Manipulating Intra-Individual Variation in Cognitive Control with Transcranial Direct Current Stimulation

Proactive vs. Reactive Control

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Abstract

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Background. Two core modes of control are proposed in the dual mechanisms of control (DMC) framework. Proactive control biases and facilitates responses to expected events, relying on the maintenance of goal- and context representations within dorsolateral prefrontal cortex (DLPFC). Reactive control is mobilized when the demanded response conflicts with the expected response. Thus, while proactive mechanisms function to minimize interference from potential conflict *before* it occurs, reactive mechanisms operate on interference *after* it has been detected. **Objectives.** The first aim of the current study was to investigate the balance of proactive vs. reactive control in young adults, and the real-time mental effort invested during the two control mechanisms. Our second aim was to investigate effects of transcranial direct current stimulation (tDCS) of brain regions involved in context representation, on task performance and effort. **Method.** 48 participants performed the AX-CPT, a task designed to assess proactive and reactive control mechanisms. Pupil dilation and constriction responses were collected to measure real time effort. Anodal tDCS was applied over right DLPFC to strengthen proactive control, allowing for the investigation of the antagonistic relationship between proactive and reactive control. All participants went through one session of stimulation and one sham session about 7 days apart. **Results.** Analysis of behavioral and pupil dilation data revealed a predominantly proactive response pattern in the task, as would be predicted in a young and healthy sample. In particular, accuracies were lower, reaction times were longer, and pupil size was larger in trials where expectations were not met. Also in line with predictions, tDCS over the brain region believed to represent cue-derived expectations, affected response patterns consistent with stronger proactive control and reduced reactive control. **Conclusion.** Our results were in line with predictions of the DMC framework, and our pupillary measures gave further support for this model of cognitive control. Also, tDCS over right DLPFC seemed to increase proactive control. Our results encourage further research on the underlying neural substrates of proactive vs. reactive control. Also, tDCS might be a useful tool in the development of interventions aiming to increase proactive control in groups showing reduction in this ability.

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Introduction

Performing tasks in our natural environment involves deciding among several alternatives, focusing on what is important, and therefore also inhibit irrelevant information and possible disruption. We are also met with situations which we can prepare for in advance if we are given some contextual cues, as well as we meet situations we consider as unexpected. We are therefore dependent on flexible adaption as we need to balance between sustained or preparatory control, detection of interfering objects or events, and finding resolution to interference when it occurs. This flexible ability of rapidly adapting thoughts and behavior to changing internal states and external environments is characteristic of human cognition (Braver, Paxton, Locke, & Barch, 2009). This ability is often referred to as cognitive control or executive functions, and is assumed to rely on prefrontal cortex (PFC) functioning(Miller & Cohen, 2001). Cognitive control has been defined as abilities of coordinating, planning, and regulating actions that correspond to internally maintained goals (Braver, 2012; D'Ardenne et al., 2012). A general idea seems to be that several brain systems interact to support executive control, but that different brain regions or systems support distinct functions. Research in the field of cognitive control has been focusing on accounting for the great range of cognitive control functions in terms of detailed anatomical specification (Braver, 2012). For instance, three main structures are often mentioned when in it comes to explaining the role of PFC in cognitive control (Purves, 2008). Dorsolateral PFC (DLPFC) has been assumed central for the selection, inhibition and abstraction of novel rules for behavior. Further, ventromedial PFC (VMPFC) plays an important role for adherence to rules of behavior, and has been linked to the process of inhibition in the adherence to well-learned rules. A third region, the anterior cingulate cortex (ACC), has been assigned an important role of conflict monitoring, and is assumed to signal the need for increased allocation of cognitive control (Purves, 2008). Although there has been an extensive progression of research in the field of cognitive control during the past 20 years, a great deal still needs more investigation (Braver, 2012).

More recently, some researchers have been shifting focus towards exploring variability within and between individuals as a core component of cognitive control. Further this shift involves capturing and explaining such variability in terms of temporal dynamics of cognitive control. According to this view the way we adapt depends on variability across situations. Research has shown that when interference is highly expected, participants prepare for the upcoming event, reflected by preparatory activity in lateral PFC. On the other hand, when

interference is not frequent and thus not expected the increase in lateral PFC activity is rather prominent after the interference or probe has been presented (Braver, 2012). Whether a preparatory and sustained form of control is utilized is therefore dependent on whether interference can be expected or not, and the type of control being used seem to be mediated by temporal dynamics within lateral PFC. Further Braver (2012) specifies that the degree to which preparatory control is utilized also depends on individual differences in cognitive abilities, motivation, and even personality (Braver, 2012). For instance, the maintenance of representations during preparatory control put demands on working memory. Working memory capacity (WMC) has been shown to vary between individuals, reflecting the ability to actively maintain goals or representations in working memory. Thus, the degree to which preparatory control is utilized should correspond with WMC (Braver, 2012). Also, how cognitive control is being utilized seems to depend on age. When it is beneficial, young adults seem to use a preparatory form of control to a greater extent than young children (Chatham, Frank, & Munakata, 2009) and older adults (Paxton, Barch, Racine, & Braver, 2008). As WMC declines with age (Jost, Bryck, Vogel, & Mayr, 2011) this further supports the assumption that preparatory control is mediated by WMC. The utilization of different mechanisms of cognitive control therefore seems to change in its dynamics over the life-span.

Dual Mechanisms of Control

Recently a theoretical account of how cognitive control is achieved has been suggested, termed the dual mechanisms of control (DMC) framework (Braver, 2012). In this framework the concept of control has been divided into two main modes of control. These are termed proactive and reactive control. Proactive control works as a form of early selection. During proactive control, goal-relevant information is maintained actively before an event occurs, to optimally bias attention, perception and action systems. This would be important for processing of contextually relevant stimulus-response associations. Reactive control on the other hand, is mobilized only as needed. Rather than early selection, this can be seen as late correction. It is usually mobilized when high interference is detected (Braver et al., 2009). Cognitive control can therefore be thought of as a dimension on which proactive and reactive control represents the two extremes. Performance on a given task will represent a mixture of the two across trials. Relatively more proactive control within a trial should be accompanied by reduced reactive control within the same trial, representing an antagonistic relationship between them.

Whether a proactive or reactive strategy is being utilized can be tested in paradigms in which the correct response to a certain stimulus does not only depend on its identity, but also upon the context in which this stimulus is presented. The original Stroop task (Stroop, 1935) involves naming the font color of written color-words, in which the font color may be congruent or incongruent with the semantic meaning of the color-word. In another version named the Switching Stroop cues are given in each trial, informing the participant about whether to name the font color or read the word when it is presented (Perlstein, Larson, Dotson, & Kelly, 2006). For this specific version it is possible test proactive and reactive control, as the correct response is dependent on the context as defined by the cue. Utilization of the cue makes it possible to prepare in advance for perceiving the relevant property of the upcoming stimulus, such as reading the color-word. This reflects proactive control, or early selection. Alternatively, it is possible to wait for the presentation of the upcoming stimulus and then retrieve the cued context from memory, reflecting reactive control or late correction (Braver, 2012).

The DMC provides predictions about the dynamics and location of brain activity during proactive and reactive control. Although these two modes represent distinct mechanisms of control, it is suggested that the same brain regions might be activated for both control modes. According to the DMC theory, sustained or anticipatory activity in lateral PFC accompany proactive control, reflecting the maintenance of task representations and goals. This would work as early selection in terms of top-down control, biasing and facilitating the processing of expected relevant task events. In contrast, reactive control is associated with transient activation of lateral PFC. According to the DMC framework, proactive and reactive control can therefore be distinguished by a dissociation between an anticipatory and sustained mode in lateral PFC and another mode that is transient and interference sensitive (Braver et al., 2009).

Proactive vs. Reactive Control Variability. As mentioned, several factors are likely to affect our decision to prepare in advance for upcoming events. This is reflected by changes in the balance between utilizing proactive and reactive control. The preparatory related activity in lateral PFC seen when interference is highly expected, is in line with the proactive control mode explained in the DMC framework. When interference cannot be expected, the preparatory lateral PFC activity is reduced. Instead lateral PFC activates after interference occurs, in line with the reactive control mode (Braver, 2012). Also, context processing tasks such as the AX-continuous Performance Task (AX-CPT) can be used to assess inter-

individual or group differences in cognitive control. The task involves one target condition and several non-target conditions, and the frequency of the trial types can be modified to assess both proactive and reactive control. The task normally includes a high frequency of target trials in which the letter A (cue) is followed by the target stimulus X in the next display (probe). All other cue-probe combinations demand a non-target response regardless of the identity of the probe stimulus letter. One of the other cue-probe combinations involves an A-cue but also a non-target probe stimulus (AY-trials). If a proactive strategy is dominating, great reliance on the cue is expected. Therefore, this might impair performance in AY-trials as the correct response (non-target) and the expected response (target) will conflict. On the other hand, if a reactive strategy is dominating, less reliance on the cue is expected. This will make it easier to respond correctly (non-target), as there has been less preparation for a target response (Paxton et al., 2008).

Further, the task includes two trial-types in which the cue is not an A, termed B-cue trials. The first one, BX trials, involves the target probe stimulus, but demands a non-target response as the cue is not valid. If a proactive strategy is being utilized, it is expected that the participant use the B-cue to in advance prepare the non-target response, as it signals the correct response to be made before the probe stimulus occurs. In contrast, if a reactive strategy is being utilized, the high frequency of AX trials might evoke dominant but inappropriate responses to the X probe in BX trials. This will in turn require reactive control to override these, by retrieving the cue from memory. Greater reliance on reactive control is therefore assumed to impair performance in BX trials (Paxton et al., 2008).

The final trial type is the BY-trials. As with BX-trials it is possible to use the B-cue to prepare a response in advance, which is expected when a proactive strategy is utilized. Still, the upcoming probe is not associated with a target response, and individuals with a reactive strategy are therefore thought to perform well in this condition. Still, one might argue that a proactive strategy is beneficial for these trials as well, as it allows for preparing a response in advance (Paxton et al., 2008).

Support for different response patterns comparing a proactive strategy with a reactive strategy in the AX-CPT was found by Paxton et al. (2008). They compared performance in a group of young adults with a group of older adults on the AX-CPT. The behavioral data revealed that young adults were using a proactive strategy, while older adults seemed to rely on a reactive strategy. As expected from the AX-CPT, this was reflected by reduced performance in AY trials in the group of young adults compared to older adults. Further, older

adults showed reduced performance on BX trials compared to young adults. It was predicted that this difference would be reflected by differences in lateral PFC activity patterns. In line with their predictions their results revealed an activity pattern in young adults associated with proactive control, showing increased cue related activity in lateral PFC. In contrast, older adults showed reduced cue-related activity, but increased probe related activity compared with the young adults, indicating a more reactive response pattern (Paxton et al., 2008).

