Effects of mid-frontal brain stimulation on sustained attention

Martine R. van Schouwenburg[1,2], Ilja G. Sligte[1,2], Michael R. Giffin[1,2], Franziska Günther[1,2], Dirk Koster[1,2], Floortje S. Spronkers[1,2], Anna Vos[1,2], & Heleen A. Slagter[1,2*]

Affiliations:

1) Department of Psychology, University of Amsterdam, Nieuwe Achtergracht 129B, Amsterdam, the Netherlands
2) Amsterdam Brain and Cognition (ABC), University of Amsterdam, Nieuwe Achtergracht 129B, Amsterdam, the Netherlands

Corresponding author: Prof. Dr. Heleen Slagter, h.a.slagter@vu.nl , Department of Applied and Experimental Psychology, Vrije Universiteit Amsterdam, Van der Boechorststraat 7, 1081 BT, Amsterdam, the Netherlands.

Keywords: vigilance; sustained attention; prefrontal cortex; tDCS; tACS

Abstract

Vigilant attention is defined as the ability to sustain attention over longer periods of time in a non-stimulating environment. Previous studies have suggested an important role for the dorsomedial prefrontal cortex (mPFC) in vigilant attention. In this manuscript, we describe two experiments in which we aimed to enhance vigilant attention by applying transcranial electrical current stimulation over the mPFC. Specifically, we were interested in reducing the often observed decline in performance with time-on-task, the so-called vigilance decrement. In the first experiment, we applied transcranial direct current stimulation (tDCS) in a between-subject design (n=97): participants received either anodal, cathodal, or sham stimulation. In contrast to our prediction, we found no effect of stimulation on the vigilance decrement. In the second experiment, we applied transcranial alternating current stimulation (tACS). Participants received alpha and theta stimulation in two separate sessions (n=47, within-subject design). Here, we found a frequency-dependent effect on the vigilance decrement, such that contrary to our expectation, participants performance over time became worse after theta stimulation, compared to alpha stimulation. However, this result needs to be interpreted with caution given that at least part of this effect seems to be driven by the intensity of side effects experienced during the two stimulation frequencies. To conclude, across the two studies we were not able to reduce the vigilant decrement using tDCS or theta tACS.

Introduction

Sustained attention, the ability to filter incoming sensory information and maintain attention to this information for longer time periods, is an important aspect of cognitive functioning. Most people will experience that it is much easier to maintain attention over a longer period of time when in an engaging environment (for example driving a car in a city), compared to when they find themselves in a rather uneventful environment (driving a car on an empty highway). Indeed, research has shown large decrements in performance over time on vigilant attention tasks that require participants to monitor and detect infrequent targets in a stream of non-targets [1,2]. Yet, vigilant attention is crucial in daily life and in particularly in jobs such as air traffic control, lifeguarding, or inspection for quality control since in these jobs a drop in attention could have large detrimental consequences. In the current study, we investigated if it is possible to improve vigilant attention using brain stimulation. Specifically, we will test whether transcranial electrical stimulation can prevent or reduce the time-dependent vigilance decrement.

According to Stuss et al., vigilant attention is thought to rely on four distinct processes [3,4]. Activation of the task-relevant schema has to be monitored (1) and if activity drops below a certain threshold, activity of the task-relevant schema has to be reactivated (2). In addition, to reduce interference, conflicting schemata have to be inhibited (3). Finally, a higher-order process monitors task performance and takes action if performance drops (4) (through reactivation of the task-relevant schema and/or inhibition of conflicting task schemata).

The question then arises which of these processes fails during the vigilance decrement. Theoretical frameworks have attributed the time-dependent drop in performance to three (not mutually exclusive) causes: enhanced mind wandering, resource depletion, and/or reduced motivation. Some have suggested that vigilant attention tasks are just not engaging enough, leading to mind-wandering [5,6]. This means that people fail to inhibit conflicting schemata and are distracted from

the main task leading to the decrement in performance [7]. Others have suggested that after sustaining attention for a certain period of time, attentional resources are depleted, leading to an inability to re-activate the task-relevant schema [8]. There is much empirical evidence that supports resource depletion and this 'mental fatigue' account is in line with the subjective experience of the task becoming harder over time [1,9]. However, studies have also shown that social comparison or monetary rewards can improve performance [10–13]. For example, a recent study by our lab showed that the vigilant attention decrement can be partly resolved by an unexpected monetary incentive [14]. This suggests that resource depletion cannot fully account for the performance decrement, but that motivation is also crucial for maintaining vigilance. This is in line with motivational control theories by Robert & Hockey [15]. Others have combined the resource depletion and motivational control accounts into hybrid models that weigh the potential reward outcome of an action against the anticipated energy expenditure [16,17]. Taken together, it seems likely that multiple factors interact to cause the vigilance decrement.

In an effort to better understand the underlying causes of the vigilance decrement, researchers have turned to neuroimaging. In a recent meta-analysis, Langner & Eickhoff (2013) identified a network of brain regions that plays a key role in maintaining vigilant attention. This network comprised a large cluster spanning the presupplementary motor area (pre-SMA), midcingulate cortex, extending into more anterior medial prefrontal cortex (PFC), as well as clusters in mid- and ventrolateral PFC, anterior insula, parietal areas and subcortical structures. The authors next built a hierarchical model of how these different network nodes might interact and their putative role in vigilant attention [7]. In this model, the large frontal cluster (which we will from now on refer to as medial PFC (mPFC)), plays a central role both due to its position on top of the hierarchy and its role in performance monitoring and task-set (re-)energizing. This view corroborates a large body of evidence that links the mPFC with error monitoring and subsequent adjustments in attentional control (for review see[18]). Improper functioning of the mPFC could lead to the inability to activate the task relevant

schema and thereby contribute to the vigilant decrement. Moreover, mPFC activity increases with time-on-task [7,19,20], which is thought to reflect enhanced effort to maintain attentional focus on the task [21]. In many of these studies, mPFC activity was measured through power in the theta band. Indeed, theta oscillations seem to be the lingua franca of the mPFC and are strongly linked to cognitive control processes [22]. In sum, midfrontal theta oscillations seem to play an important role in our ability to maintain vigilant attention over time.

