for general auditory stimuli. No such effects are expected in the occipital and sham stimulation.

Secondary analyses will shed light on how task sensitivity is different in the stimulation conditions (STG, occipital, and sham) and across varying stimulus types (voices and tones). Questionnaires will be administered to gain further insights into subjective experience of tDCS application.

The current study is not only relevant from a neuroscientific perspective in that the role of the STG in auditory perception is further investigated. It is also important from a clinical and neuropsychological standpoint since tDCS as efficacious stimulation tool will be explored, providing additional basis for investigating tDCS as clinical treatment option. In examining a non-clinical population, AVH as a distinct construct from the psychopathological representation of hallucinations will be scrutinized.

Method

Participants

Recruitment took place via newsletters, posters, and advertisement in a university participant pool at University of Groningen in 2018 and 2019. Eventually, 79 participants were reached, 55 had to be excluded, resulting in a data set of 24 participants. Reasons for exclusion were not being reached again (n = 28), not being able to follow all three consecutive sessions in the pre-determined time frame (n = 8), inappropriate medication use (n = 9), drop-out (n = 7), failure to meet all the screening criteria, and to detect all stimuli in

the hearing test, or not being eligible for tDCS studies (n = 3). The resulting 24 participants (females = 12, males = 12), aged between 18-35 years (M = 25.75, SD = 4.00), met all inclusion criteria. No further participants were removed after data analysis.

Participation was voluntary and could be terminated at any time point without indication of reason. Reimbursement was allocated by means of a €20 gift voucher and, if needed, participation pool credit. Full debriefing took place at the end of the third session.

Materials

Consent and information letter, preliminary screening and hearing test

Before starting the stimulation sessions, a consent form and an information letter were handed out to and confirmed upon by the participants (see Appendix A and Appendix B, consecutively). Further, participants were asked to fill out a screening form regarding personal information and eligibility in tDCS studies. Not fulfilling the criteria in the preliminary screening served as exclusion criteria. The screening forms can be found in Appendix C.

To assess participants hearing ability, the Siemens HearCheck Screener was used, which is a simple, safe and fast method of screening for hearing loss (Fellizar-Lopez et al., 2011). The task consisted of three tones at 1000Hz (55dB HL, 35dB HL, 20dB HL) and three tones at 3000Hz (75dB HL, 55dB HL, 35dB HL), which were presented to each ear. Participants were asked to detect each tone by raising their hand. If one tone remained undetected, the participants were immediately excluded from further participation.

Transcranial Direct-Current Stimulation

Transcranial direct-current stimulation was applied using a DC Stimulator Plus (NeuroConn), between two electrodes of 25cm² (5x5cm). The electrodes were placed in saline-soaked sponges with 0.9% NaCl, and delivered a current of 1.5mA in the STG and occipital condition and in the sham condition a current of 0.002mA, with a current density of

0.06mA/cm^2. The electrode on the scalp delivered a positive, anodal, current. The cathodal electrode, delivering a negative current, was placed on the ipsilateral upper arm, approximately in the middle between the shoulder and elbow and served as reference electrode.

To determine the exact location of the anodal electrode, the international 10-10 electroencephalogram system was utilized. The 10-10 system is an internationally recognized system to determine and apply the location of electrodes on the scalp in the context of EEG research (American electroencephalographic society guidelines for standard electrode position nomenclature, 1991). To ensure stability of the electrodes, rubber bands were used.

Electrode placement and current strength in the different conditions. In the STG condition, the anodal electrode was located over the posterior temporo-parietal cortex, which is defined as CP5 based on the 10-10 EEG system. To locate CP5, the vertex was marked (site Cz in the 10-10 system), which was determined by the midpoint between the inion and nasion and the midpoint between the left and right pre-auricular, as well as by overall scalp measurements in deciles laterally and posteriorly to CP5.

To locate the occipital cortex in the occipital condition, electrode site Oz of the 10-10 system was used which defines the primary visual cortex. Measuring one decile vertically from the inion helped to indicate the location of this electrode site.

During sham stimulation the electrodes were placed as in the occipital condition for half of the participants, while the electrodes were placed as in the STG condition for the other half of the participants. Average strength of the current was 0.002mA, while it was 1.5mA in the active stimulation conditions. Thus, this current strength and the duration of stimulation in the sham condition were too low to have reached the cortex and subsequently no changes in excitability could have been induced.

Impedance levels. If impedance levels reached ≥ 55Ω after starting the stimulation, the session was terminated and restarted as quickly as possible. For one participant, this situation occurred during each of the three sessions, probably due to arm shape or dense hair. In this case, more saline was added to the sponges and the session was restarted immediately.

In the sham condition, tDCS stimulation was only applied shortly (for 30 seconds) and the rest of the session (for 870 seconds) consisted of regular pulses. These pulses served to control for impedance levels to discover electrode disconnections and insufficient electrode contact. Additionally, it was ensured that stimulation did not exceed 120 seconds (s) as to prevent inducing any changes in cortical excitability.

Double-blinded and counterbalanced. The researchers involved in data collection were unaware which session functioned as sham stimulation and which as active stimulation. This was achieved utilizing codes specifying the nature of the conditions (sham or active), which were mentioned in the tDCS handbook and were implemented in the tDCS equipment. In that way, counterbalanced order of the sessions was ensured as well as double-blinding of participant and experimenter. The differences in electrode positions in the different conditions might have revealed some information to the experimenter on which condition was used (for example, if the electrodes were at the same head position in two sessions, one of the sessions must have been the sham condition). Nevertheless, this implies only a 50% chance of knowing which condition was the sham condition and can still be considered blinded. After the third session, the experimenters had to indicate which session they thought was the sham stimulation, including a confidence rating. These outcomes were not further explored since they were not of importance for the present study.

Auditory signal detection task

The signal detection task was programmed in Matlab (Psych toolbox) and consisted of two conditions: the voice condition, in which participants were asked to listen to voice stimuli

embedded in pink noise, and the tone condition, in which participants were asked to listen to pure tones embedded in pink noise. All participants were asked to engage in two blocks of voice detection and two blocks of tone detection in one session, with each block incorporating 36 stimulus present trials (voice or tone) and 24 stimuli absent trials (only pink noise). This resulted in a total of 240 trials in each session (4 blocks × 60 trials).

Using Audacity 2.1.1 (AudacityTeam, 2015), pink noise was created at a comfortable hearing level (~70dB). Each of the bursts of pink noise lasted 3.5s, followed by 1.5s of silence, during which the participants were asked to respond via a button press (indicating yes/no) whether they thought a target signal was present. The pink noise was identical across all sessions and participants.

The voice condition. The voice stimulus used was the same voice stimulus as used in Barkeley et al. (2007) and Moseley et al. (2014), namely a male voice reading from an instruction manual in a way that the spoken words were incomprehensible. The voice clips were segmented into 1s clips, as it was done in previous research (Moseley et al., 2014). This resulted in a total of 10 separate voice clips, which were repeated an equal number of times in each experimental session and in a random order.

The tone condition. Using Audacity 2.1.1, three 200 milliseconds (ms) tones with a sinusoidal waveform separated by 200ms were created, forming 10 clips of 1s (AudacityTeam, 2015). The frequency of the voice and tone stimuli were identical, ranging from 128Hz-145Hz, which was analyzed using Praat 6.0.28 (Boersma, 2022). The 10 tone clips were repeated an equal number of times in each experimental session and in a random order.

Detection rate. The voice and tone stimuli were calibrated at three separate volumes, each of it were presented at equal frequency in the bursts of pink noise. The volumes were set in a way that detection rate was 25%, 50%, and 75%, as in previous studies (Moseley et al.,

2014). Each of these volume levels appeared in 10 trials per block. To ensure that participants were able to detect at least some stimuli, six trials in a block were included with a detection rate of 95%, previously determined by a piloting study. To prevent habituation to the stimuli, the voice and tone stimuli started after 1s, 1.5s, or 2s, which was randomly selected in an equal number of times in each block.

Taken together, each block consisted of 60 trials, with 10 stimuli at a detection rate of 25%, 10 stimuli at a detection rate of 50%, 10 stimuli at a detection rate of 75%, and 6 trials at a detection rate of 95%. Thus, there were 36 trials in which a signal (voice or tone) was present (signal present), leaving the remaining 24 trials in each block without a signal, thus only with pink noise (signal absent). The intensity of the voice and tone stimuli and the pink noise was identical for all participants.

