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Does Anodal tDCS Over the Left Prefrontal Cortex Using the C3-RSO Montage Improve Cognitive Control?

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Abstract:

Executive function is the ability to change one's behavior in order to achieve a goal, which is supported by the prefrontal cortex (for review, Abdullah et al., 2021). Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation technique that changes the likelihood of neuronal firing by sending current through at least two electrodes on the scalp. Prior work in our lab found no enhancement of executive function on healthy participants when attempting to stimulate the dorsolateral prefrontal cortex using anodal tDCS with the F3-RSO montage (Darling et al., 2020). However, current modeling suggests that the C3-RSO montage may be more likely to stimulate dorsolateral prefrontal cortex (Datta et al., 2012). Therefore we examine whether using the C3-RSO montage to target the prefrontal cortex could enhance executive function in healthy participants.

Introduction:

Imagine you were working on a homework assignment in a noisy cafe and could not seem to focus. Would it not be nice to focus on command? Just think how efficient you would be. Just think about how much more free time you would have. Executive function — often used synonymously with "cognitive control" — is a set of mental skills that helps humans learn, work, and manage daily life tasks. For instance, executive function supports the ability to alter one's behavior to achieve a goal. Precisely, executive function can be divided into three areas: working memory, set-shifting, and inhibition (for review, Abdullah et al., 2021). In terms of working memory, this is when one is able to use relevant information while performing an activity. For example, recalling the steps of a recipe while cooking a favorite meal is using working-memory. In the case of set-shifting, this is the ability to go between different tasks or mental sets An example of this is realizing when you hear someone say "I have a record", the speaker was referring to an album rather than a criminal record. Lastly, inhibition involves suppressing attention and automatic responses to irrelevant stimuli. In other words, it can be described as thinking before acting and the ability to assess and evaluate a situation before responding to it. For example, being asked to focus on a black dot while ignoring the moving stimuli around it. Healthy cognitive control is typically associated with healthy prefrontal cortex (PFC) and related frontal lobe regions (for review, Friedman & Robbins 2021). As this would suggest, people with impaired PFC can show decreased concentration and poor planning skills.

One way to modulate PFC activity is through brain stimulation. Methods such as deep brain stimulation may indeed show promise in treating Obsessive-Compulsive Disorder and mood disorders (for review, Mi 2016), which is related to improving an impairment in the set-shifting component of executive function. However, surgically penetrating the skull is a highly invasive procedure. Conversely, non-invasive techniques – such as transcranial magnetic stimulation (TMS) and transcrainial electrical stimulation (tES) – have the potential to achieve the same goal without the limitations of an invasive technique. Transcranial magnetic stimulation uses *magnetic* stimulation to modulate neural activity. Additionally, TMS can cause neurons to fire, whereas tDCS can only change the likelihood of neurons firing by affecting their membrane potential.

Transcranial direct current stimulation (tDCS) partially composes a group of non-invasive brain stimulation methods called transcranial electrical stimulation (tES). This group uses *electrical* stimulation to modulate neural activity. The transmission of an electrical current is sent by the application of at least two electrodes — the anode and the cathode — on the scalp. By exposing neurons to positive current (depolarization), the anode electrode raises the likelihood of neuronal firing. In contrast, cathodal electrodes make neurons less likely to fire due to hyperpolarization (a more negative charge). While tDCS is less powerful than TMS, an advantage is that, tDCS (and any device that is considered a tES) tends to be much cheaper and simpler to apply (Ekhtiari et al., 2019). If the device can improve an individual's executive function, similarly to TMS, at a cheaper price, then it is worth looking at its potential.

