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Transcranial direct current stimulation over the left dorsolateral prefrontal cortex modulates auditory mismatch negativity

Michael Weigl [a,*], Axel Mecklinger [a], Timm Rosburg [a,b]

[a] Department of Psychology, Experimental Neuropsychology Unit, Saarland University, 66041 Saarbrücken, Germany
[b] Department of Forensic Psychiatry, University Psychiatric Clinics, Wilhelm Klein-Str. 27, 4012 Basel, Switzerland

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HIGHLIGHTS

- Involvement of the left dorsolateral prefrontal cortex (DLPFC) in the generation of the novelty-P3, target-P3, and mismatch negativity (MMN) was tested by tDCS.
- Left frontal anodal tDCS significantly reduced MMN to duration and intensity deviants.
- Prefrontal networks supporting preattentive deviance detection vary with the kind of deviance.

ABSTRACT

Objective: To investigate the contribution of the left dorsolateral prefrontal cortex (DLPFC) to attentive and pre-attentive stimulus discrimination via transcranial direct current stimulation (tDCS).
Methods: Novelty- and target-P3 as indexes of attentive stimulus discrimination and the mismatch negativities (MMNs) for duration, intensity, and frequency deviants as indexes of pre-attentive stimulus discrimination were recorded before and after delivering anodal and cathodal tDCS to the left DLPFC.
Results: MMN amplitudes for all kinds of deviants decreased from pre- to post-tDCS measurement. For duration and intensity deviants, this pre-post reduction was stronger after anodal tDCS, as compared to the decrease after sham stimulation. No such modulation was found for the MMN to frequency deviants. Neither the novelty-P3 nor the target-P3 was modulated by tDCS.
Conclusion: The selective MMN decrease after anodal (excitatory) stimulation of the left DLPFC suggests that this region either inhibits the processing of specific auditory changes or modulates the habituation of the MMN to certain kinds of deviances.
Significance: Our finding that left frontal anodal tDCS reduces the MMN to duration and intensity deviants further highlights the contribution of frontal brain regions to MMN generation and extends previous reports of reduced MMNs to frequency deviants after right frontal anodal tDCS.

1. Introduction

In our everyday life we are confronted with complex auditory scenes (Bregman, 1990). Extracting regularities and monitoring these scenes for unusual or unexpected events is crucial for adaptive behavior (e.g. Bregman, 1990; Näätänen, 1992; Pannese et al., 2015). Therefore, it is not surprising that several neural processes are devoted to the detection and processing of deviant stimuli that can be identified by event-related potentials (ERPs) (e.g. Escera and Corral, 2007; Grimm and Escera, 2012; Paavilainen, 2013). Such deviance-related processes are presumed to be reflected particularly in the mismatch negativity (MMN), the novelty-P3, and the target-P3.

The auditory mismatch negativity (MMN) is elicited when a rare or deviant sound occurs in an otherwise regular acoustic stimulus series (e.g. see Garrido et al., 2009; Näätänen et al., 2001; Paavilainen, 2013 for reviews). These deviant sounds can differ from the so-called standard tone in frequency, intensity, duration or any other auditory feature. The MMN amplitude increases with the magnitude of deviance (e.g. Sams et al., 1985). Attending the stimulus series is not necessary for the MMN to occur. It can even be observed in comatose patients (e.g. Daltrozzo et al., 2007). The

* Corresponding author at: Department of Psychology, Experimental Neuropsychology Unit, Saarland University, Campus, Building A2.4, 66123 Saarbrücken, Germany. Tel.: +49 681 302 6579; fax: +49 681 302 6516.
E-mail address: m.weigl@mx.uni-saarland.de (M. Weigl).

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MMN usually peaks between 100 and 200 ms and has a fronto-central distribution. It has been suggested that generators in the auditory and frontal cortices underlie the auditory MMN: whereas there is strong evidence for bilateral MMN generators in the superior temporal gyrus, evidence for an additional frontal generator is less clear (e.g. Alho et al., 1994; Doeller et al., 2003; Molholm et al., 2005; Opitz et al., 2002; Rosburg, 2003; Rosburg et al., 2005; see Alho, 1995, for a review of earlier findings). In a review of fMRI, PET, EEG source imaging, and lesion studies, Deouell (2007) concluded that, even though there is support for a frontal generator, its exact location and precise functional characteristics still remain elusive. It seems that different regions within the prefrontal cortex (PFC) are recruited depending on the type of deviance. For example, Molholm et al. (2005) reported that the MMN to duration deviants was associated with left inferior frontal gyrus (IFG) activity, whereas the MMN to frequency deviants was associated with right IFG activity. Furthermore, prefrontal regions also seem to contribute to the visual MMN, suggesting that frontal generators might generally be involved in the pre-attentive processing of stimulus deviance independently of its modality (Kimura et al., 2010).

Rare task-relevant (target) stimuli elicit a parietally distributed P300 (target-P3 or P3b) whereas rare non-target or novel stimuli elicit a fronto-centrally distributed P300 (novelty-P3 or P3a) (Polich, 2007). The novelty-P3 is supposed to reflect involuntary attentional shifts to novel or distinct stimuli, while the target-P3 seems to reflect voluntary attention allocation and stimulus evaluation. Lesions of the prefrontal cortex reduce novelty-P3 amplitudes, but leave target-P3 amplitudes unchanged indicating that the prefrontal cortex contributes to the processing of novelty (e.g. Knight, 1984). In contrast, target-P3 amplitudes to auditory and visual targets are reduced in patients with temporo-parietal lesions (e.g. Verleger et al., 1994). These results converge with dipole analyses (e.g. Mecklinger and Ullsperger, 1995), low-resolution electromagnetic tomography (LORETA) studies (Volpe et al., 2007; Wronka et al., 2012), and fMRI studies (e.g. Bledowski et al., 2004). Based on these studies, it can be presumed that – even though novelty- and target-P3 are generated by partially overlapping neural networks – the novelty-P3 is foremost generated in frontal and central regions, whereas the neural generators of the target-P3 are primarily located in temporo-parietal brain regions.

However, brain imaging methods such as fMRI or EEG can only provide limited insight in the neuronal origin of scalp-recorded ERPs due to the low temporal resolution of the hemodynamic signal or the intractability of the inverse problem in the case of source analyses of EEG data. Therefore, noninvasive brain stimulation techniques like transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) might provide more direct evidence about the involvement of a target brain region, such as the prefrontal cortex, because its activity can be experimentally manipulated by such techniques. Repetitive TMS over the dorsolateral prefrontal cortex (DLPFC) has been reported to modulate target-P3 latency (e.g. Evers et al., 2001; Hansenne et al., 2004; Jing et al., 2001). However, outside clinical settings, some preference might be given for using tDCS instead of TMS to conduct such studies, due to some risks to provoke seizures even for low-frequency TMS in thitherto neurologically unremarkable subjects (Nowak et al., 2006). In contrast, tDCS has been associated only with mild aversive effects, such as itching, tingling, and, less often, headache (Brunoni et al., 2012).

