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Test-retest reliability of prefrontal transcranial Direct Current Stimulation (tDCS) effects on functional MRI connectivity in healthy subjects

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ABSTRACT

Transcranial Direct Current Stimulation (tDCS) of the prefrontal cortex (PFC) can be used for probing functional brain connectivity and meets general interest as novel therapeutic intervention in psychiatric and neurological disorders. Along with a more extensive use, it is important to understand the interplay between neural systems and stimulation protocols requiring basic methodological work. Here, we examined the test-retest (TRT) characteristics of tDCS-induced modulations in resting-state functional-connectivity MRI (RS fcMRI). Twenty healthy subjects received 20 minutes of either active or sham tDCS of the dorsolateral PFC (2 mA, anode over F3 and cathode over F4, international 10–20 system), preceded and ensued by a RS fcMRI (10 minutes each). All subject underwent three tDCS sessions with one-week intervals in between. Effects of tDCS on RS fcMRI were determined at an individual as well as at a group level using both ROI-based and independent-component analyses (ICA). To evaluate the TRT reliability of individual active-tDCS and sham effects on RS fcMRI, voxel-wise intra-class correlation coefficients (ICC) of post-tDCS maps between testing sessions were calculated. For both approaches, results revealed low reliability of RS fcMRI after active tDCS ($ICC_{(2,1)}$ = −0.09 – 0.16). Reliability of RS fcMRI (baselines only) was low to moderate for ROI-derived ($ICC_{(2,1)}$ = 0.13 – 0.50) and low for ICA-derived connectivity ($ICC_{(2,1)}$ = 0.19 – 0.34). Thus, for ROI-based analyses, the distribution of voxel-wise ICC was shifted to lower TRT reliability after active, but not after sham tDCS, for which the distribution was similar to baseline. The intra-individual variation observed here resembles variability of tDCS effects in motor regions and may be one reason why in this study robust tDCS effects at a group level were missing. The data can be used for appropriately designing large scale studies investigating methodological issues such as sources of variability and localisation of tDCS effects.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (NIBS) technique that modifies cortical excitability by passing weak electrical current through the brain via two surface electrodes (Datta et al., 2009; Jackson et al., 2016). The current is flowing constantly from the anodal to the cathodal pole with an applied intensity of up to 4 mA and usually with 1–2 mA (Bikson et al., 2016; Edwards et al., 2013; Miranda et al., 2006). Depending on dose parameters, such as stimulation polarity, electrode positioning and applied current intensity, distinct current flow patterns as well as current density distributions are observable (Bai et al., 2014; DaSilva et al., 2015; Galletta et al., 2015; Mendonca et al., 2011; Neuling et al., 2012; Seibt et al., 2015; Woods et al., 2015). At the primary motor cortex, anodal tDCS (i.e. the anode is placed over the brain region of interest) is associated with increased motor-cortical excitability whereas the opposite is true for cathodal stimulation (Nitsche and Paulus, 2000, 2001). Such tDCS-induced excitability changes may originate from shifted resting membrane potentials towards de- or hyperpolarization (Jackson et al., 2016; Liebetanz et al., 2002; Nitsche et al., 2003). However, dose-response relations do not appear to be linear and measured responses may often be a function of the selected dose parameters (for review see Worsching et al., 2016). For example, Monte-Silva et al. (2013) found anodal stimulation of the prefrontal cortex (PFC, 1 mA intensity for 26 min) to decrease cortical excitability. Moreover, the position and size of the return electrode may influence neuromodulation within the region of the active electrode (Bikson et al., 2010). For example, for bipolar bilateral montages (Nasseri et al.,

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2015) as often used for PFC stimulation, cortex regions close to the electrodes may receive both anodal facilitation and cathodal inhibition.