Research has therefore shown that capacity of cognitive control and the choice between a proactive and reactive strategy varies between individuals and groups, but also within individuals. This within-individual variation seems to depend on situational demands and available resources (Braver, 2012) Thus, a combination of situational properties and individual characteristics determine the choice between a proactive or reactive strategy at a given moment.

Phasic Dopamine Signals during Context Updating

Functioning of the dopamine system within PFC is assumed to mediate the ability of maintaining representations actively within this region (Paxton et al., 2008). D'Ardenne et al. (2012) investigated the role of PFC and the midbrain dopamine system in working memory updating. They suggested that a gating mechanism is regulating updating. More specifically this refers to the updating of task- and goal representations. Their results suggest that phasic dopamine signals regulate the encoding, and thereby updating, of context representations in PFC. They used fMRI to identify regions associated with context representation in a modified version of the AX-CPT task, contrasting conditions in which the correct response to the probe stimulus depended on the previous display (i.e. the context) or not. Results showed bilateral activation of DLPFC, with greater activity in the right hemisphere. In a subsequent experiment involving the same participants, they aimed to test the causal involvement of DLPFC in updating of context representations. To do this, single pulse transcranial magnetic stimulation (spTMS) was used to over the individually defined BOLD local maxima in DLPFC to disrupt potential encoding of the context. Separate spTMS was given at different delays after context presentation and it was found that pulses given 150 ms after presenting context cues, slowed down responses to probes, but only in context dependent trials. This indicated a disruption of context updating. Further this was in line with previous event-related potential research on the timing of context updating (Lenartowicz, Escobedo-Quiroz, & Cohen, 2010). Follow-up fMRI data supported that this updating was regulated by a phasic

dopamine signal from midbrain regions after cue-presentation. Their results suggest that the DLPFC is critical for encoding of goal- and context representation, and that phasic dopamine signals regulate this encoding (D'Ardenne et al., 2012). As proactive control depends on encoding and utilization of these context dependent cues, it is being argued that without this phasic dopamine signal, sustaining inputs actively within PFC is not possible. Also PFC can then only be activated in a transient manner, reflecting the reactive control mode (Braver, 2012)

It has been suggested that behavioral measures of WMC can be seen as an index of dopamine functioning. It is assumed that dopaminergic modulation in the basal ganglia and PFC contributes to individual differences in WMC (Braver, Cole, & Yarkoni, 2010). Support for this has been shown as increased dopamine synthesis in the caudate predicts higher WMC (Braver et al., 2010). WMC is the number of items that can be stored and put to use over a short time period. The lateral PFC plays an important role in mediating attentional filtering in working memory, further mediated by dopaminergic modulation. Higher WMC is further related to increased proactive control, as measured WMC might indicate how easily or efficiently goals are maintained actively in working memory (Braver, 2012). It has been shown that high-WMC individuals use cue information to prepare responses to a probe only when it is likely for this probe to occur. Low-WMC individuals are less dependent on cues compared to high-WMC individuals (Redick, 2014). The physiological measure of spontaneous eye-blink rate (SEBR) has also been suggested as a reliable indicator of general dopaminergic functioning (Dreisbach et al., 2005; Tharp & Pickering, 2011). Specifically higher SEBR is associated with greater striatal dopamine functioning (Aarts et al., 2012; Dreisbach et al., 2005). SEBRs are elevated in schizophrenia patients, but reduced in Parkinson's patients. These are both conditions related to dopaminergic dysfunction. Also, studies have shown that dopamine agonists and antagonists can increase and decrease SEBRs respectively, both in nonhuman primates and humans (Chermahini & Hommel, 2010). Dopamine functioning and SEBRs have been investigated in relation to performance on cognitive tasks, and eye-blink rates seem to predict behavioral performance in cognitive tasks associated with dopaminergic functioning (Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009; Tharp & Pickering, 2011). With WMC being related to utilization of proactive control, mediated by dopamine functioning, measures of both WMC and SEBR should be associated with performance on tasks targeting the dynamics of proactive vs. reactive control.

The Norepineprine System in Cognitive Control

A wider network including additional brain regions is suggested for the reactive control mode. Reactive control might reflect a reactivation of task goals, mediated via detection of interference. This would engage conflict-monitoring regions such as ACC (Braver, 2012). Aston-Jones and Cohen (2005) specify that the ACC has been shown to robustly and reliably respond to the degree of task difficulty as well as conflicts. Conflict occurs when two simultaneous processes are competing for the expression of conflicting responses. Proactive- and reactive processes might just be an example of processes which can occur simultaneously, demanding conflicting responses. Further, the degree to which a proactive strategy is being used will have an impact on the degree of conflict when these two processes occur simultaneously. Specified control signals will then be implemented by the lateral PFC. Lateral PFC is assumed to be responsible for the regulative function of control, relating to the proactive nature of control (Shenhav, Botvinick, & Cohen, 2013). As conflict is detected, a correction or resolution is thought to be performed in this brain region.

The process of conflict correction or resolution is assumed to be mediated via locus coeruleus (LC), located on each side of the rostral pons in the brainstem. LC is the hub in the noradrenergic system to the whole brain, being the only source of the neurotransmitter norepinephrine (NE) to the cortex, cerebellum and hippocampus (Aston-Jones & Cohen, 2005). The ACC is connected with the LC, and it is thought that the ACC might drive phasic activation of the LC. This further allows for transient activation within PFC (Aston-Jones & Cohen, 2005). Research on animals has shown that LC responses are plastic, and is flexibly linked to specific sensory attributes of stimuli. Rather the LC responses are clearly task-sensitive (Aston-Jones & Cohen, 2005). Aston-Jones and Cohen (2005) suggest that LC-responses reflect an attentional filter, selecting for the occurrence or timing of specific stimuli.

Further, increasing the load within a task is thought to be associated with a proportional increased activity in the LC-NE system (Alnæs et al., 2014). In line with evidence of increased activity in lateral PFC in the inter-stimulus interval between cue and probe stimulus, reflecting utilization of a proactive strategy, it likely that this would be reflected also by increased activity in the LC-NE system during the same temporal window. Accordingly, the LC-NE system should be activated after cue-presentation, specifically when a proactive strategy is being utilized.

Pupillometry

The activity of two different muscles, the dilator and the constrictor, causes changes in pupil size. It cannot be controlled voluntarily. LC responses have a neural inhibitory effect on the parasympathetic oculomotor complex, making the pupil dilate. There is a tight link between pupillary responses and activation of the LC-NE system (Laeng, Sirois, & Gredeback, 2012). The pupil not only changes size in response to ambient light, but also in response to non-visual stimuli such as thoughts and emotions (Laeng et al., 2012). Measuring the pupil's diameter has been used as a method of investigating cognitive processes for more than 50 years (Hess & Polt, 1964; Kahneman & Beatty, 1966). The size of the pupil is also related to the amount of executive or working memory load, interference or competition between stimuli. Increased load, interference or competition is reflected by an increase in pupil size (Laeng, Orbo, Holmlund, & Miozzo, 2011; van Steenbergen & Band, 2013). Changes in pupil size driven by cognitive demands are usually modest, often not larger than 0.5 mm change (Laeng et al., 2012). Pupillary responses assumingly reflect activation in the LC, and its activation can be divided into two modes. In the phasic mode the LC activates whenever task-relevant stimuli are presented. It can be seen as a focused or exploitation mode. The second mode is the tonic mode, where the LC fails to respond phasically to task events. It can rather be seen as a diffuse mode of exploration (Aston-Jones & Cohen, 2005; Chiew & Braver, 2013; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010) Phasic processing of task-relevant events has been shown to be time-locked to quick and dramatic pupillary dilations. Still, all stimuli with some kind of relevance to the task are likely to provoke a response in form of pupillary dilation (Laeng et al., 2012).

Recently, Chiew and Braver (2013) showed how the proactive vs. reactive control is reflected by pupil responses, reflecting cognitive effort. They specifically targeted the delay period between the cue and the probe in the AX-CPT. It was found that pupil size was larger in the delay period after the presentation of cues (B-cues) of which the upcoming response could with certainty be prepared in advance. This was compared to A-cue trials in which either a target- or a non-target response is demanded, depending on whether the following probe is valid (X) or invalid (Y) respectively. These results are in line with findings of increased activity in lateral PFC during such a delay period, specifically for trials in which the upcoming response can be prepared with certainty (Paxton et al., 2008). Although Chiew and Braver (2013) was not targeting the post-probe period, their plotted results suggest increased pupillary dilation for the AY-trials, reflecting greater effort. AY-trials also demand a non-

target response. If a proactive strategy is being utilized the A-cue may create an expectation of a following X-probe, encouraging preparation for a target response. When the invalid probe (Y) appears, this will interfere with the expected outcome. The greater reliance on the preceding cue, reflecting a proactive strategy, the greater the interference will be. Conflict-related activity in the ACC will further activate the LC, and this activation is thought to be reflected by an increased phasic pupillary dilation. Chiew and Braver (2013) mention that there has been a growing interest in the use of pupillometry in the study of cognitive control. Also, it has been shown that pupillometry can be used to index changes in cognitive control mechanisms such as reactive and proactive control in relation to typical development of cognitive control during childhood (Chatham et al., 2009). However, there are still few studies that have specifically targeted variability of cognitive effort during proactive and reactive control, also in terms of temporal dynamics.

The Present Study

The extensive amount of research on cognitive control functions strongly suggests an important role of PFC, with distinct anatomical structures and systems exhibiting specific control functions (Miller & Cohen, 2001; Purves, 2008). Recently some research has shifted the focus from detailed anatomical specification towards emphasizing the importance of individual variation in explaining cognitive control. Also, there has been a growing interest in the attempt to explain such individual variability in terms of temporal dynamics of control mechanism (Braver, 2012). Evidence from fMRI research suggest a temporal difference between proactive and reactive control, in which proactive control is associated with increased cue-related activity while in contrast reactive control is associated with reduced cue-related activity combined with increased probe-related activity (Braver, 2012; Paxton et al., 2008). However, findings of temporal activity patterns associated with proactive and reactive control does not necessarily inform us about the temporal effort demanded during proactive and proactive control. The role of cognitive effort in the balance between proactive and reactive control still needs to be established.

We therefore aimed to investigate the balance between proactive and reactive control in a sample of young adults, assumed to show a proactive response pattern in the AX-CPT. Measures of accuracy and reaction times (RTs) were used to make it possible to assess whether a proactive response pattern was present. Further we included measures of pupil activity to investigate the condition specific variability of cognitive effort.