TDCS has gained some research interest in the recent time, also due to the fact that tDCS devices are much less cost-intensive than TMS devices. TDCS applies constant low currents to the scalp to alter the activity of brain regions underneath the electrodes (e.g. Nitsche and Paulus, 2000, 2001; Paulus, 2011; Priori, 2003; Utz et al., 2010). The effects of tDCS on behavior and brain responses depend on the polarity of the current flow. Anodal tDCS depolarizes cortical neurons and thereby increases cortical excitability of the target area, while cathodal tDCS has the reverse effect (Nitsche and Paulus, 2000; Stagg and Nitsche, 2011).

In general, the effect of tDCS increases with increases in current strength (Nitsche and Paulus, 2000) and stimulation duration (Antal et al., 2004; Nitsche and Paulus, 2001; Nitsche et al., 2003). Furthermore, once the duration of stimulation exceeds 10 min, the effects of tDCS can outlast the stimulation for several minutes (Antal et al., 2004; Nitsche and Paulus, 2001; Nitsche et al., 2003). Therefore, most studies apply 1–2 mA of anodal or cathodal tDCS for 10–20 min (Been et al., 2007; Brunoni et al., 2012; Utz et al., 2010). TDCS is inferior to TMS in terms of focality (Dayan et al., 2013) since most of the current gets shunted through the scalp (Miranda et al., 2006). Moreover, the current flow is modulated by the position of the "passive" (return) electrode (Antal et al., 2004; Nitsche and Paulus, 2000). Nevertheless, some conclusion about the involvement of a targeted area can be drawn, because tDCS primarily affects the cortical tissue underneath the stimulation electrodes (Miranda et al., 2006; Nitsche et al., 2007; Rush and Driscoll, 1968). In addition to behavioral changes, tDCS has been shown to modulate ERPs and oscillatory neural activity (see Miniussi et al., 2012, for a review). Due to technical considerations (e.g. amplifier saturation, interference with electrode placement) most previous ERP studies measured EEG after tDCS or were using a pre-post tDCS design (Miniussi et al., 2012). However, so far only a few studies have investigated the involvement of the DLPFC in the generation of the P300 and the MMN.

Chen et al. (2014) applied anodal and cathodal tDCS over the right DLPFC to investigate its contribution to the generation of the auditory MMN: Anodal, but not cathodal, tDCS over the right DLPFC led to a significant reduction of the MMN amplitude to frequency deviants, whereas MMN amplitudes to duration deviants were not affected by either kind of tDCS. Chen and colleagues attributed this differential effect to the differing networks presumed to be activated by duration and frequency deviants (see also Molholm et al., 2005; Opitz et al., 2002; Rinne et al., 2005). However, the MMN was recorded only once in each session, namely after the application of tDCS; therefore it remains possible that the lack of effects for duration deviants and for frequency deviants after right-frontal cathodal stimulation was due to inter-session variability.

There is some evidence that tDCS over the left DLPFC might modulate target-P3 amplitude and latency. Keeser et al. (2011) investigated the effect of anodal tDCS over the left DLPFC on ERPs and working memory performance in a 0-, 1-, and 2-back task. Anodal tDCS increased target-P3 amplitudes in the 2-back condition of the working memory task. Furthermore, this increase in target-P3 amplitude was associated with reduced reaction times and error rates. A similar increase of target-P3 amplitudes after anodal stimulation was observed in a clinical study with alcoholics (Nakamura-Palacios et al., 2012). However, other studies observed only a modulation of the target-P3 latency after tDCS. In the study of Zaehle et al. (2011), frontal cathodal tDCS decreased target-P3 latencies in a 2-back working memory task, whereas target-P3 amplitudes were not modulated by tDCS. In patients with Alzheimer's disease, repeated anodal and cathodal tDCS over the left DLPFC reduced target-P3 latencies, but did not affect target-P3 amplitudes (Khedr et al., 2014).

In an attempt to combine both, P300- and MMN-paradigms, Knechtel et al. (2014a) investigated the effect of anodal tDCS over the left DLPFC on target-P3, novelty-P3 and MMN in an active as well as in passive oddball task. In this study, neither task performance, nor any ERP component was modulated by the applied tDCS. The same experimental set-up did not produce any reliable

tDCS effects in schizophrenia patients either (Knechtel et al., 2014b).

In the current single-blind study, we sought to investigate the contribution of the left DLPFC to auditory discrimination processing as indexed by novelty-P3, target-P3, and MMN, by using anodal and cathodal tDCS. On the basis of the neuropsychological and brain imaging studies on the neural origin of the novelty- and target-P3 reviewed above, we expected that anodal frontal tDCS would enhance novelty-P3 amplitudes and frontal cathodal tDCS would reduce novelty-P3 amplitudes, whereas we expected no tDCS effects for the target-P3. However, based on the tDCS and ERP findings reviewed above, it remained possible that the target-P3 would be modulated by frontal tDCS as well. On the basis of the fMRI findings of Molholm et al. (2005), we hypothesized that left-frontal tDCS would modulate MMN amplitude to duration deviants, but would not affect the MMN to frequency deviants. No prediction was made for the MMN to intensity deviants.

2. Methods

2.1. Participants

18 healthy volunteers (6 female), ranging in age from 20 to 29 years (median age 26 years) took part in the experiment. All participants were right-handed as verified with a German version of the Edinburgh Inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. Only participants who reported unimpaired hearing were invited. Further exclusion criteria that were assessed at the beginning of the first session were a history of psychiatric, or neurological diseases, centrally acting medication or metallic implants. Prior to participation, participants were informed about the experimental procedure and tDCS application and gave written informed consent. The stimulation protocol and methods used in the present study were approved by the ethic committee of the German Psychology Society [Deutsche Gesellschaft für Psychologie DGPs]. After the final session, participants were given the opportunity to ask in which sessions they had received active stimulation. All participants were students of the Saarland University and received monetary compensation for their participation (10 €/h).

2.2. Material and procedure

The experiment consisted of three sessions, one for each kind of stimulation (anodal, cathodal, and sham), on three separate days within maximally three weeks. The within-subject order of the three conditions was counterbalanced across participants. For each session, participants came to the laboratory at the same time of day at which they came in their first session in order to minimize the impact of the circadian rhythm as confounding factor. Between each session, there was a lag of at least three days to avoid carry-over effects (e.g. Javadi et al., 2012). The median time lag was four days (range: 3–13 days). The within-session procedure was as follows (Fig. 1): before tDCS was applied, ERPs were recorded in a passive oddball and an active oddball task, followed by the recording of resting EEG. To distract the participants from the stimulation, tDCS was applied while they performed a continuous recognition task (CRT). Immediately after the tDCS, resting EEG was recorded a second time. Thereafter, the ERP recordings in the active and passive oddball paradigm were repeated. This design allowed us to compare the effect of tDCS against a baseline recorded in the same session. In contrast, other tDCS-studies either used separate baseline sessions and measured EEG only after the stimulation (e.g. Chen et al., 2014; Keeser et al., 2011) or they recorded the effects of sham and active tDCS within the same session (e.g. Knechtel et al., 2014a,b; Zaehle et al., 2011). We considered both approaches as problematic, because inter-session variability might distort the assessment of tDCS-effects in the first case and carry-over effects might hamper the interpretation of tDCS effects in the second case. Our approach allowed us to take inter-session variability into account and to avoid unwanted carry-over effects.

