

Domain-specific suppression of auditory mismatch negativity with transcranial direct current stimulation

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HIGHLIGHTS

- Mismatch negativity for duration and frequency deviants is recorded in healthy subjects following anodal and cathodal stimulation using tDCS.
- MMN to frequency deviants was significantly reduced after anodal tDCS.
- tDCS could be a useful method to manipulate MMN for experimental purposes.

ABSTRACT

Objective: To evaluate the influence of frontal transcranial direct current stimulation (tDCS) on auditory mismatch negativity (MMN).

Methods: MMN is an event related potential calculated by subtracting the amplitude of the evoked potentials in response to a “standard” stimulus from the evoked potentials produced by a rare “oddball” stimulus. Here we assessed the influence of anodal tDCS, cathodal tDCS or sham stimulation delivered over the right inferior frontal cortex on MMN in response to duration and frequency auditory deviants in 10 healthy subjects.

Results: MMN to frequency deviants was significantly reduced after anodal tDCS compared with sham or cathodal stimulation which did not change MMN to frequency deviants. Neither anodal nor cathodal tDCS had any effect on MMN to duration deviants.

Conclusions: Non-invasive brain stimulation with tDCS can influence MMN. The differing networks known to be activated by duration and frequency deviants could account for the differential effect of tDCS on duration and frequency MMN.

Significance: Non-invasive brain stimulation could be a useful method to manipulate MMN for experimental purposes.

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Introduction

There are often enormous numbers of competing stimuli for our attention at any one time, but we are typically unaware of these until they reach a certain threshold. One indication that a stimulus could be salient is that a previously established pattern has altered. It would seem likely to be biologically useful for such a change to be detected and to bias towards an “involuntary” switch in attention towards the novel stimulus. An electrophysiological measure

of this change detection mechanism is proposed to be mismatch negativity (MMN), a negative component of the event related potential (ERP) occurring at about 150–250 ms (Sams et al., 1985) and which is calculated by subtracting the ERP from a standard repeated stimulus from that produced by a rare “oddball” stimulus. The MMN has been characterized as an automatic, pre-attentive, change detection mechanism that may aid switch in attention towards a salient stimulus as well as assisting with contrast enhancement on sensory data. MMN has been most studied in the auditory domain where a variety of deviant stimuli have been demonstrated to be capable of causing MMN from simple changes in frequency or duration of a tone (Näätänen et al., 1989; Sams

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et al., 1985) to complex rule violations such as alteration in a single note of a repeated sequence (Tervaniemi et al., 1994) or even the absence of an expected tone (Yabe et al., 1997). MMN has also been reported for visual (Alho et al., 1992) and somatosensory stimuli (Friston, 2005; Friston et al., 2003; Garrido et al., 2007, 2008; Naatanen, 2009; Shinozaki et al., 1998). MMN occurs in the absence of attention towards the stimulus (Naatanen et al., 1978) and can even be recorded during sleep (Sallinen et al., 1994).

It has been proposed that auditory MMN arises from a network of hierarchically connected structures including the superior temporal gyrus and the inferior and medial frontal gyrus, with a dynamic causal model proposing that the frontal regions represent the highest point of this hierarchical system (Friston, 2003, 2005; Garrido et al., 2007, 2008, 2009). This model integrates other theories of MMN (“model adjustment”, “adaptation”) within a predictive coding model where MMN can be seen as a failure to accurately predict bottom-up sensory data resulting in a prediction error signal. Previous fMRI studies have provided evidence that cortical networks activated by frequency and duration deviants are different in some respects, with more widespread medial and superior activations in frontal regions to duration compared with frequency deviants, suggesting that the MMN does not just signal that a salient event has occurred, but also the nature of that event (Molholm et al., 2005). There is interest clinically in the MMN given its abnormality (typically absence) in a number of neurological/neuropsychiatric disorders, most notably schizophrenia (Umbricht et al., 2003a), but also dyslexia (Baldeweg et al., 1999) and in patients with more general learning difficulties (Mowszowski et al., 2012).

There has been interest experimentally in manipulating MMN, both to explore the veracity of current models for generation of MMN, and also to explore behavioral effects. This manipulation has been achieved with ketamine, though with considerable inter-subject variability of effect, small effect size, and with side effects expected with use of a psychoactive drug (Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000, 2002). Repetitive transcranial magnetic stimulation (rTMS) has been explored as a potential modulator of MMN in one study, with no measurable effect (Hansenne et al., 2004). Transcranial direct current stimulation (tDCS) utilizes weak currents to alter polarity of cortical neurons non-invasively, and depending on the type of stimulation (anodal or cathodal) long-term potentiation (LTP) or long-term depression (LTD)-like effects can be produced (Nitsche et al., 2003a). Here we sought to explore if delivering tDCS over a brain region known from fMRI studies to be activated during auditory MMN could modulate the amplitude of MMN. We chose to stimulate the right frontal region as the right inferior frontal gyrus has shown MMN related activation in both frequency and duration auditory MMN studies using fMRI, while the left frontal region shows activations with duration but not frequency MMN. We were uncertain of the likely direction of this effect given the possibility for both direct and homeostatic plastic effect on stimulated neurons. Further, we wished to exclude a placebo effect caused by the experimental set-up itself and therefore we additionally compared the effect of sham tDCS on MMN with a MMN recording session without tDCS.

