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Transcranial direct current stimulation improves executive dysfunctions in attention deficit hyperactivity disorder (ADHD): Implications for inhibitory control, interference control, working memory and cognitive flexibility

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Abstract

Objective

This study examined effects of transcranial direct current stimulation (tDCS) over the DLPFC and OFC on major executive functions (EFs) including response inhibition, executive control, working memory, and cognitive flexibility/task switching in ADHD.

Methods

ADHD children received (a) left anodal / right cathodal DLPFC tDCS and (b) sham stimulation in experiment one and (a) left anodal DLPFC / right cathodal OFC tDCS (b) left cathodal DLPFC / right anodal OFC tDCS and (c) sham stimulation in experiment two. The current intensity was 1 mA for 15 min with a 72-hr interval between sessions. Subjects underwent Go/No-Go task, N-back test, WCST and Stroop task after tDCS.

Results

anodal DLPFC tDCS most clearly affected executive control functions (e.g., WM, interference inhibition), while cathodal DLPFC tDCS improved inhibitory control. Cognitive flexibility/task switching benefited from combined DLPFC-OFC, but not DLPFC stimulation alone.

Conclusion

Task specific stimulation protocols can improve EFs in ADHD.

Keywords: transcranial direct current stimulation (tDCS), ADHD, executive control, inhibitory control, working memory, cognitive flexibility, DLPFC, OFC

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most pervasive neurodevelopmental disorders of childhood (Nezhad, Khodapanahi, Yekta, Mahmoodikahriz, & Ostadghafour, 2011; Wilmshurst, 2014) with behavioral symptoms of hyperactivity, inattention, or both (Asherson, 2012). ADHD is characterized by a variety of deficits in cognitive domains such as attention (Barkley, 1997), inhibitory control (Rubia, Smith, Brammer, Toone, & Taylor, 2014) working memory (WM) (Kasper, Alderson, & Hudec, 2012) and executive functions (EF) (Hudec et al., 2015). Cognitive deficits in ADHD include impaired inhibitory, attentional and motivational control and timing (Smith, Taylor, Brammer, Toone, & Rubia, 2006) suggesting that ADHD is a disorder of control functions. Impaired EF are among the most pervasive deficits in ADHD, such that ADHD was labelled as an executive dysfunction disorder, whose symptoms are based on a primary deficit in EF (Barkley, 1997; Castellanos & Tannock, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

Executive functioning or executive control, encompasses high-level cognitive functions that are essential for goal-directed behavior. Failure of executive control underlies many psychiatric and neurological disorders and has been specifically shown in developmental psychopathologies, especially in ADHD (Pennington & Ozonoff, 1996). Several EF domains underlie symptoms of ADHD. A meta-analysis study about the EF concept of ADHD (Willcutt et al., 2005) reported response inhibition and WM as the most consistently impaired domains in ADHD. Similarly, other studies proposed impaired inhibitory processes as the core deficit in ADHD that disrupts other EF domains (Barkley, 1997; Nigg, 2001). However, the differences between executive dysfunctions in ADHD should be considered in order to have a more realistic picture of ADHD. For example, there are different types of behavioral inhibition (e.g., interference

inhibition, prepotent inhibition) captured by different tasks on which ADHD children may perform differently. Therefore, ADHD executive deficits should be interpreted carefully.

Despite explicit heterogeneity in neuropsychological formulation of ADHD (Fair, Bathula, Nikolas, & Nigg, 2012), two major models have been proposed to account for behavioral deficits in ADHD: one is the “cognitive dysfunction or inhibition-based model” suggesting that inhibition-based executive deficits are core deficit in ADHD (Cepeda, Cepeda, & Kramer, 2000; Sonuga-Barke, 2005). According to this model, faulty inhibitory processes, especially those controlling motor responses (Nigg, 2001), lead to failure of executive control which in turn results in impulsive behavior (Patros et al., 2015) and hyperactivity. The alternative “motivational dysfunction model” emphasizes on impaired reward processing rather than cognitive deficits, suggesting that behavioral deficits in ADHD are result of deficient resource allocation or reduced arousal (Cepeda et al., 2000; Sonuga-Barke, 2005). These models are aligned with the “prefrontal hypothesis of ADHD” (Seidman, Valera, & Makris, 2005) according to which abnormalities in the frontostriatal circuitry and prefrontal cortex (PFC) are associated with behavioral deficits in ADHD. The dorsolateral PFC (DLPFC) is the primary region involved in inhibition-based models whereas the orbitofrontal cortex (OFC) is more closely implicated in motivational dysfunction models (Seidman et al., 2005; Sonuga-Barke, 2005). These models also implicate that executive dysfunctions in ADHD involves both, “hot” and “cool” EFs. Dividing EFs into cool and hot is an organizing principle of EFs in order to distinguish between the control of purely cognitive (i.e. “cold”) stimuli versus affective or reward-related stimuli (i.e. “hot”) (Ward, 2015). The former is thought to be closely associated with DLPFC functions, whereas the latter is assumed to be closely related, but not limited to OFC activity (Rubia, 2011).

It is however, of note that these models may downplay neuropsychological heterogeneity which is more common in atypically developing children like ADHD (Fair et al., 2012). Recent theoretical papers suggest that there is substantial overlap between ADHD and typically developing children in several neuropsychological measures central to ADHD and only a small minority of ADHD children could be considered clinically “affected” on the basis of any one measure (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Specifically, it is suggested that only a subgroup of ADHD children may have executive deficits implicating that more consideration should be given to the probability that only a subset of behaviorally defined children will have a deficit in a given neurocognitive mechanism which can contribute to the disorder (Nigg et al., 2005). Therefore, although the models proposed here help in classification of ADHD subtypes, they may apply to only a subset of children with ADHD.

Functional and structural abnormalities in the PFC are well-documented in ADHD and other disorders accompanied by EF impairments such as major depression (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009), obsessive-compulsive disorder (OCD) (Gonçalves et al., 2011) and schizophrenia (Callicott et al., 2000). Structural imaging studies found smaller prefrontal volumes in ADHD either in the right or left hemisphere (Bush, Valera, & Seidman, 2005) and dysfunction of DLPFC, ventrolateral PFC (VLPFC) and OFC are often reported in ADHD studies (Seidman et al., 2005). These PFC regions are associated with core cognitive deficits of ADHD; DLPFC and VLPFC are involved in vigilance, selective and divided attention, attention shifting, planning, executive control, and working memory (Duncan & Owen, 2000; Elliott, 2003) and the OFC is associated with social disinhibition and impulsivity (Rolls, 2004). Functional imaging studies also revealed abnormalities of frontal regions in children with severe ADHD, including right hypofrontality during response inhibition tasks (Langleben et al., 2001). However, other

studies have reported mixed results and showed hyperfrontality in ADHD during response inhibition (Schulz et al., 2004).