The goal of our study was to determine if electrical stimulation over the mPFC can improve the ability to sustain vigilant attention over time. To this end, we performed two experiments that used transcranial electrical stimulation. In Experiment 1, we applied transcranial *direct* current stimulation (tDCS) over the mPFC. In this technique, a small electrical current is passed between two electrodes, which is thought to depolarize (anodal stimulation) or hyperpolarize (cathodal stimulation) the underlying neural tissue [23]. We hypothesized that anodal stimulation over the mPFC would increase cortical excitability in this region, resulting in improved vigilant attention. Conversely, we predicted that cathodal stimulation over the mPFC would decrease cortical excitability, resulting in reduced vigilant attention. In Experiment 2, we applied transcranial *alternating* current stimulation (tACS) over the mPFC. tACS is similar to tDCS, except that the direction of the current alternates at a certain frequency. This is thought to entrain neurons in the underlying neural tissue to the stimulated frequency [24]. By stimulating the mPFC in theta frequency, we expected to improve vigilant attention.

Materials and methods

Experiment 1

Participants

101 healthy participants were included in the experiment and were tested in a double-blind, randomized, between-subject design. They were selected based on the following criteria; no epilepsy or (family) history of an epileptic seizure, no neurological disorders, no history of stroke or other forms of brain damage, no history of a severe concussion, no (history of) meningitis, no use of psychoactive substances, no cardiac pacemakers or other implanted medical devices, no metal anywhere in the head, no albinism, not pregnant, not recently fainted, no recent panic attack, no multiple sclerosis, no skin abnormalities on the head, and no color blindness.

All participants had normal or corrected-to-normal vision and all but three participants were right handed. Participants were instructed to abstain from alcohol, non-prescriptive medication and illicit substances 24 h prior to the experiment. If they failed to follow these instructions, they were excluded from participation.

Two participants decided not to continue with the experiment after the trial stimulation was applied. In addition, two participants did not complete the experiment (one was asked to leave because the participant was not doing the task, and the other participant accidently aborted the task). The remaining 97 participants (71 females) had a mean age of 22.3 years (sd = 2.7) and were randomly assigned to one of three stimulation groups: anodal (33 subjects, mean age 21.9 years, sd 2.9, 23 females), cathodal (34 subjects, mean age 22.6 years, sd 2.3, 25 females), or sham (30 subjects, mean age 22.4 years, sd 2.9, 23 females).

The protocol was approved by the Social Sciences ethical committee of the University of Amsterdam. All participants gave written informed consent in accordance with the Declaration of Helsinki and received course credits or a monetary reward in exchange for participation.

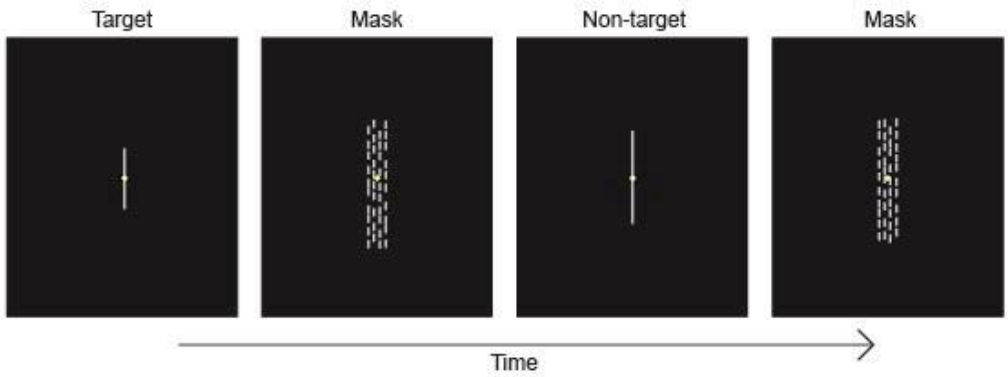

Figure 1 – In both experiments, participants performed a vigilant attention task in which they had to respond to an infrequent target stimulus (short line), and withhold responses to the non-target (long line). Presentation of stimuli (150ms) was interleaved with the presentation of masks (variable time interval, see main text).

Paradigm

Participants performed a vigilant attention task adapted from MacLean et al. (2009). In this task (**Figure 1**), participants had to discriminate between a target (short line/33% of stimuli) and non-target (long line/67% of stimuli) and respond to the target stimuli by clicking the left mouse button with their right index finger. Throughout the experiment, participants were told to fixate on a yellow fixation dot in the middle of the screen. Between stimuli, a grey mask, composed of stacked short lines, was presented to prevent an after-image of the stimuli, which would otherwise allow participants to easily compare line lengths across trials. This mask changed on each presentation to prevent participants from comparing stimulus line length to the mask. Specifically, on each presentation, the lines that comprised the mask were vertically repositioned by a random amount (-

4 to +4 pixels). Stimuli were on the screen for 150ms, while the interstimulus interval (during which the mask was presented) was randomly chosen on each trial between 1350 and 2350ms.