Some studies have already explored the association between anodal tDCS stimulation and the left dorsolateral prefrontal cortex (L-DLPFC) in order to improve executive function. One such study found that anodal tDCS has a positive influence on the motor and cognitive tasks of healthy individuals, which includes the pegboard task, finger tap tasking, the N-back task, and other cognitive tasks (Saruco & Rienzo et al. 2016). Other studies have examined whether tDCS has these positive effects on neurological disorders of executive function (or impaired executive function). For example, people with Parkinson's Disease exhibit executive dysfunction in early stages, characterized by impairments in working memory, planning, problem-solving, verbal fluency, and cognitive flexibility (for review, Combs et al., 2018). A recent study applied anodal tDCS on the L-DLPFC of sixteen patients with Parkinson's Disease and measured their phonemic fluency, part of verbal fluency (Pereira et al., 2013), which is part of the working memory aspect of executive function. Phonemic fluency requires "individuals to generate lists of words that start with a given letter" (Pereira et al., 2013). One thing to consider is that studies have already suggested improvement in phonemic fluency in healthy individuals (Iyer et al., 2005). Therefore, Pereira et al., 2013 found improvement in phonemic fluency in those with Parkinson's Disease, suggesting the potential benefits of anodal tDCS on those with executive dysfunction. Additionally, tDCS may also help people with Major Depressive Disorder who also show characteristics of characteristics of executive dysfunction, e.g., difficult planning, initiating, and completing goal-directed activities (for review, DeBattista 2005). For instance, applying anodal tDCS over the DLPFC of people with Major Depressive Disorder for 10 consecutive days improved visual spatial memory, thus exhibiting an improvement of executive function (Salehinejad et al., 2017). This is a significant improvement as visual memory is the most impaired aspect of executive function with those with Major Depressive Disorders.

Although there have been numerous studies examining whether tDCS can be used to improve executive function, not all have shown consistent results. For example, in anodal tDCS of dorsolateral prefrontal cortex during an Implicit Association Test, the researchers used the Implicit Association Test to test the association between concepts and evaluations. The purpose of this test is to make a response much quicker when the items are really closely related. In this case, they hypothesized that the incongruent trials (where items are not closely related) would decrease their response time by using anodal tDCS. However, their results contradicted their hypothesis since "tDCS did improve reaction times, but in the congruent rather than the incongruent" conditions (Gladwin et al., 2012). In other words, tDCS can show promising results, but it might demonstrate conflicting results. In a meta-analysis, they support this even further by stating how larger sample sizes may have been required since researchers "may have lacked sufficient statistical power to reliably test hypotheses based on categorical outcomes" (for review, Meron et al., 2015). Possible contradictions surface as a result of inter-subject variability and, perhaps most commonly, from the use of different parameters.

In tDCS studies, several parameters determine the amount and how the electric current will be sent to the brain region of interest. One such parameter is *current density,* which is the flow of electric charge in a specific area. Current density is determined by the amount of current and the area over which it is applied. Using larger electrodes results in a low current density, as the electric current is sent through a greater area (Brunoni et al., 2012). In contrast, smaller electrodes will allow more electric charge within a smaller area. Stimulation duration is a second parameter, because studies have shown that using anodal tDCS for more than 26 minutes actually produced *inhibition*, which is the *opposite* of what anodal tDCS is typically thought to do (Paulus 2011). The same reversal may also occur for cathodal tDCS, which is typically thought to produce *inhibition*, though the results were inconsistent (Paulus 2011). In other words, applying *cathodal* tDCS for a longer time, such as 18 minutes, did not change its *inhibition* effects to *excitation*. A third parameter is electrode placement — or "montage" — because relatively small changes in the electrode placement will result in significant changes in current flow and intensity, thus stimulating a different brain region (Ramaraju et al., 2018).

When attempting to test cognitive control via the prefrontal cortex, the classic montage is F3-RSO (for review, Splittgerber et al., 2020). This is a montage consisting of two electrodes, where the anode is placed over the left prefrontal cortex, and the cathode is placed over the right suborbital region (RSO).

Figure 1: *The F3-RSO montage used in the study done in the University of Connecticut*

In a study at the University of Connecticut, the investigators tested the effects of anodal tDCS over PFC using the F3-RSO montage and found no impact on cognitive control (Darling et al., 2020). However, in recent years, current modeling has become available to determine the likely flow of current for a given tDCS montage. Using this method to assess the likely current flow for the F3-RSO montage suggests that rather than targeting the intended area (DLPFC), this montage targets an area slightly medial to this area. It is therefore possible that failure to stimulate DLPFC is the reason that this prior study did not show any effects on cognitive control.

I hypothesize that transcranial direct current stimulation (tDCS) over the left prefrontal cortex will augment cognitive control via the C3-RSO montage. In this case, the anode will now be placed over the left cerebral cortex (C3). To measure cognitive control, I will use the Stroop and Flanker tasks (described below). Based on prior studies, we will stimulate only for 20 minutes maximum because using anodal tDCS for longer can convert activation into inhibition (Paulus 2011).

