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# EFFECT OF FRONTAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON WORD FLUENCY IN HEALTHY ADULTS

Faculty of Medicine and Health Technology
Master's Thesis
March 2020

# ABSTRACT

Riikka Havela: Effect of Frontal Transcranial Direct Current Stimulation on Word Fluency in Healthy Adults
Master's Thesis
Tampere University
Licentiate Degree Programme in Medicine
March 2020
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**Introduction:** Transcranial direct current stimulation (tDCS) is a noninvasive and well tolerated method for stimulating the brain in a subthreshold manner. It has shown some promise e.g. in treatment of major depressive disorder. The prefrontal cortex is an interesting target for tDCS studies, since the executive functions it performs are compromised in many diseases of the brain. Verbal fluency tasks are one way of measuring executive functions, albeit inherently being a combined task that measures several other functions, such as verbal ability, as well. In this study, we wanted to explore whether tDCS targeted to the dorsolateral prefrontal cortex influences performance in phonemic and semantic word fluency tasks in healthy adults.
**Materials and methods:** 23 healthy participants, aged 21-34 years, were randomized into two groups, one receiving active tDCS stimulation and the other one receiving sham stimulation. They performed a one-minute phonemic and semantic fluency test before (session 1) and after (session 2) performing Executive reaction time test, a computer-based test engaging several executive functions simultaneously, during which the active or sham stimulation was administered. The number of words produced during the verbal fluency tests was analyzed for the full one-minute test period, and in 15 second intervals using analysis of variance and Student's T-test.
**Results:** The semantic fluency task proved to be easier for the participants, as expected. There was also a tendency to perform better in session 2 (post-stimulation) than session 1 (pre-stimulation) in both fluency tasks and in both active and sham stimulation groups, implying learning. Interestingly, there was a statistically significant difference in the semantic fluency test session 2 (post-stimulation) second quarter (15-30 s from the beginning of the test) between the number of words produced by the active and sham stimulation groups with those having received tDCS producing more words.

**Conclusions**: The results indicate significant learning in repeated verbal fluency tasks influencing the assessment of an intervention on executive functions. tDCS improved verbal fluency in the second quarter of the fluency test. We speculate based on the exponential decay curve of performance in the fluency task that the second quarter is most dependent on executive functions, and thus subtle alterations in executive functions may be more easily detected during this quarter. This is in contrast to the first quarter that relies on semiautomatic access of frequent words rather than effortful retrieval of infrequent words. Furthermore, it may be that in the third and fourth quarter vocabulary may be the limiting factor on the performance rather than the efficiency of executive functions. Thus, while caution is warranted and these preliminary results should be confirmed in future studies, it is possible that there was a subtle improvement in executive functions due to tDCS that was observed only in the second quarter of the fluency task.

Keywords: tDCS, prefrontal cortex, verbal fluency

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# Review of the Literature

## The prefrontal cortex

The frontal lobe comprises approximately one third of the human brain. In an evolutionary sense, it is the newest and proportionally most prominent part of the brain compared to other non-primate mammals. It is the area maturing latest as a person grows, reflecting the complex tasks it performs. (Stuss & Knight 2002, Gazzaniga, Ivry, & Mangun, 2013; Schoenemann, 2006)

The frontal lobe, pictured from different anatomical orientations in Figure 1, is anatomically separated by the central sulcus from the parietal lobe, and by the lateral fissures from the temporal lobes. It is divided by function into three larger areas, namely primary motor area which resides in the gyrus in front of the central sulcus; the secondary motor area ventrally to the primary one and partly deep in the interhemispheric fissure; and prefrontal cortex comprising the most ventral part of the brain. The prefrontal cortex especially is very prominent in the primate and human brain (Gazzaniga et al., 2013; Schoenemann, 2006).

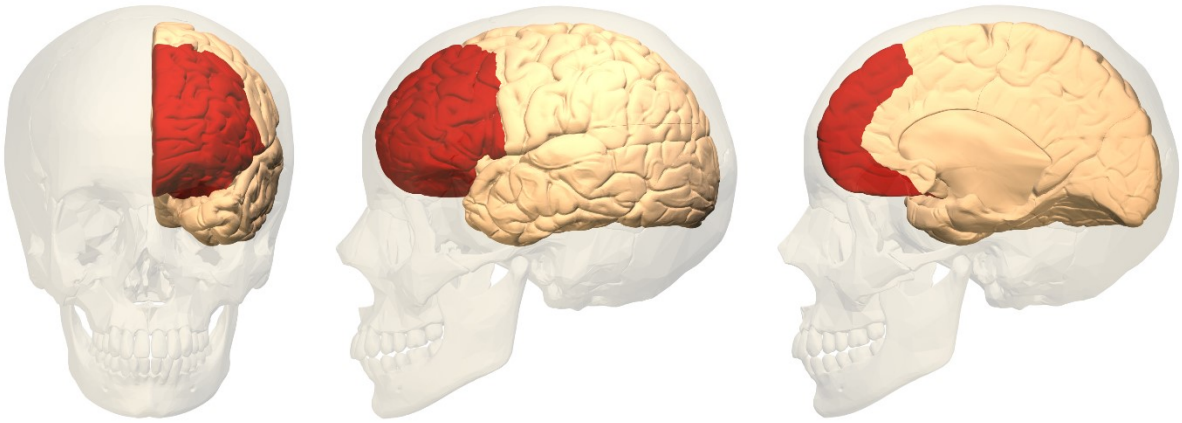

*Figure 1. The prefrontal cortex seen from a frontal, lateral and medial view, respectively. Published under a Creative Commons Attribution 2.1 Japan license by BodyParts3D, © The Database Center for Life Science licensed under CC Attribution-Share Alike 2.1 Japan.*

The prefrontal cortex is divided further into four regions: orbitofrontal cortex, lateral prefrontal cortex, medial frontal cortex and frontal polar region. The cortex can also be further divided into so called Brodmann areas (Figure 2) (Brodmann, 1909), out of which areas 9, 10, 11, 12, 13, 14, 24, 25, 32, 44, 45, 46, and 47 are part of the prefrontal cortex (Murray, Wise, & Graham, 2017). The prefrontal cortex is one of the most extensively connected area of the cerebral cortex. It receives input from motor, perceptual and limbic regions, almost all regions of the temporal and parietal cortices, as well as the prestriate regions of the occipital cortex. The most extensive input connections to the prefrontal cortex come through the thalamus, connecting it with subcortical structures such as the brainstem nuclei, cerebellum, and basal ganglia. The prefrontal cortex also reciprocally projects to almost all of the areas it receives input from. It widely projects to the contralateral hemisphere as

well, including homologous prefrontal areas as well as premotor and subcortical regions (Gazzaniga et al., 2013).

Functionally, the prefrontal cortex is organized along three axes. The ventral-dorsal axis is thought to be organized in a way that reflects maintenance and manipulation of information, similar to the organization principles more posterior parts of the cerebral cortex. The anterior-posterior axis is organized in terms of increasing levels of abstraction, more abstract representations activating the anteriormost regions and least abstract activate posteriormost regions. The lateral-medial axis is organized reflecting the amount to which working memory is influenced by personal history information and emotional states (more medial) or information about the environment (more lateral) or (Gazzaniga et al., 2013; Koechlin, Ody, & Kouneiher, 2003; Stuss, 2011).

## Executive functions

One of the major tasks of the prefrontal cortex is controlling attention (Hartikainen & Knight, 2001, Hartikainen, Ogawa& Knight 2012) cognition, emotion and behavior, i.e., executive functions (Funahashi & Andreau, 2013). They allow one to use one's perceptions, knowledge and goals to choose and execute actions. They allow one to override automatic thoughts and behaviors, promote cognitive flexibility, and suppress some thoughts or behaviors in order to function towards a goal. Executive functions are essential for goal-oriented behavior and decision making while performing a task. (A. Diamond, 2013; Jurado & Rosselli, 2007)

Executive functions are not easy to measure, largely because they cannot be measured by themselves but in the context of a task they are being applied on (Miyake, Emerson, & Friedman, 2000). Any task designed to measure executive functions thus inevitably also measures another property, e.g. verbal or motor skills (see further about fluency tests).

Executive functions comprise of many different functions, which all work towards a goal. According to the current view, there are three core executive functions. Updating refers to constant monitoring and rapid addition or deletion of working memory contents. Shifting means switching between tasks or mental sets. Inhibition means the deliberate overriding of immediate responses in order to allow for choosing a more thought out action (A. Diamond, 2013; Miyake et al., 2000). These three core functions also constitute higher order executive functions such as reasoning, problem solving and planning (Collins & Koechlin, 2012).

Diseases or disorders affecting the frontal lobes can lead to executive dysfunction. In addition to the frontal cortex, basal ganglia and striatal pathologies also cause impairment in executive functions (Elliott, 2003). This can have a stark impact to everyday life, as executive functions are needed in all planned behavior.