Based on the role of the PFC in cognitive domains and neuropsychiatric disorders (Mega and Cummings, 1994; Tandon, 2013) and in consideration of the potential of prefrontal tDCS to specifically modulate cognitive functions (for review see Tremblay et al., 2014), tDCS of PFC regions seems to be especially promising for therapeutic applications. Accordingly, the behavioural effects of prefrontal tDCS have been investigated in neurological (for review see Flöel, 2014; Schulz et al., 2013) and psychiatric disorders (for review see Kekic et al., 2016; Kuo et al., 2014). To elucidate the neural substrate of NIBS effects, tDCS can be combined with functional magnetic resonance imaging (fMRI). For instance, effects of prefrontal tDCS on the blood oxygenation level dependent (BOLD) signal in task fMRI can be observed in areas under or close to the electrode position as well as in regions distant from the electrode site (Hauser et al., 2016; Holland et al., 2011; Meinzer et al., 2012; Meinzer et al., 2013; Meinzer et al., 2014; Sacco et al., 2016; Weber et al., 2014). Instead of investigating activity in isolated brain regions, functional-connectivity MRI (fcMRI) provides the possibility to identify coordinated or integrated activity across regions (Beckmann et al., 2005; van den Heuvel and Hulshoff Pol, 2010), which is a central characteristic of healthy brain functions (Catani et al., 2013; Park and Friston, 2013). Such functional relations involve spatially distinct networks that can be extracted by analysis of the temporal coherence between spontaneous BOLD-signal fluctuations measured in different brain areas (Friston et al., 1993). In the resting state (RS), functional networks are reproducible across (Biswal et al., 2010; Damoiseaux et al., 2006) and within subjects (Blautzik et al., 2013; Braun et al., 2012; Laumann et al., 2015). Moreover, functional networks acquired under resting conditions – so called resting-state networks (RSN) – resemble functional networks during activation (i.e. task performance) (Smith et al., 2009) and are highly relevant for cognitive functions and behaviour (Laird et al., 2011; Tavor et al., 2016). For this reason, the impact of tDCS on RS fcMRI entails important information about the effectiveness of this method regarding its influence on cognition without requiring an active task. Previous studies examining the influence of prefrontal brain stimulation have shown that tDCS modulates RS fcMRI (Keeser et al., 2011; Meinzer et al., 2012; Meinzer et al., 2013; Meinzer et al., 2014; Palm et al., 2013a; Palm et al., 2016; Park et al., 2013; Pena-Gomez et al., 2012; Pereira et al., 2013; Volpato et al., 2013). For example, increased connectivity within the Frontal Parietal Network (FPN) was found following anodal tDCS of the PFC (Keeser et al., 2011; Pena-Gomez et al., 2012), potentially reflecting a cognitive state of enhanced alertness. Consequently, tDCS may bear the potential to restore altered connectivity patterns (Meinzer et al., 2013; Meinzer et al., 2014) which are often found in neuropsychiatric disorders (Buckholtz and Meyer-Lindenberg, 2012; Filippi et al., 2013; Fornito et al., 2015; Insel, 2010; Menon, 2011; Zhou et al., 2012). Though imaging stimulation, i.e. imaging the on- and offline effects of NIBS on RS fcMRI, may theoretically provide an ideal paradigm to investigate how tDCS affects neural integration and to test state, disorder and course dependency of tDCS effects, combined fMRI-tDCS investigations have methodologically not yet been developed to this point and the neurophysiological response to tDCS is still not completely understood (Parkin et al., 2015). One major issue is the intra- and inter-individual stability of tDCS effects. For both the therapeutic application of tDCS and the investigation of tDCS-induced neuromodulation and tDCS-related plasticity, it is essential to know whether the same stimulation protocol produces predictable effects across different treatment sessions. However, only few studies have tested the test-retest (TRT) reliability of tDCS effects and that only in motor-evoked potential (MEP) paradigms (Chew et al., 2015; Dyke et al., 2016; Horvath et al., 2016; Jamil et al., 2016; Lopez-Alonso et al., 2015). To our knowledge, this is the first study investigating the TRT reliability of prefrontal tDCS-induced modulation in RS fcMRI. For this purpose, effects of active or sham tDCS on RS fcMRI were measured on three different days in the same healthy subjects. In a first step, RS fcMRI at baseline and post tDCS was determined at an individual level. In a second step, reproducibility of intra-individual baseline and post-tDCS RS-fcMRI was tested using voxel-wise intra-class correlations, enabling comparisons between baseline RS-fcMRI reliability and reliability following active-tDCS or sham-tDCS intervention.

Methods

Participants and sociodemographics

We tested 20 healthy male participants (mean age: 23.85 years, age range: 18–32 years) in a total of 60 tDCS-fMRI sessions. They were all right-handed (M = 99, SD = 3.08, $range$ = 90 – 100) according to the Edinburgh Handedness Questionnaire (Oldfield, 1971). Exclusion criteria were a history of neurological and psychiatric diseases and the intake of neuroactive medication. Participant selection was also restricted to non-smokers and to people without drug consumption during the past 6 months. The study was approved by the local ethics committee (Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Germany) and all patients gave their written informed consent for participation in this study.

Experimental procedure

This study followed a sham-controlled and double-blind design with parallel groups, such that neither participants nor investigators were aware of the stimulation condition. The 20 participants were pseudo-randomised into two groups: one active-tDCS and one sham group. Each participant received 20 min of either active or sham tDCS in the MRI scanner, always preceded, accompanied and ensued by a RS-fcMRI examination (combined on- and offline measurements, though only offline results are presented here). This procedure was conducted three times with at least seven days between each testing session. Within one participant, the stimulation condition (active vs. sham tDCS) was the same across all testing sessions. Daytime of measurement was kept constant for each participant across all testing sessions (see Fig. 1).

Participants were asked to abstain from alcohol the day before and from caffeine the morning before each testing session. At the beginning of each session and prior to fMRI scanning, participants filled in several questionnaires based on an in-house digital Android tablet system. Afterwards, participants went into the MRI scanner and were asked to keep their eyes closed, to not fall asleep, to think about nothing in particular and to avoid movements. During each session, RS scans were repeated three times, directly following each other: baseline/pre tDCS (10 min), during tDCS (20 min), post tDCS (10 min) (see Fig. 1). Instructions were repeated before each RS scan started and participants were informed before stimulation started. At the end of each session, participants again filled in several questionnaires in order to assess possible stimulation effects on mood and other variables.

Questionnaires

Several questionnaires were administered once at the overall baseline including the Edinburgh Handedness Questionnaire (Oldfield, 1971), the trait scale of the Positive And Negative Affect Schedule (PANAS, missing the item “enthusiastic” on the positive affect scale) (Krohne et al., 1996; Watson et al., 1988), the trait scale of the State Trait Anxiety Inventory (STAI) (Laux, 1981; Laux and Spielberger, 1981; Spielberger et al., 1970) and a questionnaire for sociodemographic data. Additionally, the PANAS state scale and the STAI state scale were completed prior to each stimulation. After each stimulation, the PANAS state scale was filled in again in addition to the Comfort Rating Questionnaire (CRQ) (Palm et al., 2014).