Our second aim was to further investigate the antagonistic relationship between proactive and reactive control by manipulating the balance. During the recent years there has been an exponential increase in the application of non-invasive brain stimulation as research a tool. Transcranial direct current stimulation (tDCS) is one method, and involves passing a mild current between two or more electrodes placed on the scalp. The current passed between the electrodes is thought to affect the brain mostly at sites located close beneath the electrodes (Filmer, Dux, & Mattingley, 2014; Nitsche et al., 2007). tDCS is thought to modulate the resting membrane potential in a polarity dependent manner. The neuronal excitability is assumingly elevated or lowered through the anodal and cathodal electrodes respectively (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Jacobson, Ezra, Berger, & Lavidor, 2012; Nitsche et al., 2007; Stagg & Nitsche, 2011) Several studies have found that tDCS over frontal areas effects functions related to cognitive control such as task switching (Leite, Carvalho, Fregni, Boggio, & Goncalves, 2013), stimulus-response integration (Zmigrod, Colzato, & Hommel, 2014), attentional bias (Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014), error awareness (Harty et al., 2014) and vigilance (Nelson, McKinley, Golob, Warm, & Parasuraman, 2014). In the present study we therefore wanted to manipulate brain substrates of context representation directly through sustained tDCS, and observe the effects on the balance of proactive vs. reactive control, as well as on condition-specific variability of cognitive effort. D'Ardenne et al. (2012) found effects of non-invasive stimulation on context processing when it was applied over DLPFC. Also the activity related to context processing is this structure was stronger in right hemisphere. We therefore chose to apply tDCS over right DLPFC.

Hypotheses and Predictions. As our sample consisted of young adults, we expected to find a response pattern that reflected a proactive strategy in the AX-CPT. The high-frequency target AX-condition was used to manipulate towards a proactive strategy, and we were not specifically interested in performance in this condition. We expected high reliance on cue-information in general, in both A-cue and B-cue trials. Regarding the antagonistic relationship of proactive vs. reactive control, we expected lower accuracy and slower RTs in the AY-trials in which the probe is invalid. On the other hand higher accuracy and faster RTs were expected in B-cue trials, in which the cue can be used to prepare in advance for responding to the probe, whether the probe is valid (BX) or invalid (BY). We further expected to see greater cognitive effort in the AY-trials, reflected by larger pupil dilation after probe letter presentation, compared to B-cue trials. We were also interested in how cognitive effort would

unfold in the delay period before probe letter presentation. In line with findings of increased brain activity during this delay period when a proactive strategy is being utilized, we also expected on average larger pupil size in this delay period for B-cue trials compared to A-cue trials. This is because B-cue trials can be used with 100 percent certainty to prepare the upcoming response.

We further expected that anodal tDCS over right DLPFC would have a strengthening effect on proactive control, while reducing reactive control. We predicted that this would be reflected by reduced accuracy and a slowing of RTs in AY-trials in combination with increased accuracy and faster RTs in BX- and BY trials. We also expected this strengthening of proactive control to affect the condition specific variability of cognitive effort. It was therefore expected to see an increase in the pupil dilation after probe letter presentation in the AY trials reflecting increased cognitive effort. We also expected to see decreased pupil dilation in BY trials reflecting less cognitive effort. We were not certain that we would find such an effect on the BX trials, as the X-probe in general was associated with a target response, and therefore could elicit a response that was not necessarily related to proactive or reactive control. DLPFC has been assumed to be a central structure also for bottom-up visual attention during detection of salient stimuli (Katsuki & Constantinidis, 2012), and modulating activity within this structure with tDCS might therefore also affect other processes than what was targeted in the present study.

Finally, we included measures of WMC and SEBR. As these have been related to dopamine functioning, they might also relate to the phasic dopamine signal assumed to mediate context updating during proactive control. We therefore predicted that these measures would be positively correlated with performance and negatively correlated with effort in BX- and BY- trials, as performance in these trials benefit from a proactive strategy.

Method

Participants

Forty-eight participants were recruited for the experiment from the University of Oslo. Three participants were excluded from the study because they did not complete the experiment. Another five were excluded because of technical issues. A total number of 40 (N=40; females = 23) participants were therefore included in the analyses. Inclusion required participants to be within the range of 18-35 years of age (M = 23.4, SD = 2.58). Participants were told that they needed to be healthy, and have normal- or corrected to normal vision for participation in the study. They were also informed beforehand that they could not take part in the experiment if they were using psychoactive medication. All participants were fluent Norwegian speakers. Before taking part in the experiment participants read and signed an informed consent. The experiment was approved by the Department of Psychology's Research Ethics Committee at the University of Oslo.

Setup and Materials

Stimuli were presented on a 24-inch BenQ XL2420T LED monitor. Participants were seated 60 cm from the computer screen, and a chin rest was used in order to minimize head movements. E-Studio 2.0 (Psychology Software Tools) was used for presentation of stimuli. Throughout all sessions pupil diameter and blink rates were measured. This was done using an iView X Eye-Tracking Device by SensoMotoric Instruments (SMI) recording at a sampling rate of 60Hz. This meant that pupil measures were recorded every 16 ms. An integrated iView X Software provided by SMI was used to collect the data Serial Response Box Model 200a (Psychology Software Tools) was used to collect responses.

Stimulus Display. The AX-CPT was used to assess proactive and reactive control. Letters were presented on a screen in a cue-probe manner. Subjects were told to make a specific response (right index finger button press) when the letter *A* was followed by the letter *X*. Another response (left index finger button press) was required for all other stimuli. *AX* trials were "target trials". They can be explained as a valid cue that is followed by a valid probe. The task included three types of "non-target trials". These consisted of trials in which a valid cue is followed by an invalid probe (*AY* trials), or invalid cues followed by either a valid or an invalid probe (*BX* or *BY* respectively). The *AX*-condition occurred in 64% of all trials. High frequency of this trial might create an *expectancy bias* in *A* cue trials, or a *target bias* in

X probe trials. In what way a participant is biased depends on whether they are dominantly proactive or reactive in their response strategy. Specifically, a stronger proactive strategy will lead to an increased expectancy bias. The consequence of a strengthened proactive strategy will be reduced target bias. In the AX-CPT this will be reflected as reduced performance in the *AY* condition combined with increased performance in the *BX*- and *BY* condition.

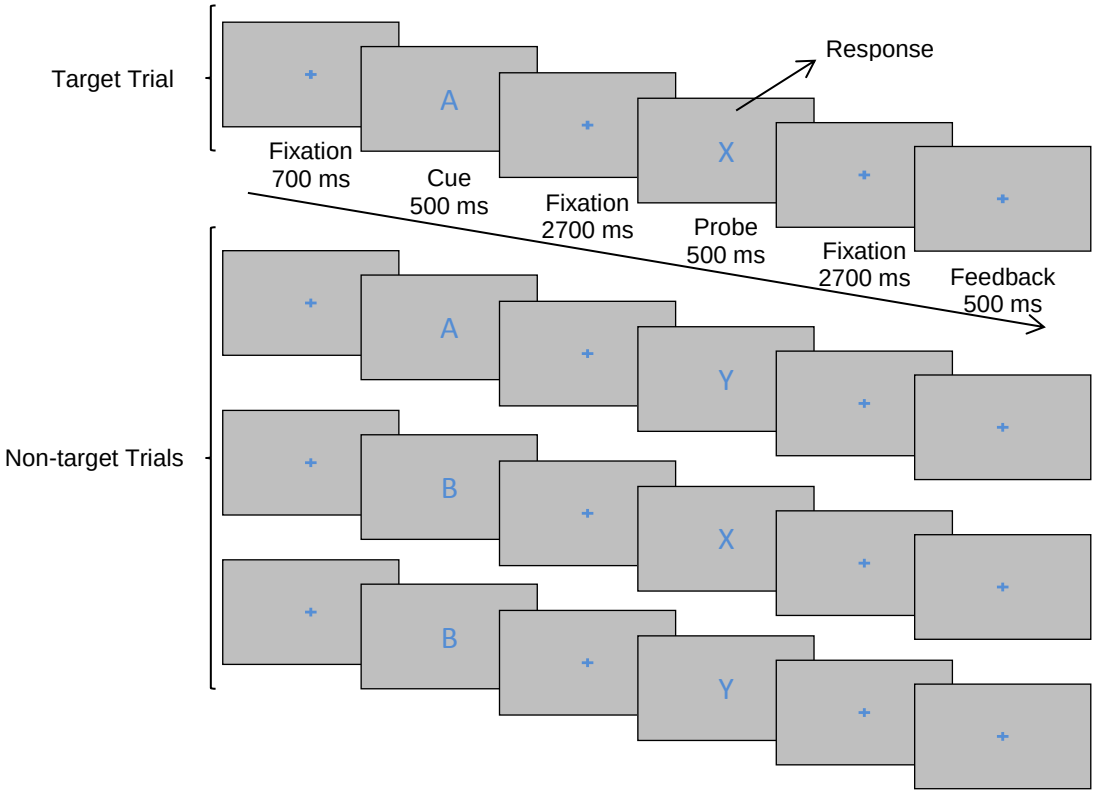

Figure 1. Illustration of the sequence of events in target- and non-target trials. The target "AX" condition is presented followed by the non-target conditions "AY", "BX" and "BY" respectively. The target AX-condition required a right index finger button press, while all non-target conditions required a left index finger button press.

Each trial started with a 700 ms baseline fixation cross in the middle of the screen. A cue was presented for 500 ms followed by an inter-stimulus fixation of 2500 ms. The probe would appear for 500 ms, and the time limit for responding was set to 1500 ms. A fixation of 2700 ms was then presented, followed by a feedback slide of 500 ms, also consisting of a fixation cross. The last 2700 ms fixation would allow for the pupil diameter to return back to baseline. In the 500 ms feedback slide the fixation would turn red in combination with a

sound after both unregistered and incorrect responses. The sequence of trial events is illustrated in Figure 1. The AX-CPT consisted of 200 cue-probe pairs divided into two blocks. In each block, consisting of 100 trials, there were 64 AX-trials and 12 of each of the other three conditions (AY, BX, BY). Within each block the different cue-probe pairs were presented in random order.

Transcranial Direct Current Stimulation. A DC-Stimulator from neuroConn was used to perform tDCS. The size of the electrodes was 5x7cm^2. The electrode montage was the same in both tDCS-conditions. The placement of the anode was over right DLPFC, corresponding F4 using the 10-20 electroencephalogram (EEG)-system. The placement of the cathode was left supraorbital area, corresponding Fp1. It has been argued that placing the anode over DLPFC and the cathode over supraorbital area makes it possible to stimulate the DLPFC unilaterally (DaSilva, Volz, Bikson, & Fregni, 2011). The two stimulation conditions consisted of stimulation and sham. We did not include a third session reversing the electrodes, often referred to as cathodal stimulation. In a meta-analytic review by Jacobson, Koslowsky, and Lavidor (2012) they concluded that placement of the anode have greater effect on outcome performance compared to cathodal electrode placement when targeting complex cognitive functions. Stimulation involved a current density of 1mA, 30 seconds fade in, 1500 seconds (25 minutes) stimulation time, and 30 seconds of fade out. The same setting was used for the sham, except stimulation time was only 30 seconds. In the Sham condition participants would get the same initial sensation of stimulation on the scalp without it affecting cortical activation as it is too short. Impedance was always kept below 10kΩ.