Problems of inhibition result in impulsive behavior, inability to evaluate consequences before acting or inability to wait in general, and socially inappropriate behavior (A. Diamond, 2013). Working memory deficits, either verbal or visuo-spatial, lead to problems with e.g. reading, writing, mathematical deduction, planning, and learning or processing new information (A. Diamond, 2013). Problems with shifting lead to rigid behaviors, inability to solve problems through switching views, and inability to switch between tasks (A. Diamond, 2013). Disorders associated with executive dysfunction include Alzheimer's disease, frontal dementia, Parkinson's disease, ADHD, major depressive disorder and schizophrenia, to name just a few (Elliott, 2003). Also conditions such as alcohol abuse (Le Berre, Fama, & Sullivan, 2017), sleep deprivation (Nilsson et al., 2005) and even stress (Shields, Sazma, & Yonelinas, 2016) impair executive functions. Thus, the consequences of executive dysfunctions are present in our everyday lives even if we personally do not suffer from them.

## Verbal fluency

Verbal fluency tests were developed in the late 1960's as means to assess the patients' performance in cognitive tasks requiring the use of language and executive control. The first category fluency test was published by A.L. Benton in 1968, (Benton, 1968), and the first letter fluency test by B Hughes in 1970 (Hughes, 1970). In the test, the subject is asked to list as many words as possible in a specified category, excluding proper nouns and repetitions, for a minute. The subject's performance is then estimated based on how many correct words they produced. Commonly used verbal fluency tests are phonemic fluency test, where the subject lists words starting with a specified letter, and semantic fluency test, where the subject lists words belonging to a specific category such as foods, animals or vehicles.

Nowadays verbal fluency tests are used in many standardized neuropsychological test batteries. For example, the Montreal Cognitive Assignment test (MoCa) (Nasreddine et al., 2005), also used in Finland, utilizes a test of verbal fluency. In the MoCa test, one measured skill is phonemic fluency using the letter S as the que, and eleven or more correct words per minute is considered a normal result in the Finnish version of the test.

Verbal fluency tasks measure both verbal ability and executive control (Sharp, 2004). Either of these could be affected in various neurological disorders. There is also considerable variability in these functions among healthy individuals. Because verbal fluency tasks are a hybrid requiring both retrieval of words and the ability to monitor one's performance and inhibit inappropriate responses, intact functioning of both verbal ability and executive control is required for good performance. For example, participants with a smaller vocabulary produce less words in these tests than those with a larger vocabulary (Raboutet et al., 2011). It is not clear what is the relative effect of each component of executive control on performance in verbal fluency tasks.

Other types of fluency tests have been designed as well. These also test executive functions, but without the need for use of vocabulary. Such tests include free or constrained design fluency (Jones-Gotman & Milner, 1977), ideational fluency (Eslinger & Grattan, 1993), gesture fluency (Jason, 1985) and motor movement generation tasks (Deiber et al., 1991). However, despite avoiding the need for good verbal ability, these tests are hybrids as well, measuring other skills in addition to executive functions. These tests are not as widely used as verbal fluency tasks as part of test batteries for patients.

Verbal fluency has wide interindividual variation. Some demographic factors correlating with verbal fluency performance have been identified. No difference between sexes have been found in either of the fluency tasks, but there is a small negative correlation between age and semantic fluency (Harrison, Buxton, & Husain, 2000). This has not been observed for phonemic fluency. There is a modest positive correlation between years of education and IQ with both types of fluencies (Harrison et al., 2000). There may also be other demographic factors that influence either type of fluency, that are yet unknown.

Considering the measurable variables related to verbal fluency, age has been shown to relate to all other measures except vocabulary size in a way decreasing the number of produced words in the verbal fluency test (Shao, Janse, Visser, & Meyer, 2014). Vocabulary size was only related to operation span, which is a measure of working memory capacity. Updating ability has been shown to significantly predict the mean score of both phonemic and semantic fluency tasks and the mean subsequent reaction times (i.e. the time taken to come up with the next word) of the semantic fluency task. The vocabulary score has been shown to significantly predict the first reaction times of both phonemic and semantic verbal fluency tasks. Average lexical speed, which means the speed at which words are retrieved from lexical memory, has been shown to contribute to the first and average subsequent reaction times of the semantic fluency task, but not phonemic (Shao et al., 2014).

Verbal fluency tests have a very good reproducibility in single test subjects, and between different testers (Harrison et al., 2000). The excellent test-retest-reliability makes the verbal fluency tasks a useful clinical tool in assessing the prefrontal cortex functions of a single patient. This is an especially important feature when assessing the performance of a patient for example in follow-up of attempted treatment. However, since performance in these tests depends on several cognitive processes such as attention, psychomotor speed and memory, they cannot be used to pinpoint the localization of a cerebral dysfunction (Cohen & Stanczak, 2000). Challenges of using verbal fluency tests include the relatively work-intensive procedure of reliably recording and evaluating the produced words. Additionally, some measures used in the protocol require subjective appraisal of the fluency of pronunciation of each produced word.

Verbal fluency is compromised in many neuropathological conditions, including ADHD (Andreou & Trott, 2013), Alzheimer's disease (Zhao, Guo, & Hong, 2013), Parkinson's disease (Pettit, McCarthy, Davenport, & Abrahams, 2013). Children with specific language impairment or dyslexia have also been shown to have a diminished verbal fluency compared to children without these language deficits (Weckerly, Wulfeck, & Reilly, 2001). Considering that executive dysfunction is a symptom in a wide spectrum of diseases, verbal fluency deficits are expected to be present in many of them.

## Brain regions involved in verbal fluency

With advances in neuroimaging technologies, more detailed anatomical localization of lesions has been possible and thus facilitated research in this area. However, the results have so far not been unambiguous, and are even partly conflicting. This probably stems from great variability of the recruited patient or healthy subject material as well as differing study designs, and imaging techniques. The imaging techniques have their own challenges, such as movement artefacts. Table 1 lists some of the results obtained so far. Based on these results, brain areas engaged in phonemic fluency tasks are the left dorsolateral, anterior and superior prefrontal cortex, left perisylvian regions, left temporal lobe, and parietal lobe. Semantic fluency tasks engage the left dorsolateral prefrontal cortex and the right frontal cortex as well as parietal lobe (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Biesbroek et al., 2016; Costafreda et al., 2006; Grogan, Green, Ali, Crinion, & Price, 2009; Katzev, Tüscher, Hennig, Weiller, & Kaller, 2013; Robinson, Shallice, Bozzali, & Cipolotti, 2012; Schmidt et al., 2019; Szatkowska, Grabowska, & Szymańska, 2000; Tupak et al., 2012).

*Table 1. Short review of research results of brain regions implicated in phonemic fluency tasks. For anatomical reference of the mentioned Brodmann areas (BA) see Figure 2.*

| Author | **Phonemic fluency** | **Semantic fluency** | **Both equally** | **Studied groups** | **Used Method** |
|---|---|---|---|---|---|
| Szatkowska et al. (2000) | Left dorsolateral prefrontal cortex | Right ventromedial cortex within the posterior part of gyrus rectus | dorsolateral cortex BA 46/39 | 24 patients with unilateral prefrontal lesions<br>10 healthy controls | Verbal fluency task, no imaging |
| Baldo et al. (2006) | frontal cortex, especially BA 4, 6 and 44<br>Parietal cortex BA 1-3, 7, 39, 40 and 43 | temporal cortex, especially left temporal lobe BA 22, 37, 41, 42 and postcentral gyrus<br>Parietal cortex BA 39 and 40 | | 48 left-hemisphere stroke patients | Voxel-based lesion symptom mapping (MRI or CT) |
| Costafreda et al. (2006) | More dorsal than semantic | More ventral than phonemic | No difference in anterior-posterior or medial-lateral axes compared to phonemic | Review of a total of 197 healthy subjects | BOLD |
| Grogan et al. (2009) | Pre-supplementary motor area<br>Head of caudate bilaterally | Left inferior temporal cortex | | 59 healthy subjects | MRI |
| Tupak et al. (2012) | Anterior and superior prefrontal areas | lateralized on the left cortical areas (frontal and temporal)<br>**Lateralized left** | Frontotemporal cortices | 50 healthy subjects | fNIRS |
| Robinson et al. (2012) | left lateral and superior medial frontal<br>**Lateralized left** | left inferior frontal gyrus | Left or right frontal lesions | 47 focal frontal lesion patients<br>20 posterior lesion patients<br>35 healthy controls | CT or MRI |
| Katzev et al. (2013) | BA 44 | Dorsal BA 45 | | 62 healthy subjects | fMRI |
| Biesbroek et al. (2016) | Left frontal<br>Left perisylvian regions | Left frontal<br>Left medial, right dorsolateral | | 93 patients with ischemic stroke lesions | Assumption-free voxel-based and region-of-interest (CT or MRI) |
| Schmidt et al. (2019) | Left inferior frontal gyrus<br>Left inferior frontal adjacent to phonemic area | Left superior and middle temporal gyrus<br>Left inferior frontal area adjacent to phonemic area | | 85 chronic patients with ischemic stroke of the left middle cerebral artery | Voxel-based lesion-behavior mapping (MRI) |