The Stroop task (Stroop 1935) is a common way to measure executive function. It requires the participant to view a list of words printed in a different color than the word's meaning, and to name the ink color or indicate it via a button press. For example, if the word "green" were printed in blue ink, the participant would respond "blue". This test measures cognitive control because the participant has to simultaneously inhibit irrelevant — or interfering — stimuli (the printed word) with the stimuli of interest (the color in which the word is printed). Looking at congruent trials, the word and ink color are the same. However, incongruent trials occur when the word and ink color are not the same. As a result, incongruent trials display slower responses when compared to congruent trials. Thus, slower responses demonstrate how cognitive control is challenged in the incongruent trials.

Figure 2: *Representation of the Stroop Task breakdown for this study*

The Flanker task (Erikson & Erikson, 1974) is another common way to test cognitive control. It is similar to the Stroop task because the participant has to inhibit irrelevant stimuli to respond to the relevant stimuli. This test presents a series of arrows and participants respond with the direction of the central arrow when asked. There are three types of stimuli used: congruent, incongruent, and neutral stimuli. In a congruent stimulus, all arrows face in the same direction. In contrast, the incongruent stimulus has all of the other arrows facing the central arrow's opposite direction. Lastly, the neutral stimulus has four crosses surrounding one arrow. Out

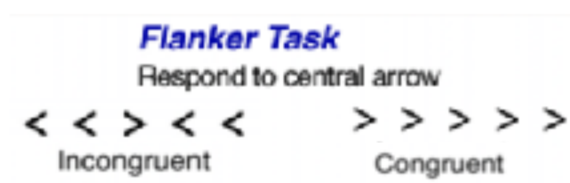

Figure 3: *The congruent and incongruent Flanker Task that was presented to our participants*

of the three stimuli, the incongruent stimulus measures cognitive control because the participant has to disregard the other arrows and focus primarily on the central arrow. To measure cognitive control, this study will also use the Flanker task.

My study will control for individual differences in executive function through a pre-and post- test design. That is, we will first test participants on the tasks described below before stimulation to get a baseline and then test them on the same tasks afterward to assess any change. This is important because, in the study described above (Darling et al., 2020), they observed that if they had not compared the pre-and post- tasks, then a significant detriment on performance (of 7%) would have emerged when comparing only the post-tasks (Darling et al., 2020). We predict that, the incongruence effect will decrease between pre-and post-test task scores in the anodal condition compared to the sham condition.

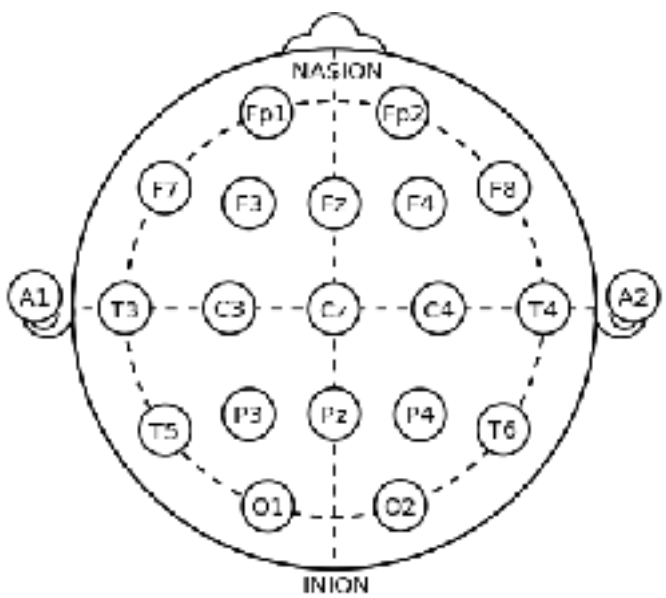

Figure 4: *The 10-20 International system of EEG electrode placement. This study will be changing the location of the anode electrode from F3 to C3. Note: the nose is the area where it says "nasion".*

Methods:

Participants were gathered from the University of Connecticut Psychological Sciences participant pool. The sham condition results will be from the study done at the University of Connecticut (Darling et al., 2020). Due to our sample size of two participants, we will discuss predicted results.

Before beginning the experiment, participants were asked to fill out questionnaires to ensure their safety in order to receive stimulation. The procedure and possible side effects of stimulation were explained to participants before they signed the consent form. Possible side effects included itching, burning, and redness at the location of the electrode.