The settings of the stimulation were set according to safety guidelines. It has been suggested that stimulation involving current densities of 1-2mA for about 20 minutes is considered safe, and the size of the electrodes is usually between 25 cm² and 35 cm² (Stagg & Nitsche, 2011). Current densities up to 2mA have been used in several studies, with durations up to 30 minutes (Jacobson, Koslowsky, et al., 2012; Stagg & Nitsche, 2011).

Working Memory Capacity Screening. WMC was assessed using the Letter-Number-Sequencing task. The task is a subtest from the Wechsler Adult Intelligent Scale Third Edition (WAIS-III) (Wechsler, 1997). Participants are presented with strings consisting of both numbers and letters combined, which are unsorted. These strings vary in length, and the task is to organize the numbers in ascending order and the letters in alphabetic order. The test is quickly administered and is also highly correlated with laboratory measures of WMC (Hill et al., 2010).

Arousal Ratings. Halfway through data collection we decided to include a self-assessment scale of arousal after each session. We used the "arousal" dimension of the Self-Assessment Manikin (SAM) Scale, a non-verbal nine-point scale illustrating experienced arousal (Bradley & Lang, 1994). Participants were told to rate their experienced arousal in the present moment after each tDCS-session.

Procedure

All participants performed the letter-number-sequencing task only at the beginning of the first session. Instructions were given on the AX-CPT, following a practice consisting of 20 trials (12 AX, 2 AY, 3 BX, 3 BY). The tDCS-equipment was set up after the practice trials, using a 10-20 positioning EEG-cap. The cap was removed after locating right DLPFC and left supraorbital area. The electrodes were attached with conductive gel. The settings for the session, stimulation or sham, was then set ready but not turned on. Eye-tracking calibration was then performed, with the aim of values below 0.5, but for some participants this was not possible. This was not critical as gaze positions were not of interest for this particular study. After performing the calibration, impedance was checked to be below 10kΩ and the tDCS session was started. The experimenter made sure the participant was comfortable with the situation. The researcher then instructed the participant to begin the task immediately after the researcher had left the room. They had also been instructed that for the 5 first minutes a fixation cross would be present on the screen, and that they were supposed to look at the fixation cross in a relaxed state. This was for the collection of SEBR. After 5 minutes the cross would disappear and reappear, indicating the beginning of the AX-CPT. Each participant went through two sessions, separated by approximately one week. They had one session when there was real stimulation and one session with sham. The order of the sessions was randomized.

Pupil Data and Blink Rate Pre-Processing

Pupil data were pre-processed in R (version 3.1.1) using RStudio (version 0.98.1049). Baselines were calculated as mean pupil size during the 700 ms baseline period. Trials in which the baseline exceeded 1.5 standard deviations from the mean baseline pupil size were excluded from the analyses. This made it possible also to reduce noise in the pupil data if participants had received negative feedback in the previous trial. Pupil responses for each trial were further calculated as percent change from baseline of that trial. Further pupil data were

filtered on E-prime RTs and accuracy. Only trials with correct responses were included in the pupil analyses. Trials showing RT's shorter than 200 ms and longer than 1300 ms were excluded. The exclusion of short and long RT's is further explained in analysis below.

The collected blink rates (BR), as measured during the 5 first minutes before the computerized task, were processed into a measure of spontaneous eye-blink rate (SEBR). As a blink normally lasts for longer than 100 ms, blinks with shorter durations were excluded from the analyses. Also, blinks with durations longer than 500 ms were excluded to avoid including data reflecting deliberately closing the eyes. The exclusion of short and long blinks was done in accordance with previous research on SEBR (Aarts et al., 2012). After exclusion of short and long blinks, the mean BR per minute was calculated for the sham-session of tDCS. We only used data from the sham-session to avoid disruption of tDCS on the SEBR-measure. We residualized these data for gender and age, as previously done by Dreisbach et al. (2005). This was to minimize influence of demographic variables on SEBR. The mean and standard deviation were calculated for each participant, and participants with SEBRs exceeding 3.0 SDs were excluded from the analyses.

Design and Data Analysis

Measures of the AX-CPT were mean accuracy, RTs, pupil dilation responses during the interstimulus interval, and after probe letter presentation. RTs for each participant were calculated as the median RT within the range 200-1300 ms. Very fast or slow responses might indicate that the observation has been influenced by processes other than what was intended to be measured. Fast responses might indicate that the participant has not processed the actual presented stimuli. Also, slower responses might indicate that the participant has been distracted during the task, either by incidental visual, auditory, or somatosensory input, or cognition that is task-irrelevant (Ulrich & Miller, 1994). We also only included trials in which correct responses had been made.

The time window for the pupil response after probe letter presentation was chosen according to the plotted results of Chiew and Braver (2013). Their illustration of the pupillary responses for the different conditions in the AX-CPT task, indicate that the response to the probe peak around 1100 ms after probe presentation, and lasts for about 1000 ms. For our experiment this same time window would be represented as 5000-6000 ms after trial start, and was set as the time window for pupil response after probe letter presentation.

For the pupil response during the delay between the cue and the probe, we chose to use a time window for the analyses that was wider than previously done by Chiew and Braver (2013) who used a 250 ms pre-probe interval. Instead we included data from an 800 ms pre-probe interval. Specifically this window was set to 2000-2800 ms after trial start, starting approximately as the same time point as done by Chiew and Braver (2013) who had the starting point for this interval at 1950 ms after trial start. Chiew and Braver (2013) were using a shorter inter-stimulus interval, of 1500 ms. As our inter-stimulus interval was 2700 ms, we had the opportunity of using data from a larger time-window for the cue pupil responses.

Z-scores were calculated for each participant, and those with z-scores exceeding 3.0 in accuracy, RTs, or pupil responses, in any of the four task conditions, where excluded from the analyses. We wanted to exclude participants who might not have understood the task instructions, and low accuracy may be an indication of this. Also, RT's far from the mean, as discussed above, make it more difficult to make sure other brain processes are not affecting the RTs. Noise in the pupil data was removed already during the step of preprocessing. This left a total of 35 participants for the analyses.

Main Analysis. The main analysis involved a 2 (tDCS; Stim and Sham) by 4 (Condition; AX, AY, BX and BY) by 2 (Treatment Order; "Stimulation – Sham" and "Sham – Stimulation") mixed-designs ANOVA. *tDCS* and *condition* were treated as within-subject factors, while *treatment order* was treated as between subject factor. This analysis was performed on accuracy-, RT-, and pupil dilation responses after probe letter presentation. In accordance with our predictions of strengthened proactive control and weakened reactive control during stimulation compared to sham, we performed planned contrasts in the main analysis. As we were specifically interested in the difference between AY-performance and BX- and BY performance, we compared both the BX- and BY condition against the AY-condition. This allowed us to investigate the main effect of condition. It also allowed us to see if the difference between the AY-condition and the BY- and BX condition would be changed during stimulation compared to sham.

We performed paired samples t-tests comparing stimulation and sham in each condition separately for all of the three measures accuracy, RTs and pupil response after probe letter presentation. This would allow us to investigate the effect of stimulation within each task condition. Bivariate correlations were performed to investigate the relationship between WMC and SEBR and accuracy, RTs and pupil response after probe letter presentation in each task condition for both stimulation and sham.

As we wanted to investigate the pupil responses in the inter-stimulus interval, we did a 2 (cue; A and B) by 2 (tDCS: stimulation and sham) by 2 (treatment order; "Stimulation – Sham" and "Sham – Stimulation") repeated measures mixed ANOVA. Cue and tDCS were set as within-subject factor, while treatment order was set as between-subject factor.

Arousal analysis. We also wanted to investigate the effects of tDCS on general arousal. This would allow us to make more certain conclusions about effects of tDCS on cognition, and that these were not merely an effect of arousal. We therefore conducted a 2 (tDCS; Stim and Sham) by 2 (Treatment Order; "Stimulation – Sham" and "Sham – Stimulation") repeated measures mixed ANOVA, with tDCS as within-subject factor and treatment order as between-subject factor. In addition to the measure arousal from the SAM Scale, we calculated the mean pupil size during baseline periods comparing stimulation and sham for each participant. We did this as tonic pupil activity is assumed to indicate the general level of arousal reflected by tonic activity in the LC-NE system, and that baseline pupil measures can be used as a measure of tonic pupil activity (Blaser, Eglington, Carter, & Kaldy, 2014; Laeng et al., 2012). Accordingly we included two measures of arousal in the analysis, SAM-scale rating and mean baseline pupil size. As not all participants had filled out the SAM-scale, only 20 participants were included in this analysis.

Results

The results of the ANOVA performed on SAM-scale ratings and on mean pupil size at baseline revealed no significant main effects of *tDCS* or of *treatment order* and no *tDCS* by *treatment order* interaction. In the main analysis we therefore interpreted effects on behavior- or pupil data to be of cognitive nature, and not as changes in the level of arousal.

Behavioral Data

For both accuracy and RTs we found no effect of treatment order as main effect or in interaction with tDCS or condition. Also there was no main effect of tDCS on accuracy or RTs. Descriptives from the accuracy analysis is presented in Table 1, showing the means and standard deviations for each task conditition in both tDCS conditions.

Table 1

Mean (M) accuracy and standard deviations (SD) during sham and stimulation for each task condition.

	Sham		*Stimulation*				
Condition	*M*	*SD*	*M*	*SD*	*t*	*p*	Cohens' *d*
AX	.99	.01	.99	.01	-0.39	.70	.07
AY	.94	.08	.92	.09	-2.15	.04	.36
BX	.99	.02	.99	.02	.22	.83	.04
BY	.98	.03	.98	.02	1.29	.21	.22

In the mixed-designs ANOVA for accuracy, Mauchly's test indicated that the assumption of sphericity had been violated for the main effect of *condition* on accuracy, χ^2 (5) = 112.89, p = < .001, and for the *tDCS* by *condition* interaction, χ^2 (5) = 39.49, p = < .001. Therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = .39 for the main effect of *condition* and .58 for the *tDCS* by *condition* interaction). Results revealed a significant main effect of *condition*, F(1.16, 38.16) = 21.31, p = < .001, partial η^2 = .39. Further the results revealed a significant *tDCS* by *condition* interaction, F(1.73, 57.09) = 4.15, p = .03, partial η^2 = .11.