More specifically, neuroimaging studies suggest that decreased activity in the right lateral prefrontal cortex (rLPFC) and right inferior frontal gyrus (rIFG) (Depue, Burgess, Willcutt, Ruzic, & Banich, 2010; Soltaninejad, Nejati, & Ekhtiari, 2015b; Verbruggen, Aron, Stevens, & Chambers, 2010) are responsible for poor inhibitory control. Other studies link poor inhibitory control in ADHD to reduced activation in the pre-supplementary motor area (Pre-SMA) (Hsu et al., 2011) and increased activity in the frontal eye field (FEF) (Juan & Muggleton, 2012). For deficient WM and attentional control functions, left DLPFC (lDLPFC) hypoactivity seems to be involved (Brunoni & Vanderhasselt, 2014; Salehinejad, Ghanavai, Rostami, & Nejati, 2017). In sum, decreased activity in the rLPFC is suggested to be responsible for impaired inhibitory control which is aligned with overall right hypofrontality in ADHD (Langleben et al., 2001) and decreased activity in the lDLPFC seems to be relevant for impaired WM and executive control.

Recent studies highlight the relevance of noninvasive brain stimulation for modulating cortical excitability (Lefaucheur, 2016). Transcranial direct current stimulation (tDCS) is a brain stimulation technique by which a weak direct current applied on the scalp modulates cortical excitability by shifting resting neuronal membrane potential. Anodal stimulation increases cortical excitability while cathodal stimulation decreases it at the macroscopic level (Nitsche et al., 2009). tDCS has been shown to improve impaired components of EF not only in ADHD (Soltaninejad, Nejati, & Ekhtiari, 2015a) but also in other disorders accompanied by impaired EF such as depression (Salehinejad et al., 2017) and OCD (Brem, Grünblatt, Drechsler, Riederer, & Walitza, 2014) as well as in healthy populations (Salehinejad, Nejati, & Derakhshan, 2016) depending on the targeted cortical area. Feasibility and safety of tDCS application in children has been

documented in previous studies (Andrade et al., 2013; Krishnan, Santos, Peterson, & Ehinger, 2015).

Recent brain stimulation studies in ADHD tried to modulate cortical excitability of regions supposed to be relevant especially for inhibitory control. Hsu et al (2011) showed that anodal tDCS over the pre-supplementary motor area (Pre-SMA) improved inhibitory control, while cathodal tDCS impaired it. In a recently published study, we found that cathodal tDCS over the IDLPFC improved inhibitory control in prepotent response inhibition explored by a Go/No-Go task, while anodal tDCS over the same area impaired it (Soltaninejad et al., 2015a). This was the first tDCS study targeting the IDLPFC for improving inhibitory control. The foundation for this effect might be an indirect increase of cortical activity in the rDLPFC, which is suggested to enhance inhibitory control (Depue et al., 2010), by cathodal tDCS over the IDLPFC due to transcallosal connections (Kobayashi & Pascual-Leone, 2003; Lindenberg, Nachtigall, Meinzer, Sieg, & Flöel, 2013).

While most of the available brain stimulation studies have focused on inhibitory processes in ADHD, there is lack of evidence about the effectiveness of brain stimulation with regard to other impaired EF domains in ADHD. Moreover, previous studies have shown mixed results regarding either hypofrontality or hyperfrontality in ADHD (Langleben et al., 2001; Schulz et al., 2004), and the way different PFC regions contribute to different EF domains in ADHD is still incompletely understood. Therefore, this study aims to investigate effects of tDCS of the DLPFC and OFC, which are the most involved PFC regions in ADHD deficits, on some of the significantly impaired executive functioning domains such as response inhibition (measured by the Go/No-Go task), interference control (Measured by the Stroop task), WM (measured by the N-back test) and task switching/cognitive flexibility (measured by the Wisconsin Card Sorting Test) in two

experiments. In experiment one we only targeted the DLPFC using anodal/sham tDCS. In experiment two, we also targeted the OFC using anodal/cathodal/sham tDCS.

Based on findings of previous tDCS studies discussed above we have three hypotheses. First, we hypothesized that anodal IDLPFC tDCS would improve WM, measured by the N-back test, and interference inhibition, measured by the Stroop task in ADHD (hypothesis 1). This was based on the large body of evidence that hypoactivity of the IDLPFC is involved in impaired WM and executive dysfunction in disorders marked with frontal abnormalities. Secondly we expected to observe improved prepotent response inhibition via cathodal stimulation of the IDLPFC (supposed to increase activity in the rLPFC) but not after anodal tDCS over the IDLPFC or cathodal tDCS over the rDLPFC, as these stimulation protocols are supposed to decrease activity in the rLPFC (hypothesis 2). This was based on the finding suggesting that decreased activity of the rLPFC is responsible for poor inhibitory control in ADHD (Soltaninejad, Nejati, & Ekhtiari, 2015a). Finally, with regard to cognitive flexibility / task switching, which is measured by the Wisconsin Card Sorting Test (WCST), we expect to observe improved WCST performance after simulation montages involving both, DLPFC and OFC (hypothesis 3). Although the WCST depends on DLPFC activity, performance on it is dependent on feedback and motivational processing that are related to medial regions of the PFC. (Summerfelt, Alphas, Funderburk, Strauss, & Wagman, 1991; Zanolie, Van Leijenhorst, Rombouts, & Crone, 2008). Indeed, the WCST measures some aspects of both hot (e.g., task switching, disinhibition) and cold EFs (i.e., executive control) implicating that it would benefit from activation of both DLPFC and OFC (Cepeda et al., 2000; Rolls, 2004).