2.2.1. Active oddball

The stimuli and procedure of the active oddball experiment were adapted from Kipp et al. (2010). Three kinds of stimuli were presented, one standard tone (600 Hz, 200 ms duration, 70 dB intensity) in 80% of the trials, one target tone (1000 Hz, 200 ms duration, 70 dB intensity) in 10% of the trials, and different environmental sounds as novels in another 10% of the trials. The environmental sounds were taken from Mecklinger et al. (1997). The active oddball consisted of 500 trials. Stimuli were presented with a stimulus onset asynchrony (SOA) of 1500 ms. Within each session, different environmental sounds were used in the pre- and post-tDCS recordings. The presentation of novel sounds was counterbalanced across sessions and participants. The participants' task was to press the "M"-key on a computer keyboard whenever targets appeared. In each session, participants performed 20 practice trials in which only standard tone and target tone were presented.

2.2.2. Passive oddball

Four kinds of stimuli were presented, one standard tone (800 Hz, 50 ms duration including 5 ms of fade in and fade out, 70 dB intensity) in 70% of the trials and three different kinds of deviants in 10% of the trials each (frequency deviant: 880 Hz; duration deviant: 100 ms; intensity deviant: 60 dB). In total, 1000 stimuli were presented. The SOA was 1098 ms. Tones were presented in random order with the constraint that two deviants never appeared in succession. Participants watched silent sequences of the films *Powaqqatsi* and *Koyaanisqatsi* during the recording, with no further task required.

2.2.3. Resting EEG

Resting EEG was recorded with eyes closed and eyes open, twice for 30 s each. Participants were instructed to close their eyes when the phrase "close your eyes" appeared on the computer screen and open their eyes again when they heard a signal tone. Because the results of the resting EEG do not contribute to elucidating the ERP results, we will not further report on these data in this article.

2.2.4. Continuous recognition task (CRT)

The stimuli and procedure of the CRT was adapted from Sprondel et al. (2011). It consisted of three blocks, with 76 trials in each block. Within each block 19 objects and 19 nonobjects were presented in randomized order and were repeated once with variable lags. For every item, participants had to indicate whether this item has been presented before or not by pressing the "C"- and "M"-keys of the computer keyboard. After each trial, visual feedback indicated whether the participant's response was correct (see Sprondel et al., 2011, for a more detailed description of the task and material). Because the CRT was mainly intended to distract participants from the stimulation and because performance on this task was not modulated by tDCS, we will not further report on these data.

2.3. tDCS

A direct current of 1 mA for 15 min (5 s ramp in and 5 s ramp out) was delivered by a battery-driven DC stimulator (neuroConn, Ilmenau, Germany), using two saline-soaked surface sponge

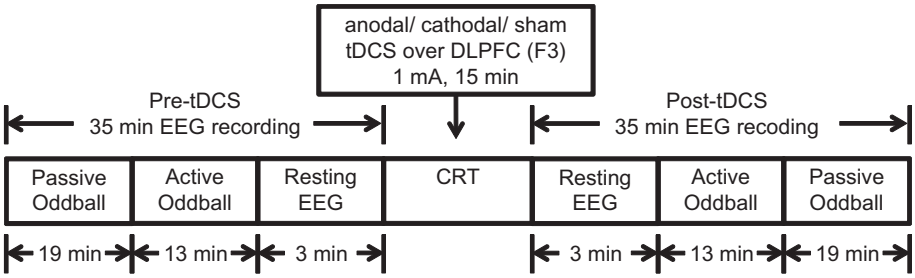

Fig. 1. Within-session procedure: Each session started with the passive oddball task followed by the active oddball task and the resting EEG recording. After the tDCS during the continuous recognition task (CRT), the recordings were repeated in reversed order. Time indications are approximate (±2–3 min).

electrodes (7 × 5 cm, 35 cm^2). One electrode was placed above the left dorsolateral prefrontal cortex (F3 according to the 10–20 system), the second was placed over the right supraorbital area (Fig. 2). This montage has been used in previous research to modulate DLPFC activity (e.g. Chen et al., 2014; Dockery et al., 2009; Iyer et al., 2005; Javadi et al., 2012; Keeser et al., 2011; Knechtel et al., 2014a,b) and was therefore chosen to enhance the comparability of our results. During sham stimulation, the current was only delivered for the first 25 s (including 5 s ramp in and 5 s ramp out). For anodal and sham stimulation, the left frontal electrode was used as anode and right supraorbital electrode as cathode. For the cathodal stimulation, the current was reversed. Electrodes were placed underneath the EEG cap immediately before the CRT in order to avoid the drying-out of the saline-soaked sponge. The EEG cap was not removed during tDCS. At the beginning and the end of each session, participants filled out a questionnaire to monitor current state and potential side-effects, as well as to check whether participants could identify the test condition (active vs. sham tDCS).

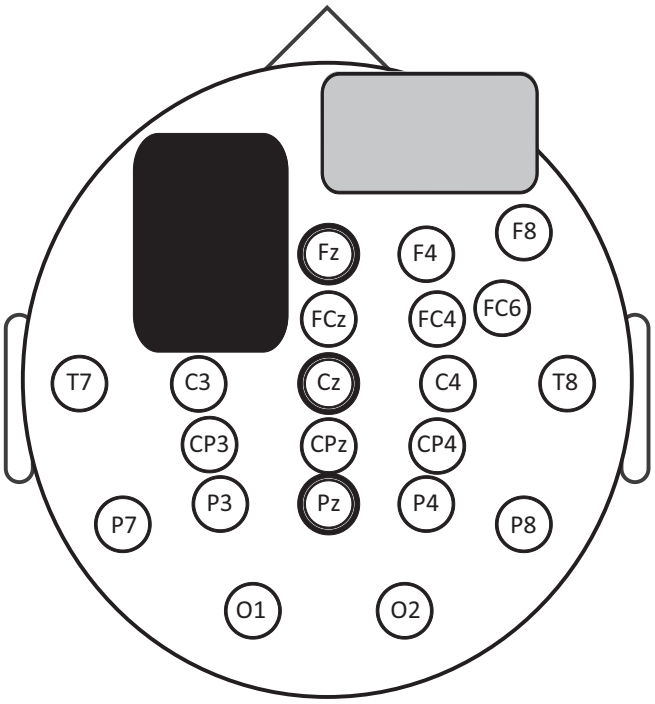

Fig. 2. tDCS and EEG recording montage: The electrodes marked by bold circles (Fz, Cz, and Pz) were chosen for the statistical analyses. The black square represents the active electrode and the gray rectangle represents the return electrode. Please note that the displayed width of the gray electrode is reduced by the top view and due to the electrode placement, as compared to the black electrode. However, the actual size of both tDCS electrodes was the same (5 × 7 cm).