Visual stimuli were presented using Presentation software (Neurobehavioral Systems) on a 24-inch monitor with a 1920 x 1080 resolution. Non-targets and targets had a width of 2 pixels. The height of non-targets (long line) was consistent across participants (122 pixels), while the height of the target (short line) was defined individually to balance task difficulty across participants (average=93.4 pixels, SD=13.0, range:20-112).

Individual target line length was determined with a Parameter Estimation by Sequential Testing (PEST) procedure [25,26]. During this calibration procedure, participants performed the vigilant attention task described above while the length of the target line was adaptively changed according to a 3-down, 1-up staircase until performance stabilized at 80% accuracy. To help participants to learn the task, auditory feedback was provided following correct identification of a target and following a miss or a false alarm.

Study design

The study followed a double blind randomized between-participants design. At the start of the session, participants were checked for exclusion criteria and asked about drug and alcohol use in the last 24h. Next, participants were seated 57 cm from the monitor, received task instructions and performed the PEST procedure. Completion of the PEST procedure lasted approximately 10 minutes, but exact length varied between subjects due to the dynamic stopping rule used by the PEST titration. Upon completion of the PEST, stimulation electrodes were attached and participants were informed about any possible side effects that could occur. Participants then received one minute of trial stimulation (5 seconds ramp up, 60 seconds stimulation, 5 seconds ramp down). Participants were asked about their experience both during and after trial stimulation. If a subject reported

uncomfortable side effects and/or impedance was above 25 mΩ, the set-up was adjusted to lower impedance. In this case, trial stimulation was applied again to ensure that participants felt comfortable with the stimulation. After trial stimulation, participants performed the vigilant attention task for a total of 60 minutes divided over three blocks of 20 minutes. In the second of these 20-min blocks, stimulation was applied. Before the start of each block, and at the end of the experiment, participants answered two questions about how motivated they were and how much aversion they felt toward the task by moving an arrow over an 1100 pixels wide scale by scrolling the mouse wheel. Stimulation electrodes were removed after the second 20-minute block. After the experiment ended, the participants filled out a questionnaire about possible side effects of the stimulation, as well as the perceived effect of stimulation on task performance. Side effects were scored on a linear scale from 0 to 100, with a score of zero representing 'not at all applicable to me' and a score of 100 representing 'completely applicable to me'. The perceived effect of stimulation on task performance was rated as worse, similar or better performance compared to the blocks without stimulation.

tDCS

tDCS (NeuroConn DC-Stimulator MR, NeuroConn, Germany) was administered via two rubber electrodes. Electrodes were placed in saline soaked sponges and attached to the head via straps and tape. One electrode (9 cm2) was placed between electrode locations FCz and Cz on the 10-20 international EEG system and a second electrode (35 cm2) was placed on the left cheek [27]. Stimulation intensity was set to 1 mA (current density of 0.11 mA/cm at mPFC electrode). During the anodal stimulation condition, the anode was placed at Cz/FCz and the cathode at the cheek, while the opposite was true for the cathode condition. Stimulation was ramped up for 60 seconds, and after the 20-minute stimulation period, ramped down again for 60 seconds. In the sham group, half of the participants received 'anodal' sham stimulation, while the other half received 'cathodal' sham

stimulation. In this control condition, stimulation was ramped up for 60 seconds and then ramped down again over 60 seconds.

Data analysis

Data were analyzed using Matlab (The Mathworks, Inc.), SPSS (IBM SPSS Statistics, version 23.0) and JASP (version 0.8.2). Per 20-minute block (pre, during and post stimulation), we determined the hit rate and false alarm rate and subsequently calculated the non-parametric perceptual sensitivity measure A' as formulated by Stanislaw and Todorov [28] (and implemented cf. [14,26,29]). A' is based on signal detection theory and indicates a subject's ability to discriminate between targets and non-targets. Values typically range from 0.5 (subjects cannot distinguish targets from noise) to 1 (subjects distinguish all targets from noise) [28]. In addition, we calculated the average reaction time per block.

Data were submitted to repeated measures ANOVAs with the between-subject factor stimulation condition (sham vs. cathodal vs. anodal) and the within-subject factor time (pre stimulation vs. during stimulation vs. post stimulation). Post-hoc paired t-tests were used when significant results were found. In addition, two-sample t-tests were used in order to assess whether reported side effects and target line length differed across stimulation conditions.

Experiment 2

Participants

The methods were the same as in Experiment 1 except for the following changes. 55 healthy participants were included in the experiment and were tested in a randomized, within-subject design. In addition to the exclusion criteria mentioned for Experiment 1, we also screened for spondylosis, scoliosis, arthritis and frequent occurrences of dizziness or headaches.

All participants were right handed and had normal or corrected-to-normal vision. Three participants decided not to continue with the experiment after the trial stimulation was applied and three participants were eliminated due to technical reasons (stimulation was automatically aborted at some point during the stimulation block due to high impedance levels). One participant drank alcohol within the 24h before the experiment and was therefore excluded. Finally, one participant dropped out after the first session. The remaining 47 participants (34 female) had a mean age of 21.5 years (SD=2.6).