Contrasts revealed that the AY-condition was significantly different from the BX-condition, F(1, 33) = 23.37, p = <.001, partial η^2 = .42, and the BY-condition, F(1, 33) =

17.43, p = <.001, partial η^2 = .35. This effect is illustrated in Figure 2, showing lower accuracy rates in the AY-condition compared to the BX- and BY-condition. This reflects the presence of an expectancy bias for the AY-condition, as predicted indicating a proactive response pattern in our sample.

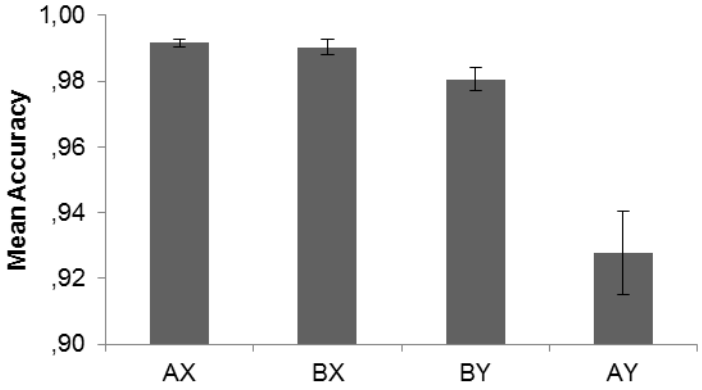

Figure 2. Mean Accuracy for each task condition. Bars indicate the standard error of the mean.

We first investigated the *tDCS* by *condition* interaction performing paired samples t-tests. *Stimulation* and *sham* were compared within each task condition. This revealed a significantly lower accuracy rate during *stimulation* (M = .92, SD = .09) compared to *sham* (M = .94, SD = .08) for the AY-condition, $t(34) = -2.15$, $p = .04$. Accuracy was not significantly different during *stimulation* compared to *sham* within any of the other task conditions. *t*-values, *p*-values and Cohens' d for the difference between *stimulation* and *sham* in each task condition are presented in Table 1.

The *tDCS* by *condition* interaction was further investigated with planned contrasts in the mixed-designs ANOVA. A significant difference between *stimulation* and *sham* was revealed when comparing the AY-condition against the BX-condition, $F(1, 33) = 4.41$, $p = .04$, partial η^2 = .12, and when comparing the AY-condition against the BY-condition, $F(1, 33) = 6.12$, $p = .02$, partial η^2 = .16. This effect was reflected by decreased accuracy in the AY-condition during stimulation combined with increased accuracy in the BX- and BY-condition. This was in line with the predictions of weakened reactive combined with strengthened proactive control during stimulation. It reflects an increased expectancy bias in the AY-condition

combined with reduced target bias in the BX- and BY condition. The effect is illustrated in Figure 3 showing both contrasts separately.

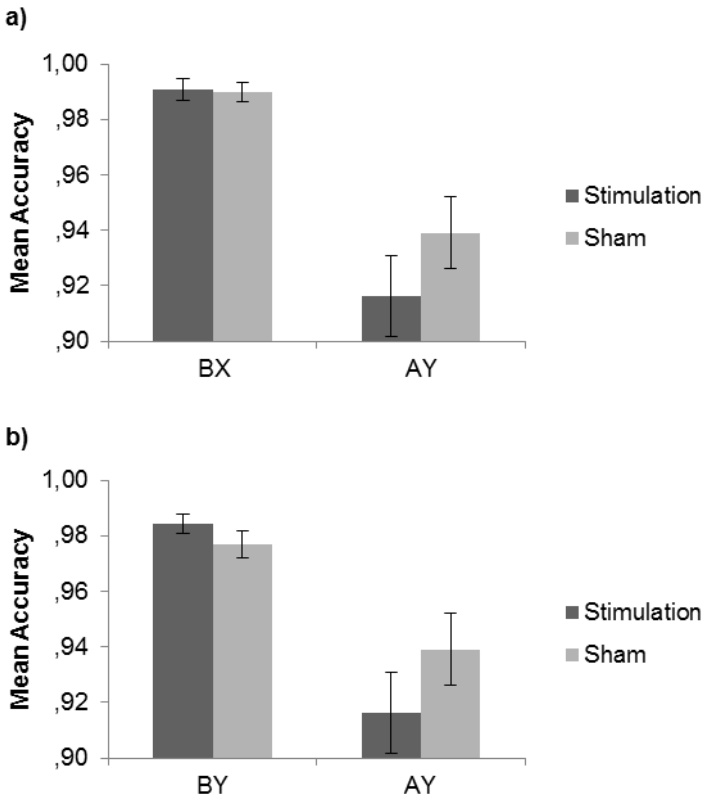

Figure 3. Mean accuracy during stimulation and sham for both contrasts. The figure illustrates the comparison between the BX-condition and the AY-condition (a), and the comparison between the BY-condition and the AY-condition (b). Bars indicate the standard error of the mean

RTs were then analyzed and descriptives are presented in Table 2, showing the mean RTs and standard deviations in each task condition for both tDCS conditions.

Table 2

Means (M) and standard deviations (SD) for reaction times (in ms) during sham and stimulation for each task condition.

	Sham		*Stimulation*				
Condition	*M*	*SD*	*M*	*SD*	*t*	*p*	Cohens' *d*
AX	355	45	357	49	.43	.67	.07
AY	488	52	492	61	.53	.60	.09
BX	308	73	302	58	-0.67	.51	.11
BY	321	73	302	56	-1.90	.07	.32

In the mixed-designs ANOVA Mauchly's test indicated that the assumption of sphericity had been violated for the main effect of *condition*, χ^2 (5) = 39.79, p = < .001, and for the *tDCS* by *condition* interaction, χ^2 (5) = 13.73, p = .02. Therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = .65 for the main effect of *condition* and .77 for the *tDCS* by *condition* interaction).

A significant main effect of *condition* was shown, F(1.94, 63.94) = 264.57, p = <.001, partial η^2 = .89. Further the results revealed a significant *tDCS* by *condition* interaction, F(2.31, 76.06) = 5.13, p = < .01, partial η^2 = .14. Planned contrasts revealed that the AY-condition was significantly different from the BX-condition, F(1, 33) = 386.97, p = <.001, partial η^2 = .92, and the BY-condition, F(1, 33) = 454.64, p = <.001, partial η^2 = .93. The effect is illustrated in Figure 4, showing slower RTs for the AY-condition, and faster RTs for the BX- and BY-condition. As with accuracy, these results are in line with the prediction that a sample of young adults will show a proactive response strategy in the AX-CPT. The RTs reflects the accuracy rates, illustrating an expectancy bias in the AY-condition, which slows down the responses. At the same time, the target bias is not present in the BX- and BY-condition, reflected by faster responses in these conditions.

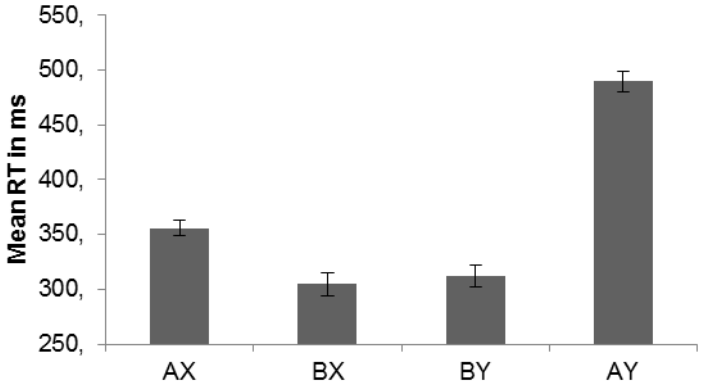

Figure 4. Mean reaction time (RT) for each task condition. Bars indicate the standard error of the mean.

Paired samples t-tests were performed to investigate the *tDCS* by *condition* interaction. No significant difference between *stimulation* and *sham* was revealed within any of the task conditions. Still, there was a trend in the BY-condition towards faster RTs during *stimulation* (M = 302.47, SD = 55.81) compared to *sham* (M = 320.94, SD = 72.96), $t(34) = -1.90$, $p = .07$. *t*-values, *p*-values and Cohens' d effect size for the difference between *stimulation* and *sham* RTs in each task condition are presented in Table 2.

The interaction was further investigated with planned contrasts in the mixed-designs ANOVA. The interaction was only significant for the difference between *stimulation* and *sham* when comparing the AY-condition against the BY-condition, $F(1, 33) = 8.85$, $p = < .01$, partial $\eta^2 = .21$. This interaction was reflected by decreased RTs during stimulation in the BY-condition, combined with increased RTs for the AY-condition. This further supported our predictions of strengthened proactive- and weakened reactive control. As with accuracy, we might say that this interaction reflects a further reduced target bias in the BY-condition, which is expected with strengthened proactive control. A consequence of this will then be an increase in the expectancy bias, reducing reactive control in the AY-condition. For the RTs analysis the interaction was not significant when comparing the AY-condition against the BX-condition, $F(1, 33) = 2.42$, $p = .13$, partial $\eta^2 = .07$. Figure 5 illustrates the interaction for both contrasts.

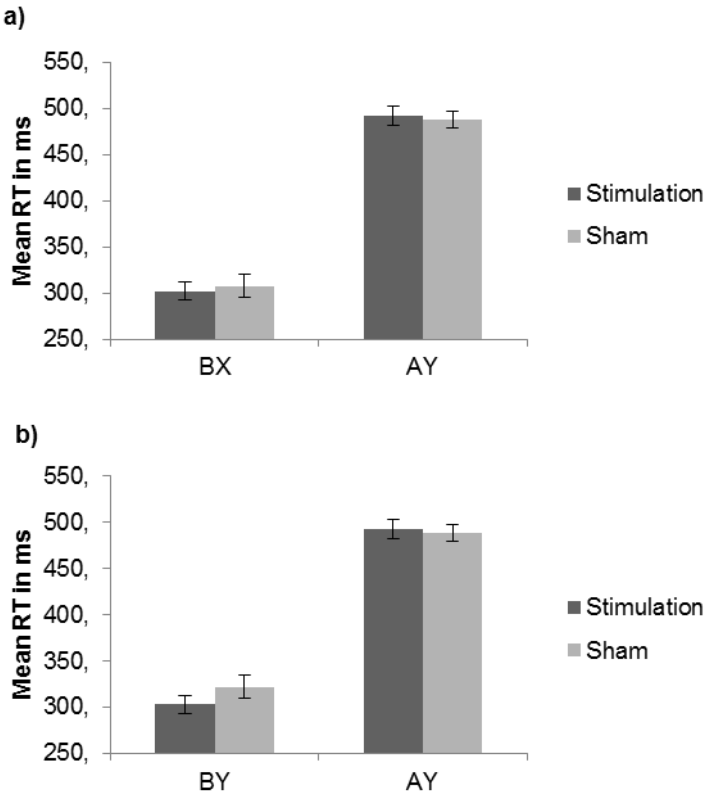

Figure 5. Mean reaction time (RT) during stimulation and sham for both contrasts. The figure illustrates the comparison between the BX-condition and the AY-condition (a), and the comparison between the BY-condition and the AY-condition (b). Bars indicate the standard error of the mean.