Questionnaire about tDCS perception

After completing the third session, participants were asked to fill in a questionnaire reporting on their experience during tDCS stimulation. Participants had to rate their experience in all three sessions on a 5-point rating scale, 1 (*not at all*) to 5 (*severe*), indicating their amount of discomfort (e.g., “headache”). This questionnaire can be found in Appendix C. They were moreover provided with the option to report on any other complaints during stimulation outside of the questionnaire.

For the purpose of completeness, Appendix C additionally entails questionnaires about the experience after the tDCS sessions and about sham efficacy including a confidence rating that the participants were asked to complete. These outcomes were not of interest for the current study and are thus not further discussed. After finalizing all questionnaires, participants were once more given the opportunity to report on any difference they noticed. Some of these statements are included as to gain a more exhaustive understanding of subjective experience of tDCS.

Procedure

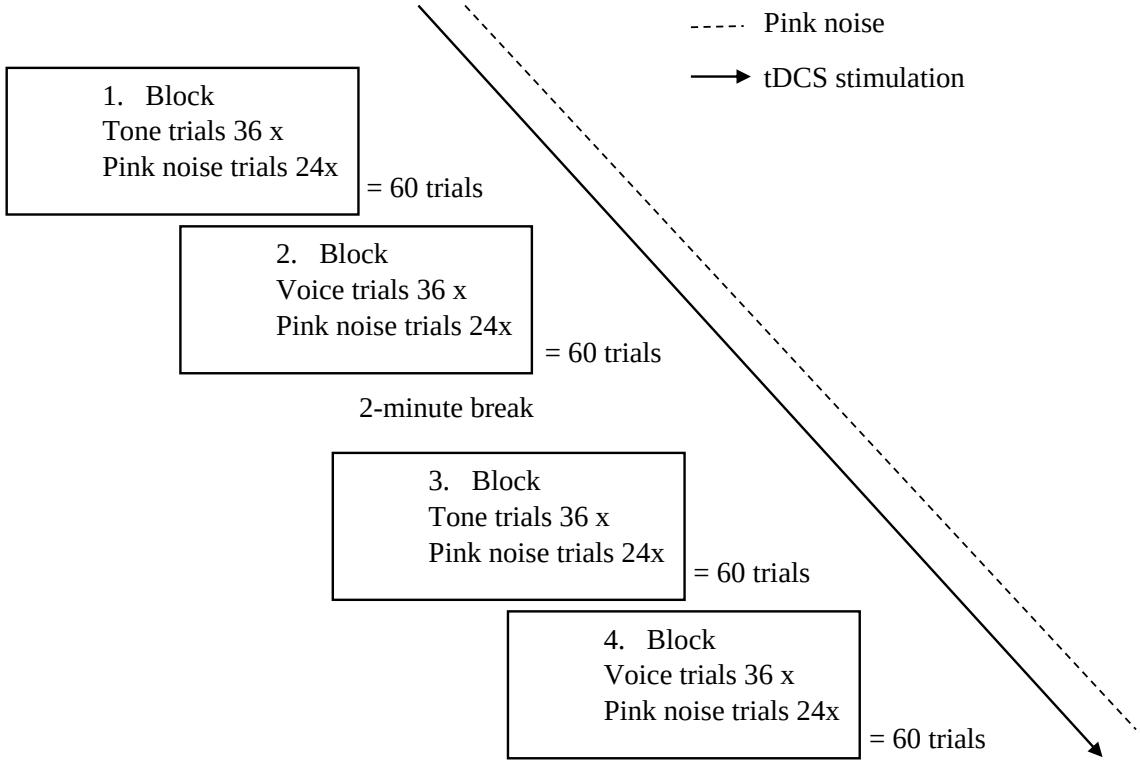
Firstly, participants underwent the screening procedure via email or telephone and the details were verified upon arrival. In total, participants were asked to come to the lab for three consecutive sessions, separated by no less than 4 days and no more than 10 days. The starting time of each session was controlled for, so that each subsequent session began within 90 minutes of the first session. Testing took place in a darkened room on a desktop computer and stimuli were presented via Creative EP-630 earphones.

At the beginning of the first session, participants completed the hearing test. Upon completing this test without any mistake, the session began. Thereafter, the tDCS equipment was placed on the scalp and the upper arm as described above. Participants were asked to complete five practice trials of voice and tone detection. If necessary, more practice trials were administered.

In the STG and occipital condition, the procedure was identical. The session began with applying tDCS stimulation for 916s. The current faded in for 8s, then full tDCS stimulation followed, and after 308s the auditory signal detection started. The task lasted for 600s, during which tDCS stimulation was applied. A fade-out of 8s tDCS followed. Participants were asked to remain seated quietly for the beginning of the session until the signal detection task started. After the first two blocks, participants did a 2-minute break while having the electrodes removed from the scalp. Thereafter, they were asked to fulfill the third and fourth block of signal detection. In total, each session consisted of four blocks of signal detection task with tDCS, summing up to a total duration of 916s per session. A schematic representation of an example STG and occipital session can be found in Figure 1.

Figure 1.

Schematic Representation of Signal Detection Task during tDCS in STG and Occipital Condition.



Note. Transcranial direct-current stimulation was turned on 308s before onset of the first block of the signal detection task (including fade-in of 8s), lasted during the whole procedure of the signal detection task for 600s, and faded out for 8s in the end. This resulted in a total of 916s tDCS stimulation, during which pink noise was presented.

In the sham stimulation, as opposed to the experimental conditions, tDCS stimulation was applied for 30s (plus 8 seconds fade-in and 8 seconds-fade out) and the remaining 870s consisted of regular pulses sent at 550ms, at 110µA over 15ms (peak current for 3ms).

Participants were given the opportunity to voice any experience of discomfort during tDCS at any time. At the end of the third session, participants were asked to complete the perception of tDCS questionnaires. Full debriefing took place and a 20€ voucher was handed out.

Design

The design employed was a 3x2 within-subjects analyses of variance (ANOVA) with dependent variable response bias and within-subject variable stimulation condition and stimulus type. Response bias, analogous to the theoretical externalizing bias, represents the willingness of participants to respond to auditory stimuli (i.e., voices or tones) in ambiguous situations (such as when pink noise is presented) in signal detection tasks.

The first within-subject variable was stimulation condition of the different sites (STG, occipital, or sham). All participants took part in each of the three sessions in a counterbalanced order to ensure that all six orders were represented equally in the sample. A random number generator was used to randomly assign the participants to fulfill the three conditions in one of these six orders.

Stimulus type (voice, tone) functioned as second within-subject variable. In each session, two blocks of voice and tone detection were presented, leading to a total of 240 trials in each session. These blocks were partially counterbalanced, in that 50% of the participants were presented with the order voice-tone-voice-tone, and the other 50% were presented with the order tone-voice-tone-voice. In that way, practice effects were prevented that could have been arisen due to presenting the same blocks after each other (e.g., voice-voice-tone-tone).

Task sensitivity was investigated as dependent variable in a 3x2 within-subject analyses of variance with within-subject factors stimulation condition and stimulus type, and their interaction.

Data analysis

Before analyzing the data, trials were removed in which participants did not respond to the presented stimuli at all (i.e., no yes/no button press was recorded), $M = 6.13$, $SD = 5.169$. The maximum number of trials that were removed per participant was 17 out of 240 trials, which was the case for one participant only. It was decided to include every participant in the main analysis since the number of removed trials per participant was < 80%, indicating that each participant engaged with the auditory signal detection task fully.

By utilizing the DC Stimulator Plus (NeuroConn) handbook, the coded sessions for each participant were assigned to the corresponding stimulation condition, either STG, occipital or sham. Thereafter, the statistical software SPSS Statistics for Windows, version 25 was employed to calculate hit rate and false alarm rate across all stimulation conditions and stimulus types (IBM Corp. Released, 2017). Within RStudio (RStudio Team, 2020), the signal detection theory (SDT) parameters response bias and task sensitivity were calculated for each participant by employing an R-script programmed by Peter Moseley (P. Moseley, personal communication, December 3rd, 2021).

The R-script was based on the formulas defined by Stanislaw and Todorov (1999): the formula $\beta = e^{\left\{\frac{Z(FA)^2 - Z(H)^2}{2}\right\}}$ was utilized to derive at response bias, while $d' = Z(H) - Z(FA)$ served to calculate task sensitivity. *Z(FA)* corresponds to the standardized false alarm rate (proportion of trials in which a participant erroneously responds that a stimulus was present even though no stimulus was presented), while *Z(H)* corresponds to the standardized hit rate (proportion of trials in which a participant correctly detected a stimulus type when it was actually presented). In that way, a lower β value refers to a liberal way of responding to stimuli; so, participants with a lower β value tend to erroneously detect voices or tones embedded in noise even though none are actually presented more often than those with a higher β value.