Materials and methods

We studied 10 subjects (8 men and 2 women, mean age 32 years; range 23–38 years). Subjects had no history of major neurological or other illness and were not taking medication at the time of the study. They gave written informed consent to participate in the study, and all of the procedures were approved by

the National Hospital of Neurology and Neurosurgery and the Institute of Neurology Research Ethics Committee, UK.

Each subject was assessed on four different occasions (non-tDCS, sham tDCS, anodal tDCS, and cathodal tDCS), and each experimental session was separated by at least 7 days. In the three tDCS recordings (sham, anodal and cathodal) electrodes were applied for 25 min and then removed immediately. Hair was dried with a hair-dryer within 30 s. After that, an EEG cap was put on and gel was infused. The order of all 4 recording sessions was counterbalanced across subjects.

Assessment of MMN

Auditory stimuli were delivered via a single speaker placed 0.5 m in front of subjects. In order to ensure that the stimuli were clearly audible, the intensity was set at 65 dB which was considerably above the auditory threshold of all subjects. The experiment consisted of two blocks: duration deviation and frequency deviation. Each block included 1000 trials; blocks were separated by 2 min and the orders of the blocks were counterbalanced across subjects. Oddball stimuli were pseudorandomly delivered in 20% of the trials. The interstimulus interval was 0.51 s. The overall EEG recording was 19 min. Standard and oddball stimuli for the duration difference MMN were played for 50 ms and 100 ms, respectively, with a constant pitch frequency of 333 Hz while standard and oddball stimuli for the frequency difference MMN had a pitch of 333 Hz and 353 Hz, respectively, and were played with a constant duration of 50 ms.

Transcranial direct current stimulation

Electric stimulation was applied via two saline rinsed sponges of 5 × 7 cm. Depending on the type of stimulation, the anodal or cathodal electrode was placed over the right frontal cortex (F4) and the reference electrode placed over the left supraorbital area. A constant current of 2.0 mA was applied for 25 min, with a linear fade in/fade out of 10 s in anodal and cathodal conditions. Sham stimulation was applied with the sponges placed in the same position, but the stimulation was stopped unbeknownst to the subject after 30 s of stimulation, also with a linear fade in/fade out of 10 s. (Galea et al., 2009; Hamada et al., 2012).

EEG recordings and analysis

Subjects sat on a comfortable chair with their hands supported on a pillow. A self-chosen video with no sound was played during the experiment with the monitor placed 0.5 m away from the subjects. Thirty Ag/AgCl scalp electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, O2) placed according to the 10–20 system were used for electroencephalogram (EEG) recording. Electrode impedance was kept below 5 kΩ. During recording, the sampling rate was set at 512 Hz, and data were online filtered with 0.3–100 Hz band-pass filter. After recording, the data were band-pass filtered at 1–30 Hz and average reference was used both online recording and offline analysis. Epochs of –50 to 500 ms were extracted using EEGLab V.11 software (<http://sccn.ucsd.edu/eeglab/>). Baseline correction was applied with respect to a time window 50 ms prior to stimulus onset. Artifacts exceeded 100 μV were automatically rejected. EEG sweeps were averaged per individual and the MMN was calculated by subtraction of deviants from standard ERPs.

Data were analyzed using SPSS (version 20.0). Averaged mismatch negativity waveforms of the anodal tDCS, cathodal tDCS, and sham tDCS stimulation conditions were first compared for duration and frequency oddball stimuli to test the effect of tDCS.

We assessed the peak amplitude and peak latency of MMN in a time window from 150 ms to 250 ms, which is in line with other auditory MMN studies (Naatanen et al., 2007). Also, in order to examine the possibility that differences in the MMN between tDCS stimulation conditions could be due to differences caused by an alteration of auditory processing and not by deviant detection, we further analyzed the peak amplitude and peak latency of P1, N1, and P2 components of the ERP to standard stimuli. The P1 component was defined as the most positive peak occurring in the first 100 ms after stimulus onset, the N1 component as the most negative peak in the 50–150 ms window and the P2 component as the most positive peak between 100 and 250 ms. (Gallinat et al., 2003; McKetin et al., 1999). Additionally, to test it was reasonable to compare effect of the anodal and cathodal stimulation sessions with the sham stimulation session, we compared the peak amplitude and latency of MMN for the non-tDCS session with the sham condition.