Next, participants in both conditions completed the Flanker Task for six minutes. Fifty percent of the trials were congruent, while the other fifty percent were incongruent. Participants then completed the Stroop task for five minutes. Half of the trials were congruent trials, which is when the ink color and word were the same, and the rest were incongruent, which is when the ink color and word did not have the same color.

Next, the participants' heads were measured to determine the size cap to use. The electrodes were then marked on the participant's skull using a washable pen. The montage used was C3-RSO, in which the anode was placed over the left cerebral cortex (C3) and the cathode was placed over the right supraorbital region. The electrodes were placed in 5x7 cm saline-soaked sponges and then put on the participant's scalp. Then, the electrodes were held with two plastic straps.

After beginning stimulation in both conditions, the gradual increase to 1.5mA occurred over the course of 30 seconds. Then, those in the anodal tDCS condition received stimulation, unlike the sham condition where the stimulation was turned off. After this 30 second interval, participants watched a nature video for three minutes to allow the stimulation to have an effect before performing the two tasks.

Next, participants post-stimulation did the Flanker and Stroop tasks. A pre- and post-test design was used to accurately compare baseline differences in cognitive control between the stimulation and sham groups. After completing the tasks, the tDCS machine gradually decreased for 30 seconds and then plastic strips and electrodes were removed. Then, participants completed forms that asked them if any side effects were experienced and for any questions.

Predicted Results:

Since only 2 of our target of at least 60 participants were tested during this study, we were only able to make predicted results on the Flanker Task and the Stroop Task.

When focusing on the Flanker Task and Stroop Task, reaction time and accuracy were prioritized. Precisely, our interest lays in the difference in reaction times between congruent and incongruent trials in the pre- and post- tests in both the sham and anodal conditions. One thing to consider is the "incongruency effect", which is the expected result of the correct response times being longer in the incongruent trials when compared to the congruent trials. If data was gathered, this would be measured by subtracting the average reaction time for congruent trials and average reaction time for the incongruent trials for each participant in both pre- and post-test Flanker and Stroop Tasks.

As shown in Figures 5 and 6, we still expect the “incongruency effect” for the sham condition to decrease in the post-test due to the testing effect. However, we expect the anodal post-test “incongruency effect” to decrease even further. In the case of accuracy, we also expect to see a decrease in accuracy difference between congruent and incongruent trials with the sham group, however similar to the “incongruency effect”, we expect more of a decrease with the anodal post-test group.

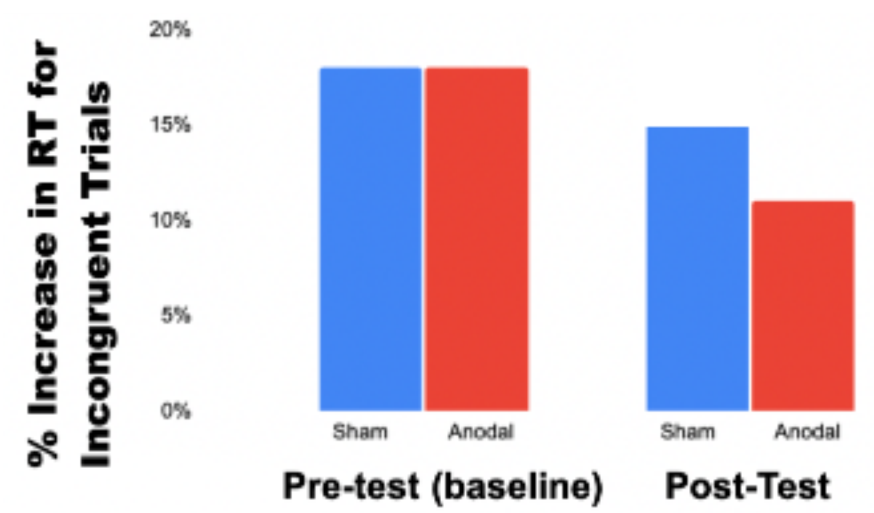

Figure 5: *The predicted percent increase in reaction time for incongruent vs congruent trials in both pre-test and post-test Flanker Tasks in the anodal and sham conditions.*