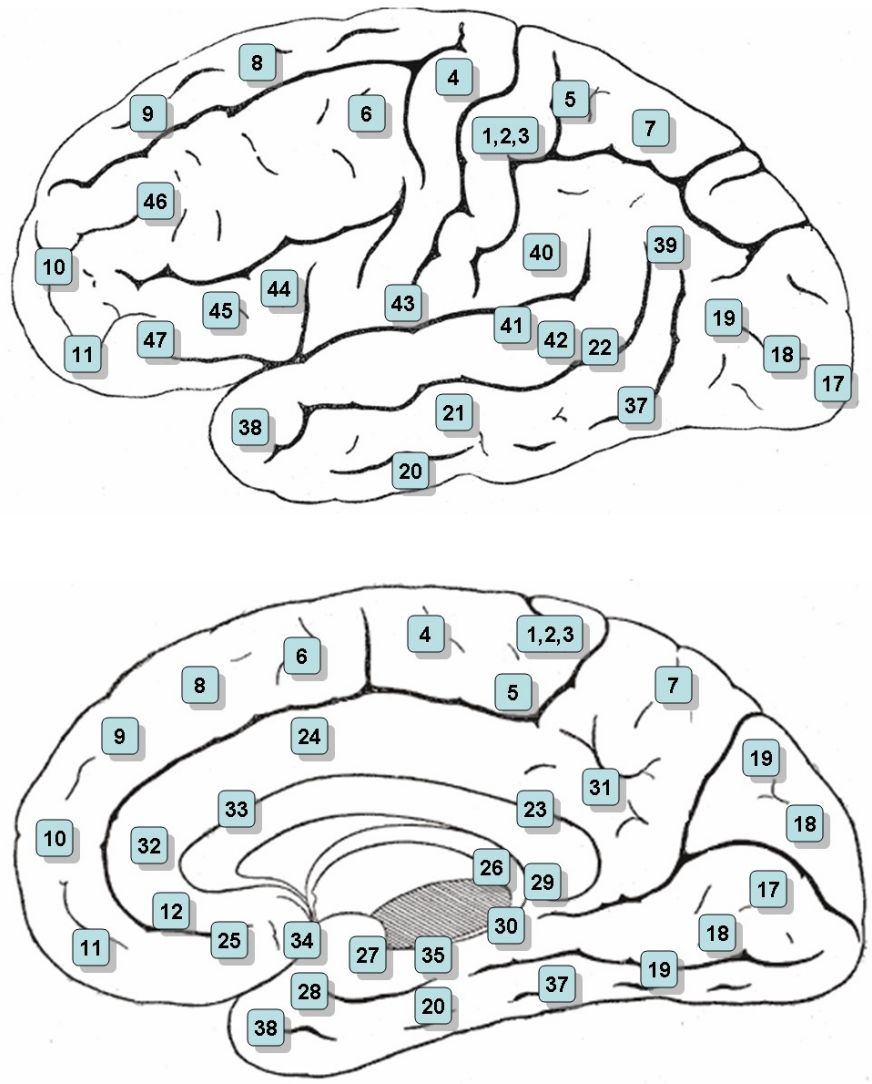


*Figure 2. Brodmann areas viewed laterally (above) and medially (below). From Gray* (1918)*, published under Public Domain in Wikipedia.*

## Transcranial direct current stimulation (tDCS)

Originally, direct electrical stimulation of the brain was tested in the end of the 19th century on dogs with part of their skull removed, and soon in a human subject suffering from a brain tumor. Methods resembling modern day tDCS were first tested in the 1960s and 1970s. In the 1980's, development of transcranial stimulators took a sprint again with introduction of very high voltage one-pulse stimulators which were able to produce visible responses in the subject (Rothwell, 2018). Modern tDCS uses considerably smaller currents and does not aim to produce visible responses.

As the current used in modern tDCS protocols is very low, it is not capable of directly activating neurons (Rothwell, 2018). Instead, it changes their membrane potential, either facilitating or suppressing their ability to become depolarized. Current flows from the positive electrode (anode) to the negative electrode (cathode), slightly depolarizing neuronal cell bodies near the anode and slightly hyperpolarizing those near the cathode. In some animal experiments, this has been shown to induce BDNF-dependent increase in synaptic efficacy (Fritsch et al., 2010). In a brain without cortical gyri and sulci, neuronal cell bodies are arranged approximately in a plane perpendicular to scalp surface. In such a situation, tDCS applied on the scalp surface can relatively straightforwardly reach the somas nearby. However, in humans with a complex cortical shape, the situation is more complex, and the exact effects of tDCS in humans are not currently known. Mathematical models of the effects of tDCS on neurons are currently being developed (Rothwell, 2018).

Studies have shown that a minimum of 10 minutes of tDCS can lead to changes persisting for minutes or hours on the cortex (Ziemann et al., 2008). However, in its current form, tDCS is not completely reliable or high accuracy. It may affect many different types of neurons nonselectively, producing varied effects that are difficult to reproduce. Accuracy of stimulation targeting is currently not high. This could be improved by using multiple electrodes to focus the stimulation better (D'Ostilio et al., 2016). In addition, tDCS can only reach superficial cortical areas, supposedly only gyri and not sulci in the human brain and cannot penetrate deeper into the brain tissue.

Soares et al. (2018) studied the effect of the orientation of tDCS electrodes in relation to the stimulated brain area on the motor cortex to the changes in the excitability of the neurons in the area. They did this by observing changes in the motor evoked potentials of M1 in the central sulcus produced by simultaneous TMS. They found out that tDCS oriented orthogonal, but not parallel to the central sulcus produced changes in the excitability of the neurons in M1. This implies that orientation of the simulation electrodes might play a large role in how the neuronal tissue responds to stimulation.

### tDCS in healthy subjects

In general, there have been two approaches to studying the effects of tDCS in healthy adults. In the first type, a single session of active tDCS can be administered either "online", i.e. while the test subject is performing a task, or "offline", before or after the task. The second type of experimental setup is where the tDCS is repeated over several sessions, either online or offline. The latter has also inspired some healthy self-experimenters to attempt to use tDCS as means to boost their cognitive performance (Fitz & Reiner, 2015; Hamilton, Messing, & Chatterjee, 2011). Some studies have found no effect of repeated tDCS on cognitive functions (Motohashi, Yamaguchi, Fujii, & Kitahara, 2013). At least one study has found improved response inhibition (Metzuyanim &

Nira, 2016). Other types of effects, such as improved mood (Newstead et al., 2018) have been observed in healthy adults with repeated tDCS.

Single session tDCS is usually applied for 10-20 minutes, either online or offline, and with this setup structure-function relationships can be studied. Although in healthy populations tDCS studies have often yielded negative results, some studies have been able to show a positive effect on cognitive functions. For example, tDCS has been shown to increase learning rate in a verbal learning task when anodal tDCS was applied to the left parietal lobe during encoding in healthy test subjects (Jones, Gözenman, & Berryhill, 2014). tDCS to dorsolateral prefrontal cortex (DLPFC) has also been shown to improve executive functions (Dubreuil-Vall, Chau, Ruffini, Widge, & Camprodon, 2019). There is much heterogeneity in experimental findings concerning specific cognitive functions and experimental setups. The reason for this is suspected to be large interindividual variability in neurophysiological condition prior to the studies, as well as initial skill levels and age-related differences. See (Berryhill & Martin, 2018) for a more comprehensive review of studies. Further studies regarding variability between individuals and optimization of research protocols are clearly warranted.

### tDCS in clinical populations

tDCS has also been studied in clinical populations, in hopes of finding therapeutic options with minimal invasiveness. In these populations there are also two approaches, single session and multiple session longitudinal study. tDCS has been intensively studied e.g. for treatment of depression, with some promising results (Palm, Hasan, Strube, & Padberg, 2016). It has been incorporated into the Finnish Current Care Guidelines for major depressive disorder with level B evidence for treatment of depression that at best reaches the efficacy of antidepressant medications ("Depressio. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society.," 2020).Some positive results concerning information processing speed, working memory and affective processing have been achieved using single session tDCS. Some studies have shown that the cognitive effects of single session tDCS were only visible at 24 hours after stimulation, and no effect was observed immediately after stimulation (Gögler et al., 2017). Studies that have compared stimulation intensities have shown that in some cases, a higher current intensity is required for observable increase of accuracy in a memory task, but this has not been a consistent finding (Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014; Jane, James, Crow, & Collinson, 2004).

After multiple sessions of anodal tDCS to left dorsolateral prefrontal cortex while practicing a naming task, stroke patients with aphasia has been shown to improve in their verbal fluency skills of these patients (Baker, Rorden, & Fridriksson, 2010). Studies of repeated sessions of tDCS in neuropsychiatric conditions have also yielded some very promising results. A review by Bennabi and Haffen (2018) concludes that tDCS is a promising new treatment for major depressive disorder

## Aims of this study

The aim of this study was to study the immediate effects of tDCS, administered during a single experiment, to the dorsolateral prefrontal cortex on semantic and phonemic word fluency of healthy adults. This work is a part of a larger study investigating on the effects of tDCS on cognitive functions in healthy adults. The hypothesis was that anodal stimulation of the DLPFC will improve either one or both measured verbal fluency types.

## Materials and methods

23 healthy adults participated in this study. The inclusion criteria were age between 20 to 50 years and righthandedness. The exclusion criteria were focal neurological symptoms, a diagnosed brain disease or brain injury, considerable use of alcohol and/or drugs, a chronic psychiatric disease, a considerable sensory deficit, cranial or intracranial metal or active implants, and pregnancy.

