Improving Visual Working Memory Capacity with Prefrontal Brain Stimulation.

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Abstract

In previous research, transcranial direct current stimulation (tDCS) applied over the left dorsal lateral prefrontal cortex (DLPFC) showed enhancement of working memory performance, however the effect on the right DLPFC is unexplored yet. This study attempted to investigate if visual working memory (VWM) capacity could be improved by applying tDCS over the right DLPFC. This double blind, sham-controlled study recruited 16 participants. The experiment consisted of three sessions: a training, tDCS and sham stimulation session. The order of the tDCS and sham stimulation session was counterbalanced. In each session a change detection task was performed before, during and after 20 minutes of 1mA anodal or sham stimulation. Electric stimulation compared with sham stimulation did not significantly improve VWM performance. Remarkably, an effect of sham stimulation was found, indicating a placebo effect. No learning effects were detected. In conclusion the study did not accomplish to confirm the hypothesis, however did found a placebo effect.

Introduction

Visual working memory (VWM) is a memory system limited to information within the visual domain. It stores information for a few seconds, so that this information can be used for ongoing cognitive tasks (Luck, 2008). In other words it keeps visual information active, as a temporary storage buffer. VWM is considered to be the visual storage component of a bigger system, working memory (Luck, 2008). The capacity of VWM is limited and varies among individuals. The maximum capacity is four objects, whereas people differ in capacity from one and a half to four objects (Luck& Vogel, 2013)

A lot of evidence indicates that the dorsolateral prefrontal cortex (DLPFC) is important for VWM. Studies with transcranial direct current stimulation (tDCS) explored the relation between the DLPFC and VWM (Coffman, Clark & Parasuraman, 2014). TDCS is a non-invasive method that involves the passage of a constant small electric current, typically 0.5 to 2.0 mA, through the scalp to modulate brain activity (Coffman et al., 2014; Keshvari, Pouretemad &
Ekhtjari, 2013). TDCS stimulates the cerebral cortex and can induce long lasting changes, in a painless and safe manner. The direction of the induced effect depends on the polarity of the current (Zaehle, Sandmann, Thorne, Jäncke & Herrmann, 2011). Anodal tDCS has an excitatory effect on the underlying cerebral cortex; it depolarizes the membrane potential. Cathodal tDCS has an opposite, inhibitory effect due to hyperpolarization of the neurons in the membrane (Marshall, Mölle, Siebner & Born, 2005). Thus, anodal tDCS increases excitability of the cortex while cathodal tDCS decreases excitability (Andrews, Hoy, Enticott, Daskalakis & Fitzgerald, 2011).

Recent tDCS studies suggested that the DLPFC plays a crucial role in working memory. For example in a study in which macaque monkeys performed a delayed matching task that required VWM. It was found that there was a high delay activity in prefrontal neurons during the delay interval. During this delay information had to be held active, which suggested the implication of prefrontal cortex in VWM processes (Miller, Erickson & Desimone, 1996). In humans, disruption of the activity in the DLPFC trough transcranial magnetic stimulation (TMS) impairs working memory capacity, implying a causal role in working memory processes (Sligte, Wokke, Tesselaar, Scholte & Lamme, 2011). Furthermore, neuroimaging studies suggested that the DLPFC is one of the most important areas correlating with working memory in humans (Keshvari et al., 2013).

The increase of excitability through anodal tDCS in the DLPFC is explored as a way to enhance working memory (Zaehle et al., 2011). Research has focused on enhancing working memory in a clinical setting, for example in Parkinson patients. A significant improvement has been found in working memory after stimulation of the left DLPFC with anodal tDCS compared to sham stimulation (Boggio et al, 2006). This also applies for rehabilitation of patients who suffered from a stroke (Jo et al., 2009). In healthy people as well it has been found that anodal tDCS of the left DLPFC led to enhancement of working memory performance. People made fewer errors on a working memory task, after only 10 minutes of anodal tDCS (Fregni et al., 2005). Later research suggested that this enhancement works in a time-dependent way (Ohn et
This means that the accuracy of response significantly increased after 10 minutes of tDCS application and was further enhanced after 30 minutes of stimulation (Ohn et al., 2008).

