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Non-invasive brain stimulation shows possible cerebellar contribution in transfer of prism adaptation after-effects from pointing to throwing movements

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Abstract

Whether sensorimotor adaptation can be generalized from one context to others represents a crucial interest in the field of neurological rehabilitation. Nonetheless, the mechanisms underlying transfer to another task remain unclear. Prism Adaptation (PA) is a useful method employed both to study short-term plasticity and for rehabilitation. Neuro-imaging and neuro-stimulation studies show that the cerebellum plays a substantial role in online control, strategic control (rapid error reduction), and realignment (after-effects) in PA. However, the contribution of the cerebellum to transfer is still unknown. The aim of this study was to test whether interfering with the activity of the cerebellum affected transfer of prism after-effects from a pointing to a throwing task. For this purpose, we delivered cathodal cerebellar transcranial Direct Current Stimulation (tDCS) to healthy participants during PA while a control group received cerebellar Sham Stimulation. We assessed longitudinal evolutions of pointing and throwing errors and pointing trajectories orientations during pre-tests, exposure and post-tests. Results revealed that participants who received active cerebellar stimulation showed (1) altered error reduction and pointing trajectories during the first trials of exposure; (2) increased magnitude but reduced robustness of pointing after-effects; and, crucially, (3) slightly altered transfer of after-effects to the throwing task. Therefore, the present study confirmed that cathodal cerebellar tDCS interferes with processes at work during PA and provides evidence for a possible contribution of the cerebellum in after-effects transfer.

Key-words: prism adaptation, after-effects, transfer, cerebellum, tDCS, plasticity

Introduction

Over a lifetime, human beings remain capable of producing smooth and precise movements despite continuously varying demands. Indeed, the plasticity of the nervous system allows the learning of new motor programs and the modification of those previously acquired to face new conditions. The possibility of transferring formerly acquired motor transformations from the one context to others brings important information on the nature of the processes involved to face perturbations (Poggio & Bizzi, 2004). Moreover, the understanding of the mechanisms underlying transfer represents a crucial interest in the field of neuro-rehabilitation (Roemmich & Bastian, 2018).

Prism Adaptation (PA) is an experimental paradigm used to study sensorimotor plasticity processes (Prablanc et al., 2019; Redding et al., 2005; Welch, 1974). In a typical PA protocol, individuals are actively exposed to a shift of the visual field induced by prismatic lenses while performing a pointing task. Initially, subjects make errors in the direction of the prismatic deviation (terminal error). Following a few trials, subjects rapidly reduce terminal error gaining accurate performance. When prisms are removed, following sustained exposure, subjects experience errors in the direction opposite to the initial prismatic deviation. These errors are called “after-effects” and attest the presence of “true” adaptation (Prablanc et al., 2019; Redding et al., 2005; Weiner et al., 1983).

According to several authors (e.g. O’Shea et al., 2014; Redding & Wallace, 2002; Rossetti et al., 1993; Weiner et al., 1983), two mechanisms seem to be at work during PA. The first mechanism aims to quickly reduce errors during the first trials of exposure by means of a strategic adjustment of motor plan on the subsequent trial based on the previous errors (O’Shea et al., 2014; Rossetti et al., 1993). These cognitive-compensatory modifications of motor commands are referred to with the term strategic control and include conscious and voluntary strategies such as pointing-off target or mental rotation. The second mechanism is a slow and automatic process that is necessary to re-organize the sensory maps (visual and proprioceptive references frames) that have been disrupted by the prismatic shift. This process, called realignment, is related to “true” adaptation and is thought to be relevant for developing after-effects (O’Shea et al., 2014; Petit et al., 2017; Prablanc et al., 2019; Redding et al., 2005).

Although these two processes are frequently described within the PA literature, distinguishing their specific contributions remains contentious. After-effects need to be assessed in a context that is different from the exposure context (without goggles and toward different unexposed target) to reflect the presence of true adaptation (Petit et al., 2017; Prablanc et al., 2019). However, after-effects may also contain a part of cognitive after-

effects, related for example to a pointing-off target strategy that leads to use-dependent modifications of movements' trajectory (McDougle et al., 2016; Redding & Wallace, 2002). Therefore, testing the transfer of after-effects allows to better capture sensorimotor after-effects that are not specific to the context of exposure (Fleury et al., 2020).

Using the classical prism exposure procedure, after-effects could be easily measured in a different context, as an instance by using other target locations (Bedford, 1993; Redding & Wallace, 2006), other limb (Girardi et al., 2004; Michel et al., 2008; Morton et al., 2001), or other tasks (Fernandez-Ruiz et al., 2003; Jacquin-Courtois et al., 2008). Recently, inter-task transfer between a throwing and a pointing task was investigated in a prism exposure study (Fleury et al., 2020). Results revealed a clear-cut unidirectional transfer from pointing to throwing but not from throwing to pointing. The authors attributed the absence of transfer from throwing to the fact that throwing is more variable than pointing. Indeed, reduced variability in individuals with throwing expertise (expert dart throwers) made the transfer reciprocal (Fleury et al., 2020). The type of task practised during exposure seemed to affect the transfer of after-effects to a task that was not practised under the prismatic deviation, possibly suggesting that different processes have been involved to face the perturbation. Crucially, the classical assessment of after-effects on the task practised during exposure (e.g. after-effects on pointing for participants who practised pointing during prism exposure) did not allow to unravel the presence of different processes because the magnitude of after-effects was comparable regardless the task practised during exposure. By contrast, the assessment of transfer might have revealed important information concerning the nature of processes involved in sensorimotor adaptation (Fleury et al., 2020). However, the mechanisms underlying inter-task transfer remain unclear and brain regions involved in transfer properties have not been yet identified.

The neural correlates of PA have been examined through lesion studies, neuro-imaging studies, and recently by means of non-invasive brain stimulation techniques (see Panico et al., 2020 for a review on neuro-imaging and neuro-stimulation studies in PA). Neuro-imaging studies showed an involvement of several parietal areas in the processes of error detection and early error correction (Chapman et al., 2010; Clower et al., 1996; Danckert et al., 2008; Luauté et al., 2009). These studies also highlighted the role of cerebellar areas from early (Küper et al., 2014) to late exposure until the development of after-effects (Chapman et al., 2010; Luauté et al., 2009), i.e. realignment. Although neuro-imaging studies allow the correlational observation of dynamics changes in brain activity and are characterized by a high temporal and spatial resolution, some constraints of these methods are not compatible with optimal PA experimental settings (Bultitude et al., 2017). As a consequence, non-invasive brain stimulation methods represent a complementary approach that enables to

directly investigate causal relationships between brain and behaviour by modulating activity in targeted-brain areas in an inhibitory or facilitatory way. Although they suffer a weaker spatial resolution as compared to neuro-imaging, non-invasive brain stimulation techniques can be applied in ecological settings and are more compatible with prism exposure procedure experimental requirements, in a causal perspective (Panico et al., 2020).

