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Relevance of Dorsolateral and Frontotemporal Cortex on the Phonemic Verbal Fluency – A fNIRS-Study

Martin J. Herrmann,* Anna K. Horst, Sophia Löble, Mira T. Möll, Andrea Katzorke and Thomas Polak
Department of Psychiatry, Psychosomatics and Psychotherapy, University Clinic Würzburg, Würzburg, Germany

Abstract—Non-invasive brain stimulation is widely used to investigate and manipulate specific brain functions to broaden knowledge about healthy people, and also to provide for a potential treatment option for people with various psychopathological disorders that do not adequately benefit from traditional treatments. Nevertheless, the underlying mechanisms have not been fully investigated yet. The aim of the present study was to investigate whether we could alter the brain activity during a test for executive functioning. Therefore, we measured the activity in the prefrontal cortex (PFC) using near-infrared spectroscopy (NIRS) while applying bilateral anodal and cathodal transcranial direct current stimulation (tDCS, 1 mA) to the left and right dorsolateral PFC (dlPFC) during the phonemic part of the verbal fluency test (VFT). A total of 61 young and healthy participants were divided into three groups: left anodal/right cathodal, left cathodal/right anodal stimulation or sham. All participants performed the letter-cued part of the VFT and a control task. Brain activation was simultaneously measured using NIRS. We found only the frontotemporal cortex (FTC) but not the dorsolateral prefrontal cortex (DLPFC) to be activated. Furthermore, stimulating the DLPFC bilaterally by tDCS showed no significant differences between the three different groups when performing the VFT, neither in performance nor in cortical activation. Instead, we found a significant increase in deoxygenated hemoglobin [HHb] while performing the control task in the left anodal/right cathodal stimulation group compared to sham. Interestingly, also an influence on the mood of our participants was observed. These results are of importance especially regarding a better understanding of the influence of the dlPFC on the VFT.

Key words: transcranial direct current stimulation (tDCS), near-infrared spectroscopy (NIRS), dorsolateral prefrontal cortex (dlPFC), fronto-temporal cortex (FTC), verbal fluency test (VFT).

INTRODUCTION

Transcranial direct current stimulation (tDCS) has been widely investigated and used as a treatment for various psychiatric disorders (Brunelin et al., 2012; Kalu et al., 2012). It is a non-invasive method that is able to change neuronal excitability of the brain (not inducing action potentials per se) by depolarizing the resting potential of the membrane through anodal stimulation and hyperpolarizing it through cathodal stimulation (Nitsche et al., 2003). Bilateral stimulation of the dorsolateral prefrontal cortex (dlPFC) via tDCS (left cathodal/right anodal stimulation) in alcohol-dependent patients for example has been shown to decrease craving (Wietschorke et al., 2016) and relapse (Klauss et al., 2014). Using the reverse electrode positions with left anodal/right cathodal stimulation over bilateral dlPFC in contrast reduces depressive symptoms in patients with major depression (Brunoni et al., 2013). Nevertheless, the underlying mechanisms of this bilateral tDCS have not been fully investigated yet.

In both psychiatric disorders mentioned above, reduced brain activation during executive functions, especially the verbal fluency task (VFT) has been reported (depressive patients: (Herrmann et al., 2004); detoxified alcohol-dependent patients: (Schecklmann et al., 2007)) even though their behavior in a VFT did not differ from the healthy control group. The VFT is not only used to examine word production abilities and speed, but is also a valid measurement for executive functions (Shao et al., 2014) and is widely used to investigate prefrontal brain functions (Ravnkilde et al., 2002). In detail, the VFT is associated with activation in frontotemporal (FTC) and dlPFC (Tupak et al., 2012). These findings therefore suggest an important role of frontal activation

*Corresponding author. Address: Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Margarete-Höppel-Platz 1, 97080 Würzburg, Germany. Fax: +49-931-20177550.
E-mail address: Herrmann_m@ukw.de (M. J. Herrmann).
Abbreviations: ADS-K, Allgemeine Depressionsskala; ASRS, ADHD self-report scale; CES-D Scale, Center for Epidemiological Studies Depression Scale; dlPFC, dorsolateral prefrontal cortex; DPF, differential path length factor; FTC, frontotemporal cortex; HHb, deoxyhemoglobin; IFC, inferior frontal cortex; NIRS, near-infrared spectroscopy; O_2Hb, oxyhemoglobin; PANAS, Positive and Negative Affective Schedule; PFC, prefrontal cortex; ROI, region of interest; tDCS, transcranial direct current stimulation; VFT, verbal fluency test.

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in the successful treatment of psychiatric patients (Ehlis et al., 2012). For this reason, the aim of this study was to elucidate the effect of bilateral prefrontal tDCS on the neural correlates of executive function, by means of VFT. As positive therapeutic effects of bilateral tDCS have been found with reverse electrode positions (left cathodal or left anodal tDCS respectively), we investigated the tDCS-induced changes in brain activity during VFT with both electrode placements compared to a sham condition. To the knowledge of the authors, this is the first study to contrast these specific bilateral tDCS electrode positions.