Previous research results are mostly generated through unilateral anodal stimulation of the left DLPFC therefore they ignore bilateral stimulation. It was found that bilateral stimulation of the DLPFC was not a useful method to improve working memory (Keshvari et al., 2013; Marshall et al., 2005). This suggests that unilateral anodal stimulation is useful for enhancing working memory contrary to bilateral stimulation. Previous research also concentrates mainly on stimulation of the left DLPFC. All this research shows that tDCS on the left DLPFC improves working memory, but there is also some evidence that stimulation of the right DLPFC plays a role in VWM (Sligte et al., 2011). A different study suggested a more dominant role of the right DLPFC on image-based visual working memory than the left DLPFC (Keshvari et al, 2013). However, this evidence is unexplored yet. We’ll explore this further in our research.

In this research we’ll use anodal tDCS on the right DLPFC in comparison with a sham stimulation condition. The main question of our study is if visual working memory capacity can be improved by increasing neural activity in the right DLPFC. Due to previous research the expectation is that an improvement in working memory capacity can be found in the stimulation condition compared to the sham stimulation condition.

Exploring tDCS in a way for enhancing working memory might be good for practical applications. An example of such practical applications is the development of new tools for treatment and rehabilitation of patients with neurological and psychiatric diseases (Coffman et al., 2014; Boggio et al., 2006). Other domains could be education (learning a new language), daily work, the military and more domains (Meinzer et al., 2014). So exploring the enhancement of visual working memory can be socially relevant for a much broader domain.
Method

Subjects

18 healthy right-handed adults (13 females) participated in the experiment. All had normal or corrected-to-normal vision. None of the subjects had a history of brain seizures, neurological diseases or other risk factors. Participants underwent the tDCS and sham stimulation conditions in a counterbalanced manner. All participants gave their written informed consent before participating, which was approved by the ethics committee of the department of Psychology of the University of Amsterdam. In the end, 16 subjects (11 females, mean age 20.4 +/- 1.7 years) completed the entire experiment. One participant quit the experiment because she was unable to schedule the last two sessions. The other participant was double booked for the second session and did not want to reschedule. For their participation the subjects received five participation points.

Materials

Exclusion criteria

For screening we used a 19-item exclusion criteria questionnaire with a yes/no response option. For example: 'Do you have epilepsy or did you ever had an epileptic attack or absence? yes/no'. This screening questionnaire was included in the information brochure and informed consent. The information brochure contained information about the goal of the research, instructions and procedure, possible side effects, voluntariness, compensation, confidentiality of research data, insurance and further information.

VWM Task design

We used a change detection paradigm, presented on a computer screen (size, x Hz). The programme used for the experiment was Presentation version 18.1 of Neurobehavioral Systems Incorporated. (Albany, California, US). The distance from the participant to the screen was 57 centimetres. This task contained five different arrays in the following order: a begin array, a
fixation array, a memory array, a delay array and a test array. In all the arrays a black fixation cross was presented at the centre of the screen. In the fixation array the cross turned green to indicate the start of the trial. The memory array contained eight black rectangles on a grey screen oriented in a circle around the fixation cross. The rectangles could be oriented horizontal, vertical, 45° to horizontal or 135° to the horizontal orientation. The orientation of the rectangles was randomized and all rectangles had each orientation equally often. The delay array only contained a fixation cross. One rectangle was presented in the test array. The trial design is shown in figure 1.

At the start of the experiment the fixation cross was black and after 1s it turned green for 0,5s. After that the memory display appeared for 0,25s. Subjects were instructed to remember the orientation of each rectangle in this display the best they could. After that the delay array was shown for 1s. Finally only one rectangle was presented in the test array whereas in 50% of the trials the orientation of the rectangle had the same orientation as the one on the memory display (‘No-change trial’). In the other 50% of the trials there was a change of 90° contrary to the orientation in the memory array (‘Change trial’). During the test array the subjects were instructed to respond by button press for change or no change. The z button, red sticker, had to be pressed for no change and the m button, green sticker, for change. The test array was presented for 3s. One complete trial had duration of 5,75s. If a participant gave the right answer he/she would hear a tone (beep), if wrong no sound would be heard.

The participants conducted three blocks. Each block contained 160 trials, divided in three parts. A complete block was as follows: first 53 trials followed by a 1,35 minute break, 54 trials again followed by a 1,35 minute break and finally again 53 trials. After that, there was another 1,35 minute break. After the first block a screen with the text ‘Wait for further instructions’ would appear, the participant then had to call for the instructor. This whole block was repeated twice. During the first break the tDCS device was turned on. After the second block there again is a 1,35 minute break wherein the tDCS device was shut down. Thus in total the participant executed 480 trials with a total duration of 60 minutes.
Experimental design