Stimulation effect comparison

Our statistical analyses proceeded in two steps. First, to identify the electrode with maximal MMN or P1, N1, P2 effects separately and to test for differences in scalp distribution between the experimental session and stimulus type (frequency/duration deviant), multivariate repeated measures analyses of variance were performed with normalized data on 9 leads (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4). Data were normalized for this first step in order to equate amplitude differences between conditions which might distort distribution effects (McCarthy and Wood, 1985). 4-way repeated measures GLM on normalized data with the factors laterality (3 levels: left, medium, right), anterior–posterior (3 levels: frontal, central, parietal), tDCS conditions (3 levels: sham, anodal, cathodal), and stimulus type (2 levels: duration and frequency deviants) were run to identify the electrode with maximal MMN or P1, N1, P2 across conditions. Having identified the electrode with the maximal effect of the MMN or P1, N1, P2, we then assessed in a second step tDCS condition and stimulus type effects on non-normalized data in a two-way repeated measures GLM. In these analyses, we focused only on the electrode which emerged as the electrode with the maximal effect from the localization analyses. Finally, follow-up pairwise comparisons were run to assess the effect within levels of the tDCS condition or stimulus-type factor. Only effects with effect sizes $>.35$ (based on the intraclass correlation coefficient: ρ_I) were considered for follow-up analyses to avoid reporting non-essential effects. Greenhouse-Geisser corrected results are reported when assumptions of sphericity were not met and Bonferroni correction was used for pairwise comparisons.

The peak latency of MMN or P1, N1, P2 was later tested at the electrode selected by the peak amplitude in stimulation effect comparison. Two-way repeated measures GLM on non-normalized data for tDCS condition effects, stimulation type effects and interaction effect was run.

Placebo effect comparison

As described above, a 4-way repeated measures GLM on normalized data with the factors laterality (3 levels: left, medium, right), anterior–posterior (3 levels: frontal, central, parietal), tDCS conditions (2 levels: non-tDCS, sham TDCS), and stimulus type (2 levels: duration and frequency deviants) were run to identify the electrode with maximal MMN across conditions. Following this, a two-way repeated measures GLM of non-normalized data focused on the maximal effect electrode and then follow-up pairwise comparisons were performed. The peak latency of MMN was separately

assessed with the same procedure at the electrode selected by the peak amplitude.

Results

Average time between tDCS stimulation and recording was 8.1 ± 0.9 min. Of the 10 subjects tested, neither of them was aware of the different stimulation types nor reported any side effect except an itching sensation during the start of the stimulation.

Mismatch negativity

The number of accepted trials was comparable between pitch and duration deviants and between the tDCS conditions. An MMN was observed after both frequency and duration deviants. Fig. 1 shows the grand average of MMN in each condition at the Fz electrodes.

Stimulation effect comparison

In a first step, a four-way repeated measures GLM for localization (stimulation condition*stimulus type*anterior–posterior*laterality) on normalized data was conducted to examine the electrodes with the largest MMN effects across conditions for later tests of the condition effects. In line with a previous study (Garrido et al., 2008), we observed the largest MMN effect at the Fz electrode (anterior–posterior*laterality interaction; $F(2,0,18.4) = 5.5$, $p < 0.01$, $\rho_I = 0.60$). As can be seen in Fig. 2, the distribution of the MMN did not differ across stimulation conditions (tDCS condition*anterior–posterior*laterality interaction; $F(3.4,30.8) = 0.4$, $p = 0.77$) or stimulus types (stimulus type*anterior–posterior*laterality interaction; $F(4,36) = 0.8$, $p = 0.55$) and was largest at frontocentral electrodes. Accordingly, we focused in a second step on the Fz electrode for further 2-way repeated measures GLM of non-normalized data to assess the tDCS condition and stimulus type effects. A significant main effect of stimulus type ($F(1,9) = 9.8$, $p = 0.01$, $\rho_I = 0.81$) indicated larger MMNs in the duration condition (cf. Fig. 3). No main effect of tDCS condition was observed ($F(2,18) = 0.8$, $p = 0.47$). However, a significant tDCS condition*stimulus type interaction effect was observed ($F(1.2, 10.7) = 4.8$, $p = 0.04$, $\rho_I = 0.63$). As can be seen in Fig. 3A, follow-up repeated measures GLM for stimulus-types were applied separately and showed no stimulation effect on duration MMN ($F(2,18) = 0.5$, $p = 0.62$), but a significant stimulation effect on frequency MMN ($F(2,18) = 11.7$, $p = 0.00$, $\rho_I = 0.78$). For frequency MMN, follow-up pairwise comparisons with Bonferroni correction showed a smaller MMN following anodal tDCS stimulation (mean difference anodal-sham: $0.57 \mu\text{V}$, $p = 0.01$, $t = 3.71$; anodal-cathodal: $0.92 \mu\text{V}$, $p = 0.01$, $t = 4.43$) whereas the other stimulation conditions did not differ from each other (cf. Fig. 3A). A consistent reduction in MMN amplitude with a mean reduction of 37% (range 5–93%) was shown following anodal stimulation for frequency MMN compared to sham stimulation (Fig. 4). The latency of MMN showed no significant main effect or interaction effect with stimulation type*tDCS condition at Fz (two-way repeated measures ANOVA, stimulation type: $F(1,9) = 3.4$, $p = 0.10$; tDCS condition: $F(2,18) = 1.6$, $p = 0.22$; stimulation type*tDCS condition: $F(3,27) = 0.6$, $p = 0.55$). (Fig. 3B).