Neuro-imaging findings were completed by neuro-stimulation studies, in which cathodal cerebellar stimulation during prism exposure resulted in larger errors during early, middle, and late exposure, as well as during post-test measures (increased after-effects; Panico et al., 2016). Moreover, in a multiple step PA protocol (Panico, Sagliano, Nozzolillo, et al., 2018), cathodal cerebellar stimulation induced larger errors in the direction of the prismatic deviation during both initial and late exposure at each increment step and reduced after-effects. In this procedure, participants were unaware of the optical deviation because of stepwise increases of the prism shift (Michel et al., 2007), thus preventing strategic corrections of pointing movements (i.e. recalibration). Findings from this study supported a causal role of the cerebellum in realignment since stimulation affected performance during late exposure and after-effects assessment. In addition, as stimulation affected also the initial component of exposure, authors pointed out a possible contribution of the cerebellum in online motor corrections and feedforward control of reaching movements (Panico, Sagliano, Nozzolillo, et al., 2018). Two neuro-stimulation studies also emphasized a possible role of the primary motor cortex in the persistence and the reactivation of after-effects (O'Shea et al., 2017; Panico et al., 2017; for an opinion paper, see Panico et al., 2021). Altogether, findings from neuro-imaging and neuro-stimulation fields are compatible with results of patient studies concerning cerebellar function in PA. Indeed, cerebellar damage impairs primarily after-effects and accessorially error-reduction (Baizer et al., 1999; Hanajima et al., 2015; Pisella et al., 2005; Weiner et al., 1983), while cortical injuries lead to altered error reduction during exposure but spared after-effects (Newport & Jackson, 2006; Pisella et al., 2004).

As a matter of fact, to date clinical neuropsychological, neuro-imaging, and neuro-stimulation studies have not provided detailed investigation of brain structures involved in inter-task transfer of prism acquired after-effects. Assessment of after-effects transfer should attest the presence of true adaptation because the classical measure of after-effects might not be sufficient to unravel the presence of different processes at work during exposure (Fleury et al., 2020; Prablanc et al., 2019). A likely hypothesis is that transfer of after-effects might depend on the initial magnitude of after-effects on the task practiced during exposure. Therefore, processes involved during exposure might directly determine the nature of after-effects and whether they could be transferred to another task or not. Thus, given the above-

mentioned evidence of a crucial role played by the cerebellum in the development of after-effects (i.e. realignment), one possible hypothesis is that the cerebellum may also be involved in after-effects transfer.

Hence, a crucial unanswered question relates to the role of the cerebellum in generating after-effects that are transferable to a task that was not practiced under prism exposure. Therefore, the aim of the present study was to investigate the influence of cathodal cerebellar transcranial direct current stimulation (C-tDCS; Nitsche & Paulus, 2000) on the magnitude of inter-task transfer. As transfer was already observed from pointing to throwing (Fleury et al., 2020), we specifically tested whether cathodal stimulation of the cerebellum would decrease the magnitude of after-effects transfer from pointing to throwing. Our main hypothesis was that cathodal stimulation of the cerebellum would impair individuals' ability to transfer after-effects from pointing to throwing because it would alter adaptive processes during exposure that allow the development of transferable after-effects (i.e. "true" adaptation). Therefore, we also expected that cerebellar tDCS would affect PA mechanisms (i.e. error reduction during exposure and development of pointing after-effects) in line with previous studies (e.g. Panico et al. 2016).

Methods

The study followed a pre-post design including a total of 27 healthy participants. Every participant gave informed consent to take part in this experiment. All procedures were designed following relevant guidelines and regulations and were approved by an ethics evaluation committee of Inserm ("CPP SUD-EST IV", ID-RCB: 2010-A01180-39).

Participants

27 right-handed participants were involved in the study. They had normal or corrected to normal vision, no neurological disorders and had never experienced prisms before the experiment. Participants performed two goal-directed visuomotor tasks –throwing and pointing. They were divided into two groups accordingly to the tDCS parameters: an experimental "C-tDCS" group (n=16, 8 males and 8 females, mean age = 22.8 ± 3.0) and a control "SHAM" group (n=11, 5 males and 6 females, mean age = 26.7 ± 8.2). Both groups followed the same procedures except that participants in the C-tDCS group received a cathodal cerebellar stimulation while participants in the SHAM group received a placebo cathodal stimulation.

Experimental paradigm:

The experimental procedure involved four stages (familiarization, pre-tests, exposure, and post-tests) as illustrated in **Figure 1**.

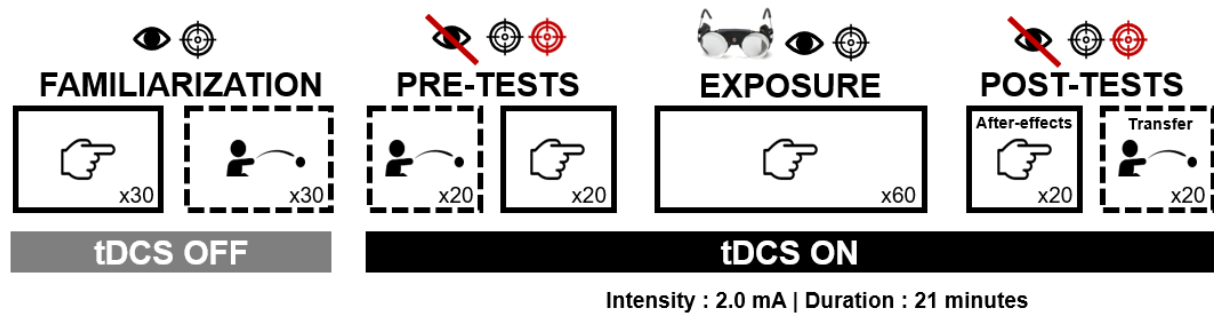


Figure 1 – Experimental procedures. The figure depicts the different steps of the study and the conditions in each step, i.e. the task performed (throwing or pointing), the availability of visual feedback (bared eye or normal eye), the number of trials (i.e. 20, 30 or 60), the presence of prism goggles, the number of targets (one black target, or two targets – black and red), and tDCS conditions (Off or On). Solid boxes refer to the practice of the exposed task (i.e. pointing) while dotted boxes refer to the practice of the unexposed task (i.e. throwing).