Paradigm

The paradigm was adapted in two ways. First, the target/non-target ration was adapted, so that now 25% of stimuli was a target (compared to 33% in Experiment 1). Second, the inter-stimulus interval lasted a minimum of 1550ms and a maximum of 2150ms (compared to 1350 – 2350ms in Experiment 1). Again, the height of the target (short line) was defined individually, on each session, to balance task difficulty across participants (average over two sessions=95.1 pixels, SD =8.3, range: 55-111).

Study design

In contrast to the first experiment, we used a within-subject design in the second experiment. Participants participated in two sessions separated by 1 week (except for 6 participants in which the sessions were separated somewhere between 6 and 15 days). The two sessions were similar except for the frequency of the applied tACS stimulation. The order of the stimulation condition was randomized and both participants and the experimenter were blind to the stimulation condition (double blind design). The general outline of the sessions was similar to the one in the first experiment with the exception of the following: 1) trial stimulation consisted of one minute of alpha stimulation (10 seconds ramp up, 30 seconds stimulation, 10 seconds ramp down), 2) participants performed the vigilant attention task for a total of 50 minutes (15 minutes before and after

stimulation, and 20 minutes during stimulation), 3) side effects were scored on a five-point scale with a score of one representing 'not at all applicable to me' and a score of five representing 'completely applicable to me'. In addition, we tried to minimize breaks during the task as much as possible. Therefore, the questions about motivation and aversion were eliminated from the design and we did not remove the stimulation electrodes until after the end of the experiment. Thus, there were no pauses during the experiment except for the time required to start stimulation in between block one and two, which lasted approximately one minute. No interaction with the participants took place during this minute to minimize the duration of the task break. Participants were seated approximately 65 cm from the screen.

tACS

tACS (NeuroConn DC-Stimulator MR, NeuroConn, Germany) was administered via three rubber electrodes. Electrodes were placed inside saline soaked sponges and attached to the head via straps and tape. The target electrode (9 cm^2) was placed between electrode locations FCz and Cz on the 10-20 international EEG system as in Experiment 1. Two reference electrodes (35 cm^2) were placed on the cheeks. This set-up has previously been used by van Driel et al. (2015) and is aimed to direct current flow through the mPFC. Stimulation intensity ranged between -1 and +1 mA and was set to sinusoidal (current density of 0.11 mA/cm at mPFC electrode). Fading in and out of the stimulation lasted for ten seconds each.

For the active condition, stimulation frequency was set to 4 Hz (theta band). During the control condition and trial stimulation, 10 Hz (alpha band) tACS was applied. Alpha band stimulation instead of sham was used for the control condition because tACS is often accompanied by phosphenes (visual disturbances) and cutaneous sensations under the electrodes, which possibly enables participants to differentiate between active stimulation and the sham condition [30]. A control condition producing similar side effects is thus needed to ensure that the active and control sessions

are as similar as possible. The current study used alpha band tACS because van Driel et al. (2015), who also used theta band stimulation as the active condition and alpha band stimulation as the control condition, reported that theta and alpha tACS resulted in similar side effects. Furthermore, stimulation with higher frequency bands, such as beta frequencies, has been associated with higher phosphene intensity compared to theta band tACS [31].

Data analysis

A' and reaction time were calculated as in Experiment 1. Next, data were submitted to repeated measures ANOVAs with the within-subject factors Stimulation Frequency (alpha vs. theta) and Time (pre, during and post stimulation). Post-hoc paired t-tests were used when significant results were found. In addition, Wilcoxon Signed Rank tests were used to assess whether side effects differed between stimulation frequencies. Because, indeed, some self-reported side effects were significantly different (see Results), we re-analyzed A' using a linear mixed model, allowing us to include these side effects per stimulation frequency as a covariate. The model tested for main effects of stimulation frequency and time. In addition, it tested for main effects of tingling sensation and light flashes. The model also included a time x stimulation frequency interaction.

Lastly, a paired samples t-test was used to assess whether target line length differed significantly between stimulation frequencies.

Results

Experiment 1

We found no significant differences in target line length between the different stimulation groups ($F(94)=2.269$, $p=0.109$), indicating that task difficulty was similar across groups (anodal, cathodal and sham stimulation).

In line with previous studies, perceptual sensitivity, as measured by A', declined with time on task (main effect of Time: $F(1.8, 167.2)=16.872$, $p<0.001$) (Figure 2, left). However, there was no Time x Stimulation Condition interaction ($F(4,188)=0.325$, $p=0.861$), nor a main effect of Stimulation Condition ($F(2,94)=1.534$, $p=0.221$). Thus, in contrast to our main prediction, perceptual sensitivity was not modulated by anodal or cathodal tDCS over the mPFC. To determine the strength of evidence for the null hypothesis we applied Bayesian statistics. We computed a Bayes factor comparing a model that only contained the main effect of Time and main effect of Stimulation Condition versus a model that contained both main effects and the interaction of both factors (see supplementary materials)[32]. With a Bayes factor of 35.5, we find strong evidence for the null hypothesis [33], confirming that anodal or cathodal tDCS had no effect on the time-dependent decline in perceptual sensitivity.

For RT, no effects were found (main effect of Time: $F(2,188)=1.469$, $p=0.233$, main effect of Stimulation Condition ($F(2,94)=1.161$, $p=0.318$), Time x Stimulation Condition interaction ($F(4,188)=0.681$, $p=0.606$)).