2.4. EEG recording

An elastic cap (Easycap, Herrsching, Germany) with 22 embedded silver/silverchloride EEG electrodes was attached to the participant's head. EEG was continuously recorded with reference to the left mastoid from the following electrode position (10–20 system): Fz, F4, F8, FCz, FC4, FC6, T7, C3, Cz, C4, T8, CP3, CPz, CP4, P7, P3, Pz, P4, P8, O1, O2 (Fig. 2). In accordance with current safety standards (e.g. Loo et al., 2011), the electrodes Fp1, Fp2, F3, F7, FC3, and FC5 were not used to avoid the risk of skin burns during tDCS after the use of abrasive EEG gel. This also allowed us to apply tDCS without removing the EEG cap and to start EEG recording immediately after the end of the stimulation. EOG activity was recorded with two electrodes placed on the outer canthi and by a pair of electrodes placed above and below the left eye. Electrode impedances were kept below 5 kΩ throughout the whole session.

2.5. ERP data processing

EEG data were processed with the Brain Vision Analyzer 2.03 (Brain Products, Gilching, Germany). For offline data processing, data were downsampled to 250 Hz. Ocular artifacts were removed via an independent component analysis (ICA) based algorithm implemented in Brain Vision Analyzer after using a 0.1 Hz high pass filter. Then data were re-referenced to linked mastoids. For all oddball recordings, data were filtered from 0.1 Hz to 30 Hz (48 dB/oct). Data were segmented into epochs of 1000 ms for the passive oddball experiment and 1200 ms for the active oddball experiment (including 200 ms pre-stimulus baseline each). After baseline correction data were screened for remaining artifacts and any segment that contained amplitudes outside the range of −70 to 70 μV or voltage steps exceeding 50 μV/ms was removed.

For the EEG recordings in the active oddball task, we quantified the mean amplitudes of ERP components at the electrodes Fz, Cz, and Pz. The time windows were selected on the basis of grand average data (across all sessions). In the active oddball task, we measured the novelty-P3 (P3 to novel stimuli) between 260 and 360 ms and the target-P3 (P3 to target stimuli) between 280 and 380 ms. Furthermore, we quantified the N100 amplitude as the mean amplitude between 76 and 108 ms separately for standards, novels, and targets and the P200 amplitude for standards from 160 to 208 ms, as well as the N2b amplitude in the difference waveform between standard and targets between 160 and 220 ms.

In the passive oddball task, we quantified the MMN as the mean amplitude of the difference potential between the ERPs to each kind of deviant and standards. The time windows were selected on the basis of grand average data (across all sessions). The time windows varied between the kinds of deviant (frequency deviant: 120–180 ms, intensity deviant: 152–212 ms, duration deviant: 152–212 ms). Additionally, the N100 mean amplitude was

quantified from 76 to 108 ms, separately for each kind of tone, as well as the P200 amplitude for standards from 160 to 208 ms.

2.6. Data analysis

All statistical analyses were conducted by using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

The ERP data of the active oddball task were analyzed using separate repeated-measure ANOVAs for novelty- and target-P3 mean amplitudes. Participants who did not show a novelty-P3 (absence defined as mean amplitude at Fz < −1 μV) or a target-P3 (absence defined as mean amplitude at Pz < −1 μV) were excluded from analysis. Using this criterion, two participants were excluded from the analysis of the novelty-P3. However, this exclusion did not change the pattern of the results. No participants had to be excluded from the analysis of the target-P3. Novelty- and target-P3 were analyzed using separate repeated-measure ANOVAs with factors ELECTRODE (Fz vs. Cz. vs. Pz), TDCS (anodal vs. cathodal vs. sham), and TIME (pre-tDCS vs. post-tDCS). In order to assure that any tDCS effects for novelty- and target-P3 were not attributable to tDCS effects on earlier ERP variations, we additionally analyzed the components N100, P200, and N2b.

For the analysis of the MMN, participants that did not show a MMN (absence defined as mean amplitude of the difference between deviant and standard >+1 μV) were excluded from analysis. Using this criterion, two participants were excluded from the analysis of the MMN for frequency deviants and three participants were excluded from the analysis of the MMN for intensity deviants. Given this, the calculation of an overall ANOVA with TYPE OF DEVIANCE as an additional factor would have resulted in a substantial loss of statistical power and, therefore, we opted for investigating the tDCS effects on the MMN for each kind of deviant separately. The exclusion of participants did not change the pattern of the reported results. The same analytical procedure was performed on the MMN mean amplitudes for each kind of deviant. Analog to the P3 analysis, we conducted a repeated-measure ANOVA with the factors ELECTRODE (Fz vs. Cz. vs. Pz), TDCS (anodal vs. cathodal vs. sham), and TIME (pre-tDCS vs. post-tDCS). Significant interactions involving the factors TDCS and TIME were followed up by comparing anodal and cathodal tDCS separately with sham stimulation using lower level ANOVAs. We additionally compared anodal with cathodal tDCS in order to test whether the effect was polarity-specific. Simple effect analyses for each electrode were used to determine the location of the effect when TDCS × TIME × ELECTRODE interactions were observed. In addition to the MMN, we analyzed the N100 and P200 components to preclude that tDCS effects on the MMN were due to changes in the processing of standard tones.

In this study, genuine tDCS effects were defined as an interaction between TDCS (anodal vs. cathodal vs. sham) and TIME (pre-tDCS vs. post-tDCS). Furthermore, to be considered a genuine tDCS effect, this interaction had to be qualified by a difference of active stimulation (anodal or cathodal) compared to sham stimulation.

For all repeated-measure ANOVAs, sphericity was checked with the Mauchly test and a Greenhouse–Geisser correction was applied when necessary, as is indicated by the citation of ε. Significance level was set to $p = .05$ for all analyses.

3. Results

All participants completed all three sessions. Post-experimental ratings indicate that active tDCS was well tolerated by all participants. Ratings for itching, headache, agitation and nausea did not indicate any discomfort (all means and medians <1 on a scale from 0 = "not present" to 10 = "very strongly present") and did not differ between conditions as assessed with a Friedman's ANOVA (all $ps > .46$). Participants were moderately tired after the experiment. However, the level of tiredness was the same for all three kinds of stimulation ($\chi^2(2) = 1.2$, $p = .55$). Participants were unable to discriminate between active and sham tDCS ($\chi^2(2) = .7$, $p = .70$).

3.1. Active oddball

3.1.1. Behavioral results

Participants showed a high level of accuracy in the active oddball task. There were virtually no misses and only few false alarms (mostly to novels). Therefore, the total number of errors was calculated for the data analysis (Table 1). A Friedman's ANOVA on the difference between pre-tDCS and post-tDCS error scores revealed a marginally significant effect ($\chi^2(2) = 5.4$, $p = .07$), but these differences are attributable to pre-tDCS differences between the sham-condition and tDCS-conditions ($\chi^2(2) = 6.3$, $p = .04$). Reaction times for targets were averaged across correct trials (Table 1): a TDCS (anodal vs. cathodal vs. sham) × TIME (pre-tDCS vs. post-tDCS) repeated measure ANOVA revealed no significant effects (all $Fs < 1.0$, $ps > .37$).

