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Transcranial direct current stimulation over the primary motor cortex during fMRI

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ABSTRACT

Measurements of motor evoked potentials (MEPs) have shown that anodal and cathodal transcranial direct current stimulations (tDCS) have facilitatory or inhibitory effects on corticospinal excitability in the stimulated area of the primary motor cortex (M1). Here, we investigated the online effects of short periods of anodal and cathodal tDCS on human brain activity of healthy subjects and associated hemodynamics by concurrent blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) at 3 T. Using a block design, 20 s periods of tDCS at 1 mA intensity over the left M1 altered with 20 s periods without tDCS. In different fMRI runs, the effect of anodal or cathodal tDCS was assessed at rest or during finger tapping. A control experiment was also performed, in which the electrodes were placed over the left and right occipito-temporo-parietal junction. Neither anodal nor cathodal tDCS over the M1 for 20 s stimulation duration induced a detectable BOLD signal change. However, in comparison to a voluntary finger tapping task without stimulation, anodal tDCS during finger tapping resulted in a decrease in the BOLD response in the supplementary motor area (SMA). Cathodal stimulation did not result in significant change in BOLD response in the SMA, however, a tendency toward decreased activity could be seen. In the control experiment neither cathodal nor anodal stimulation resulted in a significant change of BOLD signal during finger tapping in any brain area including SMA, PM, and M1. These findings demonstrate that the well-known polarity-dependent shifts in corticospinal excitability that have previously been demonstrated using measurements of MEPs after M1 stimulation are not paralleled by analogous changes in regional BOLD signal. This difference implies that the BOLD signal and measurements of MEPs probe diverse physiological mechanisms. The MEP amplitude reflects changes in transsynaptic excitability of large pyramidal neurons while the BOLD signal is a measure of net synaptic activity of all cortical neurons.

Introduction

Modulation of cortical excitability can be achieved by using external stimulation methods such as transcranial direct current stimulation (tDCS), also known as brain polarization. An early example of the clinical application of a brain polarization technique was done in 1802 shortly after invention of the voltaic pile (Hellwag, 1802). Over the centuries the method was tried several times and abandoned mainly due to lack of a sufficiently suitable evaluation method. This changed as soon as transcranial magnetic stimulation (TMS) was used for quantification of acute effects (Priori et al., 1998) and plastic aftereffects (Nitsche and Paulus, 2000). Anodal stimulation of the primary motor cortex (M1) increased the amplitude of motor evoked potentials (MEPs) while cathodal stimulation decreased them. Although MEPs are the most robust evaluation method, perceptual effects of tDCS applied over the visual areas were also found to be in accordance with its physiological effect and mirrored those after-effects achieved in the M1 (for a recent review see: Antal and Paulus, 2008).

tDCS is now a well-established non-invasive, painless technique for interventional use in research with potential therapeutic use in neurorehabilitation, chronic pain, focal epilepsy, and neuropsychiatric disorders (Webster et al., 2006; Fregni et al., 2006; Liebetanz et al., 2006; overview in Nitsche et al., 2008). tDCS induces membrane potential shifts dependent on stimulation strength, cortical layer and spatial orientation of stimulated neurons (Radman et al., 2009). Given sufficient stimulation duration the effect of stimulation can outlast the duration for several hours (Bindman et al., 1964; Nitsche and Paulus, 2001).

Neuroimaging techniques have the advantage of measuring correlates of neuronal activity both under the stimulating electrodes and also in remote brain regions during electrical stimulation, and was first implemented for tDCS studies using positron emission tomography (PET) (Lang et al., 2005) however, at the expense of radiation exposure. Combining blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) with

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concurrent tDCS allows for a non-invasive detailed examination of tDCS-induced effects throughout the brain. According to our knowledge, there is only one study published using concurrent fMRI and tDCS (Kwon et al., 2008). In this study anodal tDCS was applied to the scalp over the precentral knob of the left M1 using 4×21 s stimulation phases (resting-tDCS-tDCS-tDCS-tDCS). No cortical activation was detected in any of the stimulation phases except the fourth tDCS phase. Activation was found under the electrode but also in the left supplementary motor cortex and the right posterior parietal cortex. Here, cathodal stimulation was not applied. In the present study, therefore, we first addressed the question as to whether anodal and cathodal tDCS result in BOLD fMRI signal changes during a rest condition. Secondly, we examined the effects of tDCS on the brain network activated by a voluntary finger tapping task.

Materials and methods

Subjects

The study involved altogether 20 healthy volunteers (11 women; mean age, 25 ± 6 years; age range, 21–32 years). 13 subjects participated in the main experiment and 13 in the control session. Subjects were informed about all aspects of the experiments and all gave informed consent. Twelve of the subjects (from 20) were naive with regard to tDCS and all of the subjects were naive with regard to the purpose and aims of the study. None of the subjects suffered from any neurological or psychological disorders, had metallic implants/implanted electric devices, or took any medication regularly, and none of them took any medication in the 2 weeks before their participation in any of the experiments. All subjects were right handed, according to the Edinburgh handedness inventory (Oldfield, 1971). We conformed to the Declaration of Helsinki, and the experimental protocol was approved by the Ethics Committee of the University of Goettingen.