Pupil Data

As with accuracy and RTs, we found no main effect of or interaction by *treatment order* on pupil dilation responses after probe letter presentation, and also no main effect of *tDCS*. Descriptives from the analyses are presented in Table 3, showing the mean percent change from baseline in pupil dilation after probe letter presentation, and standard deviations in each task condition for both tDCS conditions.

Table 3

Means (M) and standard deviations (SD) for percent change from baseline in pupil dilation response after probe letter presentation in each task condition for both tDCS conditions.

	Sham		*Stimulation*				
Condition	*M*	*SD*	*M*	*SD*	*t*	*p*	Cohens' *d*
AX	2.0	2.7	2.0	3.1	.12	.91	.02
AY	3.8	3.9	4.6	4.6	1.39	.17	.23
BX	1.7	2.8	2.4	3.6	1.33	.19	.22
BY	1.8	2.7	1.1	3.1	-1.53	.13	.26

In the mixed-designs ANOVA Mauchly's test indicated that the assumption of sphericity had been violated for the main effect of *condition*, χ^2 (5) = 24.20, p = < .001, and for the *tDCS* by *condition* interaction, χ^2 (5) = 13.77, p = .02. Therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = .67 for the main effect of *condition* and .84 for the *tDCS* by *condition* interaction). As with accuracy and RTs we found a main effect of *condition*, F(2.02, 66.60) = 17.91, p = < .001, partial η^2 = .54. The results also revealed a *tDCS* by *condition* interaction, F(2.51, 82.68) = 3.04, p = .04, partial η^2 = .08.

Planned contrasts revealed that the AY-condition was significantly different from the BX-condition, F(1, 33) = 15.62, p = <.001, partial η^2 = .32, and the BY-condition, F(1, 33) = 30.65, p = <.001, partial η^2 = .48. This effect is illustrated in Figure 6 showing an increased change from baseline in the AY-condition compared with the BX- and BY-condition. This

indicates that the AY-condition demands more effort, which supports our predictions as well as our behavioral results. The increased expectancy bias in the AY-condition as a consequence of a proactive response pattern makes the responding in this condition more demanding. Further as the target bias is reduced in the BX- and BY-condition, as the proactive strategy is being utilized, this makes these conditions less demanding. These results therefore support our predictions of a proactive response strategy in a sample if young adults. Figure 7 illustrates the time course of pupillary changes from baseline for each task condition.

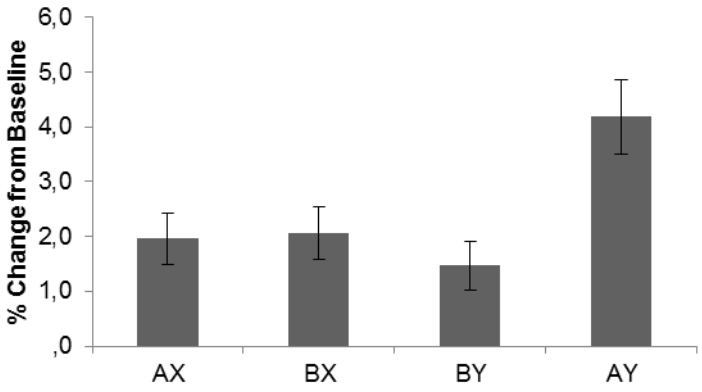

Figure 6. Percent change in pupil size from baseline after probe for each task condition. Bars indicates the standard error of the mean.

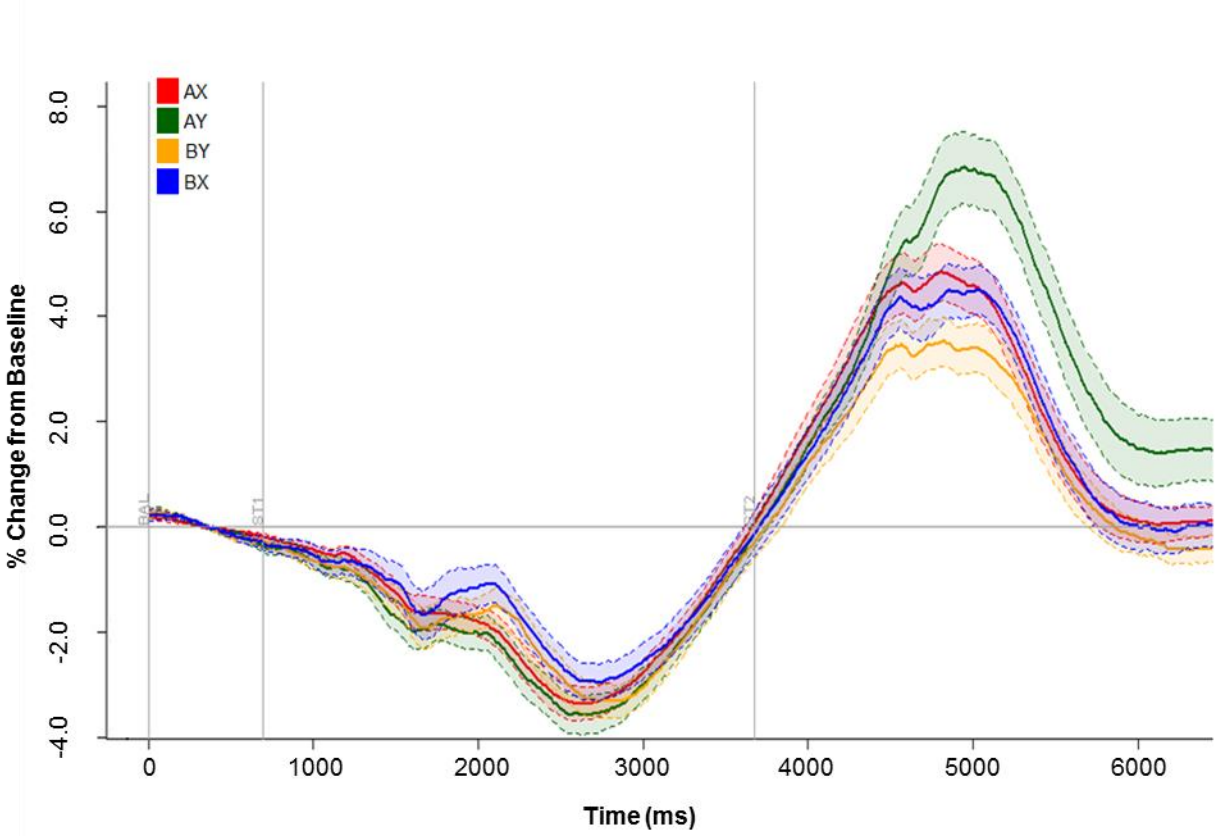

Figure 7. Time course of the percent change in pupil size from baseline by condition. The figure illustrates the time course for all four task conditions. First horizontal grey line indicated baseline onset (BAL). Second horizontal grey line indicates cue onset (ST1). Third horizontal grey line indicated probe onset (ST2). The colored transparent regions represent the standard error of the mean.

The paired samples t-tests performed to investigate the interaction did not reveal any difference between *stimulation* and *sham* within any task condition. *t*-values, *p*-values and Cohens' *d* effect size for the difference between *stimulation* and *sham* for each condition is presented in Table 3.

Further investigation of the planned contrasts in the mixed-designs ANOVA revealed that the interaction was specific for the difference between *stimulation* and *sham* when comparing the AY-condition against the BY-condition, $F(1, 33) = 4.80$, $p = .04$, partial $\eta^2 = .13$. This interaction was reflected by an increased change from baseline in pupil dilation response during *stimulation* for the AY-condition combined with a decrease in the BY-

condition. This further supports the predicted changes in the proactive vs. reactive control dynamics. The increased expectancy bias in the AY condition reflected by accuracy- and RTs data, is reflected by increased demands in this condition shown by the pupil data. In addition, this expectancy bias seems to have a positive effect in the BY-trials, reducing the demands which are further reflected by a decrease in pupil change from baseline. There was no significant interaction when comparing the AY-condition against the BX-condition, $F(1, 33) = .00$, $p = .98$, partial $\eta^2 = < .000$. The two contrasts are illustrated in Figure 8.

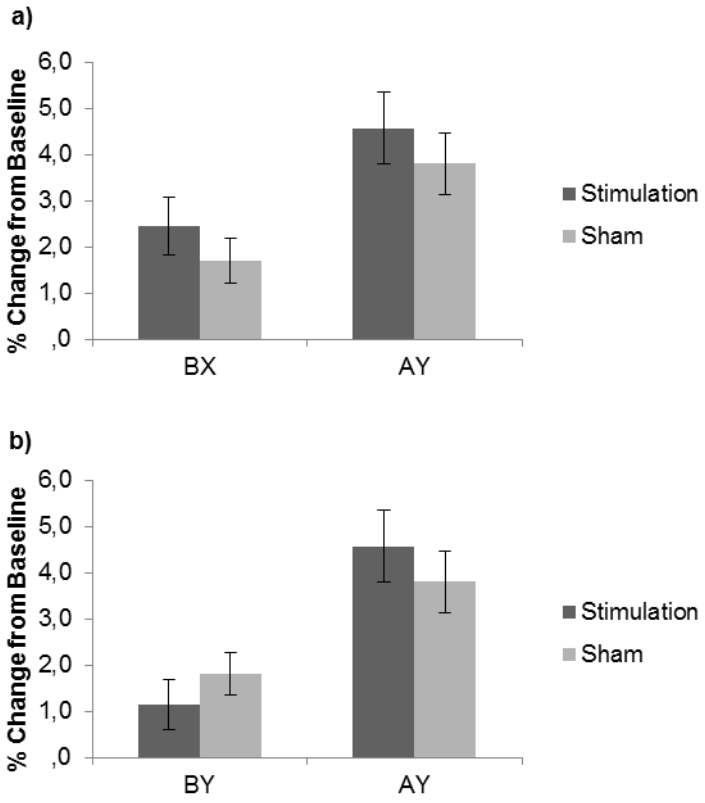

Figure 8. Percent change in pupil size from baseline after probe onset during stimulation and sham for both contrasts. The figure illustrates the comparison between the BX-condition and the AY-condition (a), and the comparison between the BY-condition and the AY-condition (b). Bars indicate the standard error of the mean.