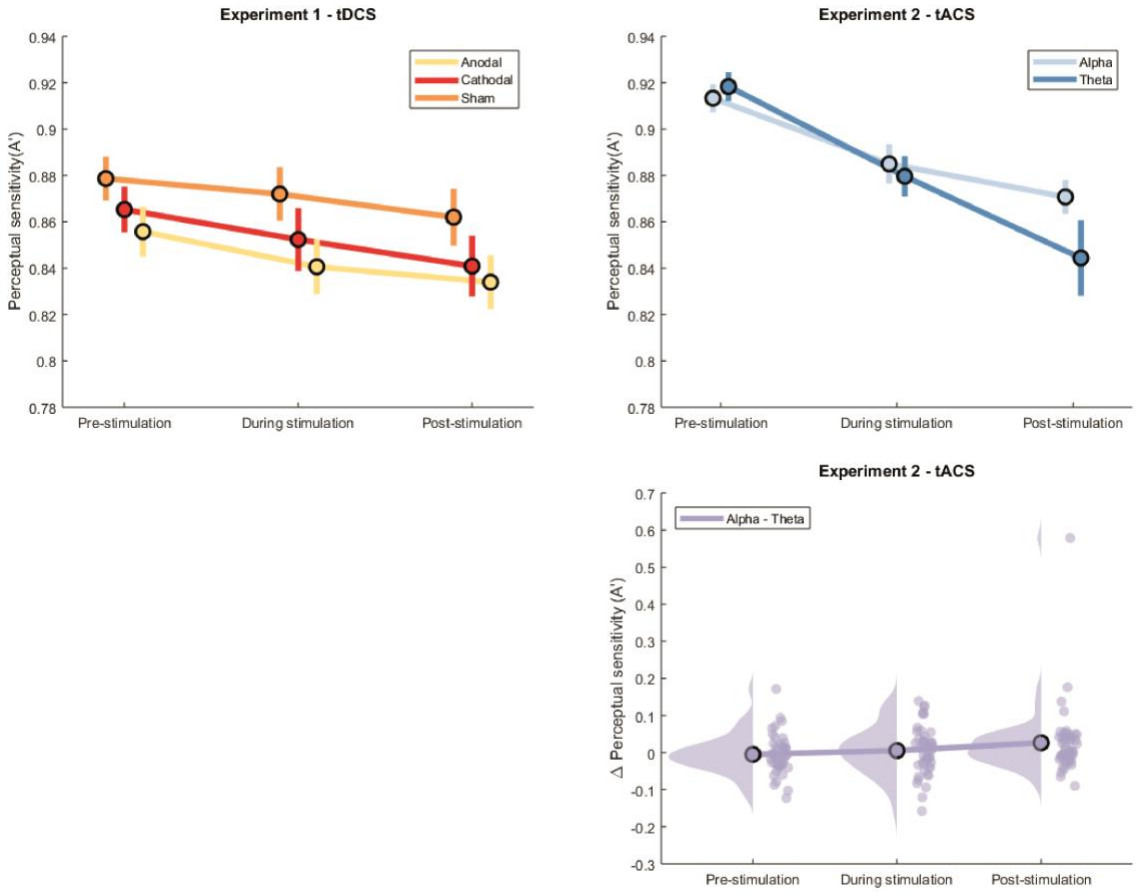

Figure 2 – In both experiments, a robust vigilance decrement was observed, as perceptual sensitivity (A') decreased significantly over time. In Experiment 1 (left), we found no significant effect of stimulation on the vigilance decrement. In experiment 2 (right), we found a significant Time x Stimulation frequency effect, such that perceptual sensitivity decreased more over time after theta stimulation compared to alpha stimulation. The upper right plot shows the data for alpha and theta stimulation separately. For the lower right plot we subtracted data from the theta condition from the data from the alpha condition for each individual. Next, we plotted the mean difference as well as the distribution and the individual data points [34].

The three different stimulation conditions led to a significant difference in self-reported headache. Specifically, a series of one way ANOVAs showed a main effect of Stimulation Condition on the amount of headache ($F(2,94)=4.926$, $p=0.009$), which was driven by the fact that participants that received anodal stimulation reported a higher amount of headache compared to the other participants (anodal vs. cathodal: $t(41.0)=2.394$, $p=0.021$; anodal vs. sham: $t(41.1)=2.356$, $p=0.023$; sham vs. cathodal: $t(62)=0.062$, $p=0.951$)(median values per stimulation condition: anodal: 3; cathodal: 0; sham: 0))(mean values per stimulation condition: anodal: 12.3; cathodal: 4.1; sham: 4.2). It should be noted that when correcting for multiple comparisons (we ran an ANOVA for each of the seven self-reported side effects), the effect of stimulation condition on headache is not significant. In the anodal group, 12 participants thought their performance worsened during the stimulation block, 11 participants thought their performance remained the same during the stimulation block, and 10 participants thought their performance improved during the stimulation block. For the cathodal group and sham group, the distributions were as follows: cathodal: 13 (improved); 12 (same); 8 (worsened); 1(data missing), sham: 7 (improved); 13 (same); 10 (worsened); 1 (data missing).

Experiment 2

We found no significant differences in target line length between the different stimulation frequencies sessions ($t(46)=0.264$, $p=0.793$), indicating that task difficulty was similar across conditions.

Again, perceptual sensitivity, as indexed by A', declined with time on task (main effect of Time: $F(1.4, 65.9=40.264$, $p<0.001$). Consistent with our hypothesis, we found a significant Time x Stimulation Frequency interaction ($F(1.5, 71.1)=5.435$, $p=0.011$)(Figure 2, right). However, in contrast to our prediction, this interaction was driven by the fact that performance declined more in the theta

stimulation condition than in the alpha stimulation condition in particular after the stimulation had ended. Although the post-hoc t-test did not reach significance ($t(46)=1.891$, $p=0.065$), numerically, perceptual sensitivity was lower after theta stimulation than after alpha stimulation. (Note that the outlier in the bottom right plot is not driving the results, but is actually reducing the significance of the effect (F-value: 5.4 vs. 5.9; p-value: 0.011 vs. 0.004).)