The values for β and *d'* were used as dependent variables in a repeated measures ANOVA, with stimulation condition and stimulus type as within-subject factors within SPSS (IBM Corp. Released, 2017) to investigate our primary and secondary hypotheses, respectively. In case of any significant outcomes of the repeated measures ANOVA, post hoc-pairwise comparisons using Bonferroni correction were employed.

To account for the subjective experience of tDCS, mean responses of the questionnaires regarding the participants' tDCS experience were calculated and some individual statements about complaints outside of the questionnaires were examined.

Results

Firstly, the main hypothesis investigated whether response bias *(β)* was lower in the STG condition compared to the other two conditions (occipital and sham) for stimulus type (voice and tone). Examining boxplots, four individuals were identified as outliers across stimulation conditions. It was decided to keep these data within the analysis in order to preserve valuable information. Mauchly's Test of Sphericity revealed that the assumption of sphericity had not been violated for response bias, neither for stimulation condition ($\chi^2(2) = 0.751$, $p = .687$), nor for the interaction between stimulus condition and stimulus type ($\chi^2(2) = 3.514$, $p = .173$). Q-Q plots and the Shapiro-Wilk test revealed that response bias was not normally distributed across the stimulation conditions and stimulus types (all p's $< .001$). Since repeated measures ANOVA are fairly robust against violations of normality and only require approximately normally distributed data, it was decided to perform a frequentist repeated measure ANOVA nonetheless. Additionally, due to the nature of the current study employing a within-subject design, participants function as their own control condition which provides baseline scores across condition.

Descriptive statistics are provided in Table 1. Figure 2 displays standard errors along

the sample means as a measure of variance and the accuracy to which our sample means represent the true population means.

Table 1.

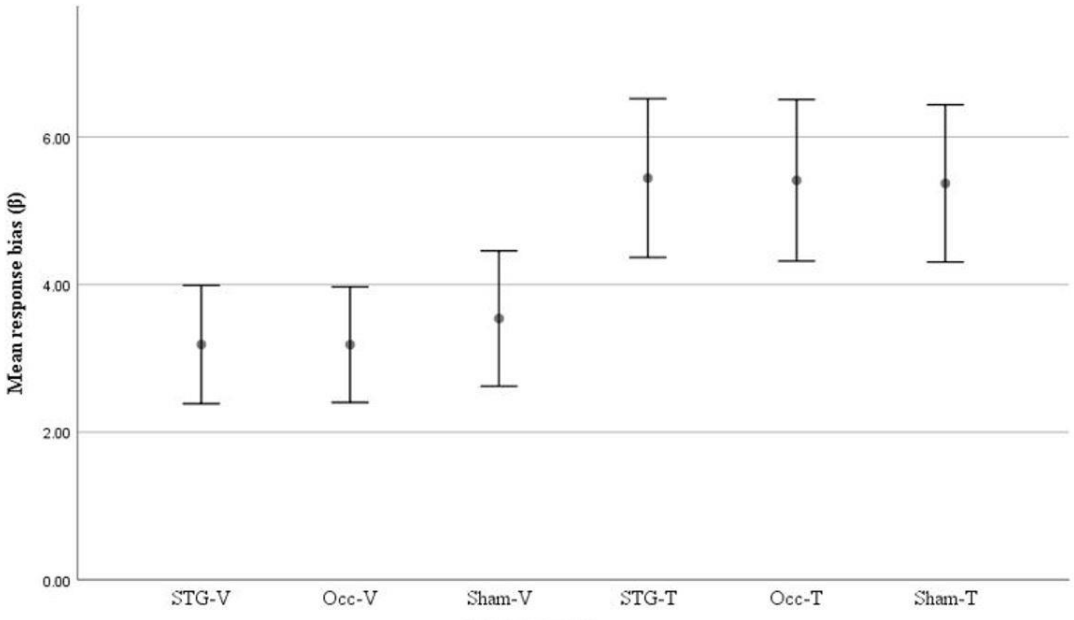
Descriptive Statistics of Response Bias (ß) and Task Sensitivity (d') across Stimulation Condition (STG, Occipital, Sham) and Stimulus Type (Voice and Tone).

Stimulation condition – stimulus type	Descriptive Statistics			
	ß		*d'*	
	M	*SD*	*M*	*SD*
STG – voice	3.19	3.93	1.23	.80
Occ – voice	3.18	3.84	1.27	.95
Sham – voice	3.54	4.5	1.4	.98
STG – tone	5.44	5.27	1.42	1.04
Occ – tone	5.41	5.36	1.57	1.17
Sham – tone	5.37	5.23	1.7	1.16

Note. $N = 24$. M = mean, SD = standard deviation. STG = superior temporal gyrus, Occ = occipital cortex, Sham = sham stimulation.

Figure 2.

Error Bars of Mean of Response Bias (β) across Different Stimulation Conditions (STG, Occipital, Sham) and Stimulus Type (Voice and Tone).



Note. Error bars +/- 1 standard error of mean (SE). Stimulation condition (STG, occipital, sham) – stimulus type (voice and tone). V = stimulus type voice. T = stimulus type tone.

Repeated Measures ANOVA: Response Bias (*β*)

To examine the main hypothesis, a repeated measures ANOVA was applied. The effect of stimulus condition and the interaction between stimulation condition and stimulus type yielded non-significant results, while stimulus type was significant. The results of the analysis are presented in Table 2. Effect sizes are evaluated by partial effect sizes of 0.01 indicating small effects, 0.06 indicating medium effect size and 0.14 or higher representing large effect size.

Table 2.

Outcomes of Repeated Measures ANOVA of Dependent Variable Response Bias, Within-subject variables Stimulation Condition and Stimulus Type, and Their Interaction.

Within-subject factors	Repeated Measures ANOVA				
	N	*df*	*F*	*p*	ηp^2
Stimulation condition	24	1	0.016	.098	.001
Stimulus type	24	1	9.840	.005*	.300
Stim. condition x stim. type	24	1	0.063	.939	.003

Note. Stim. condition x stim. type = interaction stimulation condition and stimulus type. ηp^2 = partial effect sizes. *. $p < .05$ (one-tailed).

Post-hoc pairwise comparisons between the different stimulus types voice and tone were performed using Bonferroni correction. The response bias was shown to be lower for voice stimuli compared to tone stimuli with a mean difference of -2.105 ($p = .005$).

Given that the data was not normally distributed, it was decided to repeat the repeated measures ANOVA by applying natural log transformation on the response bias data as an inspection of the results. No significant result was found, neither for stimulation condition ($F(2,46) = 0.045$, $p = .956$, $np = .002$), nor interaction between stimulation condition and stimulus type ($F(2,46) = 0.063$, $p = .939$, $np = .003$). A significant result was found for stimulus type ($F(1,23) = 12.446$, $p = .002$, $np = .351$). For interpretation, outcomes of the initial repeated measures ANOVA, without transformed data, were utilized.

Repeated Measures ANOVA: Task Sensitivity *d'*

To test whether task sensitivity was different in the STG condition compared to the other two conditions occipital and sham, another repeated measures ANOVA was performed with task sensitivity as dependent variable and stimulation condition and stimulus type as within-subject variables within SPSS. By examining boxplots four outliers were revealed,

which were decided to be kept within the analysis, as to preserve information. Mauchly's test of sphericity revealed that sphericity is violated for stimulation condition ($X^2(2) = 7.062$, $p = .029$), therefore a Huynh-Feldt correction was applied for stimulation condition ($\varepsilon = 0.832$). Sphericity was not violated for the interaction stimulation condition and stimulus type ($X^2(2) = 0.665$, $p = .717$), thus no correction was applied. Shapiro-Wilk test statistics revealed that the dependent variable task sensitivity was not normally distributed in all conditions (i.e., stimulation condition STG and stimulus type voice: $W(24) = .868$, $p = .005$; stimulation condition STG and stimulus type tone: $W(24) = .900$, $p = .022$).

The repeated measures ANOVA yielded non-significant results for stimulation condition ($F(1.664, 46) = 0.389$, $p = .642$, $\eta p^2 = .17$) and for the interaction stimulation condition and stimulus type ($F(2, 46) = 0.346$, $p = .709$, $\eta p^2 = .015$). A significant effect was reported for stimulus type ($F(1, 23) = 4.244$, $p = .051$, $\eta p^2 = .156$).