Two recent studies investigated the influence of tDCS on VFT with a focus on word production. In the first study (Meinzer et al., 2012), the authors stimulated the left inferior frontal cortex (IFC; about 1.5 cm more lateral compared to the crossing point between T3-Fz and F7-Cz, with the reference electrode over the right supraorbital region) and confirmed improved word-retrieval after anodal tDCS. Additionally, they found reduced task-related activation in the left ventral IFC. In the second study, (Ehlis et al., 2015) also stimulated the left inferior frontal cortex (again with the reference electrode over the right supraorbital region), but measured the hemodynamic changes using NIRS simultaneously. In contrast to the previous study (Meinzer et al., 2012), no behavioral effects of tDCS on VFT performance, but increased activation in IFC was found. It was argued that methodological differences between both studies might account for these differences. In detail, Ehlis et al., 2015 measured after, while Meinzer et al., 2012 measured brain activity during tDCS.

In contrast to both studies cited above (Meinzer et al., 2012; Ehlis et al., 2015), we were more interested in the executive part of the VFT, namely the dorsolateral prefrontal (dlPFC) cortex instead of stimulating Broca's region. Based on recent studies in psychiatric patients (Brunoni et al., 2013; Klauss et al., 2014), we were stimulating the left (F3) and right (F4) DLPFC using left anodal/right cathodal as well as left cathodal/right anodal electrode positions and compared them to a sham group. Like Ehlis et al., 2015 we were also using NIRS to determine brain activity by measuring changes in the concentration of oxygenated [O_2Hb] and deoxygenated [HHb] hemoglobin. In contrast to Ehlis et al., 2015, we were stimulating and measuring the brain activity simultaneously during the VFT. We expected to find increased activation in the frontal lobe in the left anodal/right cathodal tDCS group compared to the sham group.

EXPERIMENTAL PROCEDURES

Participants

Participants were 61 (31 men, 30 women) healthy, right-handed people (mean age 24.3 years) recruited via Internet or personal announcements to test the effect of tDCS over the dlPFC on the VFT. Participants were randomly assigned to one of the three tDC-stimulation groups: 20 participants received sham (sham-group), 21 participants received left anodal/right cathodal tDCS (group 1), and 20 participants received left cathodal/right anodal tDCS (group 2). Exclusion criteria were mental, neurological or physical illness, current use of psychopharmacological medication or psychotherapeutic treatment. Contraindications regarding tDCS safety guidelines such as epilepsy, cochlea implants, use of cardiac pacemakers or pregnancy were ensured. All participants included in the study provided informed, written consent. The study was in accordance with the latest version of the declaration of Helsinki (World Medical, 2013), and all procedures were approved by the local ethics committee of the medical faculty of the university of Würzburg.

Questionnaires

A German version (Krohne et al., 1996) of the Positive and Negative Affective Schedule (PANAS) (Watson et al., 1988) was administered, where subjects were asked to rate 20 adjectives according to their current mood on a 5-point scale ranging from "very low" or "not at all" to "extremely". This questionnaire was used to evaluate current positive and negative affects before and after the task. In addition, a short form of the Allgemeine Depressionsskala (ADS-K) (Hautzinger et al., 2012), the German version of the Center for Epidemiological Studies Depression Scale (CES-D Scale) (Radloff, 1977), was used to assess individual depression levels. The Edinburgh Inventory of Handedness was used to acquire subjects' handedness (Oldfield, 1971). Additionally we used the ADHD self-report scale (ASRS) for the assessment of ADHD symptoms (Kessler et al., 2005). As shown in Table 1, the participants in the three groups did not differ with regard to age, VFT performance and in symptoms associated with attention deficit-hyperactivity disorders or depression. Most participants were college students ($N = 55$). The rest of the sample had 10 years of school education and were equally distributed over the three groups (left anodal/right cathodal: $N = 3$; left cathodal/right anodal: $N = 1$; sham: $N = 2$; $Chi^2 = 1.0$; $P = 0.61$).

Verbal fluency test (VFT)

The VFT is a test used for measuring word production, executive function, and cognitive flexibility. In our case, we only evaluated the phonemic part. Participants were prompted to name as many words as possible in a short period of time. The instructions and answers were delivered to the participant and back to the examiner via speakers so that the participant was able to sit still while performing the task. The VFT procedure took 6 min in total. During the relaxation times, participants were instructed not to talk, move or think of anything. During word production, the participants were asked to name as many words as possible starting with the letter A, F or S, respectively in 30 s without using (proper) names. Alternating with word production and relaxation, the participants were requested to slowly name the weekdays in the correct order and as many times as possible. The examiner listed the number of valid words and weekdays. Participants were provided with detailed instructions before the measurements to ensure they could perform the task. Recent studies of our lab

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