3.1.2. ERPs

Fig. 3 shows the grand average ERP waveforms of the novelty-P3 at the Fz electrode and of the target-P3 at the Pz electrode in the active oddball condition for the three stimulation protocols. The results of the main analyses for the novelty- and target-P3 are shown in Table 2 and descriptive statistics are shown in Table 3. Post-tDCS novelty- and target-P3 amplitudes were generally lower than pre-tDCS novelty- and target-P3 amplitudes (Fig. 3). However, neither the novelty-P3 nor the target-P3 was modulated by tDCS (Table 2).

3.1.3. Further analyses

In order to assure that the lack of tDCS-effects on novelty- and target-P3 was not due to altered early auditory processing and attention processes, we also analyzed the components N100, P200, and N2b. Neither the N100 to standards, targets and novels, nor the N2b showed any tDCS effects (all $Fs < 2.4$, $ps > .10$). For the P200, there was a significant interaction between ELECTRODE, TDCS and TIME ($F(4,68) = 3.9$, $p = .02$, partial $\eta^2 = .19$, $\varepsilon = .57$). However, follow-up ANOVAs revealed that this interaction was due to diminished pre-tDCS P200 amplitudes in the cathodal condition ($F(2,34) = 11.0$, $p = .002$, partial $\eta^2 = .39$, $\varepsilon = .66$).

3.1.4. Summary

Behaviorally, participants showed a high level of accuracy in the target detection task. The novelty- and target-P3 amplitudes decreased from pre- to post-measurement. However, we found no evidence for a modulation of task performance and novelty- and target-P3 amplitudes by tDCS.

Table 1
Reaction times and total number of errors in the active oddball task.

		Pre		Post	
		M	SD	M	SD
RT	Anodal	384	49.3	376	59.7
	Cathodal	387	54.9	385	77.5
	Sham	371	52.2	374	55.7
Errors	Anodal	1.3	2.7	1.9	4.7
	Cathodal	1.3	1.8	1.2	1.8
	Sham	2.3	3.5	1.5	3.5

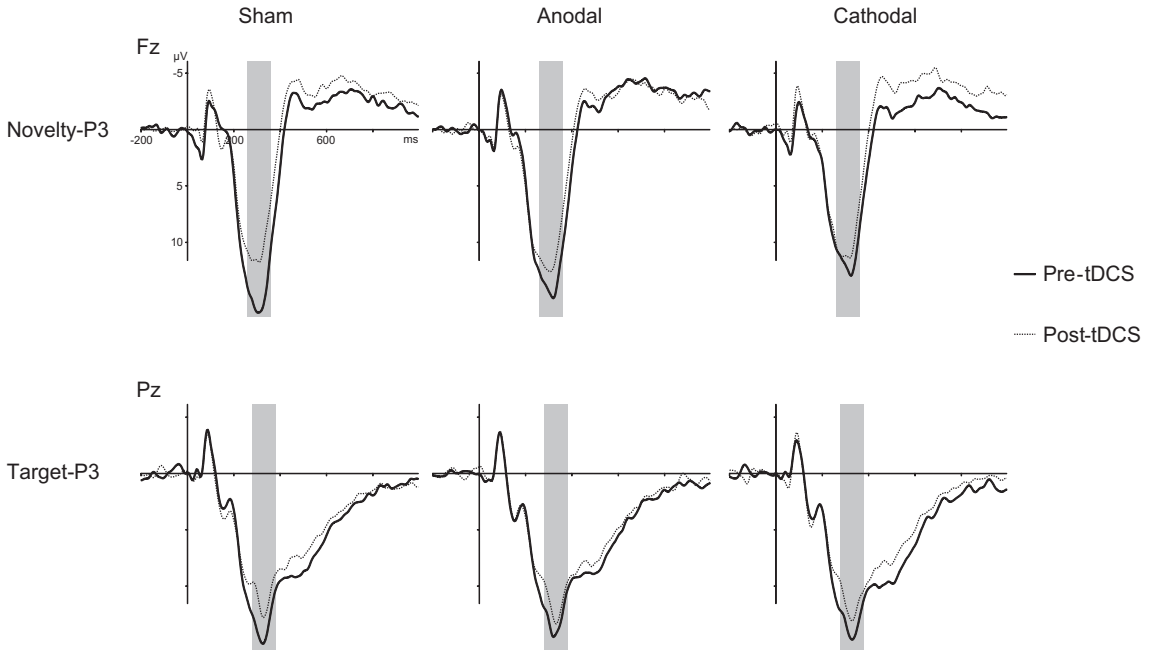

Fig. 3. Pre- and post-tDCS novelty- and target-P3 for the sham, anodal and cathodal conditions at the electrodes Fz and Pz: The gray bars indicate the selected time windows for calculating the mean novelty- and target-P3 amplitudes (260–360 ms and 280–380 ms for novelty- and target-P3, respectively). Positive values are plotted downwards.

Table 2
Main analyses of the novelty- and target-P3 amplitudes, as well as the three MMN amplitudes for duration, frequency, and intensity deviants. When sphericity assumption was violated, Greenhouse–Geisser corrected degrees of freedoms were used for calculating the *p* values, as indicated by the presence of the correction factor ε.