Post hoc-pairwise comparisons using Bonferroni correction revealed a significant difference in task sensitivity between voice and tone stimuli, namely showing reduced task sensitivity of -0.265 for voice stimuli averaged across the three levels of stimulation condition ($p = .051$).

Due to the data not being normally distributed, additional repeated measures ANOVA utilizing natural log transformations within SPSS were employed. No significant results were found for stimulation condition ($F(2, 46) = 0.184$, $p = .833$, $np^2 = .008$). Significant effects were found for stimulus type ($F(1,23) = 6.107$, $p = .021$, $np^2 = .210$) and the interaction between stimulus condition and stimulus type ($F(2,46) = 10.29$, $p = .000$, $np^2 = .309$). Outcomes of the repeated measures ANOVA without transformed data were consulted for interpretation.

Descriptive Statistics and Individual Statements: tDCS Perception

To assess the subjective experience of tDCS perception during stimulation, descriptive statistics were calculated and are represented in Table 3. Mauchly's test of sphericity revealed that the assumption of sphericity has not been violated ($X^2(2) = 1.627$, $p = .443$).

Table 3.

Descriptive Statistics of tDCS Perception Questionnaire. Level of Discomfort rated from 1 (not at all) to 5 (severe).

Stimulation Condition	*M*	*SD*
STG	1.82	0.46
Occipital	1.78	0.43
Sham	1.75	0.48

Note. *M* = mean, *SD* = standard deviation.

Two items, being "tingling where the electrode had been" and "itching where electrode had been" seemed to cause the most discomfort for the individuals, with a total of 25% and 26.7% indicating moderate discomfort and 11.7% and 18.3% of the participants indicating severe discomfort, for the two items respectively. Participants were additionally given the option to report on complaints during tDCS outside of the questionnaire. One participant reported sensation of eyestrain and trouble focusing after the first session (after encoding: STG condition), and after the third session (occipital session) the experience of tinnitus was described.

After completing the remaining questionnaires, participants could report on further differences they noticed during and between stimulation conditions. One participant described the discomfort as being worse when electrodes were placed in the back of the scalp regardless of stimulation session, another one experienced a stronger pulse in the STG session, while

another participant experienced the occipital session as very tingling and the STG session as very itchy.

Discussion

The present study intended to expand our knowledge on whether transcranial direct-current stimulation (tDCS) over the superior temporal gyrus (STG) modulates the experience of auditory verbal hallucinations (AVH) in healthy individuals. Specifically, it was investigated whether the response bias, which corresponds to the theoretical externalizing bias and signifies the willingness to respond to stimuli in ambiguous situations, is lower when anodal tDCS is applied over the STG while healthy participants were asked to detect speech stimuli (namely, voice and tone stimuli) in a signal detection task.

The results of the repeated measures ANOVA contradicted this hypothesis in that no evidence was found for the response bias being significantly lower in the STG condition than in the occipital and sham condition, neither for voice nor for tone stimuli. Our findings did further not provide evidence for a significant interaction effect between stimulation condition and stimulus type. It appears that the anodal tDCS did not have the anticipated excitatory effect on the STG. Several reasons might account for this.

Firstly, the sample was recruited from the non-clinical population and it was not accounted for hallucination-proneness. Previous studies made use of questionnaires such as the Launay–Slade Hallucination Scale (LSHS-R) to assess how prone individuals are to experiencing both auditory and visual hallucinations (McCarthy-Jones et al., 2011). This questionnaire was utilized by, among others, Moseley et al. (2016b) to subdivide participants into either being high or low in hallucination-proneness. They found a reduced response bias for participants high on hallucination-proneness compared to those low on it. In the current study no distinction was made between these two groups, hence it might be that some individuals were more likely to experience auditory hallucinations, and consequently more

likely to showing a reduced response bias, while others did not have that tendency to experience hallucinations, thus not being likely to show a reduced response bias. This is mirrored in the current data by considering the outliers (n = 4), highlighting exceptional variation in expression of response bias between individuals. It is to be noted however, that findings about how the response bias changes in hallucination-prone and none hallucination-prone individuals are still inconclusive, in that some studies could not find a difference in response bias between these two groups (McKague et al., 2012).

Considering the population of healthy individuals further, research has found that tDCS application, both anodal or cathodal, seems to be only effective for healthy individuals when the task at hand is familiar and several follow-up stimulation sessions take place (Dockery et al., 2009). In that way, neuronal connections can be formed and strengthened over time. This might explain why stimulating the STG in our healthy sample did not influence their way of responding to ambiguous speech stimuli in the auditory signal detection task. The tasks used by Dockery et al. (2009) concerned tackling complex planning abilities, while in our study the task was less demanding (responding to stimuli). However, the set-up and procedure of the auditory signal detection task may still be considered unfamiliar, limiting effectiveness of tDCS. It seems essential for efficacious tDCS application to utilize adequate tasks and to include follow-up tDCS sessions.

Another aspect worth considering when interpreting our results is the mechanism of transcranial direct-current stimulation (tDCS). It is possible that tDCS is in fact not an adequate tool to modulate auditory cortices. Kunzelmann et al. (2018) have applied tDCS over the left posterior temporal cortex to examine modulatory properties of tDCS in terms of changes in auditory evoked potentials (AEP). They could neither detect a difference in AEPs between sham and anodal tDCS of the auditory cortex, nor between measurements before, during and after stimulation session. Hence, tDCS might not be considered a suitable tool in

modulating the auditory cortex.

Yet, other studies have found an effect on tDCS on the auditory cortex. This inconsistency in the literature might be due to the high variability across tDCS studies. On the one hand, some research that has found tDCS to be effective has utilized a current of 1.25 mA for 11 minutes (Zaehle et al., 2011), while Kunzelmann et al. (2018) applied tDCS with 1 mA for 20 minutes and did not find any effect of tDCS. Adding to this, the current study applied tDCS for 2mA over 15 minutes, failing to find any modulating effect of tDCS. This inconsistency in current application points to the importance of optimizing and standardizing tDCS set-up and procedure, including stricter guidelines for current intensity and duration to ensure efficacious stimulation.

Inspecting tDCS mechanism further, it is sensible to consider neuronal baseline activity of the desired area. tDCS utilizes direct electrical current to stimulate underlying brain areas. The effectiveness of that stimulation depends on baseline activity of the neuronal connections. Research by Homan et al. (2012) has found repetitive transcranial magnetic stimulation (rTMS) to be most effective in reducing hallucinations in schizophrenic patients when individuals already possessed hyperactivity in the STG. Due to the similar mode of action of rTMS and tDCS, similar effects can be expected for tDCS efficacy (Čukić, 2020). Being hallucination-prone also implies altered STG activity (Hughdal, 2009), which in turn could have been modulated by tDCS application. If the participants in our study were non-hallucinating and thus did not have pre-existing altered STG activity, tDCS might not have stimulated and excited the STG as expected. Consequently, no reduced response bias could have been detected in the STG condition, which is in line with the data presented in this study.

Other reasons for why tDCS stimulation might not have excited the STG as desired could be the involvement of other brain networks that were active simultaneously and

competing with tDCS' effectiveness. Previous studies have employed decision making tasks, such as the moving dot task (MDT), which can be considered similar to the signal detection task used in the current study, since both tasks tackle perceptual decision-making (Georgiev et al., 2016). It was discovered that the dorsolateral prefrontal cortex (DLPFC) is highly active during this task as it is responsible for goal-directed decision-making processes. It may be possible that in our study participants possessed high DLPFC activity due to the nature of the task of making decisions, which might have overshadowed and hindered the effect of tDCS on the STG, thus not inducing a change in response bias.

Taken together, tDCS in the present study did not seem to modulate STG activity, explaining the absence of a reduced response bias in STG condition. Reasons for this might be that in the current sample hallucination-proneness was not accounted for, as well as inappropriate tDCS application. It appears questionable whether tDCS constitutes a suitable mechanism to excite auditory cortices. Missing neuronal baseline effects coupled with competing involvement of other neuronal networks might serve was further explanation for the absence of an effect.

Based on the non-significant finding, as well as the multitude of alternative explanations, we cannot assume that the tDCS in our study has had the desired excitatory effects on the STG, therefore limiting our conclusions regarding whether tDCS stimulation of the STG is voice or non-voice specific. However, our analysis yielded evidence for a significantly lower response bias for stimulus type voice, regardless of stimulation condition. Since we cannot conclude that the tDCS application has exhibited excitatory effects on the STG, this reduced response bias to react to voice stimuli in ambiguous situations might be due to the tendency to perceive and react to voices that is innate to everyone. Voices play an essential role in our social and cultural environment (Belin, 2004). This everyday exposure to voices may serve as an explanation why participants in ambiguous situations still tend to

detect a voice, even though none was actually presented.