According to each specific experimental stage, pointing and throwing tasks were performed either with vision of the movement (except the starting position) and of endpoint accuracy (closed-loop) or without (open-loop). Depending on the stage, movements were directed to one central targets (0°) or alternatively to two targets (0° and 10° right).

Pointing task set-up

Participants sat in front of a pointing table, with their head on a chinrest. This was used to prevent participants to see their hand starting position, thus precluding any static recalibration of the prism induced shift and slowing down the error reduction. The starting position of the finger was located below the chinrest, lined up with the body midline. Two targets were placed on the pointing table in front of the participants, at 57.5 cm from their eyes. The central target (exposed target) was situated straight-ahead of the participant's body midline (0 degrees) and the right target (non-exposed target) at 10 degrees to the right.

During open loop pointing (pre, early, post-tests), no vision was allowed during the entire movement. Participants wore electronic liquid-crystal glasses connected to a switch placed on the starting position. The participants were able to see the targets while their index lied on the starting position. Upon movement initiation, the glasses turned opaque and the subjects were deprived of visual feedback. When they went back to the starting position, the glasses turned transparent again.

During closed-loop condition (familiarization and post-tests), the participants had to reach the central target. They did not wear the liquid-crystal glasses and had visual feedbacks about

their pointing movements (except the starting position) and their outcomes (endpoint errors). The investigator gave the starting signal for each trial. A colour code indicated which target to reach in open-loop conditions and a vocal « go! » was provided during closed-loop conditions (using only one target).

Throwing task set up

Participants sat in front of a vertical board, at 2 meters from their body axis and wore a ball-dispenser helmet. Similarly to the pointing set-up, two targets were presented on the board. The central target (exposed target) was situated forward the participant's body midline (0 degrees) and the right target (non-exposed target) at 10 degrees to the right. All the setting was surrounded by light spots connected to a switch placed on the helmet.

During open-loop throwing, participants had to pick a ball and to press down the light-switch mounted on the helmet, to be able to see the target. Once they initiated movement and released the switch, lights were immediately turned off so they had no visual feedback about their movement and its outcomes.

During closed-loop throwing (familiarization and exposure), lights were turned on and participants saw their movement all time. As for pointing, in both conditions, participants were asked to throw as fast and accurate as possible. The starting signal was given by the investigator for each trial: the target colour to reach in open-loop conditions and « go » during closed-loop conditions.

General procedures

Specific pointing and throwing conditions for each stage of the experimental protocol are detailed in the following sections and illustrated in **Figure 1**.

Familiarization: to familiarize with both tasks and with experimental settings, participants in each group performed 30 trials of the pointing task, then 30 trials of the throwing task. All trials were performed in a closed-loop condition toward the central target.

Pre-tests: baseline performances were assessed for each task during pre-tests. Participants of both groups performed 20 trials of the throwing and the pointing tasks. Trials were performed in open-loop condition and toward both targets in a pseudo-randomized order (which was the same for all participants).

Exposure: participants performed 60 pointing trials while wearing prismatic goggles that shifted laterally the visual field 10 degrees toward the right (OptiquePeter.com, Lyon). Trials were performed in a closed-loop condition toward the central target, as fast and accurate as possible. Before positioning the goggles, participants were asked to keep their eyes closed.

They were also instructed not to look at their own body or to move before starting the experimental tasks while they were wearing the prismatic goggles.

Post-tests: once the prisms were removed, after-effects were assessed on the pointing task: participants performed 20 pointing trials in an open-loop condition toward both targets. Then, transfer was measured on the throwing task. To this purpose, participants performed 20 throwing trials in an open-loop condition toward both targets.

Order of the tasks

The design of the study required testing participants in two distinct tasks during pre-tests and post-tests. The experimental set-up for the two tasks necessitated the participants to be moved from the throwing set-up to the pointing set-up. Yet, it was crucial that participants had no access to vision during these transitional phases and did not actively move, to prevent any de-adaptation during post-tests. To that purpose, participants sat in an adjustable and movable chair throughout the whole experiment and wore eyes patches during each transitional phase. They were not allowed to move the chair and investigators were in charge to move participants between the throwing and the pointing task set-up according to the experimental procedure. Nevertheless, to limit the number of transitional phases, we specified the order of the tasks throughout the experimental procedure in a fixed manner that was identical for all the participants: pointing – throwing (familiarization); throwing – pointing (pre-tests); pointing (exposure); pointing – throwing (post-tests).

tDCS protocol

tDCS settings were based on the protocol used in a previous study by Panico et al. (2016). tDCS was turned on before pre-tests and turned off right after post-tests. A battery-driven stimulator (neuroConn, neuroCare Group, Germany) delivered a constant current of 2.0mA intensity through a pair of surface saline-soaked sponge electrodes (area = 25cm²).

The cathodal electrode was placed over the right cerebellum (1 cm below and 4 cm right to the inion) and the anodal electrode was placed over the right deltoid muscle, to ensure selective stimulation over the right cerebellum.

Stimulation was delivered over the right cerebellum as participants used their right arm to perform the tasks (Schlerf et al., 2015). Sham stimulation was performed in the same way as active stimulation, but the stimulator was turned off after 30 s. This procedure ensured that participants felt the same itching sensation at the beginning of tDCS as participants assigned to the experimental group, and were thus blinded for the stimulation condition they had been assigned to (Gandiga et al., 2006). For both sham and active conditions, stimulation was gradually increased to 2mA with a fade-in of 30 seconds.

Safety guidelines recommended a maximum stimulation time of 21 minutes (Nitsche & Paulus, 2000; Woods et al., 2016). Therefore, participants were timed to complete the experimental tasks within 21 minutes after the stimulation was turned on. Participants who did not manage to complete the procedure within this time were excluded from the analysis (n=2 in the C-tDCS group).

Data collection

An opto-electronic motion capture system (9 cameras, Vicon Motion Systems Ltd, Oxford, 1984; *Mouvement et Handicap* platform, *Hospices Civils* of Lyon) was used to record ball impact on the vertical board for each throwing trial. Reflective markers were placed on the throwing board to localize the targets and the projectiles were reflective themselves. The motion capture system was also used to track movement trajectories during pointing trials. Reflective markers were positioned on the index, the wrist and the elbow of the subject.