First, the tDCS equipment was attached to the head. To locate the F4, the circumference of the participant head was measured with a tapeline. Next, a suitable EEG-cap was placed over the head to mark F4 on the scalp. One stimulation electrode (3x3 cm) had to be applied on F4 above the right DLPFC and one reference electrode on the left forehead (5x7 cm). The electrodes were held in place with rubber straps. The order of real or sham stimulation was counterbalanced between subjects and was carried out in a double blind manner. The experimental session existed of the visual working memory task without stimulation in the first 20 minutes in block 1, than 20 minutes of stimulation during block 2 and in the last 20 minutes again without stimulation in the third block. The current was gradually built up from 0-1mA in 60 seconds. In the sham stimulation condition there was no real stimulation at all during the three blocks of the visual working memory task, although there was a ramp-up and a ramp-down. We measured accuracy in percentage of correct answers (dependent variable). The independent variable was real or sham stimulation.

tDCS device

The tDCS was delivered with the use of a DC-stimulator Plus with a maximum output of 10mA (neuroConn GmbH, Germany). The tDCS device was connected with two electrodes. The tDCS device was a battery-powered device that gave a constant 1 mA current. The device required a code to get it started. There were two types of codes; one code started tDCS and kept it running during the second block and (tDCS condition) the other code started tDCS for one
minute (ramp up) and then stopped it from working (sham stimulation condition). In the sham stimulation condition it started again in the last minute of the block after which it shut again (ramp down) for a double blind measurement.

*Side effects questionnaire*

After completion of the second and third session, the subject was asked to complete a questionnaire for possible side effects at the moment. This questionnaire contained seven statements (for example: headache) to be scored on a 5-point scale whereas 1 stands for not at all applicable to me and 5 for completely applicable to me.

*Data analysis*

The data script was written using the MATLAB_R2014b software of MatWorks Incorporated (Natick, Massachusetts, United States). Results were analyzed using the statistical software SPSS version 20.0 of IBM Corporation (Armonk, New York, United States). A 2x3 repeated measures ANOVA was executed to look for an effect of tDCS over sham stimulation. To check for learning effects two paired samples t-tests were used. T-tests were conducted to explore the effect of time, for both tDCS as sham stimulation. The statistical significance refers to a value of p<0.05.

*Procedure*

First of all, the experimenter called the participant to make three appointments, with at least 72 hours apart from each other to avoid long lasting effects of the tDCS. The participant was also instructed not to use alcohol or drugs the day before the experiment. He/she received the information brochure via email before the first session. If the participant answered yes at any of the exclusion criteria, exclusion was necessary. If the subject was permitted to participate in the research an informed consent needed to be signed as well by participant as experimenter.
The experiment included three sessions, one screening and two experimental sessions. During the first session participants were informed about the research, screened and trained. During the screening they filled in the ‘informed consent’ form with a screening questionnaire and an eye test. The aim of the eye test was to determine if sight was normal or corrected to normal. After the screening the subject underwent a trial stimulation of 1mA, after which the subject could decide to participate or not. In case the subject decided to participate, he/she was trained on the visual working memory task. The instructions of the task appeared on screen, accompanied by further instructions of the experimenter. The participant was told that at every moment of the experiment it was possible to stop the experiment. The duration of the first session was 1,5 hour.

During the second and third session, an instructor with a first aid certificate was always present, in case something went wrong. The subject received real or sham stimulation, dependent of the condition. After the session the participant received a questionnaire about possible side effects at the moment. The participant had to wait for an hour and was offered to be accompanied home. The day after the session the subject was contacted telephonically to check for possible side effects. The third session precedes the same as the second session. The duration of both the second and third session was one hour.

After the last session the subject received a debriefing and the reward.

**Results**

We applied tDCS or sham stimulation to 18 subjects DLPFC during the change detection task. Two of them did not complete the entire experiment. The third block of the first session was not stored for participant four due to technical difficulties. Also one participant was distracted and missed three trials. Missed trials or early responses were not included in the data analysis. One of the participants drank over 10 alcoholic beverages the night before the second session. The data of this particular subject was not excluded, because his performance did not
differ substantially from the rest of the data. An important observation was that there were some side effects throughout the entire experiment, an itchy feeling due to real stimulation.

First we wanted to determine if there was an effect of tDCS and time on task performance. In order to do this a repeated measure ANOVA was conducted over the performance of the participants with two factors: condition (tDCS or sham stimulation) and time (block 1/ block 2/ block 3). There was no significant effect of tDCS on performance compared to sham stimulation, $F(1,15)=0.78$, $p=.39$. However, an effect of time was found, $F(2,30)=5.15$, $p<.05$ (Figure 2). Further, there was no significant interaction effect between condition and time, $F(2,30)=0.534$, $p=.59$. Surprisingly, this analysis shows no significant effect of electrical stimulation on performance and no interaction between tDCS and sham stimulation.