For RT, we found a main effect of Time ($F(1.7, 78.7)=19.280$, $p<0.001$), but no main effect of Stimulation Frequency ($F(1,46)=0.134$, $p=0.716$), nor an interaction ($F(1.6,74.7)=1.674$, $p=0.193$).

In terms of side effects, we also found a difference between the stimulation conditions. Specifically, participants perceived more tingling sensations ($Z=-4.053$, $p<0.001$) and more phosphenes ($Z=-4.981$, $p<0.001$) during alpha stimulation. This could confound our findings on perceptual sensitivity. In an attempt to control for these potentially confounding side effects, we performed another analysis, in which we tested for a Time x Stimulation Frequency interaction on perceptual sensitivity using these two side effects as a covariate. Again, we found a main effect of Time ($F(2,230)=33.587$, $p<0.001$), indicative of a decrease in performance over time, but now the Time x Stimulation Frequency interaction did not reach significance ($F(2,230)=2.508$, $p=0.084$).

Discussion

Vigilant attention is crucial in many everyday life and professional settings that require continuous monitoring to detect rare and difficult to predict events, such as when driving a car or in air traffic control. In two experiments, we aimed to improve people's ability to maintain vigilant attention over time using transcranial electrical stimulation over mPFC, a key region involved in vigilant attention [7]. However, in neither experiment, we found convincing evidence that electrical stimulation over mid-frontal cortex can enhance vigilant attention. These findings contribute to a growing body of studies that report no effect of electrical brain stimulation on behavior [35,36], but contrast with studies that did observe positive effects of electrical stimulation on vigilant attention [37,38]. In the below, we discuss our findings in greater detail with respect to the current literature, and discuss potential explanations and necessary follow-up studies.

In Experiment 1, neither anodal nor cathodal tDCS over mPFC modulated vigilant attention compared to sham tDCS. It is possible that our stimulation did not reach the mPFC or that mPFC is not critical to vigilant attention. In previous studies looking at the effect of tDCS on vigilant attention, it was found that tDCS over bilateral dorsolateral prefrontal cortex (DLPFC) could prevent the vigilance decrement [37,38]. However, replication of these effects are warranted since some of the effects ascribed to tDCS were already apparent before tDCS stimulation started [37]. Also, correction to the baseline block, as was applied in these studies, can lead to artificially induced effects. Alternatively, it is possible that we did not choose the most optimal settings in the design of our experiment. Although 1mA is a common current strength used for tDCS in attention studies (see for example Reteig et al. 2017), the effects of tDCS may vary as a result of the applied stimulation intensity [40], though not necessarily in a linear fashion [41]. Another reason for the null findings could be the fact that we used a between-subject design. tDCS effects are generally subtle and might therefore surface only in a within-subject design which is more sensitive because it takes out

individual variance in baseline task performance and the degree of vigilance decrement over time (although we tried to control for the first with the staircase procedure). However, compared to many tDCS studies that previously reported effects on attentional performance using a between-subjects design [39], our sample size was relatively large with 30 to 34 participants in each stimulation group. It should also be noted that the effects of tDCS in general are debated [42]. As we pointed out in an earlier review, the wide range in stimulation parameters that is used in tDCS studies and individual differences in the effects of tDCS might contribute to the failure to find (consistent) effects [39]. Also, the neural effects of tDCS itself may be smaller than assumed, as it was recently shown that the strength of the electric field in the brain is at the lower bound for it to be physiologically effective [43,44]. To summarize, using anodal tDCS over mPFC we were not able to improve vigilant attention.

In Experiment 2, using a within-subject design with 47 participants, we found effects of tACS on the vigilance decrement. However, we have to be cautious about the interpretation of these results. First, in contrast to our expectations, participants' vigilance decrement became worse after theta stimulation compared to alpha stimulation. As explained in the introduction, we anticipated that theta stimulation would improve performance based on previous studies showing that theta oscillations originating from the mPFC are involved in performance monitoring and task-set (re-)energizing [22]. It is possible that we interfered with an already optimally functioning system (in healthy individuals) and therefore found the opposite of what we anticipated. Also, we did not use individually determined theta frequency, but stimulated everyone at 4 Hz. It has been suggested that effects of tACS might be strongest when stimulation happens in sync with the individual intrinsic frequency [45,46]. Perhaps by entraining mPFC neurons to a frequency that did not match their intrinsic frequency in some of our participants, we disrupted the system, rather than helped it. Alternatively, it is also possible that theta stimulation had no effect, but that alpha stimulation improved performance. Indeed, in a recent study, Clayton et al. found that alpha stimulation over

occipital cortex stabilized performance on a visual attention task [47]. The researchers speculated that the alpha stimulation may have prevented top-down reorienting signals from changing the attentional state of the visual system. Alpha stimulation may similarly have stabilized the monitoring state of mPFC. Yet, without the presence of a sham condition, we cannot dissociate whether the effects that we found are driven by effects in the alpha stimulation condition, the theta stimulation condition, or a combination of both. However, as described in the methods section, including a sham condition has its own disadvantages.