2. Methods

2.1. Subjects

We enrolled twenty-five children (age $M_1 = 10$, $SD_1 = 2.23$; $M_2 = 9$, $SD_2 = 1.8$) diagnosed with ADHD symptoms according to the DSM-5 diagnostic criteria examined by a professional child psychiatrist. We monitored clinical symptoms via the SWAN Rating Scale (Swanson et al., 2006), and results of this questionnaire confirmed symptoms of ADHD in childhood in the children. Participants who scored 1.67 or higher were selected as subjects with ADHD symptoms according to the SNAP-IV parent version questionnaire (Swanson, Nolan, & Pelham, 1992). The cut-off point for inattentive and hyperactivity/impulsivity subscales were 1.78 and 1.44 respectively. In order to ensure the absence of other psychiatric diseases the Symptom Checklist 25 (SCL-25) questionnaire was completed by all participants. Demographic information is shown in Table 1. Inclusion criteria were: 1) not being on ADHD medication (e.g., methylphenidate) during the experiment 2) being free from present or past history of neurological or psychiatric disorders, epilepsy, seizures, and head injury or loss of consciousness 3) moderate to severe ADHD scores on the Swanson rating scale. Both experiments were separate and none of the subjects from the experiment one participated in experiment two. The study was performed according to the latest version of the Declaration of Helsinki ethical standards and approved by the local Institutional Review Board and the Ethical Committee of the local University. Given that participants were under legal age, their parents were instructed about experimental procedures. They then gave their informed consent before participation. Participants were free to withdraw from the experiment at any stage.

2.2. Experimental Protocol

We conducted a randomized, double-blinded sham-controlled trial. The design was a cross-over study in which subjects were randomly assigned to a sequence of tDCS treatment. Participants were randomly assigned to each stimulation condition. In experiment one ($N = 15$) participants

received anodal and sham tDCS and in experiment two ($N = 10$) they received anodal, cathodal and sham tDCS. EF domains (inhibitory control/WM/task switching/cognitive flexibility) were assessed right after each stimulation condition in the same session. The order of stimulation conditions and EF tasks were randomized and counterbalanced across participants in both experiments in order to control for “order effects”. Both experimenters and data collectors were blind to the study hypothesis.

2.3. Procedure

Given that participants were children, we intensified standards and safety aspects of tDCS application in term od electrode size and current intensity based on previous studies on children (Minhas, Bikson, Woods, Rosen, & Kessler, 2012). The tDCS device in use was “ActivaDose II Iontophoresis” Delivery Unit manufactured by Activa Tek, battery-driven with a 9-volt battery as its source. Electrical direct current generated by the stimulator was applied through a pair of saline-soaked sponge electrodes with size of 25 cm² (5 × 5) for 15 min. Given that subject are children with smaller head circumference, this electrode size was selected. The current was constant and of 1 mA in intensity, with a 30 s ramp up and down. Participants in experiment one and two received anodal/sham and anodal/cathodal/sahm tDCS respectively for 15 minutes at 1 mA intensity with a 72-hr washout period between sessions. The stimulation montages of experiment one were: (a) anodal tDCS over the F3 (IDL PFC) and cathodal tDCS over the F4 (rDLPFC) according to the international EEG 10/20 system; and (b) sham stimulation of the same regions. In experiment two we had three stimulation modalities: (a) anodal electrode applied over the F3 and cathodal electrode placed over the Fp2 (OFC) at a minimal distance of 6 cm from the anodal electrode to decrease the probability of shunting of current through the scalp (Nitsche et al., 2007); (b) cathodal electrode over F3 and anodal electrode over Fp2; (c) and a sham condition which served as control.

During sham condition, electrical current was ramped up for 30 seconds to generate the same sensation as active condition for the participant in the sham group and then turned off without the participants' knowledge (Palm et al., 2013). This method of sham stimulation has been shown to be reliable (Gandiga, Hummel, & Cohen, 2006). All patients were blind to the type of tDCS delivered in each session. A side-effect survey was done after tDCS sessions (See Figure 1).

2.4. Cognitive Assessment

In this study we measured response inhibition, interference control, WM and cognitive flexibility / task switching with the Go/No-Go, Stroop, N-back and WCST respectively. We need however, to note to some similarities and differences between the tasks. While the Go/No-Go and Stroop task rely on a global inhibitory mechanism (Verbruggen, Liefoghe, Notebaert, & Vandierendonck, 2005), each may capture different aspect of response inhibition. For example, some evidence suggest that both tasks measure prepotent response inhibition (Khng & Lee, 2014), it's been shown that the two tasks may index different constructs such as the response inhibition and interference control with unique neural contributions (Dimoska-Di Marco et al., 2011). On the other hand, there other task that capture response inhibition (e.g., Stop Signal Task) and interference control (e.g., Flanker task) differently. It is essential therefore to consider such minor differences in different aspects of each cognitive construct and their respective tasks when interpreting results.

Go/No-Go task: To measure inhibitory control, we used the Go/No-Go task which is a less difficult measure of response inhibition compared to the Stop Signal Task (SST). Participants are presented with stimuli in a continuous stream. They need to make a binary decision on each stimulus by pressing a button (Go) for a specific stimulus and not pressing the same button (No-Go) for a different stimulus. In this study, participants were presented with a plane which appeared on the

screen in four directions, up, down, left, and right. They were instructed to press the button aligned with the plane (the Go condition), but to withhold pressing any button when the sound “Beep” was heard (the No-Go condition). Participants were then asked to focus on a cross on the screen and to press the response button “as quickly and accurately as possible” for all Go stimuli. This task consisted of 50 stimuli that required response execution on 75% of trials, and the inhibition of a response on the remaining 25%. The planes (7×7 cm) were static and black and were presented on a white screen. The task was counterbalanced across runs and subjects. The dependent variables were accuracy for the Go and No-Go categories and reaction time (RT) of Go stimuli. The correct response to No-Go stimuli examines prepotent response inhibition as an index of inhibitory control. This task takes about 7 minutes to complete. Details about duration of stimuli, fixation time and latency of beep are displayed on Figure 2.

It is noteworthy that the Go/No-Go task procedure used in this study resembles the Stop Signal Task (SST) paradigm (Logan, 1994). Indeed, the Go/No-Go task is specially similar to the Stop Signal Reaction Time (SSRT) in that both investigate the ability to inhibit a response (Georgiou & Essau, 2011) but the SST is actually a more difficult variation of the Go/No-Go paradigm. In standard Go/No-Go paradigm participants are presented with certain stimuli that re asked to respond and certain stimuli that are asked not to respond to. In contrast, the SST requires participants to respond to stimuli, but on some trials, they will get a "stop" signal meaning that they need to stop the response they might already have initiated (Morein-Zamir & Sahakian, 2010). In other words, in the Go/No-Go paradigm stimuli are consistently associated with going and stopping, than in the stop-signal paradigm, where stimuli are inconsistently associated with going and stopping (Verbruggen & Logan, 2008) which is why response inhibition is more difficult in the Stop-signal than Go/No-Go task (Johnstone et al., 2007).