Data processing

Throwing and pointing terminal errors

Markers' trajectories were recorded for each trial and filtered with a Butterworth low-band pass filter at a cut-off frequency of 6Hz. For the throwing trials, the time-point corresponding to the contact between the projectile and the board was automatically detected. This time-point was used to compute the lateral errors between the impact of the projectile and the aimed target using MatLab customized routines. Thus, we computed performances on each trial, i.e. the angular deviation between the ball impact and the aimed target.

For pointing trials, the endpoint of each pointing movement was computed automatically (using in-house custom software written in Matlab). Movements were detected using the following threshold: onset was defined as the point at which hand velocity exceeded 80mm/s while offset was defined as the time-point at which velocity dropped below this threshold (O'Shea et al., 2014). After automatic detection, all trials were cross-checked visually and adjusted manually if necessary. Index endpoints were then used to obtain the lateral endpoints errors from the aimed target.

Pointing kinematics analysis

We used in-house software written in MatLab to compute kinematics of pointing movements. Two phases constitute a pointing movement: an acceleration phase (initial ballistic component) and a deceleration phase, referring to the target approach phase (Elliott et al., 2010). The initial part of the trajectory reflects feedforward movement planning while the second part of the trajectory involves online feedback corrections (O'Shea et al., 2014). We

analysed trajectories of pointing movements by specifically investigating the orientations (i.e. angles between the velocity vector and the line formed by the starting position and the central target) of velocity vectors at acceleration, velocity and deceleration peaks. Only pointing movement kinematics were investigated.

Statistical analysis

We analysed two main dependent variables. First, we computed terminal errors between index endpoint (pointing task) or ball impact (throwing task) and the aimed target for each trial. Moreover, pointing trajectories orientations were computed as the magnitude of velocity vectors at acceleration peak (initial orientation), velocity peak (intermediate orientation) and deceleration peak (terminal orientation).

It is worth mentioning that all values for post-tests are baseline subtracted, i.e. for each group, we subtracted pre-tests values for each individual and for each task, as recommended in PA literature (Prablanc et al., 2019). In fact, quantifying after-effects requires to take into account the physiological baseline deviation within the same group of testing.

We computed linear mixed models (Singer & Willett, 2003) separately for each stage of the experiment and for each dependent variable, i.e. terminal errors and pointing trajectories orientations at initial, intermediate, and terminal directions. All analyses were conducted using R package *lme4* (Bates et al., 2015). A p-value of 0.05 was used to indicate statistical significance.

Linear mixed models were chosen to analyse not only mean individuals' values (e.g. mean of 20 post-tests trials) but also their longitudinal evolution. Moreover, linear mixed models are a flexible method to deal with intra-individuals' variability within each group (Wright & London, 2009). This approach allows to assess inter-subject differences considering the intra-individual changes over time (through trial-by-trial repetition).

Each trial during the different phases of the procedure represented a time point. These time points were the level-one unit nested in the different individuals (level-two units). We used a by-subject random intercept to test the effect of trials' repetition and the effect of the stimulation condition on the dependent variables. The factor TIME, the factor GROUP (C-tDCS versus SHAM), and the interaction term GROUP*TIME were set as fixed effects. Results from these models provide estimates for each of the factors tested and indicate whether their effects are significant. The reference group was set up as the C-tDCS group. Estimate for the factor TIME allows to evaluate the mean evolution of the dependent variable from the trial n to the trial $n+1$, regardless the group condition. Estimate for the factor

GROUP enables to assess the difference between groups regarding mean values for the dependent variable, at any time point. Finally, the interaction term GROUP*TIME allows to assess whether the slopes of the curves differed between groups, i.e., differences between groups concerning the longitudinal evolution of the dependent variables across trial repetition. Noteworthy, the slopes of the curves are considered as the average rate of change estimated by the models across trial repetition during a given period.

Moreover, to refine the longitudinal analysis of the variables, we also divided some phases of the experiment into multiples series of trials, particularly during exposure. PA literature describes several adaptive processes characterized by different timing (e.g. fast vs slow processes; Inoue et al., 2015; Petit et al., 2017; Rossetti et al., 1993; Smith et al., 2006). For this reason, we decided to analyse early exposure (trials 1 to 10) separately from the remaining trials during exposure (trials 11 to 60). We also analysed separately each block of 10 trials under exposure to obtain a complete description of pointing behaviour under prismatic perturbation, and to investigate effect of C-tDCS on this behaviour at different times of exposure. Furthermore, to provide a qualitative analysis of early exposure, we analysed the five first trials separately given that error reduction is greatest during the very first trials of exposure. Besides, we also cut post-tests phases into bins of five trials.

Finally, to test the differences between mean group terminal errors and mean group trajectories orientation during familiarization, we also performed independent samples T-test. As no stimulation and no prismatic deviation were present during familiarization, we considered no reason to test for any longitudinal variation across trials.