Another difficulty in the interpretation of the obtained results is the fact that we found differences in side effects between the two stimulation frequencies. During alpha stimulation, subjects experienced more tingling sensations and more phosphenes compared to during theta stimulation. It could be argued that these side effects mainly occurred during the block of stimulation and do not extend to the block after stimulation, in which the difference between the stimulation conditions seems to arise. Also, it seems counterintuitive that an increase in side effects, would lead to better rather than worse perceptual sensitivity. Nevertheless, when trying to control for these differences, the Time x Stimulation Frequency interaction did not reach significance any more. This suggests that at least part of the frequency-dependent tACS effects on the vigilance decrement can be explained by the differences in side effects between the stimulation frequencies. In sum, although we do find frequency-dependent tACS effects, with the current setup we cannot determine whether participants improved or worsened by the stimulation, and they could simply reflect non-specific side effects. Further research including other control conditions, for example stimulation over another brain region, is needed to determine the direction of the observed effects. Regarding the role of midfrontal theta oscillations in vigilant attention, we find preliminary evidence that theta and/or alpha oscillations play a role in vigilant attention. However, ideally, analyses should be repeated on a large enough pool of subjects that experienced similar side effects in both stimulation conditions.

Conclusions

To conclude, across the two studies we were not able to find a convincing method to prevent or reduce the vigilant decrement. More research that combines brain stimulation with neuroimaging, is needed to determine if and how electrical stimulation over mPFC may affect brain functioning and vigilant attention.

Declarations of interest: none

Acknowledgements:

This research was funded by a Marie Curie European Fellowship grant to MS and a VIDI from the Netherlands Organization for Scientific Research (NWO) to HAS.

References

[1] Warm JS, Parasuraman R, Matthews G. Vigilance Requires Hard Mental Work and Is Stressful. Hum Factors J Hum Factors Ergon Soc 2008;50:433–41. doi:10.1518/001872008X312152.

[2] Robertson IH, O'Connell RG. Vigilant attention. In: Nobre AC, Coull JT, editors. Atten. time, Oxford, England: Oxford University Press; 2010, p. 79–88.

[3] Norman DA, Shallice T. Attention to action: Willed and automatic control of behaviour. Conscious. self-regulation, 1986. doi:10.1098/rstb.1996.0132.

[4] Stuss DT, Shallice T, Alexander MP, Picton TW. A Multidisciplinary Approach to Anterior Attentional Functions. Ann N Y Acad Sci 1995;769:191–212. doi:10.1111/j.1749-6632.1995.tb38140.x.

[5] Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. "Oops!": Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia 1997. doi:10.1016/S0028-3932(97)00015-8.

[6] Smallwood J, Schooler JW. The restless mind. Psychol Bull 2006. doi:10.1037/0033-2909.132.6.946.

[7] Langner R, Eickhoff SB. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. Psychol Bull 2013;139:870–900. doi:10.1037/a0030694.

[8] Helton WS, Warm JS. Signal salience and the mindlessness theory of vigilance. Acta Psychol (Amst) 2008;129:18–25. doi:10.1016/j.actpsy.2008.04.002.

[9] Grier RA, Warm JS, Dember WN, Matthews G, Galinsky TL, Szalma JL, et al. The Vigilance Decrement Reflects Limitations in Effortful Attention, Not Mindlessness. Hum Factors J Hum Factors Ergon Soc 2003;45:349–59. doi:10.1518/hfes.45.3.349.27253.

[10] Boksem MAS, Meijman TF, Lorist MM. Mental fatigue, motivation and action monitoring. Biol Psychol 2006;72:123–32. doi:10.1016/j.biopsycho.2005.08.007.

[11] Lorist MM, Bezdan E, ten Caat M, Span MM, Roerdink JBTM, Maurits NM. The influence of

mental fatigue and motivation on neural network dynamics; an EEG coherence study. Brain Res 2009;1270:95–106. doi:10.1016/j.brainres.2009.03.015.

[12] Bonnefond A, Doignon-Camus N, Hoeft A, Dufour A. Impact of motivation on cognitive control in the context of vigilance lowering: An ERP study. Brain Cogn 2011;77:464–71. doi:10.1016/j.bandc.2011.08.010.

[13] Hopstaken JF, van der Linden D, Bakker AB, Kompier MAJ. A multifaceted investigation of the link between mental fatigue and task disengagement. Psychophysiology 2015;52:305–15. doi:10.1111/psyp.12339.

[14] Reteig LC, van den Brink RL, Prinssen S, Cohen MX, Slagter HA. Sustaining attention for a prolonged period of time increases temporal variability in cortical responses. Cortex 2019;117:16–32. doi:10.1016/j.cortex.2019.02.016.

[15] Robert G, Hockey J. Compensatory control in the regulation of human performance under stress and high workload: A cognitive-energetical framework. Biol. Psychol., 1997. doi:10.1016/S0301-0511(96)05223-4.

[16] Boksem MAS, Tops M. Mental fatigue: Costs and benefits. Brain Res Rev 2008;59:125–39. doi:10.1016/j.brainresrev.2008.07.001.

[17] Christie ST, Schrater P. Cognitive cost as dynamic allocation of energetic resources. Front Neurosci 2015;9:1–15. doi:10.3389/fnins.2015.00289.

[18] Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The Role of the Medial Frontal Cortex in Cognitive Control. Science (80-) 2004;306:443–7. doi:10.1126/science.1100301.

[19] Boksem MAS, Meijman TF, Lorist MM. Effects of mental fatigue on attention: An ERP study. Cogn Brain Res 2005. doi:10.1016/j.cogbrainres.2005.04.011.