Stroop Task: While the Go/No-Go task (specifically the No-Go stimuli) is a measure of prepotent response inhibition, the Stroop task is rather a measure of interference control with unique neural contributions of both tasks specially in ADHD (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011). This is relevant, since different PFC regions are supposed to be involved in interference versus prepotent response inhibition (Vendrell et al., 1995; Wager et al., 2005). The task requires participants to view color names presented in various ink colors (e.g., red, blue, yellow, green) and name the color of the ink. Participants were given four buttons marked with four colors and were instructed to select a color when presented with the word as fast as possible. During the neutral trials the word was written in black ink (e.g., “red” in black ink) and participant should press the button with the corresponding colour; during the congruent trial, the word matched the ink color (e.g., “blue” in blue ink) and in the incongruent trials, the word conflicted with the ink color (e.g., “red” in yellow ink) and participants should response to the color of the ink and inhibit the word. There were 25 stimuli for each stage with size of 7 (length) \times 5 (width) cm and the next stimulus was presented after participants’ response. Interference inhibition is measured by the proportion of false answer and reaction time of third stage that shows interfering stimuli. Details about duration of stimuli presentation are displayed on Figure 2.

N-Back Test: In order to probe WM performance we used the visual “N-back” task which is a widely used test of WM performance (Brewin & Smart, 2005) and is sensitive to the underlying neural basis of WM in the PFC (Owen, McMillan, Laird, & Bullmore, 2005). During the N-back task participants are presented with a stimulus (letter or picture) one at a time on a screen. Subjects are asked to identify the picture that repeats relative to the one presented n items before its onset. In our study, the target was any picture that was identical to the one it preceded one trial back, which is called “1-back” task. Each participant completed three runs of the task, each run consisted

of 30 stimuli, lasting around 6 minutes in total. The stimuli were consisted of 10 different images which means that each image was randomly repeated 3 times in each run (Figure 2). Participants were instructed to answer only if the 1-back picture was the same. The task was counterbalanced across runs and subjects. We used mean reaction time (RT) of correct responses and the number of correct responses on the 1-back task as measures of WM performance. Stimuli presentation in all three computerized tasks (i.e., Go/No-Go, Stroop, N-back) were controlled by a laptop with a 15.6" screen (Schneider, Eschman, & Zuccolotto, 2002), at the viewing distance from the monitor of approximately 50 cm.

Wisconsin Card Sorting Test (WCST): The WCST is regarded as the gold standard of EF (Ozonoff, Goodlin-Jones, & Solomon, 2005) which is sensitive to frontal abnormalities (Romine et al., 2004). It is primarily used to measure cognitive flexibility, planning and set maintenance (Kaland, Smith, & Mortensen, 2008) as well as task-switching abilities (Cepeda et al., 2000). PFC dysfunctions are associated with impaired WCST performance (Merriam, Thase, Haas, Keshavan, & Sweeney, 1999). WCST performance also depends on impulsive responding (Sweitzer, Allen, & Kaut, 2008) and some studies used the WCST as measure of impulsivity (Leshem & Glicksohn, 2007), implying that other PFC regions than the DLPFC may be involved. Motivational deficits have been suggested as one possible reason of poor performance on the WCST in population with frontal abnormalities. Previous studies showed that individuals with ADHD consistently exhibit poorer performance in WCST compared to healthy controls (Romine et al., 2004). In this study we used the WCST to measure cognitive flexibility and task-switching ability which are functions of executive control. The WCST requires participants to identify the sort criterion of a set of cards based upon "correct" versus "incorrect" feedback given by the examiner. After correctly matching a card according to a stimulus feature (color, form, or number) for 10 consecutive trials, the

matching feature changes. Four WCST variables, namely number of categories, perseverative errors RT and total errors were used to measure participant's performances. We used the short version of WCST with 64 cards which lasts about 7 minutes.

2.5. Statistical Analysis

We used PASW Statistics 24 for data analysis. In order to examine effect of tDCS on EFs, we used repeated measures analysis of variance (ANOVA) with stimulation condition (anodal/cathodal in experiment one and anodal/cathodal/sham in experiment two) as within subject factors. Our data met the ANOVA linear assumptions and the Leven's test was used to examine homogeneity of variances. Mauchly's test was used to evaluate the sphericity of the data before performing the repeated measures ANOVA for each dependent variable. In case that the assumption of sphericity was violated, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. A significance level of $p < .05$ was used for all statistical comparisons and Fisher's least significant difference (LSD) post hoc test was used for post hoc analysis.

3. Results

All subjects tolerated tDCS well and no adverse effects were reported except for mild itching or tingling under electrodes which are normally experienced. Descriptive statistics including mean and standard deviation of participants scores on dependent variables are shown in Table 2.

We applied repeated measures ANOVA in experiment one to examine effects of the tDCS conditions (anodal/sham) on participants' performance on the Go-No/Go, WCST, N-back and

Stroop tasks. Results showed no significant differences between tDCS conditions in the Go-No/Go measures of accuracy Go ($F = 0.19, p = 0.66$), accuracy No-Go ($F = 1.02, p = 0.32$) and reaction time ($F = 2.42, p = 0.14$). These results suggest that anodal IDLPFC / cathodal rDLPFC tDCS did not improve inhibitory control in ADHD which is in accordance with our second hypothesis. ANOVA results also showed no significant effect of anodal IDLPFC / cathodal rDLPFC tDCS on cognitive flexibility and task-switching measured by the WCST regarding perseverative errors, completed categories and total errors. For WM performance, the ANOVA results showed that anodal IDLPFC / cathodal rDLPFC tDCS did not significantly increase the number of accurate responses ($F = 0.21, p = 0.65$). However, RT was significantly reduced after anodal IDLPFC / cathodal rDLPFC tDCS compared to sham situation ($F = 21.01, p < 0.01$). Finally, the respective ANOVA showed a significant improving effect of anodal IDLPFC / cathodal rDLPFC tDCS on interference response inhibition measured by the Stroop task in terms of accuracy ($F = 9.01, p < 0.01$) and RT ($F = 7.7, p < 0.02$). In sum, the results of experiment one indicated a significant effect of anodal IDLPFC / cathodal rDLPFC tDCS on performance of the Stroop task and N-back speed but not the WCST and Go-No/Go tasks. Results of experiment one are shown in Table 3.