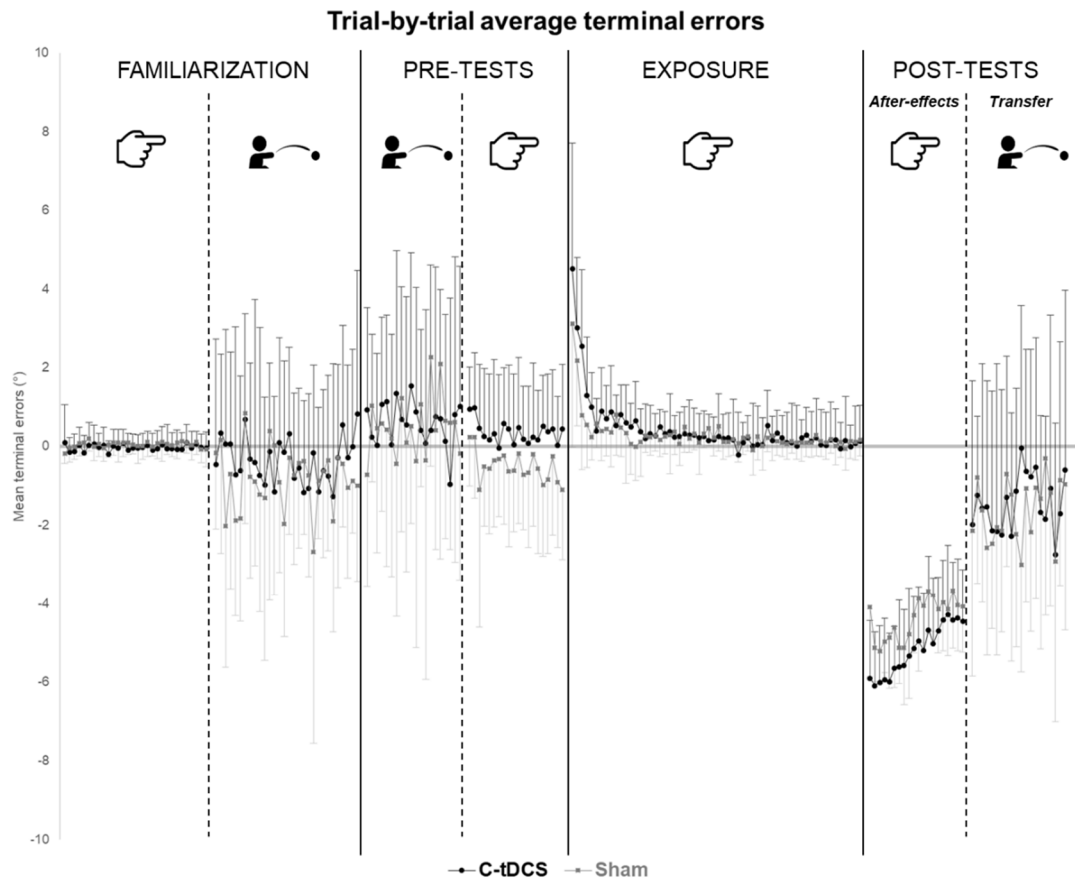
Results

Two participants in the C-tDCS group did not manage to complete the procedure within 21 minutes. These two participants were thus excluded from the following analysis. None of the participants reported any conscious awareness of the prismatic deviation during exposure. When verbally asked following the experiment, no one reported any knowledge about the stimulation condition they had been assigned to. **Table 1** presents the descriptive statistics of mean group terminal errors during the different phases of the procedure. **Figure 2** represents trial-by-trial mean group terminal errors during each step of the procedure.

Table 1 – Descriptive statistics of mean group terminal errors

		C-tDCS group	Sham group
Pre-tDCS	Pointing	-0.03 ± 0.34	0.04 ± 0.23

Familiarization	Throwing	-0.37	± 1.11	-0.84	± 0.79
Pre-tests	Throwing	0.58	± 1.99	0.52	± 2.02
	Pointing	0.35	± 1.22	-0.51	± 1.45
Exposure <i>Pointing</i>	Trial 1	4.52	± 3.20	3.10	± 3.12
	Trial 2	2.99	± 1.81	2.17	± 1.65
	Trial 3	2.53	± 1.96	0.79	± 1.39
	Trial 4	1.28	± 1.49	0.54	± 1.07
	Trial 5	0.99	± 0.86	0.24	± 0.59
	Trials 6-10	0.67	± 0.66	0.51	± 0.59
	Trials 11-20	0.45	± 0.52	0.22	± 0.45
	Trials 21-30	0.25	± 0.58	0.28	± 0.34
	Trials 31-40	0.10	± 0.65	0.16	± 0.32
	Trials 41-50	0.20	± 0.63	0.13	± 0.30
	Trials 51-60	0.09	± 0.79	0.11	± 0.34
	Post-tests	Pointing	-5.19	± 1.22	-4.38
Throwing		-1.46	± 2.06	-1.65	± 1.55



Values are reported in degrees together with standard deviations.

Figure 2 - Trial-by-trial average terminal errors. Trial-by-trial average group terminal errors are represented with standard deviations for each group (C-tDCS group in black, Sham group in grey) and for each step of the procedures

Familiarization

Independent samples t-tests revealed no difference between groups in the pointing task ($t(23)=.63$; $p=.53$) and the throwing task ($t(23)=1.17$; $p=.25$) concerning terminal errors during familiarization (**Figure 3**). Moreover, no difference between groups in mean pointing trajectories orientations during familiarization was found. Results did not show significant difference between the two groups during familiarization.

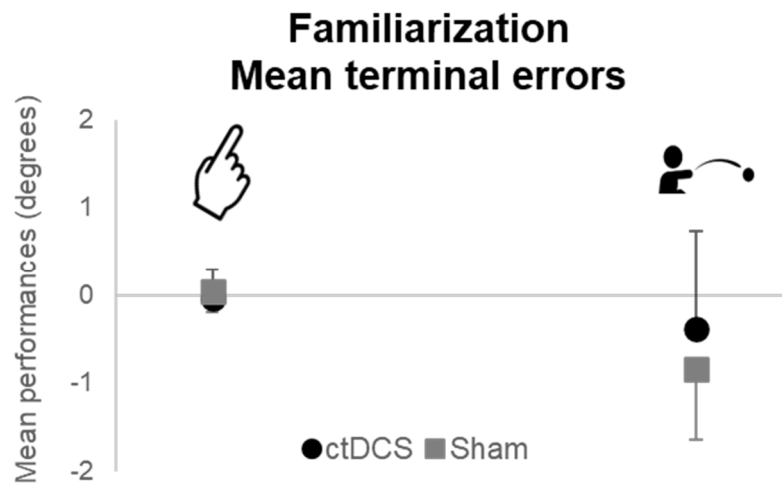


Figure 3 – Mean group terminal errors during familiarization. Mean group terminal errors are represented with standard deviations for each group (C-tDCS group in black, Sham group in grey) and for each task (pointing on the right, throwing on the left).

Pre-tests

Terminal errors

Models did not show any significant effect of TIME, GROUP, nor TIME*GROUP interaction on trial-by-trial terminal errors (i.e. longitudinal values of terminal errors) during pre-tests both on the throwing and the pointing task (Supplementary materials, **Table 2**).

Pointing trajectories orientations

A significant effect of TIME was reported on pointing trajectory orientations at initial direction on both central ($\beta = -.35$, $SE = .15$, $t(223) = -2.27$, $p = .02$) and right ($\beta = -.47$, $SE = .14$, $t(225) = -3.30$, $p < 10^{-2}$) targets; without any group distinction (no effect of GROUP neither GROUP*TIME). Concerning intermediate and final trajectory orientations, results did not reveal any no effect of TIME, GROUP, nor GROUP*TIME interaction (Supplementary Materials, **tables 3-6**).

These results indicate that C-tDCS had no significant effect on terminal errors and pointing trajectories during pre-tests. However, TIME had a significant influence on initial orientations of pointing trajectories without any group distinction: in both groups, the values of initial pointing orientations decreased across trial repetition, i.e., slightly veered toward the left across trials.