Auditory evoked potentials to standard tones

Table 1 shows the peak amplitudes and latencies of P1, N1 and P2 to standard tones for sham, anodal, and cathodal conditions for the maximal effect electrode. With the same measure in MMN analysis, we first conducted a four-way repeated measures GLM

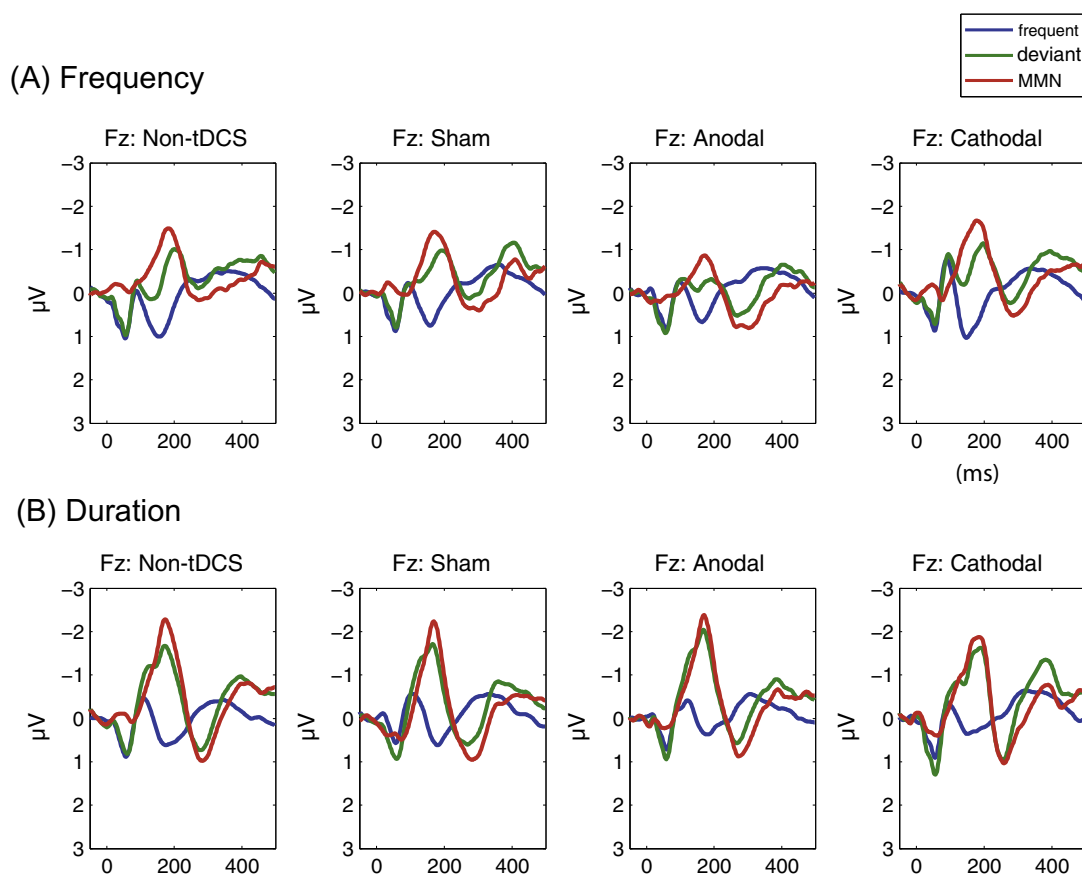


Fig. 1. (A) Grand average of standard (blue line), deviant (green line), and MMN (red line) ERPs at Fz in the frequency condition across 10 subjects in non-tDCS, sham, anodal and cathodal stimulation condition. (B) Grand average of standard, deviant, and MMN ERP at Fz in the duration condition across 10 subjects in non-tDCS, sham, anodal, and cathodal stimulation condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for localization (tDCS condition*stimulus type*anterior–posterior*laterality) on normalized data to examine the electrodes with the largest P1, N1, P2 effects separately across conditions for later tests of the condition effects. We observed the largest P1 and N1 effect at the Fz electrode (anterior–posterior*laterality interaction; $F(4,36) = 3.7$, $p = 0.01$, $\rho_I = 0.35$; $F(4,36) = 9.6$, $p = 0.00$, $\rho_I = 0.63$) and largest P2 at Cz electrode ($F(4,36) = 7.0$, $p = 0.00$, $\rho_I = 0.54$). We then focused on two-way repeated measures GLM on the maximal effect electrode to assess the tDCS condition and stimulus type effects. There was no significant stimulus type or stimulation condition main effect or condition*stimulus interaction effect for P1 latency, P1 amplitudes, N1 latency, N1 amplitudes, P2 latencies and P2 amplitudes (Table 1).