We were also interested in the inter-stimulus interval as this would allow for the investigation of whether A-cue trials were processes differently compared to B-cue trials. The results of the mixed-designs ANOVA analyzing inter-stimulus interval pupil dilation change from baseline revealed a main effect of cue, $F(1, 33) = 6.18$, $p = .02$, partial $\eta^2 = .16$. There was no interaction of tDCS by cue, $F(1, 33) = .02$, $p = .90$, partial $\eta^2 = < .01$, but we found a tDCS by treatment order interaction, $F(1, 33) = 7.41$, $p = .01$, partial $\eta^2 = .18$.

The main effect was reflected by larger pupil diameter during the inter-stimulus interval in B-cue trials compared to A-cues trials as shown in Figure 9. This effect was in line with our predictions, that B-cue trials possibly demands more effort during this interval if a proactive strategy is being utilized. As previously shown, both the behavioral data and pupil data indicated that such a strategy was being utilized in our sample of young adults. The time course of the change from baseline in pupil responses during A-cue trials and B-cue trials are illustrated in figure 10.

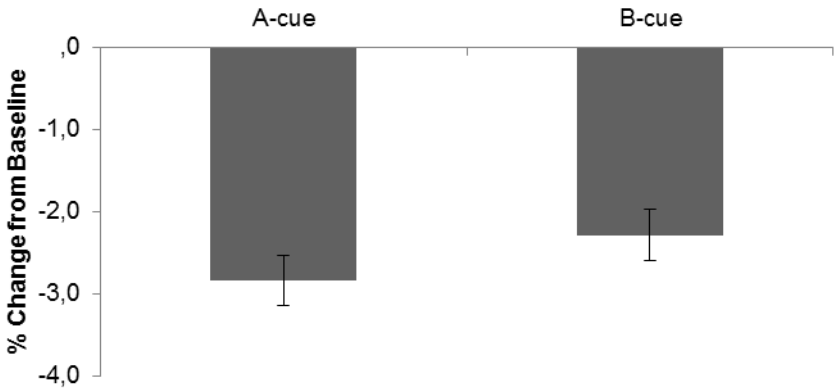

Figure 9. Percent change in pupil size from baseline during the inter-stimulus interval for each cue-type. Bars indicate the standard error of the mean.

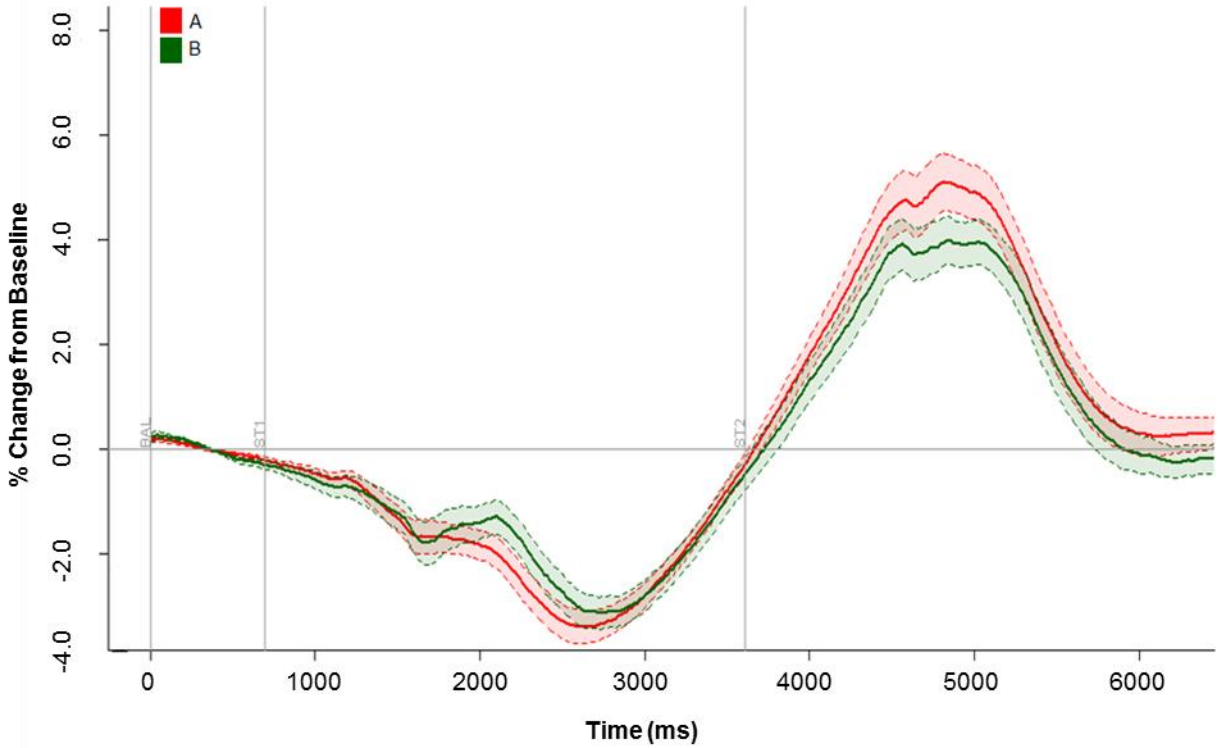

Figure 10: Time course of the percent change in pupil size from baseline by cue. The figure illustrate the times course for the two cue-types. The red line represents A-cue trials, while the green line represents B-cue trials. First horizontal grey line indicated baseline onset (BAL). Second horizontal grey line indicates cue onset (ST1). Third horizontal grey line indicates probe onset (ST2). The colored transparent regions represent the standard error of the mean.

There was no interaction of *tDCS* by *cue*, $F(1, 33) = .02$, $p = .90$, partial $\eta^2 = < .01$, but as mentioned above we found a *tDCS* by *treatment order* interaction. This effect, as illustrated in Figure 11, shows an effect of time on pupil responses during the inter-stimulus interval. In Figure 11a the data is plotted as the *tDCS* by *treatment order* interaction. In Figure 11b we have plotted the data by session (1 or 2) for a better illustration of the learning effect. As we see, this effect in reflected by larger pupil diameter in general during the inter-stimulus interval in session 2 compared to session 1.

Further, we found no interaction of *treatment order* by *cue* or any interaction of *tDCS* by *cue* by *treatment order*. There were also no significant main effects of *tDCS* or of *treatment order*.

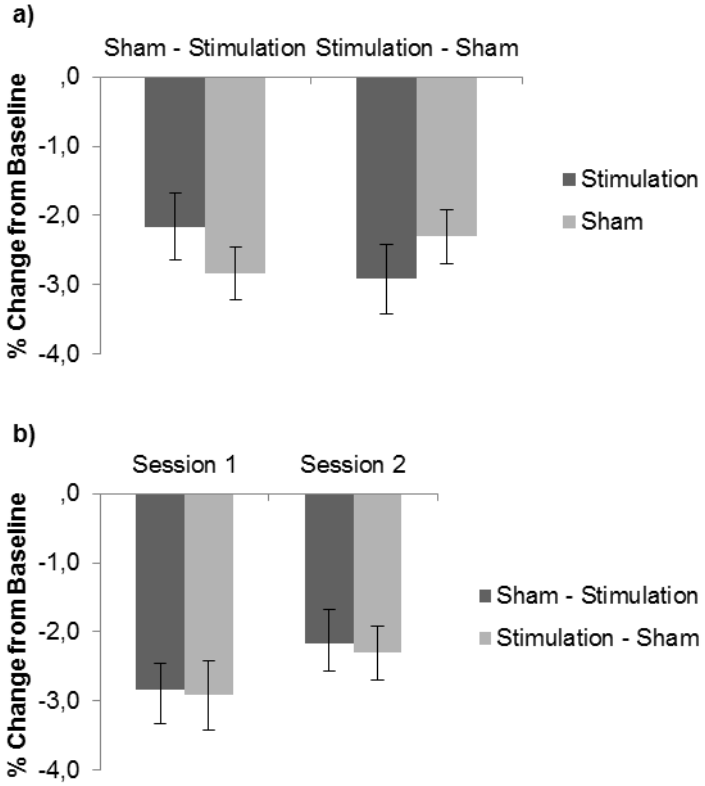

Figure 11. Percent change in pupil size from baseline during the inter-stimulus interval for each treatment order during stimulation and sham (a). The same data was plotted to illustrate that this was an effect of time, session 1 and session 2 (b). Bars indicate the standard error of the mean.

Correlations

We first looked at correlations between WMC and accuracy, RTs and pupil responses in all different task conditions during stimulation and sham. As predicted, WMC showed a significant positive correlation with accuracy in the BX condition, $r = .46$, $p = < .01$, and BY, $r = .38$, $p = .03$, only during sham. This indicates higher accuracy rates in these conditions, for high WMC-individuals. WMC is associated with utilizing a proactive strategy when this is

beneficial. Our predictions were therefore met as a proactive strategy is beneficial for the processing of the BX- and BY trials in the AX-CPT, which explains why the measure of WMC was associated with higher accuracy rates in specifically these two conditions. WMC did not correlate with accuracy on any other task condition. There were also no correlation between WMC and RTs in any of the different task conditions. For the pupil responses however, we found a positive correlation between WMC and AY pupil response after probe letter presentation during stimulation, $r = .39$, $p = .05$. Together these results support our predictions that WMC is associated with a proactive responses pattern. WMC only correlated with accuracy in the proactive conditions during sham, and not during stimulation. Finally, we looked at correlations between SEBR and we found no correlations with either accuracy, RTs or probe pupil responses.

Discussion

In our study we administered the AX-CPT to assess the dynamics between proactive- and reactive control. As predicted, our sample of young adults revealed a proactive response pattern in the AX-CPT. This was reflected by lower accuracy rates and slower responses in the AY-condition assumed to induce interference, compared to both B-cue trial conditions which allows for the preparation of the response in advance of probe letter presentation. Pupillary measures of condition-specific variability in effort supported these effects, showing increased pupil dilation after probe letter presentation for the AY-condition compared to both B-cued trial conditions.

We were also able to manipulate the assumed antagonistic relationship of proactive vs. reactive control by applying anodal tDCS over right DLPFC, the location in which goal- and context representations assumingly are being maintained during proactive control. We predicted a strengthening of proactive control, which in turn was predicted to be accompanied by reduced reactive control during stimulation compared to sham. This prediction was met as accuracy rates were decreased and RTs became slower in the AY-trials in combination with increased accuracy in both B-cue trial conditions, and RTs also became faster in the BY-condition. These effects were further supported by changes in pupillary measured of effort. Specifically, pupil dilation after probe letter presentation was increased in AY-trials, compared with decreased pupil dilation in the BY-condition. These results are also in line with developmental research, showing that a shift towards proactive control during childhood is accompanied by reduced reactive control. This shift is also associated with similar changes in pupil responses (Chatham et al., 2009; Lucenet & Blaye, 2014).