Secondary analyses investigated whether task sensitivity (the ability to distinguish between auditory stimuli and noise) was different in the three conditions. No significant difference was found, neither for stimulation condition nor for the interaction between stimulation condition and stimulus type. This might be due to the absence of efficacious tDCS as previously discussed.

Considering stimulus type, a significantly reduced task sensitivity was found for the stimulus type voice, regardless of stimulation condition. Participants seem to be less accurate in distinguishing voice stimuli from noise. Since it is not possible to conclude from the given findings that tDCS has modulated STG activity, we cannot assume that the change in task sensitivity concerning voice stimuli was due to altered STG activity.

Alternatively, a reduced signal-to-noise ratio (SNR) indicating higher level of noise than level of signal (in this case, voice stimuli), might serve as explanation as to why distinguishing between voices and noise was challenging for participants. This reduced SNR coupled with the tendency to over-detect voice stimuli embedded in noise (response bias) as shown in the current data and previous research (tae.g., Barkus et al., 2007; Moseley et al., 2014; Moseley et al., 2016b), might serve as explanation for the demonstrated reduced task sensitivity for voice stimuli.

Research by Moseley et al. (2014) has revealed similar results in that hallucinating individuals demonstrated a reduced response bias coupled with a reduction in sensitivity for voice stimuli. In their study, STG activity was altered by tDCS, hence leading to the conclusion that stimulation of the STG induces changes in response bias while at the same time making it more difficult to distinguish between actual stimuli and noise. Further clarification is required in order to comprehend how task sensitivity varies across hallucinating and non-hallucinating individuals.

To draw conclusions about the subjective experience of tDCS, participants rated their experience of discomfort during tDCS application in the three stimulation sessions, and were additionally given the opportunity to report on their experience outside of the questionnaires. As demonstrated in the descriptive statistics, no outstanding high level of discomfort was noted in any of the three different conditions. Tingling and itching sensations seem to elicit the most discomfort for the individuals. This is in line with findings by Fertonani et al. (2015) investigating over 600 transcranial electric stimulation (tES) sessions, and pointing out itching as one of the most prominent feelings of discomfort during tES.

Some individuals reported uncomfortable sensations in the STG condition, such as very itchy sensations and stronger pulses. Importantly, the current study was blinded so the participants did not know which session was the experimental condition when making these statements. In general, tDCS treatment can be considered safe and painless. However, these subjective statements point to a tendency of discomfort during experimental tDCS and high inter-individual variability which is important to consider for potentially implementing tDCS as clinical treatment option.

Limitations and Future Directions

Analytical Limitations and Future Directions

This study has some limitations that deserve to be discussed. Firstly, it is to be noted that the sample size was small (n = 24) and our data was not normally distributed, limiting statistical power. Hence, the presented results should be interpreted with caution. We decided to employ a frequentist repeated measures ANOVA within SPSS nonetheless since this analysis is fairly robust against violations of normality. The given data does not demonstrate a statistically significant effect for response bias in the stimulation condition. Yet, our results point to a marginally significant effect of response bias in stimulation condition (p = .09).

This trend was not investigated further since the current study determined statistical significance at a *p*-value of .05. This remains to be uncovered by future research.

Given that the data was not normally distributed, log transformation was applied as an inspection of the results. Repeating the analysis with log transformed data for response bias, yielded similar results to those of the analysis without log transformation. Interestingly, when applying log transformation on the task sensitivity data, the repeated measures ANOVA yielded a significant effect for the interaction between stimulation condition and stimulus type ($p = .000$), deviating from the non-significant result of the initial analysis. Since investigating the log transformed data was not an essential part of this study and research points to drawbacks in utilizing log transformations, stressing cautious application of it, these findings were not further explored (Feng et al., 2014). Nonetheless, this significant result can be considered as an interesting avenue for future research efforts.

Theoretical Limitations and Future Directions

Potential limitations of the current study might be found in that no distinction between groups that are hallucination-prone and those that are not hallucination-prone was made. Including a clear distinction between these two groups is recommended in order to reach conclusive results about how the response bias as well as task sensitivity changes in different individuals. To do so will advance the understanding of how AVH is represented in different populations.

To further disentangle the concept and representation of AVH and the role of the STG concerning perception of auditory stimuli, future research should ensure to use tDCS in a sample sensitive to its effects. It has been suggested that individuals with already existing hyperactivity in the STG, profit more from rTMS treatment than those without pre-existing hyperactivity (Homan et al., 2012). Thus, accounting for underlying neuronal baseline activity by utilizing techniques such as resting perfusion measurement before tDCS appears to be

appropriate and is recommended (Homan et al., 2012). Ensuring effectiveness is especially important when tDCS is utilized as a clinical treatment option.

Adding to this, the questionnaires used in this study supported tDCS as safe treatment without severe side-effects, however highlighting individual differences in experiencing undesirable sensations such as “tingling” and “itching” that should be considered. It further became evident in our study protocols, that one participant was very negatively aroused due to personal issues. Since tDCS’ efficacy depends highly on the mental well-being of each individual during the session, it might be advisable to account for participants’ state prior to each session (Moseley et al., 2016a).

A key finding of the current study is that tDCS did not seem to exhibit any modulatory properties on STG activity. This finding points to the need for future research to include standardized research protocols with fixed guidelines on duration and intensity of the current utilized. Implementing stricter protocols is highly important to achieve reliable results about tDCS’ efficacy.

Although tDCS did not appear to have excited the STG, a distinction in perceiving voice and tone stimuli for both response bias and task sensitivity were found. This points to the existence of different perceptual mechanisms behind perceiving various types of auditory stimuli. Henceforth, future research efforts should further investigate the distinction between perceiving voice and tone stimuli and the potential involvement of different sub-areas of the STG while applying tDCS with the above-mentioned guidelines. In doing so, signal detection task parameters such as response bias and task sensitivity can further be elucidated.

Conclusion

The present study investigated whether the response bias, corresponding to the theoretical externalizing bias, is lower when anodal tDCS is applied over the STG compared to over occipital cortex or sham stimulation, while asked to detect either voice or tone stimuli.

We could not confirm that the response bias was significantly lower in the STG condition but we observed a significantly lower response bias for stimulus type voice, regardless of stimulation condition. Conclusions regarding the role of STG in the representation of AVH are limited due to the absence of tDCS effectiveness. However, healthy participants in general seem to have the tendency in ambiguous situations to over-detect voice stimuli, coupled with a reduced sensitivity for detecting these voice stimuli.

Important implications about the effectiveness of tDCS can be drawn from the present study. First and foremost, our findings add to the existing body of literature about tDCS and is in line with previous findings in that no difference is found between different stimulation conditions of tDCS. Additionally, tDCS application did not seem to have had the desired excitatory effect on STG activity and thus our results generate doubt about the effectiveness of tDCS in modulating the auditory cortex, confirming previous research outcomes.

Additionally, the effectiveness of tDCS may seem to differ between individuals and researchers should account for these factors before starting applying it. Furthermore, it is important to consider intra- and inter-individual differences and individualize tDCS sessions as well as current mental and physical well-being of the individual. Nevertheless, our study confirms tDCS as safe treatment without severe side-effects and thus points to its potential as a clinical treatment option.

Altogether, our findings provide valuable information about speech perception in healthy participants without tDCS modulation and serve as incentive for future research to apply tDCS with stricter guidelines to investigate the role of the STG in representation of AVH.

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Appendix A

Consent form

METc 2017.
Version 1.1
30.03.2018

university of groningen / umcg / neuroimagingcenter

A study into the role of specific brain regions in false auditory perceptions, using noninvasive brain stimulation

TOESTEMMINGSFORMULIER

Voor het medisch wetenschappelijk tDCS onderzoek

"Een onderzoek naar de functie van specifieke hersengebieden bij valse auditieve waarnemingen, met gebruik van niet-invasieve hersenstimulatie"

Wetenschappelijke titel: "Using transcranial direct current stimulation to investigate speech perception: a signal detection study"

- Ik ben naar tevredenheid over het onderzoek geïnformeerd.
- Ik bevestig dat ik bijbehorende schriftelijke informatie heb gelezen, ik begrijp de informatie.
- Ik ben in de gelegenheid gesteld om aanvullende vragen over het onderzoek te stellen.
- Mijn vragen zijn naar tevredenheid beantwoord.
- Ik heb voldoende tijd gehad om goed over deelname aan het onderzoek na te kunnen denken.
- Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef op te geven.
- Ik ga akkoord dat indien er tijdens het onderzoek onverwachte medisch relevante afwijkingen worden gezien, ik hiervan op de hoogte wordt gesteld door mijn behandelend arts.
- Ik geef toestemming om mijn gegevens op de onderzoeklocatie nog 15 jaar na dit onderzoek te bewaren. Mogelijk kan dit later nog voor meer onderzoek wordt gebruikt zoals in de informatiebrief staat.