Results of experiment two revealed improving effect of tDCS (anodal/cathodal/sham) of the DLPFC and OFC on most of the EFs. With regard to inhibitory control, the respective repeated measures ANOVA showed significant differences between stimulation conditions for No-Go accuracy, which is a measure of prepotent response inhibition ($F = 4.48, p < 0.03$). Fisher's least significant difference (LSD) post hoc test showed that cathodal IDLPFC / anodal rOFC tDCS (montage 2) resulted in a significant increase of No-Go accuracy compared to sham stimulation ($p < 0.01$; $M_{\text{montage2}} = 24.2$ vs. $M_{\text{sham}} = 20.7$), suggesting that this electrode arrangement improves prepotent response inhibition in ADHD (Table 4).

Additionally, we observed a significant effect of stimulation on WCST performance. Particularly, results showed that in contrast to experiment one, anodal IDLPFC / cathodal rOFC tDCS (montage 1), cathodal IDLPFC / anodal rOFC tDCS (montage 2) and sham stimulation significantly differed regarding perseverative errors ($F = 10.70, p < 0.01$) and completed categories ($F = 15.67, p < 0.01$). The respective post hoc analyses further showed that montage one (anodal IDLPFC / cathodal rOFC tDCS) ($p < 0.01; M_{\text{montage1}} = 7.8$ vs. $M_{\text{sham}} = 14.8$) and montage two (cathodal IDLPFC / anodal rOFC tDCS) ($p < 0.04; M_{\text{montage2}} = 11.8$ vs. $M_{\text{sham}} = 14.8$) significantly reduced perseverative errors in ADHD children compared to sham stimulation although the first montage was significantly more effective compared to second one ($p < 0.01; M_{\text{montage1}} = 7.8$ vs. $M_{\text{montage2}} = 11.8$). The same pattern of results was observed for completed categories and total errors, and the respective post hoc analysis showed that montage one ($p < 0.01; M_{\text{montage1}} = 5.1$ vs. $M_{\text{sham}} = 3.9$) and montage two ($p < 0.01; M_{\text{montage2}} = 4.5$ vs. $M_{\text{sham}} = 3.9$) significantly increased categories completed by ADHD children compared to sham stimulation. Again the first montage was significantly more effective compared to second one ($p < 0.01; M_{\text{montage1}} = 5.1$ vs. $M_{\text{montage2}} = 4.5$). These results suggest that increasing activity of the IDLPFC and reduction of right OFC activity is more effective in improving cognitive flexibility, attentional shifting and task switching compared to sham situation as well as the reversed montage.

Finally, the respective repeated measures ANOVAs showed a significant difference between stimulation conditions regarding WM performance in terms of both accuracy ($F = 9.84, p < 0.01$) and RT ($F = 5.89, p < 0.01$). The post hoc tests showed that only montage one (anodal IDLPFC / cathodal rOFC tDCS) resulted in a significant increase in accuracy and RT compared to sham stimulation ($p < 0.04; M_{\text{montage1}} = 21$ vs. $M_{\text{sham}} = 17.9; p < 0.01; M_{\text{montage1}} = 103.39$ vs. $M_{\text{sham}} = 162.88$). Interestingly, montage one (anodal IDLPFC / cathodal rOFC tDCS) was significantly

superior in increasing accuracy compared to montage two (anodal rOFC / cathodal IDLPFC tDCS) ($p < 0.03$; $M_{\text{montage1}} = 21$ vs. $M_{\text{montage2}} = 19.4$)

4. Discussion

The present study investigated effects of modulating cortical activity of PFC regions, namely the DLPFC and OFC, on improving executive functioning in ADHD using electrical brain stimulation. According to the prefrontal hypothesis of ADHD (Seidman et al., 2005), behavioral deficits in this disorder are related to abnormal DLPFC (inhibition-based model) and OFC functioning (motivational dysfunction model) (Sonuga-Barke, 2005). Despite promising results of tDCS studies in disorders with frontal abnormalities, its application in ADHD has only recently been documented. These studies mostly investigated effects of tDCS on inhibitory process (Bandeira et al., 2016; Hsu et al., 2011; Soltaninejad et al., 2015a). To our knowledge this is the first tDCS study to investigate role of the DLPFC and OFC in a broader range of impaired EF domains of ADHD including inhibitory control, WM, executive control and cognitive flexibility/task switching.

Regarding inhibitory control, results of the first experiment showed that left anodal / right cathodal DLPFC tDCS does not improve response inhibition in the Go-No/Go task. This tDCS montage should lead to decreased activity of rDLPFC as a result of cathodal rDLPFC tDCS as well as anodal IDLPFC tDCS, the latter likely reducing activity of the contralateral region through inhibitory transcallosal connections (Mishra, Nizamie, Das, & Praharaj, 2010). Reduced response inhibition in ADHD is explained by unsuccessful disengagement in the Go/No-go task, which is necessary for successful performance. For this disengagement, rLPFC activity is crucial, and thus reduction of activity of this area, which was the case in experiment one, should not improve

performance. Our second experiment showed that cathodal IDLPFC / anodal rOFC tDCS significantly improved accuracy of No-Go responses, likely by indirectly activating the rDLPFC via reduction of transcallosal inhibition. Moreover, due to smaller head circumference in children, this might also have affected the rDLPFC which is close to the rOFC. These findings support the second hypothesis of the study that cathodal IDLPFC tDCS would improve prepotent response inhibition and are in accordance with findings of previous studies showing that decreased activity in the rLPFC is responsible for poor inhibitory control (Aron & Poldrack, 2005; Depue et al., 2010). Our results also replicate findings of a recently conducted tDCS study, in which cathodal stimulation of the IDLPFC significantly improved accuracy of No-Go responses (Soltaninejad et al., 2015a). In further accordance with these results, cathodal tDCS over the IDLPFC improved ADHD symptoms in adult ADHD patients (Cachoeira et al., 2017).

In addition to response inhibition, we investigated interference control measured by the Stroop task. We found that left anodal / right cathodal DLPFC tDCS improved both accuracy and RT in the Stroop task. This finding is in accordance with recent brain imaging studies showing activation of both, left and right, but relatively larger activation of the left DLPFC during Stroop task performance (Hyodo et al., 2016; Jiang, Bailey, Xiang, Zhang, & Zhang, 2016). In further accordance, high frequency rTMS over the IDLPFC has beneficial effects on both congruent and incongruent trials during Stroop task performance compared to sham stimulation (Vanderhasselt, De Raedt, Baeken, Leyman, & D'haenen, 2006). We suggest that increasing activity of the IDLPFC by anodal tDCS leads to enhanced cognitive control over relevant stimuli (naming the color but not the word) by maintaining them in WM. The observation that performance of the Go-No/Go and Stroop tasks are differently altered by DLPFC activation implicates that the activation of these regions is task-specific (Pope, Brenton, & Miall, 2015). Moreover, it also suggests that

the relevance of the interhemispheric balance for task performance is also task- or domain-specific, since an impact of suggested alterations of interhemispheric balance on performance was only observed for response inhibition, but not other EF domains.