Placebo effect comparison

As described above, we observed the largest MMN effect at the Fz electrode (anterior–posterior*laterality interaction; $F(4,36) = 11.8$, $p \leq 0.00$, $\rho_I = 0.67$). As can be seen in Fig. 2, the distribution of the MMN did not differ between non-tDCS and sham conditions (tDCS condition*anterior–posterior*laterality interaction; $F(4,36) = 0.6$, $p = 0.67$) or stimulus types (stimulus type*anterior–posterior*laterality interaction; $F(4,36) = 0.18$, $p = 0.14$) and was largest at frontocentral electrodes as well. Accordingly, we focused in a second step on the Fz electrode for further 2-way repeated measures GLM of non-normalized data to assess the tDCS condition and stimulus type effects. A weak effect of stimulus type ($F(1,9) = 4.2$, $p = 0.07$) indicated probable a trend of larger MMNs

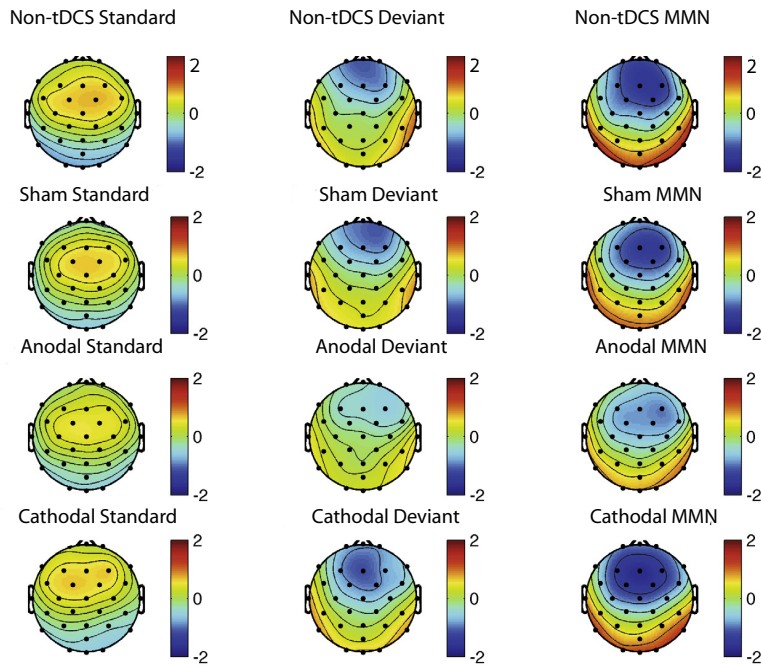
in the duration condition (cf. Fig. 3) similar to previous stimulation effect comparison. No main effect of tDCS condition ($F(1,9) = 0.2$, $p = 0.67$) or tDCS condition*stimulus type interaction effect ($F(1,9) = 0.14$, $p = 0.72$) was observed. The latency of MMN also showed no significant main effect or interaction effect of stimulation type*tDCS condition at Fz (two-way repeated measures ANOVA, stimulation type: $F(1,9) = 5.0$, $p = 0.05$; tDCS condition: $F(1,9) = 0.10$, $p = 0.76$; tDCS condition*stimulation type: $F(1,9) = 0.02$, $p = 0.89$). (Fig. 3B).

Discussion

Here we demonstrate that non-invasive brain stimulation with anodal tDCS is capable of reducing auditory MMN for frequency deviants. Anodal tDCS decreased amplitude of MMN for frequency but not duration deviants, compared with no effect from cathodal or sham stimulation. The dissociation between effects on frequency and duration MMN is consistent with previous reports that there are anatomical differences in frontal cortical areas activated during these stimuli (Molholm et al., 2005). The effect of tDCS on MMN may involve an action on NMDA dependent synapses given the similarity between the effect of anodal tDCS and some reports of ketamine administration (Umbricht et al., 2002, 2003b).