- **Ik stem toe met deelname aan het onderzoek**

Ik geef WEL/NIET* toestemming om mij te benaderen voor deelname aan eventueel toekomstig vervolgonderzoek. (*s.v.p. doorstrepen wat niet gewenst is)

Ik stem toe met deelname aan het onderzoek.

Naam:
Geboortedatum:

Handtekening: Datum:

Ondergetekende verklaart dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Hij/zij verklaart tevens dat een voortijdige beëindiging van de deelname door bovengenoemde persoon geen nadelige

effecten zal hebben voor deze persoon.

Naam:

Functie:
Handtekening: Datum:

Appendix B

Information letter

METc 2017.645
Versie 1.1
30.03.2018

university of groningen / umcg / neuroimagingcenter

De functie van specifieke hersengebieden in foutieve geluidsperceptie met tDCS

Informatiebrief

Groningen, …..2018

Betreft het medisch wetenschappelijk onderzoek:

"Een onderzoek naar de functie van specifieke hersengebieden bij foutieve auditieve waarnemingen, met gebruik van niet-invasieve hersenstimulatie"

Hartelijk dank voor uw belangstelling in dit onderzoek dat bij het Neuro Imaging Center in samenwerking met de afdeling Psychologie van de Durham University, Engeland wordt uitgevoerd.

Dit onderzoek richt zich op hoe de hersenen reageren tijdens het horen en reageren op geluiden. Met de bedoeling toekomstige behandelingen te ontwikkelen voor psychiatrische stoornissen die te maken hebben met het verwerken van taal en auditieve hallucinaties.
In de volgende pagina's van deze brief hebben wij een lijst met vragen en antwoorden opgesteld die u zoveel mogelijk informatie geven over het onderzoek. Als u nog vragen heeft kunt u altijd contact opnemen met de onderzoeker (contactinformatie vindt u onderaan de brief). Het is ook mogelijk contact op te nemen met een onafhankelijk arts die niet betrokken is bij het onderzoek maar wel van het onderzoek op de hoogte is en uw vragen kan beantwoorden.

Als u deel wilt nemen aan het onderzoek dan vragen wij u het bijgesloten toestemmingsformulier in te vullen, te ondertekenen en in de antwoordenvelop terug te sturen naar de onderzoeker. Ook nadat u het formulier heeft ondertekend kunt u zich altijd terugtrekken uit het onderzoek.

Nogmaals hartelijk dank voor uw interesse in dit onderzoek!

Met vriendelijke groet,

Dr. Branislava Curcic-Blake
Prof. Dr. André Aleman
NeuroImaging Center, Antonius Deusinglaan 2, 9713 AW Groningen

Tel. 050-3616395, e-mail: b.curcic@umcg.nl

Mogelijke vragen en antwoorden over het onderzoek

Wij vragen u vriendelijk aandachtig de onderstaande vragen en antwoorden door te lezen. Als u vragen heeft, neemt u dan contact op met dr. Branislava Curcic (contact informatie is onderaan de brief te vinden).

Wat is het doel van het onderzoek?

Het doel van het onderzoek is meer te weten te komen hoe onze hersenen actief zijn tijdens het ontvangen en reageren op geluiden. Deze kennis is belangrijk om toekomstige behandelingen te kunnen ontwikkelen voor mensen met psychiatrische stoornissen die te maken hebben met het verwerken van taal en auditieve hallucinaties. Er is evidentie dat magnetische hersenstimulatie (TMS) van taalgebieden hallucinaties kan verminderen. Stimulatie met tDCS is echter comfortabeler voor de patiënt. Wanneer bij gezonde deelnemers aangetoond kan worden dat tDCS invloed heeft op spraakwaarneming is de weg gebaand voor verder onderzoek naar tDCS als mogelijke behandeling.

Wie voert het onderzoek uit en wie zijn erbij betrokken?

Dr. Branislava Curcic-Blake voert het onderzoek uit in samenwerking met prof. dr. A. Aleman. Het onderzoek maakt deel uit van een onderzoek bij de afdeling Psychologie van de Durham Universiteit in Engeland. Zowel in Nederland als in Engeland zullen 108 vrijwilligers aan het onderzoek deelnemen.

Waar vindt het onderzoek plaats?

Het onderzoek vindt plaats in het NeuroImaging Center Groningen, Ant. Deusinglaan 2, 9713 AW Groningen.

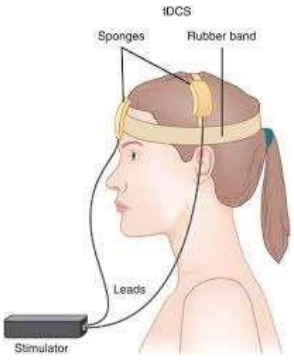
Hoe wordt het onderzoek uitgevoerd?

U zult worden gevraagd een eenvoudige taak over geluiden op de computer te doen waarbij wij u naar allerlei geluiden luistert en wij u vragen hieruit specifieke geluiden te herkennen.
Tijdens deze taak zal een bepaald deel van de hersenen worden gestimuleerd met een zwak electrische stroom, genaamd tDCS. Waarbij we langzaam het niveau van spanning onder de electrode op uw hoofd zullen wijzigen om te testen in hoeverre dit uw taakuitvoering beïnvloedt. Ook zult u dezelfde taken op de computer uitvoeren zonder hersenstimulatie.

Wat is transcranial Direct Current Stimulation (tDCS)?

Het experiment gebruikt een neurostimulatieve techniek, genaamd transcranial Direct Current Stimulation (tDCS). Met deze techniek wordt gedurende 15 minuten via twee electrodes een electrisch

stroompje gegeven. Eén electrode wordt op uw hoofd geplaatst, de andere electrode op uw bovenarm. De techniek is veilig en pijnloos, vaak voelen vrijwilligers een milde tinteling onder de electroden dit duurt meestal minder dan 1 minuut. Sommige proefpersonen hebben na stimulatie een kortdurende, lichte hoofdpijn.
Onderstaande foto's geven een beeld hoe neurostimulatie tijdens een sessie er voor u uitziet:



Hoe lang duurt de tDCS stimulatie?
Elke stimulatie duurt 15 minuten per sessie.

Hoe lang duurt het hele onderzoek?
Het onderzoek bestaat uit drie sessies, 1 sessie per week. In totaal 175 minuten. Elke sessie duurt 55 minuten, waarvan 15 minuten tDCS per sessie. Tussen de drie sessies zal minimaal 4 dagen, maximaal 10 dagen tijd zitten.

Is deelname aan het onderzoek gevaarlijk of heft het nadelen voor de gezondheid? Belangrijk om te weten is dat de effecten van tDCS tijdelijk zijn en al verdwenen zijn als de sessie is afgerond, het gaat hierbij om korte bijwerkingen zoals lichtehoofdpijn, misselijkheid of lichte duizeligheid. De stimulatie die wij toepassen zal geen auditieve hallucinaties buiten het onderzoek als effect hebben, echter als u enige zorg hierover hebt (ook na het experiment), neemt u dan contact op met Dr. Branislava Curcic-Blake, 050 - 361 6395 / b.curcic@umcg.nl

Indien ik onverhoopt schade ondervind door deelname aan dit onderzoek, ben ik dan verzekerd?
Het Universitair Medisch Centrum Groningen en de Rijksuniversiteit Groningen hebben een verzekering afgesloten die onverwachte schade dekt. In de bijlage bij deze brief treft u de volledige informatie aan over deze verzekering.

Wanneer kunt u niet deelnemen aan het onderzoek?

Vooraf aan het onderzoek vult u een veiligheidsvragenformulier in over neurostimulatie. Aan de hand van wat u heeft opgegeven beoordeelt de onderzoeker of uw gezondheid niet in gevaar wordt gebracht tijdens het onderzoek.