To establish whether results could be explained by learning effects two paired samples t-tests were performed. The paired t-tests compared the third block of the training session with the first block of the tDCS session and the sham stimulation session. No learning effects were found, $t(14)=-0.16$, $p=.88$, $t(14)=-0.03$, $p=.98$. This means that the recruited results cannot be attributed to learning effects.

Several paired samples t-tests were performed to explore the effect of tDCS and sham stimulation over time. First, the sham stimulation condition was more explored. Interestingly, a significant effect was found between the first and second block of sham stimulation $t(15)=-2.56$, $p<.05$. No significant effect was found between the second and third block of the sham stimulation condition, $t(15)=0.59$, $p=.57$.

Secondly, the blocks in the tDCS condition were compared. Contrary to the sham stimulation condition, no difference was found between the first and second block of electrical stimulation, $t(15)=-1.77$, $p=.097$. Similarly to the sham stimulation condition, the second and third block showed no significant difference, $t(15)=-0.37$, $p=.72$ (figure 3). Table 1 provides an overview of the conducted t-tests.

In summary, no effect of tDCS on VWM performance was found. Interestingly, an effect of sham stimulation was found which indicates a placebo effect.
Table 1. Overview of the paired samples t-test and associating values in mean with standard deviation t-values and p-values.

<table>
<thead>
<tr>
<th>Pairs</th>
<th>Mean (SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training block 3 – tDCS block 1</td>
<td>-0.21 (5.05)</td>
<td>-0.16</td>
<td>.875</td>
</tr>
<tr>
<td>Training block 3 – sham block 1</td>
<td>-0.42 (5.73)</td>
<td>-0.028</td>
<td>.978</td>
</tr>
<tr>
<td>Sham block 1 – sham block 2</td>
<td>-4.80 (7.52)</td>
<td>-2.557</td>
<td>.022</td>
</tr>
<tr>
<td>Sham block 2 – sham block 3</td>
<td>1.09 (7.44)</td>
<td>0.588</td>
<td>.565</td>
</tr>
<tr>
<td>tDCS block 1 – tDCS block 2</td>
<td>-2.34 (5.29)</td>
<td>-1.772</td>
<td>.097</td>
</tr>
<tr>
<td>tDCS block 2 – tDCS block 3</td>
<td>-0.70 (7.69)</td>
<td>-0.365</td>
<td>.720</td>
</tr>
</tbody>
</table>

Figure 2. This graph shows the effect of time on VWM performance displayed in mean performance with standard error of the mean. The effect is showed for all participants for all sessions and split up per block.
Figure 3. This second graph shows the performance of participants separated per block for training, tDCS and sham stimulation. The performance is displayed in mean performance with error bars (standard error of the mean).

Discussion

The impairment of working memory due to TMS applied over the right DLPFC exposed the causal role of the DLPFC in working memory (Sligte et al, 2011). Next to that, in previous research tDCS was explored in a way to enhance working memory performance. These studies showed an effect of tDCS applied over the left DLPFC on working memory performance. Our study attempted to investigate if visual working memory capacity could be improved by increasing neural activity in the right DLPFC. Nevertheless, results showed no significant enhanced performance from 1mA electrical stimulation applied over the right DLPFC compared to sham stimulation. We expected that application of tDCS on the right DLPFC would enhance working memory, however this hypothesis could not be confirmed. Remarkably, there was a significant difference between the first and second block of the sham stimulation condition. This effect could indicate a placebo effect. Contrary, significant effect was found of electrical
stimulation both compared to baseline and sham stimulation. No further significant effects were found.

As soon as the tDCS device was turned on, subjects thought to be stimulated throughout the whole session, even when they were not stimulated for real. In the sham stimulation condition this thought influenced their performance in such a manner that performance improved. Compared to previous research this is a new outcome. Earlier researches did not report any placebo effects. An explanation could be that this research was conducted in a double blind manner, whereas previous research mostly was single blinded (Keshvari et al, 2013; Fregni et al, 2005; Jo et al, 2009; Boggio et al, 2006; Andrews et al, 2011). In a single blind experiment the experimenter knows if the participant receives real or sham stimulation. This knowledge can result in an observer expectancy effect. If the experimenter knows in which condition the participant is stimulated, this could (unconsciously) raise expectations. These expectations can (unconsciously) influence his behaviour and perhaps influence the performance of the participant. Double blind testing is a simple way to control for observer expectancy effects, while in single blind research you only control for subject expectancy effects. Placebo effects can influence any psychological experiment, thus are important to control for (Coffman, 2014). A way to control for placebo effects is the addition of a sham stimulation condition. Not every earlier research used a sham stimulation condition; hence there was no controlling for placebo effects (Im et al, 2008; Brunoni & Vanderhasselt, 2014).