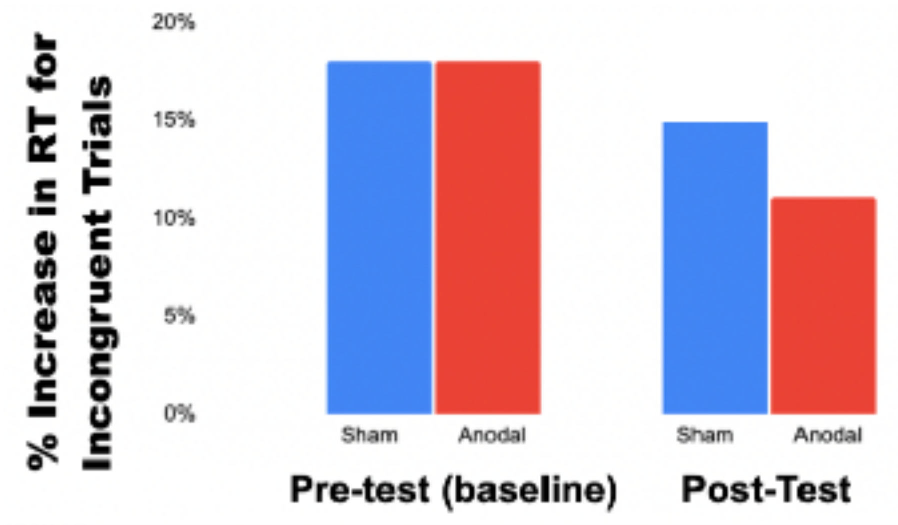

Figure 6: *The predicted percent increase in reaction time for incongruent vs congruent trials in both pre-test and post-test Stroop Tasks in the anodal and sham conditions.*

If the predicted results are true, it would be clear that anodal tDCS with the C3-RSO montage over the left prefrontal cortex has an effect on cognitive control. Since we are comparing pre-test and post-test reaction times, this takes into account baseline differences in cognitive control among individuals that was not caused by stimulation conditions.

Discussion:

If we tested participants and gathered data that matched to our predicted, then that would mean that anodal tDCS over the left prefrontal cortex with this specific montage — C3-RSO — improved executive function. In other words, it would confirm our prediction that maximum stimulation occurs between the two electrodes. Additionally, this can explain why there have been conflicting results of tDCS, where some studies see an effect on cognitive control and others have not. If this were to be true, then this will improve the accuracy of where stimulation occurs by anodal tDCS. If cognitive control can be enhanced, this could benefit those with attentional deficits, including those with neurological disorders of cognitive control, such as Parkinson's Disease (Pereira et al., 2013).

On the other hand, if any future gathered data does not match with the predicted, then that could mean that stimulation is not reaching the targeted DLPFC region. It is also possible that the stimulation is too spread out or that stimulating DLPFC does not enhance executive function. Considering that bipolar montages have widespread current distribution and are poor at spatially targeting brain areas, potentially the use of more electrodes, therefore no longer bipolar, can increase excitability to the brain area of interest (Saturnino et al., 2015). Recent studies have suggested that the use of more electrodes is more precise in the current distribution (Fisher et al., 2017).

It is also possible that changing the parameters of the study of Darling et al (2020) will elicit an increase in cognitive control. In other words, stimulation with the parameters of our study did not reach the region of interest. There is also the possibility that intensity of 1.5 mA was not enough, and higher intensity (up to 2 mA) can change our results. Potentially, the duration of the stimulation is not correct, although this should proceed with caution since stimulation over 26 minutes turns into inhibition (Paulus 2011).

Another possible reason why we do not see an effect is that the Stroop and Flanker tasks only test the inhibition component of executive function. Therefore, future studies should use other cognitive tasks to focus on the other components — working memory and set-shifting— to see if those components will be enhanced. Potentially, other tasks are more likely to be affected by tDCS in the PFC when compared to the inhibition component tasks. It is worth gathering data for this montage for the sake of accuracy of where stimulation occurs.

Overall, examining whether stimulating DLPFC can enhance executive function will require tasks to measure the different aspects of cognitive control. Even so, more work must be done to verify the significance of the DLPFC in terms of set-shifting and inhibition. (Imburgio & Orr 2018). Additionally, it requires the systematic examination of parameters, such as the montage, intensity of the current, duration of the stimulation, with a well-powered design that takes into account baseline differences. If this is done, it will one day reduce this current lack of consensus between tDCS studies.

Appendix

A Transcranial Direct Current Stimulation (tDCS) Adult Safety Screen was used to determine the eligibility of a participant in the study. If a participant had any indicators of brain injuries, history of seizures, medications, metal implants and pregnancy, then they were removed from the study. Participants were asked to remove any metal, such as piercings and jewelry and electronic devices with them.

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