	Novelty-P3 ($N = 16$)	Target-P3 ($N = 18$)	MMN to duration ($N = 18$)	MMN to frequency ($N = 16$)	MMN to intensity ($N = 15$)
ELECTRODE	$F(2,30) = 6.3$ $p = .02^*$ Partial $\eta^2 = .30$ $\varepsilon = .64$	$F(2,34) = 36.6$ $p < .001^*$ Partial $\eta^2 = .68$ $\varepsilon = .72$	$F(2,34) = 56.2$ $p < .001^*$ Partial $\eta^2 = .77$ $\varepsilon = .63$	$F(2,30) = 50.7$ $p < .001^*$ Partial $\eta^2 = .77$ $\varepsilon = .62$	$F(2,28) = 64.6$ $p < .001^*$ Partial $\eta^2 = .82$ $\varepsilon = .71$
TDCS	$F(2,30) = 0.2$ $p = .86$ Partial $\eta^2 = .01$	$F(2,34) = 0.1$ $p = .90$ Partial $\eta^2 = .00$ $\varepsilon = .72$	$F(2,34) = 1.7$ $p = .20$ Partial $\eta^2 = .09$	$F(2,30) = 1.3$ $p = .28$ Partial $\eta^2 = .08$	$F(2,28) = 1.5$ $p = .24$ Partial $\eta^2 = .10$
TIME	$F(1, 15) = 22.2$ $p < .001^*$ Partial $\eta^2 = .60$	$F(1,17) = 10.8$ $p = .004^*$ Partial $\eta^2 = .39$	$F(1,17) = 13.2$ $p = .002^*$ Partial $\eta^2 = .44$	$F(1,15) = 4.8$ $p = .04^*$ Partial $\eta^2 = .24$	$F(1,14) = 6.7$ $p = .02^*$ Partial $\eta^2 = .33$
ELECTRODE × TDCS	$F(4,60) = 4.0$ $p = .03^*$ Partial $\eta^2 = .21$ $\varepsilon = .50$	$F(4,68) = 0.8$ $p = .52$ Partial $\eta^2 = .05$	$F(4,68) = 2.4$ $p = .10$ Partial $\eta^2 = .12$ $\varepsilon = .60$	$F(4,60) = 2.9$ $p = .07$ Partial $\eta^2 = .16$ $\varepsilon = .52$	$F(4,56) = 0.6$ $p = .59$ Partial $\eta^2 = .04$ $\varepsilon = .52$
ELECTRODE × TIME	$F(2,30) = 0.4$ $p = .55$ Partial $\eta^2 = .03$ $\varepsilon = .57$	$F(2,34) = 5.5$ $p = .02^*$ Partial $\eta^2 = .25$ $\varepsilon = .68$	$F(2,34) = 1.1$ $p = .31$ Partial $\eta^2 = .06$ $\varepsilon = .64$	$F(2,30) = 0.6$ $p = .55$ Partial $\eta^2 = .04$	$F(2,28) = 6.4$ $p = .005^*$ Partial $\eta^2 = .32$
TDCS × TIME	$F(2,30) = 2.2$ $p = .13$ Partial $\eta^2 = .13$	$F(2,34) = 1.4$ $p = .27$ Partial $\eta^2 = .07$	$F(2,34) = 0.9$ $p = .40$ Partial $\eta^2 = .05$	$F(2,30) = 0.8$ $p = .47$ Partial $\eta^2 = .05$	$F(2,28) = 1.2$ $p = .32$ Partial $\eta^2 = .08$
ELECTRODE × TDCS × TIME	$F(4,60) = 1.2$ $p = .30$ Partial $\eta^2 = .08$ $\varepsilon = .50$	$F(4,68) = 0.1$ $p = .94$ Partial $\eta^2 = .01$ $\varepsilon = .64$	$F(4,68) = 4.4$ $p = .01^*$ Partial $\eta^2 = .21$ $\varepsilon = .66$	$F(4,60) = 0.7$ $p = .50$ Partial $\eta^2 = .05$ $\varepsilon = .50$	$F(4,56) = 3.9$ $p = .02^*$ Partial $\eta^2 = .22$ $\varepsilon = .63$

$^*p < .05$.

3.2. Passive oddball

Fig. 4 shows the grand average ERP waveforms of the MMN to duration, frequency, and intensity deviants at the Fz electrode in the passive oddball condition for the three stimulation protocols, as well as the ERPs to standard tones. The results of the main analyses for the MMN to all three kinds of deviants are shown in Table 2 and descriptive statistics are shown in Table 4. For all three kinds of deviants, post-tDCS MMN amplitudes were generally lower than pre-tDCS MMN amplitudes (Fig. 4).

Table 3
Mean amplitudes [in μV] of the novelty-P3 and the target-P3 at electrodes Fz and Pz, respectively: amplitudes values are based $N = 16$ (novelty-P3) and $N = 18$ (target-P3).

		Pre		Post	
		M	SD	M	SD
Novelty-P3	Anodal	13.6	8.4	11.4	7.0
	Cathodal	11.7	6.9	10.5	6.3
	Sham	14.9	7.2	10.5	6.2
Target-P3	Anodal	13.0	7.1	11.6	7.3
	Cathodal	13.4	8.1	11.7	8.0
	Sham	13.5	7.7	11.0	6.7

Table 4
MMN mean amplitudes [in μV] for duration ($N = 18$), frequency ($N = 16$) and intensity ($N = 15$) deviants at Fz.

		Pre		Post	
		M	SD	M	SD
Duration	Anodal	−4.8	1.7	−3.7	1.3
	Cathodal	−4.5	1.7	−3.6	1.8
	Sham	−4.5	1.7	−4.5	1.2
Frequency	Anodal	−4.2	1.4	−3.3	1.3
	Cathodal	−3.8	1.4	−3.6	1.9
	Sham	−3.9	1.7	−3.3	1.3
Intensity	Anodal	−4.1	1.4	−2.5	1.3
	Cathodal	−4.0	1.5	−3.4	1.3
	Sham	−3.5	1.6	−3.3	1.2

3.2.1. MMN to duration deviants

For duration deviants, the pre- to post-stimulation MMN reduction was modulated by electrode site and tDCS as evidenced by a significant three-way interaction between ELECTRODE, TDCS and TIME. Follow-up ANOVAs revealed that the three-way interaction was reliable when anodal tDCS was compared with sham stimulation ($F(2,34) = 8.1$, $p = .005$, partial $\eta^2 = .32$, $\varepsilon = .69$), but not when cathodal tDCS was compared with sham stimulation ($F(2,34) = 2.3$, $p = .14$, partial $\eta^2 = .12$, $\varepsilon = .63$) and when anodal tDCS was compared with cathodal tDCS ($F(2,34) = 2.6$, $p = .11$, partial $\eta^2 = .13$, $\varepsilon = .69$). Simple effect analyses for each electrode revealed reduced MMN amplitudes after anodal tDCS at Fz ($F(1,17) = 5.6$, $p = .03$, partial $\eta^2 = .25$), but not at Cz ($F(1,17) = .9$, $p = .35$, partial $\eta^2 = .05$) and Pz ($F(1,17) = .5$, $p = .47$, partial $\eta^2 = .03$), as compared to the sham condition.

3.2.2. MMN to frequency deviants

For frequency deviants, the pre- to post-stimulation MMN reduction was not modulated by tDCS.

3.2.3. MMN to intensity deviants

For intensity deviants, the pre- to post-stimulation MMN reduction was modulated by electrode and tDCS. There was a significant three-way interaction between ELECTRODE, TDCS and TIME. Follow-up ANOVAs revealed that the three-way interaction was reliable when anodal tDCS was compared with sham stimulation ($F(2,28) = 5.8$, $p = .02$, partial $\eta^2 = .29$, $\varepsilon = .71$) and when anodal tDCS was compared with cathodal tDCS ($F(2,28) = 6.5$, $p = .01$, partial $\eta^2 = .32$, $\varepsilon = .66$), but not when cathodal tDCS was compared with sham stimulation ($F(2,28) < .1$, $p = .94$, partial $\eta^2 < .01$, $\varepsilon = .63$). Simple effect analyses for each electrode again revealed reduced MMN amplitudes after anodal tDCS at Fz ($F(1,14) = 4.8$, $p = .046$, partial $\eta^2 = .25$), but not at Cz ($F(1,14) = 1.7$, $p = .22$, partial $\eta^2 = .11$) and Pz ($F(1,14) < .1$, $p = .85$, partial $\eta^2 < .01$), as compared to the sham condition.