Event related potentials were measured throughout the experiment using EEG. These results will be reported in future publications and are not included in this thesis.

In this study, the subjects were stimulated with active tDCS or sham stimulation. The two devices used here were identical and provided by Sooma Oy. Based on the placement of the electrodes, the electric current is expected to travel from left to right over the surface of the prefrontal cortex mainly in the subarachnoid space, through the highly conductive cerebrospinal fluid that covers it (Jiang et al., 2020). This current slightly depolarizes neurons in the left dorsolateral prefrontal cortex and slightly hyperpolarizes neurons in the right dorsolateral prefrontal cortex (see Figure 3). Size of the electrodes was 5 cm by 7 cm, so the stimulated area cannot be defined with high accuracy. The stimulation electrodes were placed on the EEG cap, anode replacing EEG channels F3, F5, FC5 and FC3, and cathode replacing channels F4, F6, FC4 and FC6.

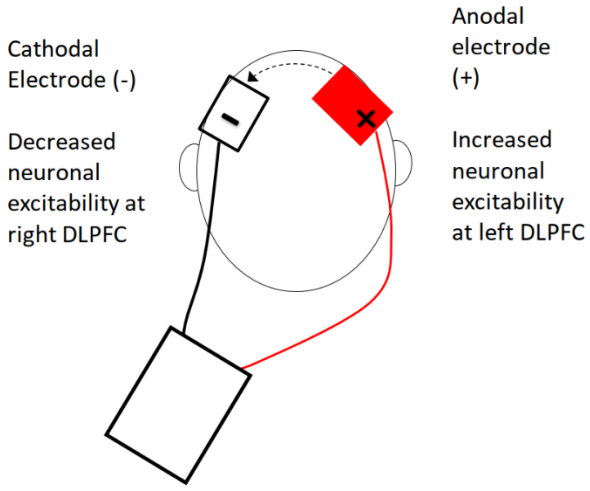


*Figure 3. A schematic drawing of the placement of tDCS electrodes on a subject's head, and their effect on the dorsolateral prefrontal cortex (DLPFC) neurons.*

Sham stimulation and tDCS experiments were randomized. Participants were blinded from whether they received sham stimulation, or active stimulation (tDCS). Sham stimulation rises initially to 2 mA and is subsequently lowered down to 0.3 mA. The tDCS is constant after rising to 2 mA. Only the rising phase, whether it be active or sham stimulation, is sensed by the subject. The subjects were not able to systematically recognize which stimulation they were given (personal communication with Dr. K. Holm, data not shown). The stimulation protocol was such that each participant receiving tDCS received a 2 mA current for a 6 min duration, 4 times in total during the experiment i.e. altogether 24 min of stimulation during the course of the whole experiment. Participants in the sham stimulation group received 0.3 mA for 6 minutes, 4 times in total.

In the beginning of the experiment both phonemic and semantic fluency tasks were performed by the subject. The test protocol was designed in such a way that different types of fluency tests were symmetrically distributed among the participants, so that an equal number of participants started with each phonemic and semantic cue in session 1. The possible combinations here are K and food, K and animal, S and food, and S and animal. Then, the subject performed a reaction time test measuring multiple executive functions simultaneously and in context of intervening threat related emotional stimuli (Executive RT test) (Hartikainen, Siiskonen & Ogawa, 2012, Erkkilä, Peräkylä & Hartikainen 2018). The executive RT test has been shown to be sensitive to subtle improvement or decline in executive functions after mild head injury (Hartikainen, Wäljas, et al., 2010), changes in emotion-attention interaction after deep brain stimulation in patients with epilepsy (Hartikainen et al., 2014; Sun et al., 2015) and improvement in cognitive flexibility following heart surgery (Liimatainen et al., 2016) Additionally, it has been shown to have good reliability in repeated testing (Erkkilä, Peräkylä, & Hartikainen, 2018). During this test, the tDCS stimulator was alternately on and off. Half of the

subjects received sham stimulation instead of tDCS at this part of the test. At the end, the Executive-RT-test was performed again, this time without cognitive strain. Finally, both phonemic and semantic fluency tasks are performed at the very end again using a different cue than initially.

The dependent variable studied in this work is the number of words produced in one minute. Changes in the number of produced words reflect changes in the processing capabilities of the brain areas responsible for phonemic and semantic word fluency. Additionally, the one-minute test period is divided into 15 second segments which are analyzed separately.

To analyze data from the word fluency tests, analysis of variance (ANOVA) was used. ANOVA was performed with main factors stimulation status (tDCS or sham), session (session 1 pre-stimulation and session 2 after tDCS or sham stimulation), verbal fluency test type (phonemic or semantic) and analyzed time interval (full one-minute test period or quarters 1-4). In addition, the same analyses were performed such that each participant was also used as their own control, i.e. their verbal fluency task result from session 1 (pre-stimulation) was used as a baseline and subtracted from the result of the same type of verbal fluency task session 2 (post-stimulation). These results were then analyzed using ANOVA with stimulation status, verbal fluency test type and analyzed time interval as factors. Post-hoc ANOVA was performed for interactions found in the initial analysis. Paired t test was used to analyze statistics of demographics and other statistics that did not include multiple factors. Statistical analyses were performed using R and its R studio graphical user interface. ANOVA was done using R's ezanova package.

## Results

There were 23 participants in this study, 12 male and 11 female. The median age of the participants was 24 (mean age 25.1 and SD 3.9 years). They had had a median number of 16.3 years of education (mean 16.5 and SD 2.2 years). The median BDI score was 3 (mean 3.9 and SD 4.1). This study is therefore representative of healthy, young and educated adults. There was no statistically significant difference in age ($p = 0.5256$), years of education ($p = 0.624$) and BDI score ($p = 0.929$) between sham and tDCS group. All participants were right-handed.

Participants produced significantly more words in the semantic fluency test 25.5 (SD 6.42) than the phonemic fluency test 18.6 (SD 6.89) in all studied time intervals ($p = 0.000003$ for the full one-minute test period). Figure 4 shows the number of words produced by each participant in sessions 1 and 2 in the phonemic fluency test. Figure 5 shows this data for the semantic fluency test. Table 2 lists the mean number of words and SD for both phonemic and both semantic fluency test types (K and S for phonemic and animal and food for semantic fluency) and all analyzed time intervals. For the two phonemic fluency tests, there was no statistically

significant difference between the number of words produced in these tests during the full one-minute test period. Neither was there any statistically significant difference between the two semantic fluency test ques in the number of produced words during the one-minute period. Table 3 lists the mean number of words and SD for active and sham groups. This data is further illustrated in Figure 6.

In general, more words were produced during session 2, post-stimulation, than during session 1, pre-stimulation. This difference was more pronounced in phonemic than semantic fluency. In semantic fluency task, there seemed to be a couple of extremely fluent subjects. These results are shown for the whole one-minute test period in Figure 6 and 7. In Figure 8, results for phonemic and semantic fluency tests are shown separately for active and sham stimulation.

To confirm that the tDCS and sham stimulation groups did not differ in their baseline performance levels, paired t-test was used to compare session 1 (pre-stimulation) verbal fluency test results of these groups. There was no statistically significant difference in the baseline between these groups in the phonemic ($p = 0.691$) or the semantic ($p = 0.258$) verbal fluency.

Table 4 and Table 5 list the results of ANOVA analysis and t-tests for different analyzed factors. For the second quarter (15-30 s), an interaction between device and session was found. Post-hoc analysis revealed that while in the session 1, before stimulation, there was no difference in the number of words produced between the groups in the session 2, after the stimulation, the groups differed in the number of produced words ($p = 0.032$). Participants in the tDCS group produced 6.42 (SD 3.09) words and those in the sham stimulation group produced 4.82 (SD 1.82) words. Since it is known that phonemic and semantic fluency require different areas of the DLPFC and have differing lateralization, this result was analyzed further to see if tDCS had a differing effect on the different fluency tasks. Participants in the tDCS group produced more words than those in the sham stimulation group in the semantic fluency test, 7.58 (SD 2.50) and 5.36 (SD 1.50) respectively. The difference was not significant in the phonemic fluency test. In the other quarters, as well as in the full one-minute test period, there was no statistically significant difference in the number of produced words between tDCS and sham groups. However, when each person was used as their own control and their baseline from session 1 was subtracted from session 2 results, and this difference was analyzed using ANOVA as described above, the result for the second quarter did not hold and no statistically significant difference was found.

In post-stimulation session 2 where the statistically significant difference between tDCS and sham stimulation was observed, different decay curves during tDCS and sham stimulation can be observed (Figure 11). With sham stimulation, word production rate decays exponentially but with tDCS, a more linear decay is observed. In pre-stimulation session 1 both groups have an exponential decay of word production rate.