WM is another impaired EF in ADHD. Although children with ADHD exhibit significant WM deficits (Kasper et al., 2012) relative to their typically developing peers, no study has investigated effects of tDCS, which is a robust technique for improving WM, on WM in ADHD (Brunoni & Vanderhasselt, 2014). Our findings show that left anodal / right cathodal DLPFC tDCS significantly improved participants' performance in the N-back task compared to sham stimulation. Interestingly, in the second experiment both accuracy and RT were improved by stimulation, while only RT benefitted in the first experiment. One explanation could be opposing effects of cathodal IDLPFC tDCS in experiment one, that could reduce increased activity of the IDLPFC. Previous tDCS studies have already shown improved WM performance after anodal stimulation of the IDLPFC (Brunoni & Vanderhasselt, 2014; Fregni et al., 2005). Our findings replicate results of these studies, and suggest decreased activity in the IDLPFC as causally relevant for impaired attentional control and WM in ADHD and other disorders with executive dysfunctions (Banich et al., 2009; Fregni et al., 2005; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009; Salehinejad, Rostami, & Ghanavati, 2015). Another explanation for these results takes the role of inhibitory control for WM performance into account, which was also improved in the second experiment. Inhibition is introduced as the central executive part of WM in Baddeley's model of WM (Hasher, 2006) and improved inhibitory control, which was only observed in the second experiment, could explain why participants' WM was more robustly improved in experiment two.

Cognitive flexibility, task switching and attentional shifting were other EF domains investigated in the present study. The stimulation conditions in experiment two, which involved both, DLPFC and OFC, significantly improved performance on these EFs compared to the first experiment, that only involved the DLPFC. WCST performance requires EF domains that clearly benefit from DLPFC-related executive functioning such as attentional and executive control (Cepeda et al., 2000) for directing behavior toward achieving a goal (sorting cards based on a criterion). However, when the rule changes, participants need to inhibit the now irrelevant response, which requires inhibition, and to apply a new rule which requires disinhibition. Disinhibition and impulsivity are OFC-related deficits in ADHD (Rolls, 2004). Therefore, stimulation montages that target both regions (i.e., DLPFC and OFC) might be optimal to enhance WCST performance. This also implies that deficits in ADHD are not limited to executive dysfunctions controlled by the DLPFC and are related to DLPFC-OFC interaction rather than imbalanced DLPFC activity marked in other disorders with frontal abnormalities.

Regarding the presumed DLPFC-OFC interaction in WCST performance, both tDCS montages (i.e., anodal IDLPFC tDCS/ cathodal rOFC tDCS and cathodal IDLPFC tDCS / anodal rOFC tDCS) significantly improved performance on the WCST in ADHD children compared to sham stimulation, although the first montage was significantly more effective than the second one. One explanation for the performance-improving effect of cathodal IDLPFC tDCS addresses cognitive flexibility, which is one of the EFs measured by the WCST. Recent tDCS studies showed increased cognitive flexibility after cathodal tDCS of the IDLPFC (Chrysikou et al., 2013). Cathodal stimulation of the IDLPFC facilitates disengagement from the current task and engagement in novel ones. This is one of the abilities required to apply new rules in the WCST and might explain why the second montage also improved WCST performance. The improving

effect of anodal tDCS of the IDLPFC could then be explained by increased cognitive control and attentional shifting. In other words, reduced DLPFC activity that affects both sustained and transient aspects of attentional control in ADHD (Banich et al., 2009) was increased by anodal tDCS, which would lead to regulation of top-down attentional control which is one of the underlying mechanisms of improved scores of performance on the WCST.

In sum, our study suggests modulation of PFC regions, namely the DLPFC and OFC, modified performance on EFs tasks; accordingly, while IDLPFC activity is more closely related to executive control, WM and interference inhibition in ADHD, rDLPFC activation is more involved in inhibitory control. Moreover, our findings suggest that cognitive flexibility / task switching and attentional shifting mostly benefit from DLPFC-OFC interactions. Interestingly, our findings suggest that the effects of activation of PFC regions, especially the DLPFC, are task-specific and domain-specific, benefiting some but not all the EFs domains in a lateralized way (i.e., left and right DLPFC involvement in Stroop performance or IDLPFC/rOFC involvement in WCST performance). However, findings of the present study should be interpreted considering what follows. Firstly, executive dysfunctions in ADHD presented in this study should not imply a homogenous description and singly core dysfunction of ADHD deficits. Instead, ADHD is a quite heterogeneous disorders in terms of impaired deficits and neuropsychological measures central to ADHD (Fair et al., 2012). Secondly, the executive dysfunctions measured in this study should be discussed based on the validity and specificity of tasks given the significant overlap and differences between executive deficits in ADHD.

This study is also an initial step towards developing clinical treatment of ADHD, especially regarding impaired EFs, by electrically stimulating the DLPFC or OFC. A recent study supports this notion by showing beneficial effects of tDCS on ADHD symptoms (Cachoeira et al., 2017).

Importantly, our results suggest using task-specific stimulation protocols to ameliorate specific deficits. For example, our study results suggest to use stimulation montages that increase activity in the rDLPFC using either cathodal IDLPFC tDCS (Soltaninejad et al., 2015a) or anodal rDLPFC tDCS for improving impulsive behavior and inhibitory control in ADHD (Beeli, Casutt, Baumgartner, & Jäncke, 2008). Anodal IDLPFC tDCS is also suggested for enhancing WM and executive control as this stimulation protocol increases cortical excitability of the IDLPFC, which its role in WM is well-documented. Finally, anodal IDLPFC tDCS / cathodal rOFC or cathodal IDLPFC tDCS might be beneficial for improving cognitive flexibility, attentional shifting and impulsivity in ADHD. The latter stimulation protocol might benefit more attentional and behavioral deficits in ADHD by ameliorating attentional deficits (through anodal IDLPFC tDCS) and impulsive behaviors (through targeting OFC).