We found a specific effect of anodal tDCS on frequency, but not duration MMN. Auditory MMN is suggested to be generated by a hierarchically organised set of structures (Garrido et al., 2009). One of these is the superior temporal gyrus (STG) which has shown activation in previous fMRI, EEG and MEG studies to pitch, inten-

(A) Frequency



(B) Duration

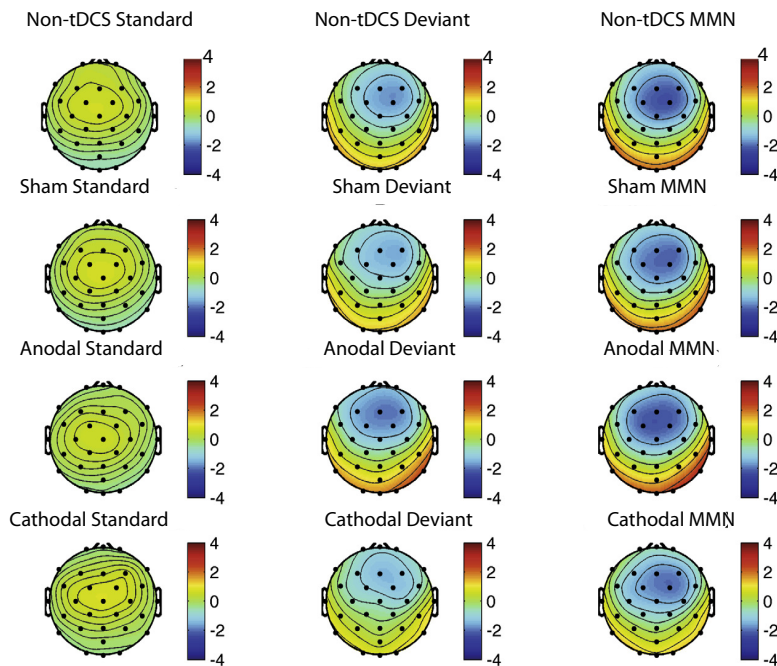


Fig. 2. Scalp topographies of standard, deviant, and MMN ERPs. Maps are based on mean amplitudes of a 50 ms interval around individually defined MMN peaks in a time window of 150–250 ms after stimulus onset (cf. Fig. 3B for average peak latencies). (A) Frequency stimulus condition, (B) duration stimulus condition. Consistent fronto-central maxima of the MMN were noted in each condition.

sity, and duration (Loveless et al., 1996; Paavilainen et al., 1991). In addition to the STG, activation is commonly reported in inferior frontal cortex (IFC) bilaterally for duration deviants and the right frontal area for frequency deviants (Rinne et al., 2005). The frontal region activated by frequency deviants (Opitz et al., 2002) is pos-

terior to and less extensive than that seen for duration deviants (Molholm et al., 2005). These anatomical differences between the networks activated by frequency and duration tDCS on frequency and duration MMN. Although it is not possible to have direct knowl-

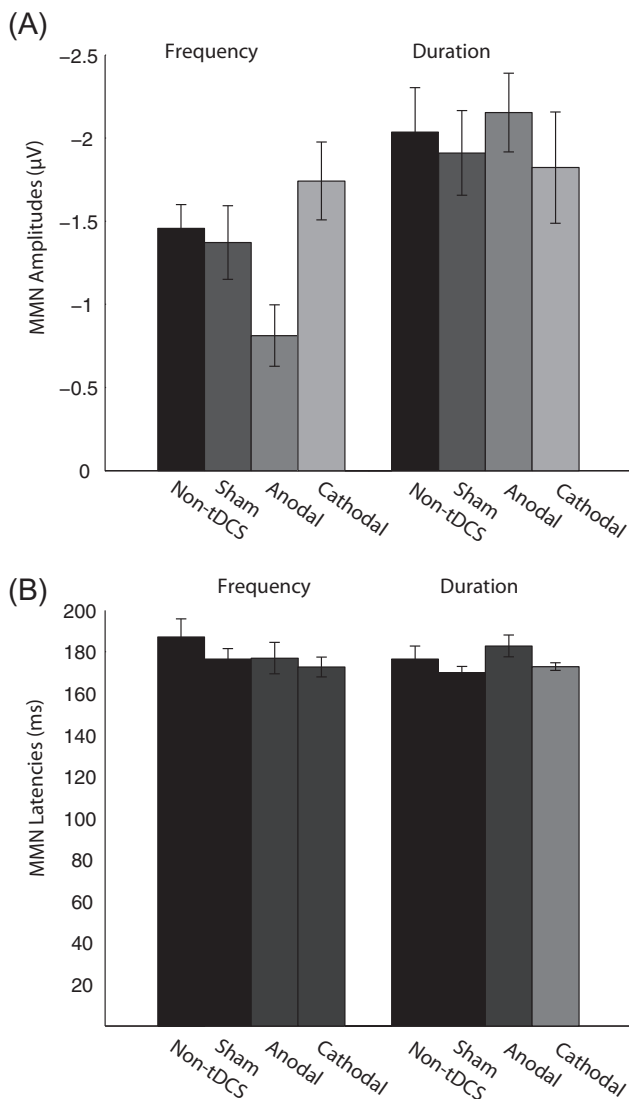


Fig. 3. (A) MMN peak amplitudes in non-tDCS, sham, anodal, and cathodal tDCS stimulation conditions for the frequency and duration stimulus condition at Fz electrode. (B) MMN peak latencies in non-tDCS, sham, anodal, and cathodal tDCS stimulation conditions for the frequency and duration stimulus condition at Fz electrode. Error bars indicate 1 SEM. MMN peak amplitudes in the frequency stimulus condition were significantly smaller after the anodal tDCS stimulation as compared to sham, or cathodal stimulation conditions.