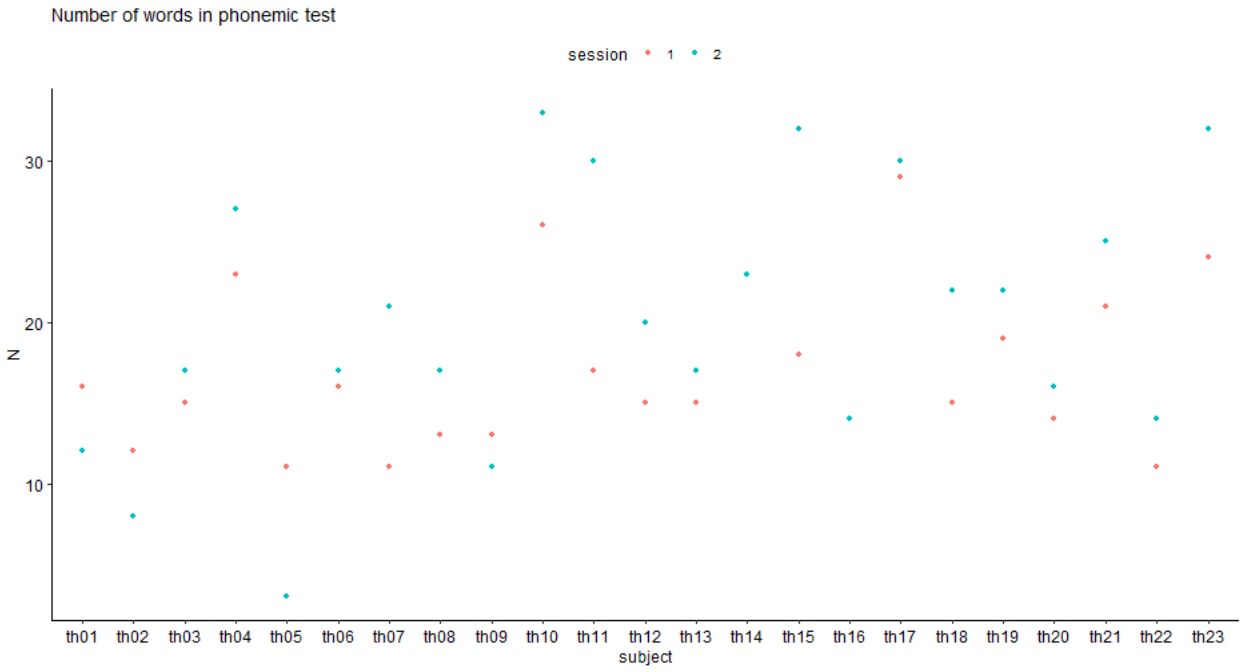


*Figure 4. Number of words produced by each participant, labeled from th01 to th23, in the phonemic fluency test in one minute. Red dots indicate results in session 1 (pre-stimulation), and blue dots session 2 (post-stimulation). The majority of participants performed better in session 2 in the phonemic fluency test.*

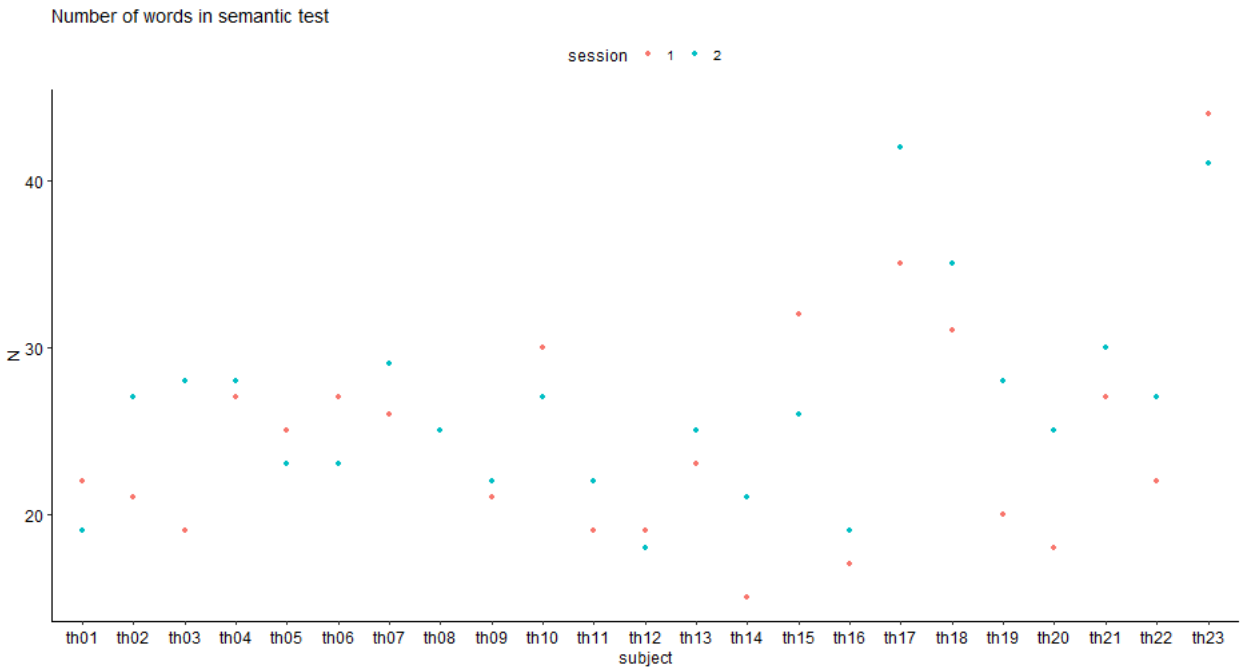


*Figure 5. Number of words produced by each participant, labeled from th01 to th23, in the semantic fluency test in one minute. Red dots indicate results in session 1 (pre-stimulation), and blue dots session 2 (post-stimulation). Most participants performed better in session 2 also in the semantic fluency test.*

*Table 2. Number of words produced in the different types of phonemic and semantic word fluency tasks, for all analyzed time intervals. Session 1 is pre-stimulation, session 2 post-stimulation.*

| **Fluency task** | **Que** | **Session** | **N** | **1 minute mean ± SD** | **1st quarter mean ± SD** | **2nd quarter mean ± SD** | **3rd quarter mean ± SD** | **4th quarter mean ± SD** |
|---|---|---|---|---|---|---|---|---|
| Phonemic | K | 1 | 23 | 17.33 ± 6.02 | 7.67 ± 2.57 | 3.42 ± 2.23 | 3.08 ± 1.78 | 3.17 ± 1.64 |
| Phonemic | K | 2 | 23 | 22.55 ± 6.64 | 8.73 ± 1.79 | 6 ± 2.41 | 3.82 ± 1.72 | 4 ± 2.76 |
| Phonemic | S | 1 | 23 | 16.64 ± 4.08 | 6.73 ± 1.27 | 3.82 ± 1.4 | 3.27 ± 2 | 2.82 ± 1.33 |
| Phonemic | S | 2 | 23 | 17.92 ± 8.98 | 8.08 ± 2.5 | 3.67 ± 2.61 | 3.83 ± 3.43 | 2.42 ± 1.83 |
| Semantic | Food | 1 | 23 | 22.42 ± 4.56 | 9.33 ± 2.23 | 4.83 ± 1.59 | 4.67 ± 2.06 | 3.58 ± 2.19 |
| Semantic | Food | 2 | 23 | 27.73 ± 8.26 | 9.91 ± 2.7 | 6.91 ± 2.81 | 5 ± 1.95 | 6.18 ± 2.4 |
| Semantic | Animal | 1 | 23 | 26.91 ± 7.97 | 11.18 ± 2.64 | 6.45 ± 2.38 | 4.64 ± 2.46 | 4.64 ± 2.8 |
| Semantic | Animal | 2 | 23 | 25.42 ± 3.34 | 9.67 ± 2.06 | 6.17 ± 1.85 | 5.42 ± 2.07 | 4.17 ± 1.4 |

*Table 3. Number of words produced in the phonemic and semantic word fluency tests, separately for active and sham stimulation, for all analyzed time intervals. Session 1 is pre-stimulation, session 2 post-stimulation.*

| **Fluency task** | **Device** | **Session** | **N** | **1 minute mean ± SD** | **1st quarter mean ± SD** | **2nd quarter mean ± SD** | **3rd quarter mean ± SD** | **4th quarter mean ± SD** |
|---|---|---|---|---|---|---|---|---|
| Phonemic | Active | 1 | 12 | 17.42 ± 5.30 | 7.75 ± 2.09 | 3.92 ± 1.83 | 2.83 ± 1.85 | 2.92 ± 1.56 |
| Phonemic | Active | 2 | 12 | 21.00 ± 9.33 | 8.25 ± 2.45 | 5.25 ± 3.28 | 3.83 ± 2.52 | 3.67 ± 2.64 |
| Phonemic | Sham | 1 | 11 | 16.55 ± 5.05 | 6.64 ± 1.96 | 3.27 ± 1.90 | 3.55 ± 1.86 | 3.09 ± 1.45 |
| Phonemic | Sham | 2 | 11 | 19.18 ± 6.88 | 8.55 ± 1.92 | 4.27 ± 2.00 | 3.82 ± 2.99 | 2.64 ± 2.11 |
| Semantic | Active | 1 | 12 | 26.08 ± 7.55 | 10.08 ± 1.93 | 5.83 ± 2.72 | 5.42 ± 2.15 | 4.75 ± 2.77 |
| Semantic | Active | 2 | 12 | 27.92 ± 7.14 | 10.17 ± 2.72 | 7.58 ± 2.50 | 5.58 ± 2.11 | 4.58 ± 2.19 |
| Semantic | Sham | 1 | 11 | 22.91 ± 5.43 | 10.36 ± 3.20 | 5.36 ± 1.29 | 3.82 ± 2.04 | 3.36 ± 2.06 |
| Semantic | Sham | 2 | 11 | 25.00 ± 4.75 | 9.36 ± 1.86 | 5.36 ± 1.50 | 4.82 ± 1.83 | 5.73 ± 2.05 |

