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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.

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 (Naatanen 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 noninvasively, 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 give 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, Fpz, 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.