Er zijn een aantal criteria waaraan u moet voldoen om deel te kunnen nemen aan het onderzoek:

- U moet tussen 18 en 35 jaar oud zijn
- U bent rechtshandig
- U hebt geen gehoor problemen (Voordat de eerste tDCS sessie begint zal bij u een gehoortest worden afgenomen. Als blijkt dat u niet alle tonen kunt horen zult u niet deel kunnen nemen aan het onderzoek.
- U verstaat goed Engels
- Alle metalen objecten (bijv. oorbellen, piercings) en haarproducten (zoals gel of hairspray) moeten verwijderd zijn van uw hoofd en armen voordat u deelneemt.
- Geen (vermoeden van) zwangerschap
- Geen geschiedenis van epilepsie in de familie
- Geen (geschiedenis van) huidproblemen (bijv. eczeem)
- Als het voor u niet mogelijk is om aan na de eerste en na de tweede sessie binnen 4 of 10 dagen bij de volgende sessie aanwezig te zijn, dan kunt niet deelnemen aan het onderzoek.

Kan het onderzoek worden afgebroken?

U neemt geheel vrijwillig deel aan dit onderzoek. U kunt zich daarom op ieder moment, ook nadat u de schriftelijke verklaring voor toestemming tot deelname hebt ondertekend, en ook tijdens het onderzoek, terugtrekken zonder opgaaf van redenen. Wij verzoeken u vriendelijk dit zo snel mogelijk te melden aan de onderzoeker. Het is niet nodig dit de onderzoeker schriftelijk mee te delen. Deze beslissing zal geen nadelige effecten voor u hebben. Ook de onderzoeker kan besluiten het onderzoek af te breken. Hij/zij zal u dan vertellen wat de reden is dat het experiment werd afgebroken.

Hoe worden de gegevens geregistreerd?

Van de onderzoeksgegevens zal een aparte registratie worden aangelegd. Deze registratie is strikt vertrouwelijk. De gegevens worden met een codenummer verwerkt. Dus zonder vermelding van naam of andere persoonlijke gegevens. Alleen de onderzoeker en de coördinerend onderzoeker zullen in staat zijn om de gegevens aan u als persoon te koppelen. In publicaties zal uw naam niet terug te vinden zijn. Als u de toestemmingsverklaring ondertekent, geeft u toestemming voor het verzamelen, bewaren en inzien van uw gecodeerde gegevens. Uw gegevens worden dan 15 jaar bewaard.

Wordt een vergoeding gegeven en worden reis- en verblijfkosten vergoed?
Voor deelname aan het totale onderzoek (3 sessies) ontvangt u een vergoeding van € 25,- . Indien u reiskosten maakt om naar het onderzoekscentrum te komen, zullen deze worden vergoed op basis van het openbaarvervoertarief. Mocht u per auto komen, dan vergoeden wij u ook de parkeerkosten. Gezien de beperkte duur van het onderzoek worden geen verblijfskosten vergoed.

Hoeveel bedenktijd heeft u voor uw besluit om wel of niet mee te doen?
U hebt in principe een week de tijd om te beslissen of u aan het onderzoek deel wilt nemen. Als u meer bedenktijd wilt, vragen wij u contact op te nemen met ondergetekende. Maximaal krijgt u twee weken bedenktijd.
Als u besluit deel te nemen, verzoeken wij u de toestemmingsverklaring in te vullen en ondertekend op te sturen in bijgaande antwoordenvelop. De onderzoeker neemt na ontvangst van de papieren zo spoedig mogelijk contact met u op. Wij willen dan weten of u nog extra vragen heeft, alles uitleggen en informeren of u aan alle inclusiecriteria voldoet. Als alles duidelijk is, maken wij een aantal afspraken met u.

Kan ik onafhankelijke informatie krijgen over het onderzoek?
U kunt contact opnemen met een niet bij het onderzoek betrokken arts (dr. S. Van Belkum, s.m.van.belkum@umcg.nl, tel. 050-3612008). De onafhankelijk arts is niet direct betrokken bij het onderzoek en kan u op onafhankelijke wijze informeren.
Aan wie kan ik eventuele verdere vragen stellen?
Mocht u nog vragen hebben vóór, tijdens of na het onderzoek dan kunt u contact opnemen met Branislava Curcic-Blake, tel. 050-361-3616395, e-mail: b.curcic@umcg.nl,

We hopen u hiermee voldoende te hebben geïnformeerd en dat u geïnteresseerd bent in ons onderzoek.

Dr. Branislava Curcic-Blake
Prof. Dr. André Aleman

Contactinformation:
NeuroImaging Center, Antonius Deusinglaan 2, 9713 AW Groningen
Tel. 050-3616395, e-mail: b.curcic@umcg.nl

Mededeling inzake verzekering voor proefpersonen voor het medisch wetenschappelijk onderzoek:

"A study into the role of specific brain regions in false auditory perceptions using noninvasive brain stimulation"

Er is een proefpersonenverzekering afgesloten voor onverwachte schade die u zou lijden door uw deelname aan dit wetenschappelijk onderzoek. Het betreft de schade door letsel of overlijden die zich openbaart gedurende de deelname aan dit onderzoek en de schade die zich openbaart binnen vier jaar na beëindiging van deelname aan dit onderzoek.

Het bedrag waarvoor de verzekering is afgesloten is maximaal € 7.500.000,- voor de totale schade die zich per verzekeringsjaar bij proefpersonen heeft geopenbaard bij alle onderzoeken die door het Universitair Medisch Centrum Groningen en de Rijksuniversiteit Groningen wordt verricht, maximaal € 3.500.000,- voor de totale schade bij dit onderzoek en maximaal € 650.000,- per proefpersoon. Bepaalde soorten van schade kennen wettelijk gelimiteerde vergoedingen.

Van de dekking door de verzekering is uitgesloten:

- schade van te verwachten risico's zoals beschreven in de schriftelijke informatie voor proefpersonen. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
- Schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- Schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen
- Schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

De verzekering is afgesloten bij verzekeringsmaatschappij Centramed, Postbus 7374, 2701 AJ Zoetermeer.

Indien u schade heeft geleden of het vermoeden daarvan heeft, dient u zich direct met de onderzoeker (contactinformatie, zie hieronder) in verbinding te stellen en de gegeven aanwijzingen op te volgen. Ook dient u in zo'n geval contact op te nemen met de juridisch stafmedewerker van het Universitair Medisch Centrum Groningen, bereikbaar via telefoonnummer 050-361 4929.

Contactinformatie:
Dr. Branislava Curcic-Blake
Prof. Dr. André Aleman

Contactinformatie:
NeuroImaging Center, Antonius
Deusinglaan 2, 9713 AW Groningen
Tel. 050-3616395, e-mail: b.curcic@umcg.nl

Afspraakbrief

Groningen, 00-00-2018

Geachte ……..,

Hiermee bevestigen wij de afspraak die met u is gemaakt voor uw deelname aan het wetenschappelijk tDCS:

"De functie van specifieke hersengebieden in foutieve geluidsperceptie met tDCS"

Wetenschappelijke titel: "Investigating the neural basis of auditory false perceptions in a signal detecting paradigm using transcranial Direct Current Stimulation"

Voor de eerste afspraak wordt u verwacht om …….. uur tot …… uur

Voor de tweede afspraak wordt u verwacht om …….. uur tot …… uur

Voor de derde afspraak wordt u verwacht om ..…….. uur tot …… uur

Alle afspraken vinden plaats in het onderzoekslaboratorium in het NeuroImaging Center van het UMC Groningen. Het NeuroImaging Centrum (zie foto en routebeschrijving) bevindt zich aan de Antonius Deusinglaan 2, recht tegenover de hoofdingang van de Faculteit Medische Wetenschappen, Tandheelkunde en Farmacie.

Bij binnenkomst loopt u rechtdoor tot de deur die toegang geeft naar de trap van de kelderverdieping. Hier kunt u aanbellen. Als u vervolgens de trap naar beneden neemt kunt u plaats nemen in de wachtruimte. Daar zult u worden opgevangen. U kunt ook in de hal plaatsnemen en daar wachten tot u wordt opgehaald.

U kunt u op ieder moment, ook nadat u de schriftelijke verklaring hebt ondertekend, zonder opgaaf van redenen terugtrekken uit het onderzoek.