*Table 4. ANOVA results for verbal fluency test results. Interactions between analyzed factors found in the analysis marked with x. Device refers to tDCS or sham, type to verbal fluency task type, session to session 1 (pre-stimulation) and 2 (post-stimulation).*

| **Number of words** | 1 min | 1st quarter | 2nd quarter | 3rd quarter | 4th quarter |
|---|---|---|---|---|---|
| device | - | - | - | - | - |
| type | x | x | x | x | x |
| session | x | - | x | - | - |
| device:type | - | - | - | - | - |
| device:session | - | - | x | - | - |
| type:session | - | x | - | - | - |
| device: type:session | - | - | - | - | - |

*Table 5. T-test p values between active and sham device experiments for all analyzed time intervals, both fluency task types and sessions 1 (pre-stimulation) and 2 (post-stimulation). The obtained statistically significant result is marked with an asterisk.*

| P values | 1 minute | 1st quarter | 2nd quarter | 3rd quarter | 4th quarter |
|---|---|---|---|---|---|
| Combined verbal fluency Session 1 | 0.328 | 0.619 | 0.396 | 0.487 | 0.329 |
| Combined verbal fluency Session 2 | 0.304 | 0.713 | 0.037* | 0.594 | 0.939 |
| Semantic fluency Session 1 | 0.258 | 0.805 | 0.599 | 0.082 | 0.186 |
| Semantic fluency Session 2 | 0.260 | 0.416 | 0.018 * | 0.363 | 0.211 |
| Phonemic fluency Session 1 | 0.690 | 0.202 | 0.419 | 0.369 | 0.784 |
| Phonemic fluency Session 2 | 0.599 | 0.750 | 0.395 | 0.990 | 0.311 |

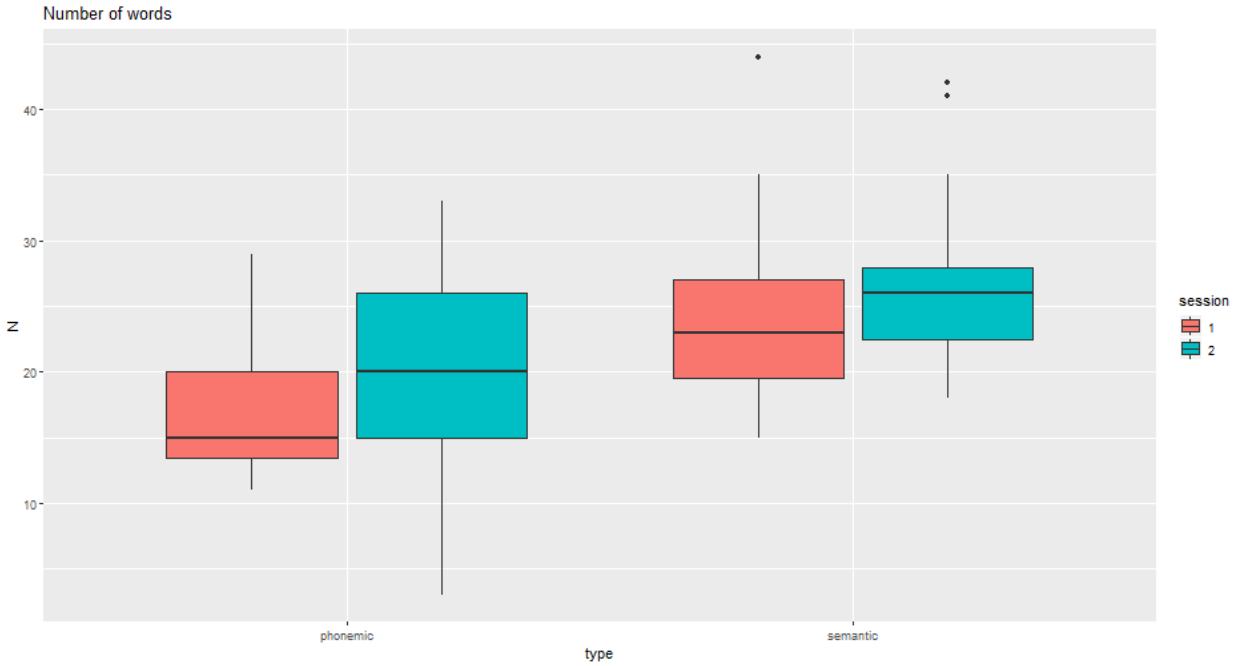


*Figure 6. Number of words produced in phonemic and semantic fluency tests. Numbers of produced words are shown separately for pre-stimulation (session1) and post-stimulation (session 2). Extremely fluent participants in the semantic fluency test are marked with a dot.*

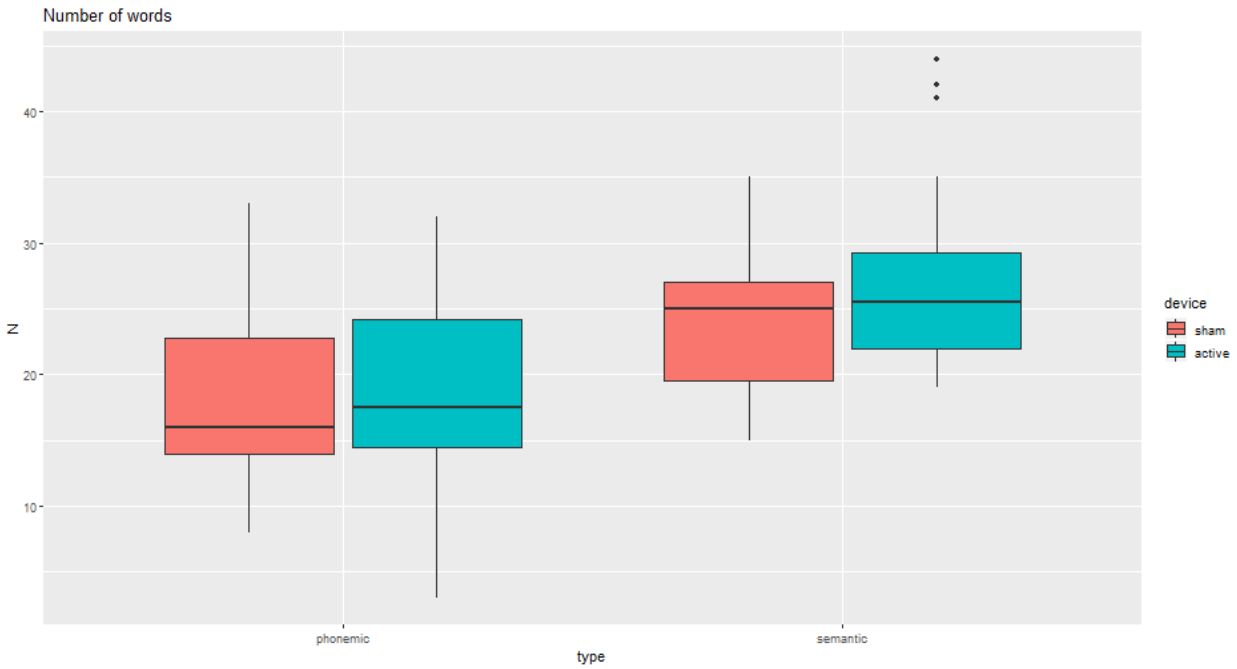


*Figure 7. Number of words produced in phonemic and semantic tests using sham device (red) and tDCS (blue). Extremely fluent outliers are marked with a dot.*