Transcranial direct current stimulation (tDCS)

Direct current was provided via a pair of square rubber electrodes (7×5 cm), manufactured to be compatible with the MR-scanner environment. The electrodes were equipped with 5.6 kΩ resistors in each wire to avoid sudden temperature increases due to induction voltages from radio frequency pulses. They were connected to a specially developed battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) outside the magnet room via a cable running through a radio frequency filter tube in the cabin wall (Fig. 1). Two filter boxes were placed between the stimulator and the electrodes. The characteristic bandwidth of the filters on the DC current path was chosen to have an approximate attenuation of 60 dB within a frequency range of 20–200 MHz to suppress the radio frequency impulse energy.

In order to properly position the electrodes over the M1 of the subjects' head, the representational field of the right hand was determined using suprathreshold TMS pulses. Before subjects entered the MR scanner, the electrodes were placed atop the respective left-hemispheric M1 hand area and above the contralateral right orbita using conventional electrode gel (Fig. 2). For cathodal tDCS, the cathode was placed above the M1, for anodal tDCS the direction of the electric flux was reversed. In the control experiment we tested whether the electrical stimulation could result in any non-specific effect due to e.g. increased attention. In order to avoid current flow through M1 and related motor areas, in a control experiment the two electrodes were placed over the occipito-temporo-parietal junction, centred between O1-P3 and O2-P4, respectively, according to the 10–20 system. Because tDCS functions in a bipolar way, in six cases the anode was placed over the right side and in seven cases over the left side.

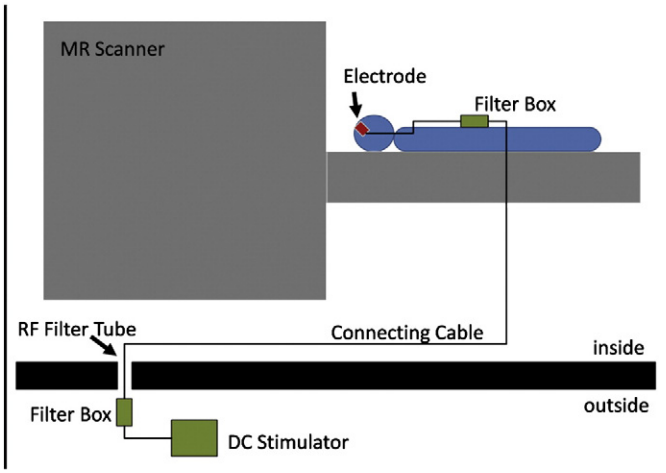

Fig. 1. Experimental setup for concurrent tDCS and fMRI. The DC stimulator is placed outside the scanner room and connected to a filter box placed very close to a radio frequency filter tube through the wall of scanner room. Via a long cable the connection to a second filter box inside the scanner room placed on the patient table is achieved, which then connects to the electrodes attached to the head of the subject.

Functional magnetic resonance imaging (fMRI)

fMRI studies were conducted at 3 T (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) using a standard eight-channel phased array head coil. Subjects were placed supine inside the magnet bore and wore headphones for noise protection. Vital functions were monitored throughout the experiment. Initially, anatomic images based on a T1-weighted 3D turbo fast low angle shot (FLASH) MRI sequence at 1 mm^3 isotropic resolution were recorded (repetition time (TR) = 2250 ms, inversion time: 900 ms, echo time (TE) = 3.26 ms, flip angle: 9°). For BOLD fMRI a multislice T2*-sensitive gradient-echo echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 36 ms, flip angle 70°) at 2×2 mm^2 resolution was used. Twenty two consecutive sections at 4 mm thickness in an

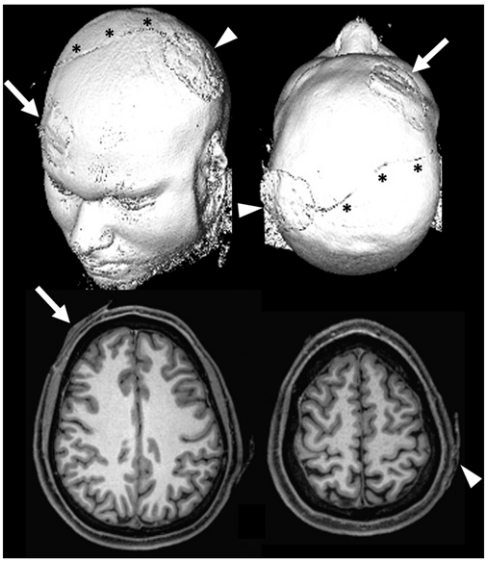

Fig. 2. Three-dimensional surface reconstruction (top) and axial cross-sections (bottom) from the T1-weighted anatomical dataset of a single subject. The electrodes over the left-hemispheric M1 hand area (arrowheads) and right-hemispheric orbita (arrows) are indicated. The cable running from the electrode over M1 across the subject's head is marked by asterisks.