In contrast with our hypothesis, no significant effect of tDCS was found on VWM performance. This finding is incongruent with previous studies, which did show a significant improvement of working memory due to tDCS (Zaehle et al, 2011; Boggio et al, 2006; Fregni et al, 2005; Ohn et al., 2008). A possible explanation for this unexpected finding is the power of our study, in which only 16 subjects participated. Sample size is thereby important because too small a sample size decreases the chance for detection of a real effect.

There are differences between our study and earlier research that apply for discussion. It was found that TMS applied over the right DLPFC results in impaired visual working memory
capacity (Sligte et al, 2011). However, the reverse effect, due to stimulation, did not show in our study. This raises questions whether the right DLPFC is the right area to stimulate for the enhancement of visual working memory or in which proportion VWM can be improved. This can lead to the idea that we perhaps should consider revising our hypothesis. In addition, no significant effects of the tDCS (or sham stimulation) after stimulation on task performance were found, whereas previous research did detected effects after real stimulation (Keshvari et al, 2013). Their finding was supported by earlier research that suggested that until 90 minutes after tDCS the excitability of the cortex was increased to 150% above baseline (Nitsche & Paulus, 2001). Our results are not in line with previous research and thus cannot confirm the enhancing role of tDCS on VWM.

A number of methodological differences with other studies are worth discussing. First, in this study a stimulation intensity of 1mA is used, while some other research used 2 mA (Keshvari et al, 2013; Boggio et al, 2006; Jo et al, 2009). The study of Boggio et al. (2006) suggested the importance of stimulation intensity because of their finding that 2mA tDCS enhanced working memory in Parkinson patients, while 1mA did not. Nevertheless, previous research also found effects after 1mA stimulation. However, those studies used different stimulation times than we did: 15 minutes (Zaehle et al, 2011) and 30 minutes (Ohn et al, 2008). The stimulation time for our study was 20 minutes. Next to that, most of the previous research was conducted over the left DLPFC (Andrews et al, 2011; Fregni et al, 2005; Ohn et al, 2008; Jo et al, 2009), while in our study the right DLPFC was investigated. Future studies could investigate the differences and similarities between the left and right DLPFC and its function. Finally, almost all previous studies used an n-back task to measure working memory (Andrews et al, 2011; Fregni et al, 2005; Ohn et al, 2008; Zaehle et al, 2011; Keshvari et al, 2013; Boggio et al, 2006; Jo et al, 2009) while this study used a change detection paradigm. All these previous researches look for working memory enhancement as we looked especially to VWM. Due to these methodological differences, no direct comparisons can be made.
Future studies could build on from the following. If more subjects had participated and an effect of tDCS on VWM performance was found, there still would be the placebo effect in the sham stimulation condition. If so, a possibility could be that the placebo effect is a component of the tDCS effect on performance. This would be a remarkable finding, because earlier research did not mention this. Therefore it is very interesting to further explore this placebo effect in research with the same design but with more participants.

Secondly, to explore whether the placebo effect is a consequence of the double blind design, a way to verify this result is to run the same research with an additional condition; a single blind condition. If the placebo effect only occurs in the double blind condition than this would implicate that the placebo effect is a consequence of the double blind design and there are possible observer expectancy effects. This finding would lead to the idea that studies involving tDCS should be conducted in a double blind way. If the placebo effect also occurs in the single blind condition the placebo effect is not a consequence of the double blind design.

In addition, this study has some potential limitations that should be controlled. Next to the limited number of subjects participated, the context may not have been optimal. For example due to a few factors as the presence of the two experimenters, a lot of people walking by and the temperature sometimes raised to an uncomfortable level. Finally, we did not register which and how many participants thought which session he/she was stimulated for real. Some participants reported that the itchy feeling of stimulation was distracting them during the task. Due to this reported distractions the question when the participant thought to be stimulated should have been included. Those limitations can be controlled for in future research.

In conclusion, the results of our study did not show that anodal tDCS over the right DLPFC had a positive enhancing effect on VWM. However, a placebo effect was found in the sham stimulation session, whereby participants showed enhanced VWM performance. Our study has raised some interesting questions which further research could build on.
References