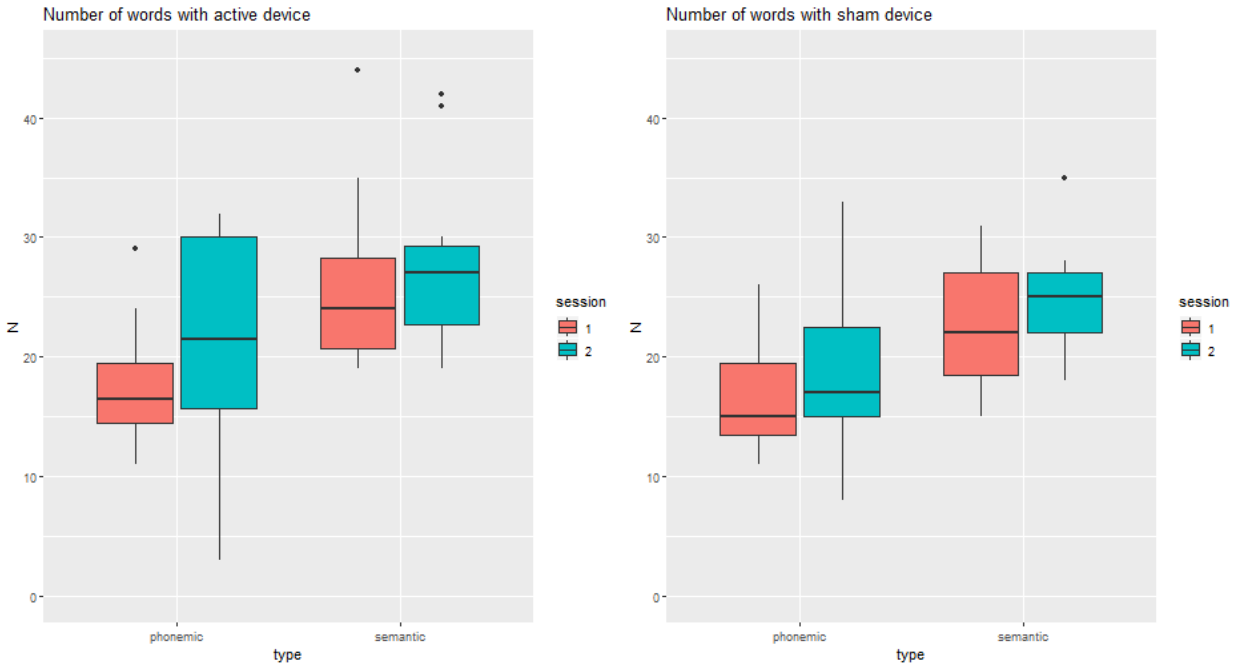


*Figure 8. Number of words produced in phonemic and semantic fluency tests using active device, or sham stimulation. Numbers of produced words are shown separately for pre-stimulation (session1) and post-stimulation (session 2). In both fluency test types, the participants produced more words in session 2 compared to session 1. Extremely fluent outliers are marked with a dot.*

Figure 9 and Figure 10 plot the statistics for phonemic and semantic fluency, sessions 1 and 2 and active and sham device separately for all analyzed quarters. From these graphs, some trends can be observed. The number of words produced is notably largest in the first quarter and declines during the one-minute test time. Session 2 tends to be more productive than session 1. In almost each graph, one or more outliers can be seen, usually very fluent performers. In some cases, there were also outliers performing more weakly compared to the average participant.

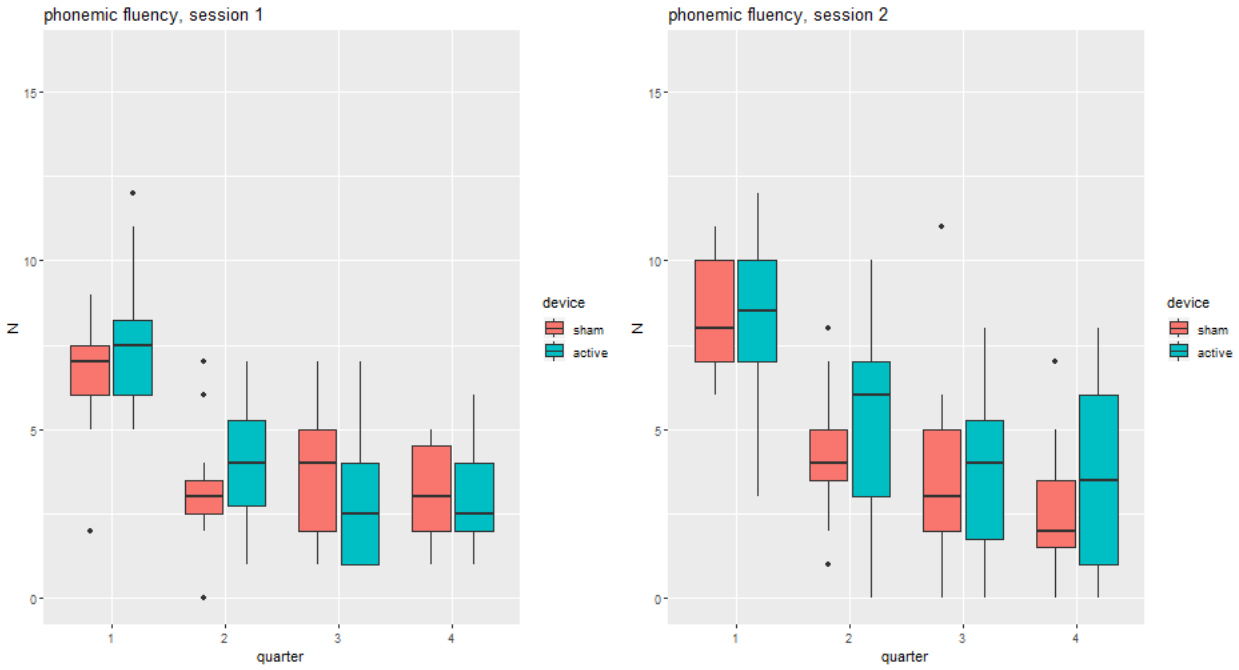


*Figure 9. Number of words produced in the phonemic fluency test in sessions 1 and 2 using the tDCS, analyzed for each quarter, pre-stimulation (session 1) and post-stimulation (session 2) tDCS or sham stimulation.*

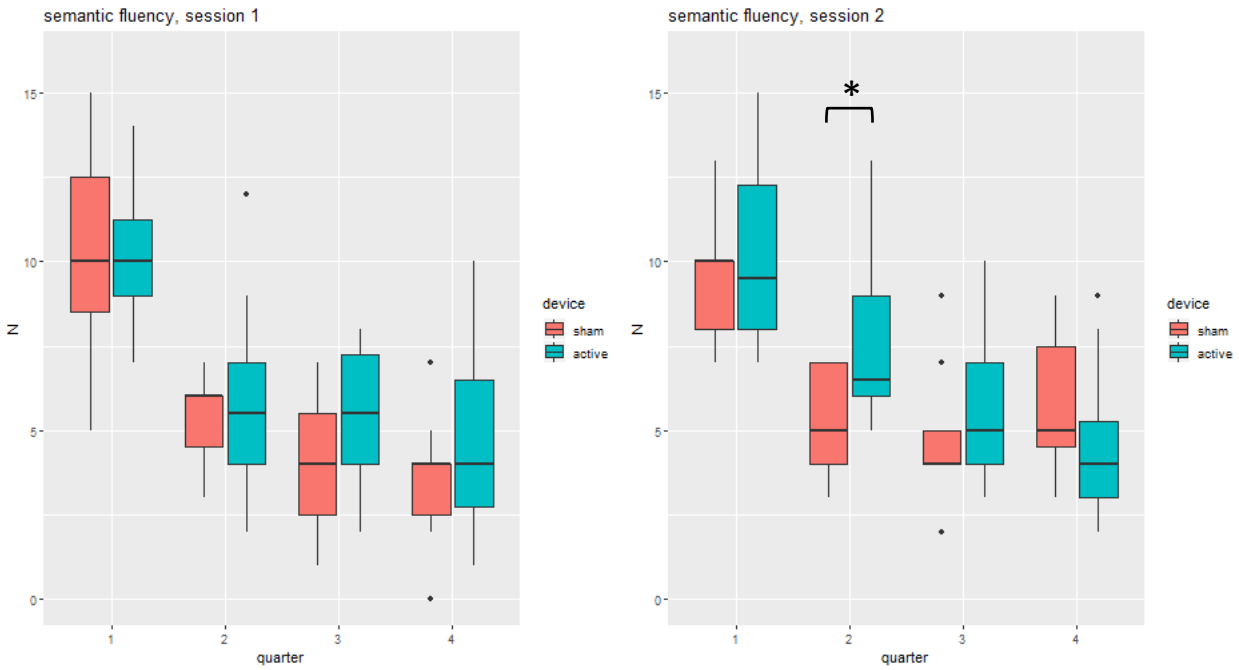


*Figure 10. Number of words produced in the semantic fluency test in sessions 1 and 2 using the sham stimulation, analyzed for each quarter, pre-stimulation (session 1) and post-stimulation (session 2) tDCS or sham stimulation. The obtained statistically significant result is marked with asterisk.*