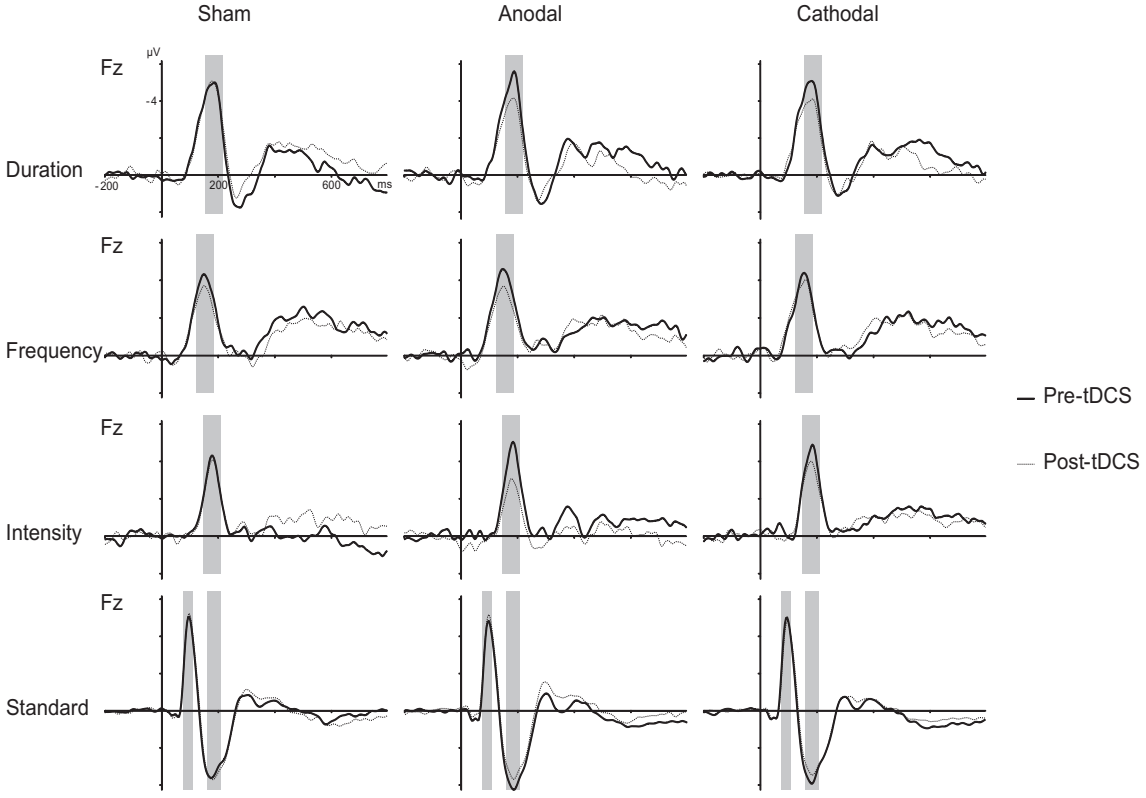

Fig. 4. Pre- and post-tDCS MMN for duration, frequency and intensity deviants and the waveform for standards for the three tDCS conditions at electrode Fz. Please note that MMNs are depicted as difference wave (ERPs to deviant minus ERP to standards). For the MMNs, the gray bars indicate the chosen time windows for calculating the mean amplitudes (120–180 ms for frequency deviants, 152–212 ms for duration and intensity deviants). For standards the first gray bar indicates the time window for calculating the mean amplitudes of the N100 (76–108 ms) and the second gray bar indicates the time window for calculating the mean amplitudes of the P200 (160–208 ms). Positive values are plotted downwards.

3.2.4. Further analyses

In order to assure that tDCS effects on the MMN are not attributable to differences in early auditory processing and attention processes, we also analyzed the components N100 and P200. There was a significant interaction between ELECTRODE, TDCS, and TIME for the N100 amplitude to standards ($F(4,68) = 3.7$, $p = .03$, partial $\eta^2 = .18$, $\varepsilon = .53$). Follow-up ANOVAs revealed that this interaction was only reliable when anodal tDCS was compared with cathodal tDCS ($F(2,34) = 5.8$, $p = .02$, partial $\eta^2 = .26$, $\varepsilon = .61$). The N100 for standards was stronger at frontal sites after anodal tDCS than after cathodal tDCS ($F(2,34) = 5.6$, $p = .02$, partial $\eta^2 = .25$, $\varepsilon = .71$). The pre-post change was significant for anodal ($F(2,34) = 5.5$, $p = .02$, partial $\eta^2 = .25$, $\varepsilon = .62$), but neither for cathodal ($F(2,34) = 1.1$, $p = .33$, partial $\eta^2 = .06$, $\varepsilon = .66$) nor sham tDCS ($F(2,34) = .6$, $p = .49$, partial $\eta^2 = .03$, $\varepsilon = .61$). No such tDCS effects were observed for the N100 for duration deviants, frequency deviants, and intensity deviants or the P200 for standards (all Fs < 2.6, $p > .07$). These findings indicate that the tDCS-induced MMN modulations were not due to altered early processing of standard and deviant tones.

3.2.5. Summary

MMN amplitudes decreased from pre-tDCS to post-tDCS. Left-frontal anodal tDCS led to significantly stronger pre- to post-stimulation reductions of the MMN at frontal recording sites, as compared to the sham condition. This effect was found for duration and intensity deviants, but not for frequency deviants. The effect was specific to anodal tDCS for intensity deviants, whereas the effects on the MMN for duration deviants did not significantly differ between anodal and cathodal tDCS. Analyses of the N100 and P200 indicated that the observed MMN modulations cannot be attributed to an impact of tDCS on the standard tone processing.

4. Discussion

In this single-blind study, we found that anodal tDCS over the left DLPFC selectively modulated the MMN to duration and intensity deviants. However, no such effect was observed for cathodal tDCS. The MMN to frequency deviants as well as the novelty- and target-P3 amplitudes were not modulated by tDCS.

4.1. Active oddball paradigm

The absence of tDCS-effects on novelty- and target-P3 amplitudes during active auditory discrimination was unexpected, because previous studies reported a modulation of the target-P3 amplitude by tDCS (e.g. Keeser et al., 2011; Nakamura-Palacios et al., 2012) and imaging and lesion studies implied that the PFC is involved in novelty-P3 generation. The absence of tDCS effects cannot be explained by a fading of such effects, because reliable tDCS effects were observed later on in the experiment during the passive oddball task (see Fig. 1). However, the absence of effects in the active oddball condition might possibly be explained by the choice of the current strength and stimulation duration. Keeser et al. (2011) found increased P3 amplitudes after 20 min of 2 mA anodal tDCS over the left DLPFC, whereas Zaehle et al. (2011) did not find such a modulation after 15 min of 1 mA tDCS over the same region. Thus, one might speculate that the stimulation parameters in our study (15 min, 1 mA) were suboptimal for observing tDCS effects on the P3. Because both, novelty- and target-P3, are supported by widely distributed networks (e.g. Bledowski et al., 2004; Wronka et al., 2012), other cortical areas might have compensated for these rather weak tDCS-induced changes in activity of the left DLPFC (Jacobson et al., 2012b). Higher current strengths and longer stimulation duration might possibly produce stronger changes in novelty- and target-P3 (Nitsche and Paulus, 2000, 2001). The absence of effects for the target-P3, however, might also indicate that the tDCS effects for the target-P3 in auditory oddball tasks observed in clinical populations (Khedr et al., 2014; Nakamura-Palacios et al., 2012) do not necessarily generalize to healthy subjects. The margin for improvement and increases in ERP amplitudes in healthy subjects with normal functioning in target detection might be smaller than in clinical populations, where tDCS is mainly applied to improve impoverished functions (e.g. Holland and Crinion, 2012; Khedr et al., 2014).