[20] Wascher E, Rasch B, Sänger J, Hoffmann S, Schneider D, Rinkenauer G, et al. Frontal theta activity reflects distinct aspects of mental fatigue. Biol Psychol 2014;96:57–65. doi:10.1016/j.biopsycho.2013.11.010.

[21] Clayton MS, Yeung N, Cohen Kadosh R. The roles of cortical oscillations in sustained attention.

TiCS 2015:1–8. doi:10.1016/j.tics.2015.02.004.

[22] Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. Trends Cogn Sci 2014:1–8. doi:10.1016/j.tics.2014.04.012.

[23] Nitsche MA, Paulus W. Transcranial direct current stimulation--update 2011. Restor Neurol Neurosci 2011;29:463–92. doi:10.3233/RNN-2011-0618.

[24] Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci 2013;7:279. doi:10.3389/fnhum.2013.00279.

[25] Taylor MM, Creelman CD. PEST: Efficient Estimates on Probability Functions. J Acoust Soc Am 1967;41:782–7. doi:10.1121/1.1910407.

[26] MacLean KA, Aichele SR, Bridwell DA, Mangun GR, Wojciulik E, Saron CD. Interactions between endogenous and exogenous attention during vigilance. Attention, Perception, Psychophys 2009;71:1461–7. doi:10.3758/APP.

[27] van Driel J, Sligte IG, Linders J, Elport D, Cohen MX. Frequency Band-Specific Electrical Brain Stimulation Modulates Cognitive Control Processes. PLoS One 2015;10:e0138984. doi:10.1371/journal.pone.0138984.

[28] Stanislaw H, Todorov N. Calculation of signal detection theory measures. Behav Res Methods, Instruments, Comput 1999;31:137–49.

[29] Slagter HA, Prinssen S, Reteig LC, Mazaheri A. Facilitation and inhibition in attention: Functional dissociation of pre-stimulus alpha activity, P1, and N1 components. Neuroimage 2016;125:25–35. doi:10.1016/j.neuroimage.2015.09.058.

[30] Davis NJ, Gold E, Pascual-Leone A, Bracewell RM. Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. Eur J Neurosci 2013;38:2973–7. doi:10.1111/ejn.12307.

[31] Turi Z, Ambrus GG, Janacsek K, Emmert K, Hahn L, Paulus W, et al. Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during

transcranial alternating current stimulation. Restor Neurol Neurosci 2013;31:275–85. doi:10.3233/RNN-120297.

[32] Wagenmakers EJ, Love J, Marsman M, Jamil T, Ly A, Verhagen J, et al. Bayesian inference for psychology. Part II: Example applications with JASP. Psychon Bull Rev 2018;25:58–76. doi:10.3758/s13423-017-1323-7.

[33] Jeffreys H. Theory of probability. 3rd ed. Oxford, UK: Oxford University Press; 1961.

[34] Allen M, Poggiali D, Whitaker K, Marshall TR, Kievit RA. Raincloud plots: a multi-platform tool for robust data visualization [version 1; peer review: awaiting peer review]. Wellcome Open Res 2019;4.

[35] Horvath JC, Forte JD, Carter O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul 2015;8:535–50. doi:10.1016/j.brs.2015.01.400.

[36] Medina J, Cason S. No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. Cortex 2017;94:131–41. doi:10.1016/j.cortex.2017.06.021.

[37] Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 2014;85:909–17. doi:10.1016/j.neuroimage.2012.11.061.

[38] McIntire LK, McKinley RA, Goodyear C, Nelson J. A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness. Brain Stimul 2014;7:499–507. doi:10.1016/j.brs.2014.04.008.

[39] Reteig LC, Talsma LJ, van Schouwenburg MR, Slagter HA. Transcranial Electrical Stimulation as a Tool to Enhance Attention. J Cogn Enhanc 2017;1:10–25. doi:10.1007/s41465-017-0010-y.

[40] Nitsche MA, Kuo M, Paulus W, Antal A. Textbook of Neuromodulation 2015. doi:10.1007/978-1-4939-1408-1.

[41] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation

intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;591:1987–2000. doi:10.1113/jphysiol.2012.249730.

[42] Horvath JC, Forte JD, Carter O. Evidence that transcranial direct current stimulation (tDCS) Generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy Human subjects: A systematic review. Neuropsychologia 2014. doi:10.1016/j.neuropsychologia.2014.11.021.

[43] Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, et al. Measurements and models of electric fields in the *in vivo* human brain during transcranial electric stimulation. Elife 2017;6:e18834. doi:10.7554/eLife.18834.

[44] Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 2018;9. doi:10.1038/s41467-018-02928-3.

[45] Schmidt SL, Iyengar AK, Foulser AA, Boyle MR, Fröhlich F. Endogenous cortical oscillations constrain neuromodulation by weak electric fields. Brain Stimul 2014;7:878–89. doi:10.1016/j.brs.2014.07.033.

[46] Romei V, Bauer M, Brooks JL, Economides M, Penny W, Thut G, et al. Causal evidence that intrinsic beta-frequency is relevant for enhanced signal propagation in the motor system as shown through rhythmic TMS. Neuroimage 2016;126:120–30. doi:10.1016/j.neuroimage.2015.11.020.

[47] Clayton MS, Yeung N, Kadosh RC, Clayton MS, Yeung N, Kadosh RC. Performance on Visual Attention Tasks Electrical Stimulation of Alpha Oscillations Stabilizes Performance on Visual Attention Tasks. J Exp Psychol Gen 2018. doi:10.1037/xge0000502.