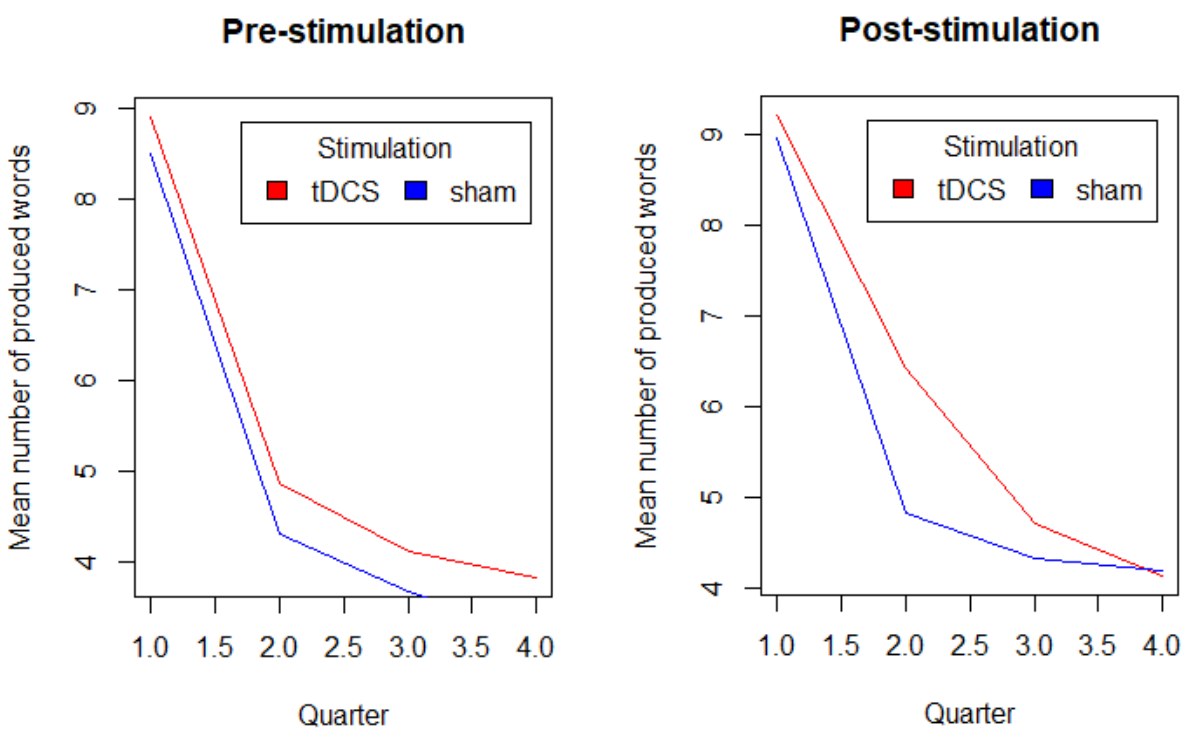


*Figure 11. Decay curves of word retrieval in session 1 and session 2. All other curves show an exponential decay, except for session 2 tDCS curve which shows a more linear decay of word retrieval. Significant difference was found post-stimulation in the second quarter of the pos*

## Discussion

The results of this study show, that there was a statistically significant difference post-stimulation only in the second quartal of the fluency task with tDCS leading to a higher number of words than sham stimulation. Post-hoc analysis, based on a-priori hypothesis of differential impact of tDCS on different fluency tasks, showed that this result was significant only in the semantic fluency task. In none of the other measured time intervals, including the whole one-minute interval, of the semantic fluency task or the phonemic fluency task significant differences were observed. The significance was lost when each subject was used as their own control and the ANOVA was conducted on the delta of stimulation effect. Thus, the results obtained in this study is marginal and preliminary and needs to be confirmed in future studies.

Recent studies suggest inconsistent outcomes in healthy participants using a single session tDCS (Horvath, Forte, & Carter, 2015a; Westwood & Romani, 2017). However, these include some positive results of improved verbal fluency (Monti et al., 2013). For example, tDCS to Broca's area (Cattaneo, Pisoni, & Papagno, 2011) and left frontal areas (Penolazzi, Pastore, & Mondini, 2013) area have been shown to improve verbal fluency. A longer stimulation duration or otherwise different stimulation parameters might be required to elicit a stronger

response. In some studies, it has been observed that effects of tDCS on executive functions might not be immediately measurable after stimulation (Gögler et al., 2017). It is also known that the effects of tDCS dissolve in a time period dependent on the type of stimulation used (Nitsche & Paulus, 2000).

The exponential decay of words retrieved when looking at the performance during different quartiles of word fluency tests suggest that initially there is immediate semiautomatic access and later a more effortful retrieval of words. It is during this later effortful retrieval that executive functions are especially needed. As test time goes on it gets harder to retrieve new words even with excellent executive functions as the extent of one's vocabulary or verbal processing may become the limiting factor. Thus, it is possible that the impact of tDCS was detected only in the second quarter of the semantic fluency test as that is the time period especially relying on executive functions that frontal tDCS may enhance. During the first quarter, responses are more automated, and the performance level does not rely on executive functions. Thus, even improved executive functions would not necessarily result in more words retrieved during the 1$^{st}$ quarter. As by the second quarter the easiest and most obvious words have been used and the need for executive functions to retrieve suitable words increases improvement in executive functions is likely to result in better performance. Yet again, towards the end of the fluency task a person's vocabulary might already be exhausted, and improvement in executive functions would not help in coming up with new words. In summary, we speculate that it may indeed be just the 2$^{nd}$ quarter of the word fluency test that is sensitive to neuromodulation aiming at enhancing executive functions such as was the case with frontal tDCS. tDCS changed the typical exponential decay curve of word fluency towards a more linear relationship between retrieved words and the lapsed time (Figure 11).

The semantic fluency task was generally easier than the phonemic one for the participants. This effect has been shown before, and it reflects the more natural, everyday production tasks requiring semantic fluency, as opposed to a more tedious retrieval and assessment process needed for the phonemic fluency task (Shao et al., 2014).

The participants generated more words in session 2 than session 1 in most studied time intervals, and it is likely because of learning. This effect is observed especially in the phonemic fluency task, which is inherently more difficult of the two. The relatively pronounced learning effect observed in the current study complicates the use of verbal fluency tests in repeated testing of executive functions for example when studying an impact of an intervention to executive functions , since the effects of an intervention on executive functions may be masked by the effects of learning.

The sample size in this study was estimated to be sufficient for showing effects of active tDCS stimulation on word fluency and indeed we were able to show a marginal impact post-stimulation on the second quarter even though the total number of words in the whole one minute task did not improve. This significance however did not survive multiple comparison and was not observed when subjects were used as their own controls, thus there may have been a problem in power with such a small sample. With a larger sample we might have obtained more robust evidence for this effect. The importance of adequate sample size has been discussed in context of lack of reproducibility of some of the tDCS effects (Minarik et al., 2016).

It is known that there is a lot of heterogeneity in subjects when it comes to measuring executive functions through a task (Berryhill & Martin, 2018). Although the subjects in this study were a rather homogeneous population by age and educational background, two significant factors contributing to heterogeneity observed in verbal fluency tests, there still might be variability to the extent that masks some of the effects of tDCS on executive functions in a small sample. Furthermore, repeated stimulation and training might be required for long-lasting effects which might be more readily measurable (Berryhill & Martin, 2018). It might also be interesting to do a follow-up to attempt to measure effects not immediately measurable after stimulation (Berryhill & Martin, 2018).

In this study, the participants were young, healthy and educated. They are thus expected to have better performance in the verbal fluency task than older or less educated subjects (Harrison et al., 2000). As their executive functions are likely to be performing on the high end of the spectrum already, the stimulation might have less capacity to induce measurable changes in these functions. Indeed in recent meta-analysis (Horvath, Forte, & Carter, 2015b) either no effect of tDCS on cognition or only weak modulation of cognitive processes (Hill, Fitzgerald, & Hoy, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016) has been observed in young, healthy participants. Nonetheless, with healthy older subjects or patients with brain disorders affecting executive functions, there might be more room for improvement. Following the Hebbian version of the Yerkes-Dawson law where the rising slope of the inverted U curve represents optimization of performance due to increasing arousal (D. M. Diamond, Campbell, Park, Halonen, & Zoladz, 2007), patients with lower performance might be on the rising slope of the inverted U-curve with their cognitive performance. For these groups, neuromodulation through tDCS might improve cognitive functions by pushing them up the curve towards more optimal cognitive performance.

Furthermore, there are several stimulation parameters that might be optimized, although using current methods they are all not possible yet. Targeting stimulation is currently somewhat approximate, depending on the skull structures and exact position of the prefrontal cortex of each subject. In this study, the exact location of DLPFC was not confirmed. Location of the electrodes could also be adjusted to produce more pronounced

effects in the desired Brodmann's areas. In addition, by moving the cathode from right frontal region to more posterior brain regions might allow for decreasing the slight hyperpolarization in the right prefrontal cortex that may interfere with optimal executive functions (Soares et al., 2018).

A practical challenge in a clinical setting is determining spoken words and their timing. Here, the verbal output of the participants was recorded and processed by a researcher afterwards. Efficient and reliable use in bedside test batteries would require at least semi-automated recording and analyzing of produced words. With current technology widely used e.g. in smartphones, this is already doable.

## Conclusions

In this study, we found that tDCS of the dorsolateral prefrontal cortex increased semantic fluency in a time period between 15-30 second from the beginning of the test. Word retrieval performance during this time period depends most likely strongly on executive functions and thus subtle improvement of executive functions may theoretically explain this finding. However, the finding is marginal and preliminary and needs to be confirmed in the future. It is possible that modifying test parameters such as strength of current, timing and length of stimulations, as well as doing repeated stimulations over a longer period of time, might bring out more pronounced effects of tDCS.

Learning might significantly mask or contribute to changes in executive functions in verbal fluency tasks limiting its use in repeated testing. Furthermore, linguistic processes influence the performance and thus word fluency tasks do not allow for isolated assessment of executive functions. These are some of the challenges in using verbal tests to measure impacts of different interventions or the course of a brain disease and its impact on executive functions in clinical populations.

While the effect of tDCS in young healthy subjects with optimal cognitive functions was marginal, it would be interesting to study whether there might be stronger effects of tDCS in older populations or patient groups with impaired executive functions and thus more room for neuromodulation to improve cognitive functions.

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