Moreover, as the effectiveness of tDCS depends on the orientation of the neurons relative to the electrical field (Miranda et al., 2006; Stagg and Nitsche, 2011), varying the exact placement of the electrodes can change the effect of tDCS (e.g. Antal et al., 2004; Nitsche and Paulus, 2000). Thus, future tDCS studies that seek to explore the involvement of the left DLPFC in the generation of the novelty- and target-P3 should vary the position of the return electrode (e.g. choosing extracranial locations like the cheek or the chin instead of the right supraorbital area) while leaving the active electrode over the left DLPFC. One especially promising approach might be oppositional tDCS (Jacobson et al., 2012a). Here, the anode can be used to excite one region (e.g. DLPFC), while the cathode can be used to simultaneously inhibit another region (e.g. temporo-parietal junction). By this approach it is possible to dissociate the contribution of two cortical regions that are activated during the same task, but associated with different cognitive processes. Jacobson et al. (2012a) have successfully employed this approach to investigate the role of the left intraparietal sulcus/superior parietal cortex and the right inferior parietal cortex in encoding of episodic information. Thus, oppositional tDCS over DLPFC and temporo-parietal junction might be more effective in modulating novelty- and target-P3 activity than stimulating either the DLPFC or the temporo-parietal junction with the return electrode placed over a neutral area.

4.2. Passive oddball paradigm

During passive auditory discrimination we observed tDCS-effects for the MMN to duration and intensity deviants. After anodal tDCS over the left DLPFC, MMN amplitudes were significantly reduced for these deviant types as compared to the sham condition. However, no such decrease was observed for frequency deviants. These results complement and extend the results of Chen et al. (2014), who found that anodal tDCS over the *right* DLPFC modulated the MMN amplitude to frequency deviants but not to duration deviants. Our finding provides further evidence that different kinds of sound deviance are processed in different regions within the PFC. This notion is consistent with a recent meta-analytical review of brain imaging studies that showed that MMN generators of frequency deviants were located mostly on the right frontal cortex, whereas the MMN generators for duration deviants were found bilaterally in the frontal cortices (Deouell, 2007; see also Molholm et al., 2005). Evidence for frontal MMN generators for intensity deviants has so far been scant (Kircher et al., 2004; Mathiak et al., 2002). Together with the findings of Chen et al. (2014), our data indicate that the involvement of the prefrontal cortex in the processing of different kinds of sound deviance varies between hemispheres: intensity and duration deviance appears to be processed predominantly in the left PFC and frequency deviance is presumably processed to a greater extent in the right PFC. However, due to the large size of the tDCS electrodes in the study by Chen et al. (2014) and in our study, it is not possible to conclude which area(s) in the PFC precisely are involved in MMN generation. Even though the tDCS montage in our study was chosen to target the DLPFC, areas surrounding the DLPFC might have been stimulated as well. Future studies should therefore aim at reducing the size of the stimulation electrode

which leads to more focal stimulation (e.g. Datta et al., 2009; Nitsche et al., 2007). However, safety concerns have to be considered in such a case, because reduced electrode sizes also increase the risk of skin irritations (Datta et al., 2009).

In the study by Chen et al. (2014) as well as in our study, the MMN amplitudes were *reduced* after anodal tDCS. At first glance, it might seem counterintuitive that anodal tDCS over the DLPFC is associated with a reduction of MMN amplitudes, since anodal tDCS is usually associated with an enhancement of neural activity (e.g. Jacobson et al., 2012b) and since tDCS over the auditory cortices leads to *increased* MMN amplitudes (Heimrath et al., 2015; Impey and Knott, 2015; see also Yang et al., 2013, for TMS evidence). However, according to Rinne et al. (2005), the frontal generators of the MMN might be part of an inhibitory system that enables the participants to ignore the changes in the auditory input that do not require a response. In this view, the excitatory effect of anodal tDCS on the PFC might have supported the inhibitory function of the PFC to suppress the change related activity. As a consequence, MMN amplitudes were reduced after anodal tDCS. However, it might also be possible that anodal tDCS led to a faster habituation to the deviant and, by this, to decreased MMN amplitudes (McGee et al., 2001; Rosburg et al., 2004). Since anodal tDCS has been shown to increase habituation to repetitive visual stimuli (Viganò et al., 2013), the reduction of the MMN amplitude to frequency deviants observed by Chen et al. (2014) and to duration and intensity deviants in the present study might actually represent more effective learning in form of an increased habituation. Still another alternative explanation for our results might be related to the depth of stimulation. Purpura and McMurtry (1965) found that the effect of anodal and cathodal DC polarization on cats was reversed for deeper cortical structures. Here, anodal tDCS led to a deactivation and cathodal tDCS led to activation. Even though tDCS is supposed mainly to affect the cortical surface (e.g. Nitsche and Paulus, 2001), it might be the case that the tDCS montage chosen for this study affected deeper cortical structures and as a consequence, anodal tDCS might have exerted an inhibitory influence on the MMN in our study. Future studies should therefore aim at varying both, tDCS-related and MMN-related parameters to decide between these different explanations.

In contrast to anodal tDCS, cathodal tDCS did not modulate the MNN, neither when the right DLPFC is targeted as in the study by Chen et al. (2014) nor when the left DLPFC is targeted as in our study. These results are in line with an rTMS study by Laloyaux et al. (2006). They found that stimulation of the left and right PFC with 1 Hz rTMS, which is also supposed to exert inhibitory effects, did not affect the MMN amplitude to frequency deviants. This result together with Chen et al. (2014) and our results might indicate that the DLPFC reacts differently to inhibitory and excitatory stimulation. Inhibitory effects of cathodal tDCS are more often observed when motor functions are studied rather than cognitive functions, while the facilitating effect of anodal tDCS is well documented for both, motor and cognitive functions (see Jacobson et al., 2012b, for a review and meta-analysis). Jacobson and colleagues speculated that this difference might be due to the fact that cognitive functions are supported by wide-spread cortical networks which compensate for the down-regulation via cathodal tDCS.

5. Conclusion

In conclusion, this study shows that anodal tDCS over the left DLPFC reduces the MMN to duration and intensity deviants and extends on previous research showing that anodal tDCS over the right DLPFC reduces the MMN to frequency deviants (Chen et al., 2014). Together, these results imply that information about the type of deviance is processed in different regions within the PFC and that the frontal MMN generator might be functionally related to inhibition of change related, response-irrelevant activity (Rinne et al., 2005) or habituation to stimulus change (McGee et al., 2001; Rosburg et al., 2004). Further studies are needed to determine the exact function of the frontal MMN generator and tDCS might be a suitable tool for this task.

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