Exposure

Terminal errors

Models showed a significant main effect of TIME ($\beta = -10^{-4}$, SE = .00, $t(1475) = -10.76$, $p < 10^{-15}$) and a significant effect of GROUP*TIME interaction ($\beta = -10^{-3}$, SE = .00, $t(1475) = 3.15$, $p < 10^{-2}$) on the whole exposure (60 trials), but no significant main effect of GROUP (Supplementary materials, **Table 2**). This indicates that terminal errors decreased across trial repetition in both groups. However, the negative slope of the error reduction curve in the Sham group was steeper in the C-tDCS group as compared to the Sham group over the whole exposure period. Although both groups rapidly recovered practice level of accuracy, between-subjects (see **Figure 1**) and within-subjects variability remained larger in the C-tDCS group.

During the 10 first trials of exposure, models showed significant effects of TIME ($\beta = -.03$, SE = .00, $t(225) = -6.86$, $p < 10^{-10}$), GROUP ($\beta = -1.09$, SE = .00, $t(42) = -2.63$, $p = .01$) and GROUP*TIME ($\beta = .02$, SE = .01, $t(225) = 2.27$, $p = .02$) on pointing terminal errors. This suggests that stimulation had an influence on terminal errors values and their evolution across time during early exposure (10 first trials). Mean terminal errors were lower in the Sham group as compared to the C-tDCS group. In addition, the slope of the error reduction curve was steeper in participants who received the Sham stimulation. During the subsequent trials (trials 11-60), results revealed a significant effect of TIME ($\beta = -.01$, SE = .00, $t(1225) = -6.58$, $p < 10^{-10}$) and GROUP*TIME interaction ($\beta = -10^{-3}$, SE = .00, $t(1225) = 2.28$, $p = .02$) but no effect of GROUP (Supplementary materials, **Table 2**). From trial 11 to trial 60, terminal errors decreased in both groups, although the slope of the curve fitted over this period was steeper in the C-tDCS group as compared to the Sham group.

Trajectories

Figure 4 plots the mean pointing trajectories during the 5 first trials of exposure. **Figure 5** represents the mean group orientation of pointing trajectories at initial, intermediate, and terminal directions. Significant results revealed by LMMA concerning pointing trajectories orientations are reported below (see Supplementary Materials, **Tables 3-6** for all effects).

Mean Pointing trajectories Exposure - Trial-by-trial n°1 to 5

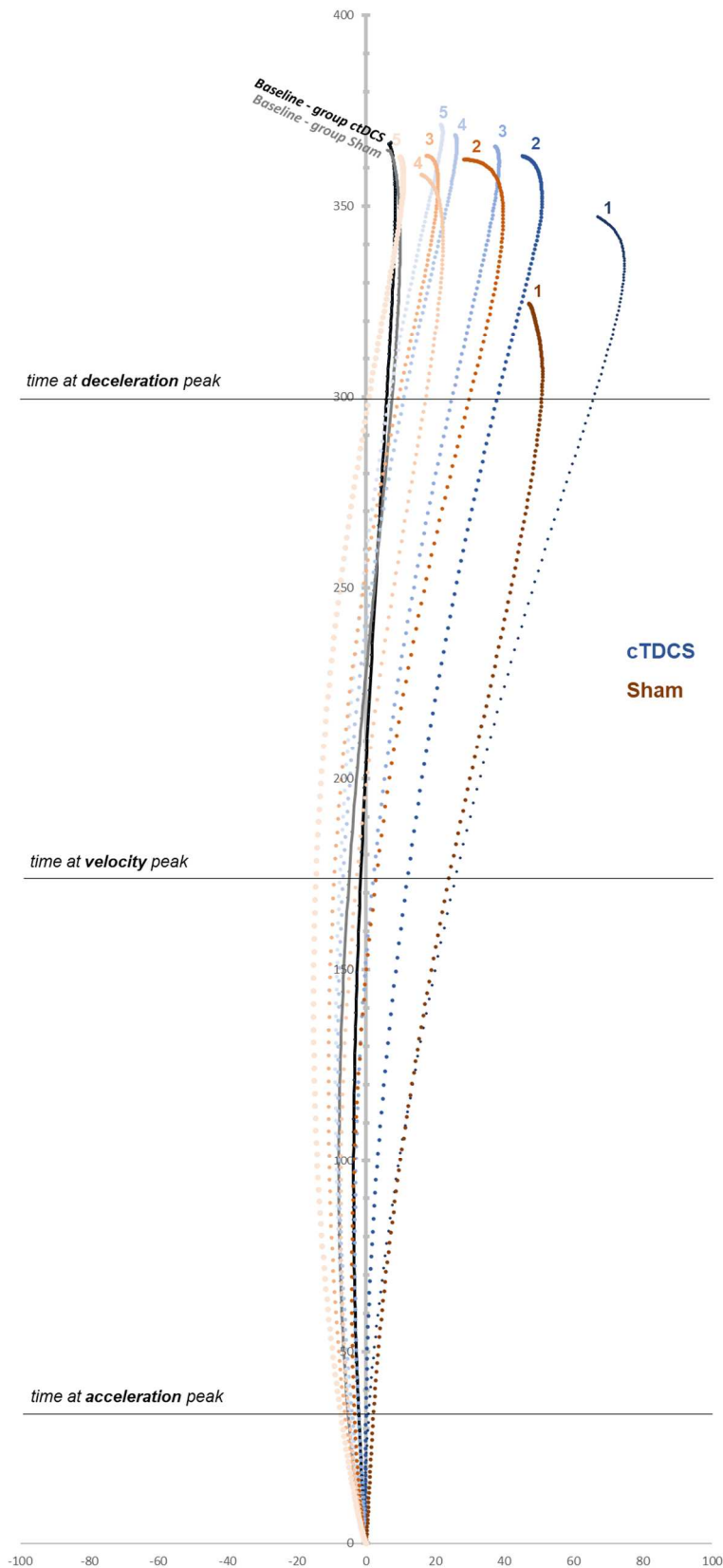
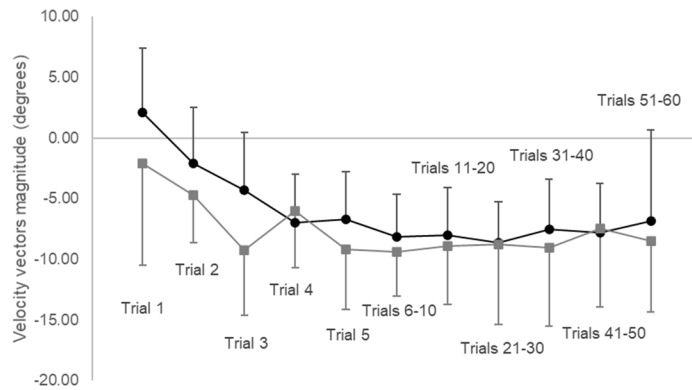
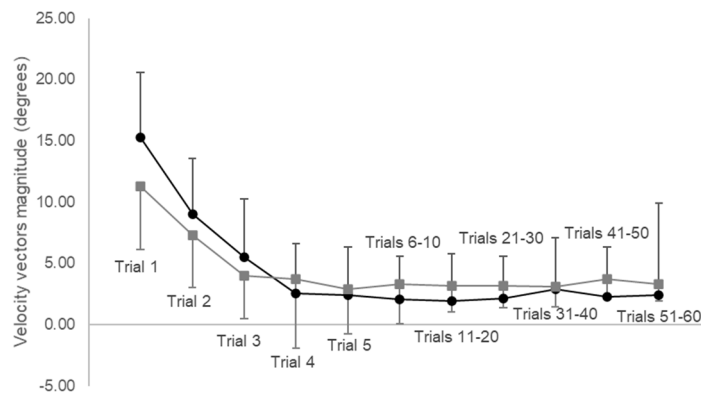