Both our behavioral and papillary restults in general supported the DMC-framework, and anodal tDCS over right DLPFC affected the dynamics between proactive and reactive control in the predicted direction of an antagonistic relationship. Our results also supported previous findings on pupillary activity during the delay between the cue and the probe (Chiew & Braver, 2013). Our sample showed larger pupil size in B-cue trials compared to A-cue trials during the inter-stimulus interval, possibly reflecting a proactive strategy. The effect can be explained by the increased need for preparatory control following B-cues (Chiew & Braver, 2013). Further this result was in line with fMRI studies showing increased activity in lateral PFC during this inter-stimulus interval when a proactive strategy is being utilized, specifically in B-cue trials (Paxton et al., 2008). On the other hand, B-cue trials were relatively rare (24%) compared to A-cue trials (76%), and another explanation of the

increased pupil size during B-cue trials might be a general effect of novelty (Chiew & Braver, 2013). Such an interpretation could be used in future investigation with the aim of clarifying this delay specific pupil activity pattern.

Finally, we found support for a positive relationship between WMC and proactive control. Specifically this was shown by a positive correlation between WMC and accuracy rates in the BX and BY trials during sham. With anodal tDCS affecting accuracy rates in these conditions, the correlation was no longer significant during stimulation. This result was consistent with our findings, as we would no longer predict a relationship between WMC and proactive control during stimulation. This is because tDCS seemed to affect proactive processes during these specific task conditions. In addition we found a positive relationship between WMC and probe pupil responses in the AY-condition during stimulation. This might be an indication that high WMC-individuals were to a greater degree affected by the stimulation, and would be an interesting question for future research on effects of tDCS on cognitive control mechanisms.

SEBR on the other hand did not correlate with any of the task measures. It would be beneficial to do a more controlled experiment for the purpose of investigating the relationship between SEBR and measures of the AX-CPT. Subjects were allowed to participate even though they were wearing contact lenses. This could possibly disrupt the measure of SEBR, as wearing contact lenses has been assumed to encourage high blink rates (Iacono, Moreau, Beiser, Fleming, & Lin, 1992). In some studies investigating SEBR they also have specifically asked participants not to consume alcohol or nicotine the day before the recording, as well as they have been told to sleep sufficiently (Colzato et al., 2009; Slagter, Davidson, & Tomer, 2010). We did not control for these factors. Future investigation of how SEBR might be associated with proactive vs. reactive control dynamics should therefore consider creating a more controlled environment than was done in the present study. Although some research has been using the eye-tracker for blink detection (Aarts et al., 2012), it has been argued that eye-trackers inaccurately detects blinks (Chen & Epps, 2013). Future investigation of SEBR might therefore consider using other methods of measuring SEBR.

Pupil responses in the BX-condition during stimulation did not reflect the predicted direction related to strengthened proactive control. Visual inspection of Figure 8 rather indicates that tDCS over right DLPFC had de opposite effect. Still, accuracy rates increased for this condition compared to the decrease in accuracy in the AY-condition during stimulation. We might therefore assume that the change in pupil response during stimulation

is the result of tDCS affecting some other cognitive processes. The X-probe is a target in approximately 70 percent of all trials. As mentioned, the LC is sensitive to task relevant events. One might argue that the X-probe is especially task relevant, as it also most frequently demands a "target" response. Supporting this interpretation Walz et al. (2014) found right-lateralized frontal activation post-stimulus as well as early in the trials in a simple visual oddball task. This task involved detection of a salient target. Also, neuronal recordings in monkeys show an early involvement of DLPFC in bottom-up visual attention during detection of a salient stimulus (Katsuki & Constantinidis, 2012). WE might therefore assume that tDCS over right DLPFC could have affected processing of salient- or target-stimuli as well.

It is possible to argue that the BX-condition involves an aspect of conflict, and that the X-probe has the role of a distractor within this specific task condition. The X-probe is associated with a "target" response, but demands a "non-target" response when following a B-cue. Some studies have found that tDCS over DLPFC also affects the conflict-monitoring structure ACC, and it's connectivity with PFC. In a recent study investigating neuronal activity in dorsal ACC in macaque monkeys, they found that dorsal ACC responded to salient, goal-irrelevant distractors (Ebitz & Platt, 2015). This response was reflected largely by increased firing rate. Research using brain imaging techniques such as fMRI has shown that prefrontal tDCS can affect task-related activity in ACC (Weber, Messing, Rao, Detre, & Thompson-Schill, 2014). As suggested by Nelson et al. (2014) the DLPFC and the ACC is strongly interconnected. As white matter tracts have greater conductivity it is therefore not unlikely that tDCS over DLPFC affects activity within the ACC. The ACC has also been suggested to be involved in target detection measured by vigilance tasks (Nelson et al., 2014).

We might therefore raise the question whether the increase in probe pupil size for the AY-condition during sham, is a consequence of strengthened proactive control or a change in conflict-monitoring processes within the ACC. Still, the changes in accuracy rates and RTs support our interpretation of strengthened proactive control, as stimulation of right DLPFC did not negatively affect performance in the BX-condition. Performance was only negatively affected by stimulation in the AY-condition.

Limitations and Future Directions

In the present study we did not include a condition of left hemisphere stimulation. D'Ardenne et al. (2012) found increased DLPFC activation during context processing, with greater activity in the right hemisphere. It would be of interest to investigate whether

specifically right hemisphere is critical for the balance between proactive and reactive control. Assuming this, we would not expect to see the same effect in a condition of left hemisphere stimulation. Still, future research should probably consider combining tDCS with brain imaging techniques such as fMRI and EEG to be able to make conclusions about the involvement of specific structures and hemispheres. Our aim was to investigate the dynamics between proactive- and reactive control in terms of cognitive effort, and whether we could manipulate the dynamics with tDCS. As we were able to do so, this opens up for further investigation of the dynamics and their neural underpinnings, as well as the neural basis of how tDCS specifically affects these.

In the present study we did not include a tDCS condition reversing the electrodes for a cathodal stimulation of right DLPFC. It has been assumed that this type of positioning might lead to an opposite effect compared to anodal stimulation. This has been called anodal-excitation and cathodal-inhibition effects (Jacobson, Koslowsky, et al., 2012). One might argue that including a condition like this could lead to the opposite effect. At the same time the dual-polarity effect has most often been found in studies targeting motor-areas. In studies targeting non-motor areas, relevant cognitive or perceptual task measures will indicate that the anode has an excitatory effect. The cathode on the other hand will rarely cause inhibition when targeting such complex cognitive functions (Jacobson, Koslowsky, et al., 2012).

In a recent review it has been argued that applying tDCS over PFC probably modulates many different cognitive functions simultaneously (Tremblay et al., 2014). With relevance to our findings, we discussed how our results might reflect changes in target detection or conflict-monitoring processes. Tremblay et al. (2014) argue that a clear *a priori* hypothesis is necessary to be able to interpret results from stimulating prefrontal areas. Also they mention the possibility that behavioural effects might also be related to parallel modulation of related cognitive function. This should be taken into consideration when interpreting effects of tDCS.

Although we may not be able to make conclusions about how tDCS might have affected right DLPFC and surrounding structures, we can most likely be certain that anodal tDCS over right DLPFC have affected the dynamics between proactive- and reactive control. As we did included measures of arousal, and analyzed these in relation to tDCS, we were able to rule out the possibility of tDCS just having affected arousal in general. It is therefore likely that the effects we found were of a cognitive nature.

As discussed, tDCS over PFC probably affects surrounding structures such as the ACC, further limiting our conclusions regarding the role of DLPFC within the DMC framework.

We used a conventional tDCS electrode configuration, which has been shown to affect cortical areas far from the electrode positions (Dayan et al., 2013). How the current flows between the electrodes will be affected by anatomical details. The scalp, skull, muscles, cerebrospinal fluid and brain tissue all have different conductivities. Also the placement of the referent electrode, seems to affect the path of the current through the brain (Bikson, Datta, Rahman, & Scaturro, 2010). An alternative to the conventional electrode montage has been investigated, referred to as high-definition (HD) 4x1 ring tDCS. In this montage a central active electrode is surrounded by four return electrodes (Kuo et al., 2013). It is argued that this montage makes it possible to avoid a spread of the current, making focal tDCS possible. It is further suggested to use HD-tDCS for cortically targeted neuromodulation (Edwards et al., 2013). Improving focality of tDCS may enable the use of tDCS for understanding larger scale functional architecture, as well as for understanding network dynamics (Dayan et al., 2013). Combining improved methods of tDCS with brain imaging techniques such as fMRI and EEG would further enable insight into the spatial and temporal underpinnings of the dynamics between proactive- and reactive control. Our results might therefore encourage future research on the dynamics between these two core mechanisms.

Understanding these dynamics, may be important for the development of interventions aiming to improve cognitive control in groups known to have reductions in these abilities. As mentioned, a change from a reactive to a proactive strategy seems to be present during childhood (Chatham et al., 2009), while during the transition into older age this pattern reverse from a proactive response style toward reliance on a reactive response strategy (Paxton et al., 2008). One might argue that future research on the dynamics between proactive and reactive control is important for the understanding of life-span changes in cognitive control. Knowing that transition into older age is accompanied reduced proactive control, interventions aiming at strengthening proactive control could be beneficial. It has been shown that calling attention toward the importance of the contextual cue information within the AX-CPT improves performance on BX-trials in older adults after progressive training and practice. In line with the assumed relationship between the two control modes, reactive control is reduced, reflected by a worsening of AY trial-performance (Paxton, Barch, Storandt, & Braver, 2006). Findings like these encourage development of interventions aiming to improve cognitive control. Further, as we found similar of tDCS, future development of such interventions should possibly consider combining tDCS with such training. This might even lead to faster improvement of proactive control.

Conclusion

In conclusion, our results support the DMC-framework. We found support for this account as participants on average showed a strong proactive strategy, reflected by reduced reactive control. This was expected as our sample consisted of young adults, normally showing a proactive response pattern. We aimed at strengthening proactive control by applying anodal tDCS over right DLPFC, and our results supported and antagonistic relationship between proactive and reactive control as strengthening of proactive control was accompanied by a reduction in reactive control. This was revealed for accuracy rates, RTs, and for pupil data reflecting cognitive effort.

Our findings may be important for future research on populations who are known to show reduced ability of proactive control. As interventions aiming at enhancing proactive control are being developed, it is useful to have in mind that a shift towards proactive control can at the same time reduce control engagement in situations that is typically driven by reactive control (Braver, 2012).

Also, future research on effects of tDCS on proactive –and reactive control mechanisms, should consider high definition-tDCS for greater local precision of stimulation. It will also be important to investigate how tDCS affects these neural mechanisms on a neurobiological level. Combining tDCS with brain imaging methods such as EEG or fMRI might therefore be a useful approach.

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