Met vriendelijke groet,

Dr. Branislava Curcic-Blake
Prof. Dr. André Aleman

NeuroImaging Center, Antonius Deusinglaan 2, 9713 AW Groningen

Tel. 050-3616395, e-mail: b.curcic@umcg.nl

Bijlage. Routebeschrijving MRI Centrum Groningen

Antonius Deusinglaan 2 9713 AW
Groningen

Voor uw MRI onderzoek gaat u niet naar het UMCG maar naar het MRI-centrum in het NeuroImaging Center, Ant. Deusinglaan 2

Routebeschrijving en parkeren

Per auto

LET OP: A. Deusinglaan is geen doorgaande weg meer, uw navigatie geeft mogelijk geen juiste routeplanning.

Ring Zuid: via SS Rosensteinlaan
Volg de borden UMCG, u rijdt via de Europaweg, Petrus Campersingel over de SS Rosensteinlaan. (Het complex van het UMCG ligt links). Bij het kruispunt met stoplichten gaat u linksaf de Vrydemalaan op. 1e afslag links.

Ring Noord: via J.C. Kapteynlaan
Bij het Borneoplein gaat u de J.C.Kapteynlaan op.
Bij het kruispunt met stoplichten gaat u rechtsaf de Vrydemalaan op. 1e afslag links.

Centrum: via Bloemsingel
U rijdt op de Oostersingel, U kunt vanaf hier de A.Deusinglaan niet op. U rijdt verder op de Bloemsingel. Voor de parkeergarage Boterdiep gaat u rechtsaf de Vrydemalaan op. 1e afslag rechts.

Via E.Thomassen a Theussinklaan.
Bij het kruispunt met stoplichten gaat u rechtdoor de Vrydemalaan op.1e afslag links.

Vanuit elke richting gaat u na de afslag een doodlopende weg in, na ca. 30 meter slaat u rechtsaf de A.Deusinglaan in. Voor de rood/witte blokkade gaat u rechtsaf het parkeerterrein van het MRI Centrum op.
Als u zich meldt via de intercom bij de slagboom dan kunt u het terrein oprijden. U kunt uw auto dan gratis parkeren op het achterliggende terrein parkeerterrein van het MRI Centrum. Daarna loopt u naar de voorzijde van het gebouw, recht tegenover de hoofdingang van de Faculteit Medische Wetenschappen, Tandheelkunde en Farmacie.

Andere parkeermogelijkheden (betaald parkeren)

U kunt ook uw auto parkeren in Parkeergarage Boterdiep (einde Vrydemalaan) of bij Parkeergarage UMCG/Noord.

Vanaf Parkeergarage Boterdiep aan de Langestraat 68 is het ca. 5 minuten lopen naar het MRI Centrum. U gaat naar buiten via de uitgang Bloemsingel, u gaat linksaf, bij het kruispunt steekt u de straat over en loopt u nog ca. 100 meter door naar de voorzijde van het gebouw, recht tegenover de hoofdingang van de Faculteit Medische Wetenschappen, Tandheelkunde en Farmacie.

Vanaf Parkeergarage UMCG/Noord is het ca. 10 minuten lopen naar het MRI Centrum, dat aan de andere kant van het gebouw ligt.

Met Openbaar Vervoer

Trein/bus: NS Station Groningen CS, daar kunt u overstappen op bus 3 (richting Lewenborg) of bus 6 (richting Beijum).

Uitstappen bij halte Bloemsingel, ga rechtsaf, na ca. 10 meter, bij het ijzeren hek, linksaf de Antonius Deusinglaan inlopen.

Tegenover de Tandheelkunde faculteit bij het blauw/witte bord “MRI Centrum” bevindt zich de ingang.

Voor een gedetailleerde routebeschrijving per openbaar vervoer kunt u ook kijken op www.9292ov.nl of bellen met Openbaar Vervoer reisinformatie 0900-9292.

Appendix C

Screening and Safety Form and tDCS and Sham Stimulation Questionnaires

METc 2017.
Version 1
29.11.2017

university of groningen / umcg / neuroimagingcenter

A study into the role of specific brain regions in false auditory perceptions, using noninvasive brain stimulation

Review Questionnaires

1. Form personal information
2. Safety form tDCS-study

Remaining questionnaires:

3. Questionnaire during tDCS stimulation
4. Questionnaire after tDCS stimulation
5. Questionnaire about sham stimulation

1. Form personal information

To define if you can participate in the tDCS-research study: **"A study into the role of specific brain regions in false auditory perceptions, using non-invasive brain stimulation",** we ask you to fill in the questions below**.** If something is not clear you can leave the question open.
In that case the researcher will contact you. After filling in the questions you can send back the form in the enclosed answering envelope. The forms will be treated confidentially.

Personal information

Name _____

Address _____

Postal Code _____ Place _____

Phone number _____

Birth date _____

Gender M / F Weight _____

Education _____

Current job _____

Name General Practitioner _____ Phone GP _____

Name researcher:	
ID-number (filled in by researcher):	
Date:	

2. Safety form tDCS-study

Questionnaire for subject of the research "A study into the role of specific brain regions in false auditory perceptions, using noninvasive brain stimulation"

Name researcher:	
ID-number (filled in by researcher):	
Date:	

The answers to the questions below are important to determine if you can safely can participate in this study. We will also use your answers for interpretation of the research results. This is the only reason why we ask these questions.

Please answer the questions precise and honest.

1. You only can participate if you are 18 years or older, not older than 35 years. What is your birthdate?
   _____
2. Are you feeling healthy? Yes / No
   a. If no, can you point out why not?
   _____
3. How many glasses alcohol do you drink in a week?
   _____
4. How much tobacco do you smoke in a week? In number of cigarettes or gram of packages.
   _____
5. How much cups of coffee do you drink per week?
   _____
6. Do you use medication? Yes / No
   a. If yes, which
   _____
7. Did you use past four weeks medication which influences the brain (Heeft u in de afgelopen vier weken medicijnen geslikt die op de hersenen werken (antidepressants, anti epileptica etc. …?)) Yes / No
   a. If yes, which

_____

8. Did you use past four weeks drugs (f.i. weed)? Yes / No
    a. If yes, which

_____

9. Did you ever have an epileptic attack? Yes / No
10. Did you ever had a consult or have been under treatment by a neurologist? Yes / No
11. Did you ever had a consult or have been under treatment by a psychiatrist? Yes / No
12. Do you have metal implants (such as a pacemaker) in your body?
    a. If yes, which

_____

13. What are your sleeping habits?

_____

14. How many hours do you sleep per night?

_____

15. During which hours do you sleep? From _____ till _____
16. Are you a morning person or a night owl?

_____

17. Are you lefthanded or righthanded? Left / Right

I declared to have filled in the above questions truthfully.

Name _____

Place and date _____

Signature _____

3. Questionnaire during tDCS stimulation

Name researcher:	
ID-number (filled in by researcher):	
Date:	

We are interested in your experience of receiving tDCS. Did you experience any of the following **during** stimulation?
Please write a number corresponding to the severity/intensity of the experience, for each of the three sessions.

1 = not at all **2 = very mild** **3 = mild** **4 = moderate** **5 = severe**

	First session	Second session	Third session
Headache			
Tingling underneath electrode			
Itching underneath electrode			
Burning sensation underneath electrode			
Neck pain			
Scalp pain			
Skin redness under either electrode			
Sleepiness			
Trouble concentrating			
Mood change			
Other (please specify below)			

4. Questionnaire after tDCS stimulation

Name researcher:	
ID-number (filled in by researcher):	
Date:	

We are interested in your experience of receiving tDCS. Did you experience any of the following **after** stimulation? Please include anything you experienced up to 8 hours following the first two sessions. Please write a number corresponding to the severity/intensity of the experience, for each of the three sessions.

1 = not at all **2 = very mild** **3 = mild** **4 = moderate** **5 = severe**

	First session	Second session
Headache		
Tingling where electrode had been		
Itching where electrode had been		
Burning sensation where electrode had been		
Neck pain		
Scalp pain		
Skin redness where electrode had been		
Sleepiness		
Trouble concentrating		
Mood change		
Other (please specify below)		

5. Questionnaire sham tDCS stimulation

Name researcher:	
ID-number (filled in by researcher):	
Date:	

You participated in three tDCS sessions, in which we asked you to perform a simple auditory perception task. One of these sessions was a ‘sham’ stimulation condition, in which the equipment was only turned on for the first 30 seconds, before it turned itself off.

In which session do you think you received ‘sham’ stimulation?

Please circle an option below. (If you don’t know, please take a guess.)

Session 1 **Session 2** **Session 3**

How confident are you about your choice? Please circle a number between 1-7.

1 Not confident at all
2
3
4 Somewhat confident
5
6
7 Very confident