Figure 4 – Mean trial-by-trial pointing trajectories during exposure (trials 1 to 5). The figure represents trial-by-trial mean pointing trajectories for trial 1 to 5 (shades of blue for C-tDCS, shades of orange for Sham). Baseline mean trajectories are also represented for each group in black (C-tDCS group) and grey (Sham group) corresponding to mean pointing trajectories during familiarization. Times at acceleration (initial direction), velocity (intermediate direction) and deceleration (terminal direction) are represented approximately (mean between C-tDCS and Sham groups) showing no substantial difference between groups (see Table 7 for exact values).

Mean orientation at initial direction during exposure



Mean orientation at intermediate direction during exposure



Mean orientation at terminal direction during exposure

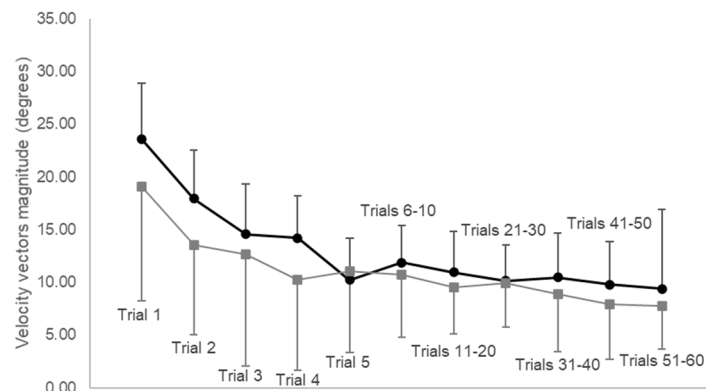


Figure 5: mean group orientation of pointing trajectories at initial, intermediate and terminal direction. The figure depicts mean group orientations of velocity vectors at initial (acceleration peak), intermediate (velocity peak) and terminal (deceleration peak) direction of pointing movements during exposure. Group mean values are plotted for trial 1, 2, 3, 4, 5 and then for subsequent blocks (mean values for trials 6-10, 11-20, 21-30, 31-40, 41-50, 51-60) in black for the C-tDCS group and in grey for the Sham group. Analyses revealed no effect of TIME during trials 11 to 60 except for terminal direction. For initial and intermediate direction, values seem to rapidly reach a plateau. However, concerning terminal direction, values still decrease during late exposure, but without any difference between groups.

Over the whole exposure (trials 1 to 60), analyses revealed a main effect of TIME ($\beta = -.04$, SE = .01, $t(1453) = -4.16$, $p < 10^{-4}$) and GROUP*TIME ($\beta = .04$, SE = .01, $t(1453) = 2.88$, $p < 10^{-2}$) for initial direction (at acceleration peak). This indicates that initial trajectory orientations gradually veered toward the left in both groups across trial repetition. Moreover, the slope of the curve was steeper in the Sham group, as compared to the C-tDCS group. Additionally, results showed a main effect of TIME for intermediate ($\beta = -.03$, SE = .01, $t(1454) = -5.58$, $p < 10^{-7}$) and terminal ($\beta = -.08$, SE = .01, $t(1455) = -8.14$, $p < 10^{-15}$) direction: trajectory orientations at velocity and deceleration peaks globally veered toward the left across trial repetition without any group distinction.

During early exposure (trials 1 to 10), results showed an effect of TIME ($\beta = -.96$, SE = .11, $t(222) = -8.44$, $p < 10^{-14}$), GROUP ($\beta = -4.04$, SE = 1.58, $t(43) = -2.55$, $p = .01$) and GROUP*TIME ($\beta = .41$, SE = .17, $t(222) = 2.40$, $p = .02$) on initial direction. In both groups, trajectory orientations at acceleration peak gradually veered to the left throughout the 10 first trials. However, the slope of the curve over this period was steeper in the Sham group. In addition, the models showed that mean values were lower in the Sham group, i.e. average initial trajectories were more oriented to the left. Concerning intermediate direction of trajectories, models showed a significant effect of TIME ($\beta = -1.13$, SE = .10, $t(222) = -11.16$, $p < 10^{-15}$), i.e. trajectory orientations at velocity peak gradually veered to the left throughout the 10 first trials in both groups, with a steeper slope for the Sham group (GROUP*TIME effect; $\beta = .46$, SE = .15, $t(222) = 3.01$, $p < 10^{-2}$). Finally, trajectories at deceleration peak also gradually veered to the left across the 10 first trials in both groups without any distinction (TIME effect; $\beta = -1.04$, SE = .17, $t(222) = -6.24$, $p < 10^{-8}$).

During the remaining part of exposure (trials 11 to 60), we found no significant effect of TIME, GROUP, nor GROUP*TIME for initial and intermediate direction. However, results showed a significant effect of TIME ($\beta = -.04$, SE = .01, $t(1207) = -3.00$, $p < 10^{-2}$) on terminal direction without any effect of GROUP neither GROUP*TIME interaction. This indicates that trajectory orientations at deceleration peak continued to veer toward the left across trial repetition until the end of exposure, without significant difference between groups.