The present study has some limitations. First of all, both experiments had a relatively low number of participants, although the total sample size was adequate considering that small sample size has been the case in many studies on ADHD children. Moreover, the first experiment sample size only included male ADHD children. Secondly and more importantly, our design involved only post-stimulation assessment whereas, assessment of task performance before and after tDCS provides a better evaluation of tDCS effectiveness. This is of importance given the neuropsychological heterogeneity of patients with ADHD which necessitates application of more robust designs such as pre & post-test designs. Thirdly, although we considered a minimal distance of 6 cm from the anodal electrode with the reference electrode, but low focality of tDCS limits interpretability of the stimulation effects regarding specific areas. Finally, despite that we had control condition by applying sham stimulation, a group of healthy control can add to data interpretation in terms of effectiveness of tDCS which is recommended for future studies. Future

studies should also explore potential long-term effects of tDCS on cognitive deficits in ADHD. Our results do not suggest a simple locus of neural dysfunction of the DLPFC in ADHD. Neuroimaging studies are required to specify accurate localizations of PFC regions involved in respective symptoms to improve targeting of stimulation approaches. Lastly, it is of note that tDCS, as a clinical intervention and neuromodulation technique (Brunoni et al., 2012) can enhance cerebral plasticity and could then be used as a tool to increase the developmental potential of children (Holt & Mikati, 2011) especially in neurodevelopmental disorders such as ADHD.

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Table 1. Demographic information of participants

Variable		Experiment 1	Experiment 2
Gender	Male (Female)	15 (0)	5 (5)
Age	Mean (SD)	10 (2.3)	9 (1.8)
Ritalin Use history	Yes (No)	15 (0)	10 (0)
SNAP inattention	Mean (SD)	1.45 (0.38)	1.82 (0.18)
SNAP hyperactivity/compulsivity	Mean (SD)	2.07 (0.48)	2.40 (0.35)
	Mean (SD)	1.76 (0.41)	1.87 (0.22)

Table 2. Means and SDs of cognitive tasks and ADHD scores.

Task		Experiment 1		Experiment 2		
		Anodal	Sham	Anodal	Cathodal	Sham
		<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Go/No-Go	Accuracy Go	93.33 (11.42)	90.90 (19.56)	100 (0.00)	100 (0.00)	98.54 (3.24)
	Time	1.08 (0.21)	1.03 (0.17)	1.33 (0.9)	1.31 (0.13)	1.23 (0.12)
	Accuracy No-Go	19.86 (7.6)	19 (7.80)	22.7 (1.33)	24.2 (1.22)	20.7 (4.39)
N-back	Accuracy	15.26 (8.32)	14.40 (7.42)	21 (2.26)	19.40 (2.27)	17.90 (2.92)
	RT*	120.23 (22.48)	175.73 (55.44)	103.39 (24.19)	120.87 (48.60)	162.88 (94.41)
WCST	Perseverative errors	17.60 (3.60)	18 (8.98)	7.8 (2.44)	11.8 (3.29)	14.80 (3.7)
	Category completed	2.46 (0.83)	2.40 (1.05)	5.1 (0.71)	4.5 (0.52)	3.9 (0.73)
	Time*	237.30 (79.75)	291.12 (106.70)	123.22 (16.85)	143.10 (30.82)	170.28 (85.94)
	Total errors	29.71 (8.3)	30.73 (9.34)	11 (2.86)	16 (4.32)	21.60 (5.36)
Stroop	Accuracy Incongruent	34.93 (15.54)	24.93 (12.01)	N/A	N/A	N/A
	RT	2.87 (2.21)	1.39 (0.44)	N/A	N/A	N/A

WCST = Wisconsin Card Sorting Test; RT = Response Time; M = Mean; SD = Standard Deviation; N/A = Not administrated; * = Values marked by (*) are in second

Table 3. Exp 1: ANOVA results for effects of tDCS conditions (anodal F3-cathodal F4/sham) on Go/No-Go task, WCST, N-back test and Stroop task.

Tasks	Source	<i>df</i>	Mean square	<i>F</i>	Significance	Partial eta ²
Go/No-Go	Accuracy Go	1,14	44.31	0.19	0.66	0.01
	Time	1,14	0.02	2.42	0.14	0.15
	Accuracy No-Go	1,14	5.63	1.02	0.32	0.06
Stroop	Accuracy Incongruent	1,14	346.80	9.01	0.01	0.39
	RT	1,14	16.46	7.07	0.02	0.33
N-Back	Accuracy	1,14	5.63	0.21	0.65	0.01
	RT	1,14	21561.75	21.01	0.01	0.62
WCST	Perseverative errors	1,14	1.20	0.03	0.86	0.01
	Category completed	1,14	0.03	0.06	0.81	0.01
	Time	1,14	21721.40	7.87	0.01	0.36
	Total errors	1,14	7.50	0.15	0.69	0.01

tDCS = Transcranial Direct Current Stimulation; F3 = left DLPFC; F4 = right DLPFC; WCST = Wisconsin Card Sorting Test; RT = Response time; Significant results are highlighted ($p \leq 0.05$) in bold.

Table 4. Exp 2: ANOVA results for effects of tDCS conditions (anodal F3-cathodal OFC/cathodal F3-anodal OFC /sham) on Go/No-Go task, WCST, and N-back test.

Tasks	Source	<i>df</i>	Mean square	<i>F</i>	Significance	Partial eta ²
Go/No-Go	Accuracy Go	2,18	7.02	2.01	0.16	0.18
	Time	2,18	0.02	2.09	0.15	0.19
	Accuracy No-Go	2,18	30.83	4.48	0.03	0.33
N-Back	Accuracy	2,18	24.03	9.84	0.01	0.52
	RT	2,18	9346.97	5.89	0.01	0.39
WCST	Perseverative errors	2,18	123.33	10.70	0.01	0.54
	Category completed	2,18	3.60	15.67	0.01	0.63
	Time	2,18	55.80	3.06	0.07	0.25
	Total errors	2,18	281.20	16.67	0.01	0.64

tDCS = Transcranial Direct Current Stimulation; F3 = left DLPFC; OFC = Orbitofrontal cortex; WCST = Wisconsin Card Sorting Test; RT = Response time; Significant results are highlighted ($p \leq 0.05$) in bold.