edge of exactly how much current is received in different regions of the brain during tDCS, a simulation study has previously suggested that electrodes placed over F4 and the left supraorbital region as in our study should produce the largest current density in right IFG and right DLPFC compared to left IFG, DLPFC or basal ganglia (Sadleir et al., 2010). We speculate that the smaller right hemisphere frontal network underlying frequency MMN might be more vulnerable to effects of tDCS compared to the more distributed bilateral network activated by duration MMN.

Previous studies have sought to manipulate MMN, mainly using the NMDA antagonist ketamine, in order to model the effects in healthy subjects of the reduction in MMN seen in neuropsychiatric disorders such as schizophrenia. However, results from these studies are inconsistent (Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000, 2002), with increased, unaltered and reduced MMN all seen in some subjects, variable effects on fre-

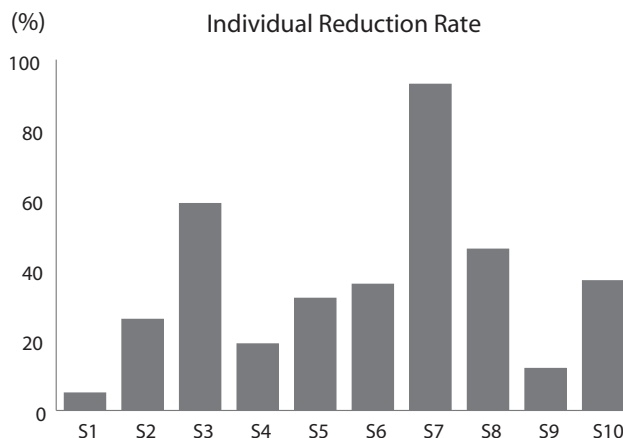


Fig. 4. Change in peak MMN amplitude for each subject comparing sham and anodal conditions. A mean reduction rate of 37% was found with a range from 5% to 93%.

quency and duration MMN, and only small (~20%) reductions in MMN seen in those subjects where ketamine does reduce MMN. rTMS has also been used in one study to alter MMN, but without any effect. rTMS may have an important limitations with regard to influencing MMN compared with tDCS, including the limited depth of stimulation, and its tendency to affect only tangentially orientated neurons (Ravazzani et al., 2002) and not radially orientated ones thought to mediate MMN (Rinne et al., 2000). In contrast, we have shown a consistent effect on frequency MMN in this study. The subjects showing a reduction in MMN amplitude with a mean reduction of 37% (range 5–94%). (Fig. 4). This demonstrates that tDCS may be a more reliable method to experimentally alter MMN non-invasively than other currently available methods.

We only found an effect of anodal tDCS on MMN, with the effect of cathodal tDCS for either frequency or duration MMN being no different from sham stimulation. Though it is difficult to speculate on the exact mechanism whereby frequency MMN is reduced by anodal tDCS, it is certainly of interest that MMN is also thought to be partly related to short-term glutamatergic plasticity (Stagg et al., 2009). The tDCS is thought to exert its effects through glutamate-dependent plasticity (for example in M1 effects of tDCS are blocked by NMDA antagonists) (Nitsche et al., 2003a), providing a clear area for interaction between the mechanism of MMN production and tDCS. While ketamine is proposed to have its effect on MMN via blockade of short-term glutamatergic plasticity due to NMDA receptor blockade, the effects we found would not be consistent with a similar mechanism of effect for anodal tDCS: one might in fact expect an enhancement of MMN via an LTP-like effect of anodal tDCS on superficial pyramidal cells that are proposed to encode prediction error and drive the MMN response. However, one explanation for our findings is that there is a homeostatic interaction where recent activity in superficial pyramidal cells renders them vulnerable to depression by an LTP-like stimulus via anodal tDCS. This would serve to decrease precision on prediction error at this level, therefore decreasing the amplitude of MMN (Friston, 2005). It is also possible to speculate that any alteration to network activity via tDCS will tend to disrupt MMN. A reduction in ERP components following anodal stimulation is not unprecedented (Accornero et al., 2007; Heimrath et al., 2012), suggesting that one cannot assume that anodal stimulation always increases ERP components. We did not find an effect of cathodal tDCS. It is of interest in this regard that some other studies have also failed to find an effect of cathodal tDCS in particular tasks when anodal tDCS has had effects, for example in a motor tapping

Table 1
 (A) Stimulation effect comparison: Mean and standard deviation of MMN, P1, N1 and P2 peak latencies and amplitudes to duration and frequency deviants for sham, anodal, and cathodal stimulation at the maximal effect electrode. A significant effect of stimulation type and stimulation type*tDCS condition was noted in the peak amplitude of MMN. (B) Placebo effect comparison: Mean and standard deviation of MMN peak latencies and amplitudes to duration and frequency deviants for non-tDCS and sham tDCS conditions at Fz electrode. No significant main effect or interaction effect of stimulation type*tDCS condition were observed.

	Frequency						Significance		
	Duration			Stimulation type			tDCS Condition	Condition*type	
	Sham	Cathodal	Anodal	Sham	Cathodal	Anodal			
(A) Stimulation									
Amplitude	MMN	-2.3 ± 1.0	-2.6 ± 0.9	-1.6 ± 0.8	-2.0 ± 0.7	-1.0 ± 0.7	F(2,18) = 0.8, p = .47	F(1.2, 10.7) = 4.8, p = .04	
	P1	0.7 ± 0.5	1.1 ± 0.9	1.0 ± 0.8	1.0 ± 0.8	0.9 ± 0.6	F(1,9) = .64, p = .44	F(1.0,9.4) = 1.0, p = .36	F(1.2,10.4) = .87, p = .39
	N1	-1.0 ± 0.5	-0.7 ± 1.0	-0.6 ± 0.8	-0.8 ± 1.2	-0.8 ± 0.6	F(1,9) = 0.0, p = .98	F(1.2,10.5) = 1.1, p = .79	F(2,18) = 0.3, p = .74
	P2	1.0 ± 0.5	1.1 ± 0.9	1.1 ± 0.7	1.3 ± 0.7	1.0 ± 0.7	F(1,9) = 1.0, p = .34	F(2,18) = 1.4, p = .27	F(2,18) = 2.2, p = .14
	MMN	172 ± 7	173 ± 15	181 ± 17	193 ± 25	179 ± 23	F(1,9) = 3.4, p = .10	F(2,18) = 1.6, p = .22	F(3,27) = 0.6, p = .55
	P1	59 ± 6	59 ± 7	52 ± 12	49 ± 14	54 ± 16	F(1,9) = 1.3, p = .28	F(1.2,10.5) = .3, p = .62	F(2,18) = .3, p = .74
Latency	N1	112 ± 18	107 ± 27	105 ± 22	93 ± 13	110 ± 25	F(1,9) = .8, p = .39	F(1.2,10.7) = 2.4, p = .15	F(1.1,10.0) = 1.0, p = .35
	P2	155 ± 11	151 ± 15	164 ± 23	155 ± 20	155 ± 29	F(1,9) = .35, p = .57	F(2,18) = .5, p = .61	F(1.3,11.4) = 0.77, p = .43
	Sham						tDCS Condition	Condition*type	
(B) Placebo									
Amplitude	MMN	-2.3 ± 1.0	-2.4 ± 0.9	-1.6 ± 0.8	-1.8 ± 0.5	-1.8 ± 0.5	F(1,9) = 4.2, p = .07	F(1,9) = 0.14, p = .72	
	MMN	172 ± 7	172 ± 6	181 ± 17	183 ± 16	183 ± 16	F(1,9) = 5.0, p = .05	F(1,9) = 0.10, p = .76	
Latency	MMN								
	MMN								

* p < 0.05.

task in fMRI study (Antal et al., 2011), a “3-back” working memory task (Fregni et al., 2005) and a motor learning task (Nitsche et al., 2003b).

We additionally tested if there was any non-specific effect of the tDCS set-up by comparing MMN recorded after sham tDCS with a non-tDCS condition. We found no significant differences between two conditions which suggest that there is no significant non-specific effect of the tDCS set-up on MMN.

It would be of great interest to explore the behavioural consequences of experimentally induced reduction (or indeed increase) of MMN. There has been surprisingly little work on behavioural correlates of MMN amplitude, and validated tasks that correlate with MMN amplitude are lacking. The clinical disorders characterised by reduction in MMN (schizophrenia, autism), while sharing some clinical characteristics also have many differences, and it is difficult to speculate on what clinical features (if any) are being driven by reduction in MMN. One could speculate that a reduction in MMN would render one relatively insensitive to involuntary shifts in attention towards potentially salient stimuli, and that this might in fact improve attentional focus, while also depriving one of orientation towards potentially important novel stimuli.

In summary, this study demonstrates that frontal anodal tDCS can reduce auditory MMN. This fits with the hypothesis that there is a frontal generator of MMN which is sensitive to non-invasive electrical stimulation. This provides a potentially useful way to modulate MMN for experimental purposes and deserves further exploration with different stimulation sites, and with a search for behavioural correlates of MMN suppression.

Conflict of interest

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