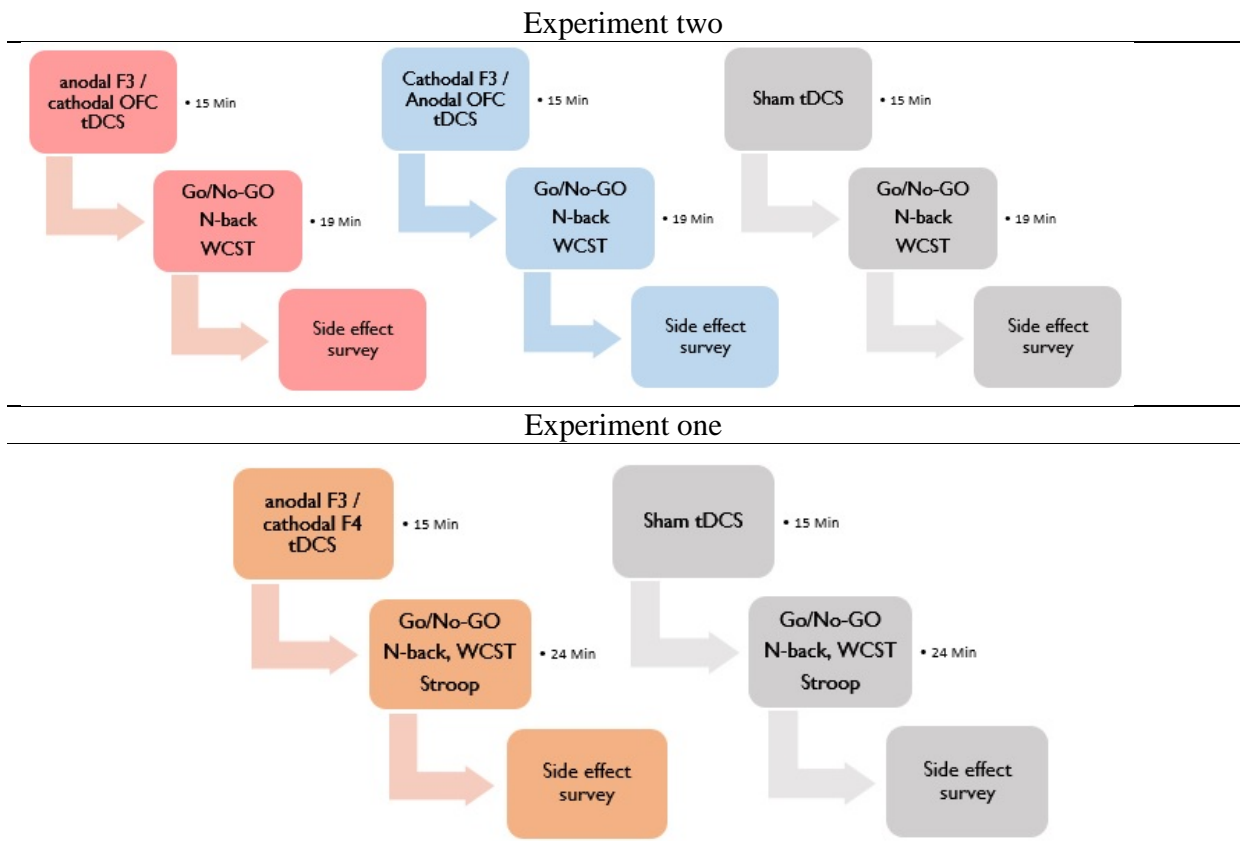


Figure 1. Procedure of tDCS conditions in experiment one (bottom) and experiment two (top); tDCS = Transcranial direct current stimulation; F3 = left DLPFC; F4 = right DLPFC; OFC = Orbitofrontal cortex; WCST = Wisconsin Card Sorting Test.

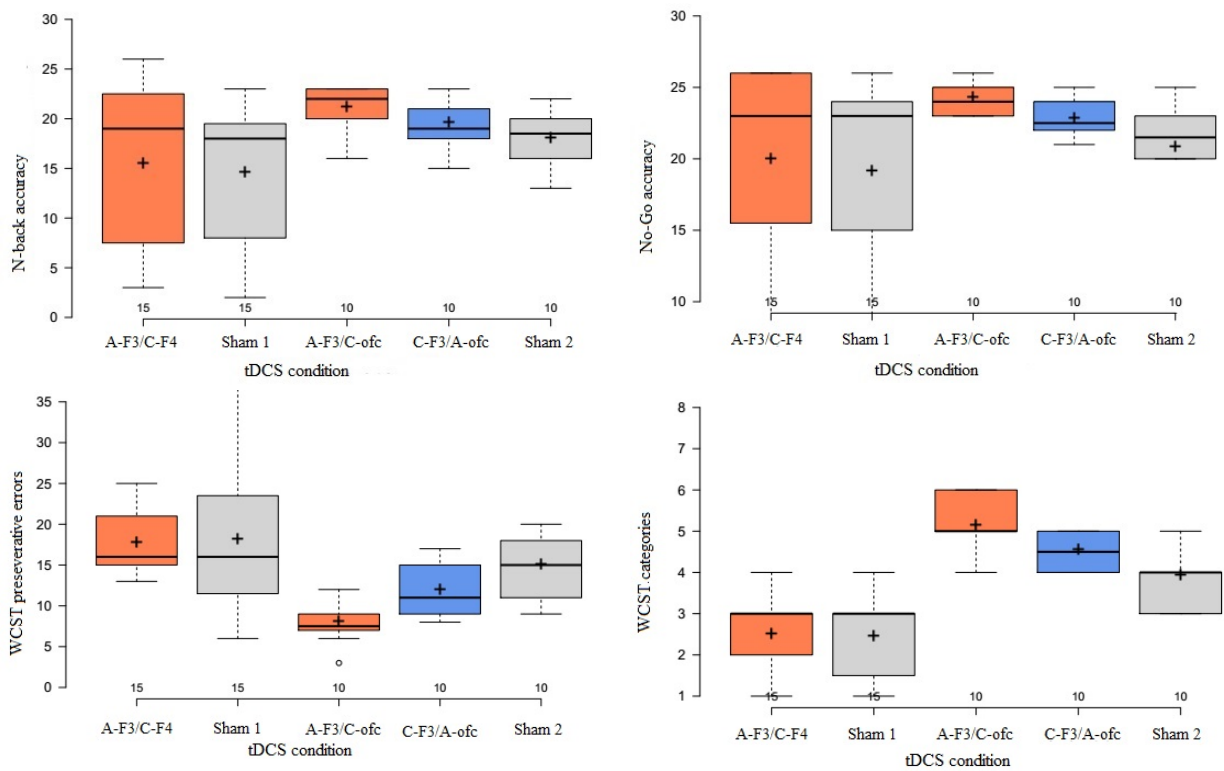


Figure 3. N-back accuracy, accuracy No-Go, perseverative errors and categories completed after each tDCS condition in both experiments. A = anodal tDCS; C = cathodal tDCS; F3 = left DLPFC; F4 = right DLPFC; OFC = Orbitofrontal cortex. Exp one N = 15, Exp 2 N = 10.