Moreover, significant effects were found in late blocks of exposure: slight effects of TIME ($\beta = -.24$, SE = .11, $t(218) = -2.11$, $p = .04$), and GROUP*TIME interaction ($\beta = .34$, SE = .17, $t(218) = 2.05$, $p = .04$) on initial direction during trials 41 to 50. We also found significant effects of GROUP ($\beta = 12.56$, SE = 4.63, $t(227) = 2.71$, $p = .01$) and GROUP*TIME interaction ($\beta = -.21$, SE = .08, $t(219) = -2.54$, $p = .01$) on intermediate direction during the 10 last trials (trials 51 to 60). These results indicate that the initial part of pointing trajectories slightly veered again to the left from trials 41 to 50 in both groups with a steeper slope for the

Sham group. In addition, during the 10 last trials of exposure, the group average intermediate orientations of pointing trajectories appeared to be more deviated to the left in the Sham group as compared to the C-tDCS group. However, the slope of the curve fitted over these 10 trials is steeper in the C-tDCS group.

Post tests

Pointing task: after-effects

Terminal errors

Analyses showed a significant effect of TIME ($\beta = .10$, SE = .01, $t(473) = 11.14$, $p < 10^{-15}$), GROUP ($\beta = 1.16$, SE = .44, $t(30) = 2.60$, $p = .01$) and GROUP*TIME interaction ($\beta = -.04$, SE = .01, $t(473) = -2.51$, $p = .01$) on pointing terminal errors values during post-tests (see **Table 2**). The positive effect of TIME shows that terminal errors values evolved to zero across trial repetition while the GROUP*TIME interaction indicates that this evolution was less pronounced in the Sham group. In addition, the GROUP effect suggests that mean terminal errors were overall larger in the C-tDCS group. These results indicate that stimulation had an influence on the magnitude of pointing after-effects and more specifically on their evolution across trials: in C-tDCS, after-effects were initially larger but decreased more rapidly compared to the Sham group. Therefore, we may conclude that after-effects in the tDCS group were about 20% larger but more labile, such that they turned similar to the ones of Sham group at the end of the testing period.

Trajectories

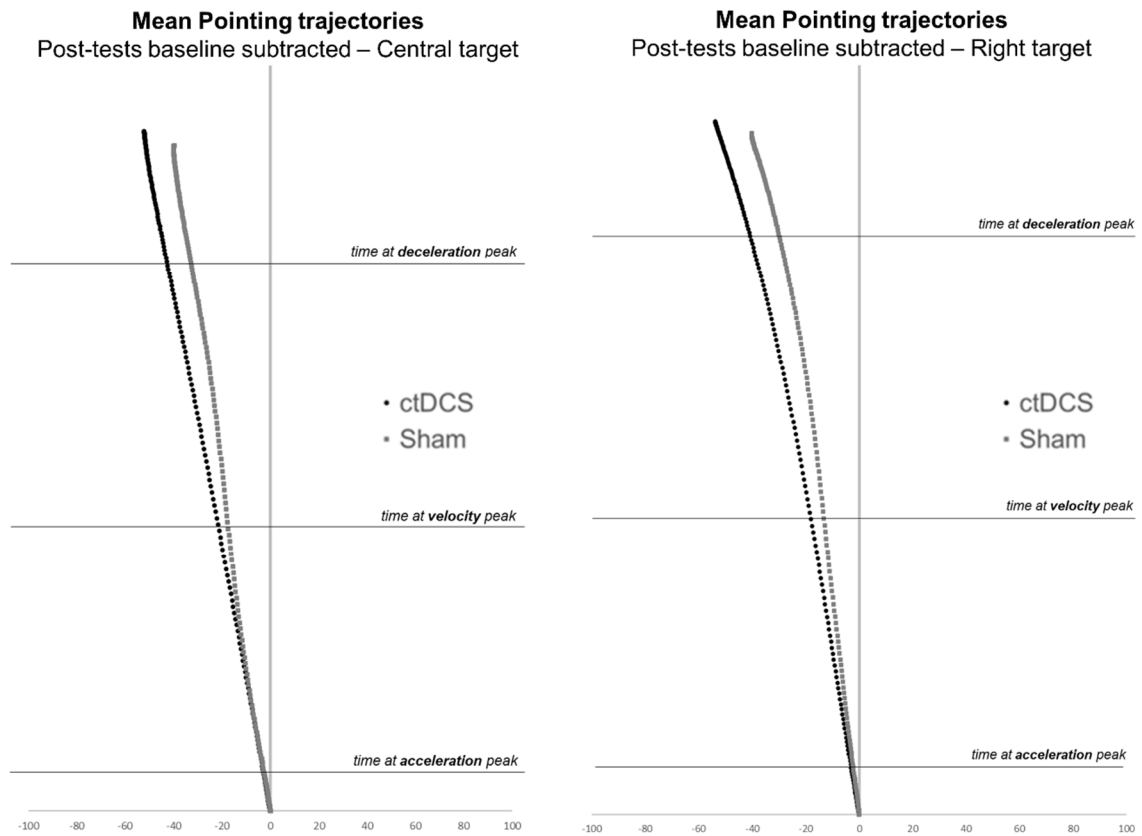
Mean pointing trajectories are represented in **Figure 6**. Models analyses were performed on pointing movements' orientations at initial, intermediate, and terminal directions. All effects are reported in **tables 3-6** (Supplementary Materials).

We found no significant effect of TIME, GROUP, nor GROUP*TIME for initial direction and for both targets. However, results showed significant effects of TIME ($\beta = .39$, SE = .08, $t(224) = 4.73$, $p < 10^{-5}$), GROUP ($\beta = 3.44$, SE = 1.23, $t(39) = 2.80$, $p = .01$) and GROUP*TIME interaction ($\beta = -.36$, SE = .13, $t(224) = -2.84$, $p < 10^{-2}$) for intermediate direction concerning pointing movements performed toward the central target.

A significant effect of TIME only ($\beta = .22$, SE = .09, $t(223) = 2.40$, $p = .02$) was found for intermediate direction of pointing movements performed toward the right target. For terminal direction, analyses revealed an effect of TIME both on central ($\beta = .28$, SE = .12, $t(224) = 2.42$, $p = .02$) and right ($\beta = .40$, SE = .16, $t(224) = 2.54$, $p = .01$) targets.

These results reveal that the initial direction of pointing movements during post-tests was similar between groups and did not evolve across trial repetition. As illustrated in **Figure 6**, trajectories differed between groups in the intermediate part of the movement. In both groups, trajectory orientations at velocity peak were initially deviated to the left, and evolved to the right across post-tests trials. Trajectory orientations were initially more deviated to the left in the C-tDCS group as compared to the Sham group. Interestingly the evolution of trajectory orientation was significantly less pronounced in the Sham group.

Figure 6 - Mean group pointing trajectories during post-tests. Mean pointing trajectories with baseline trajectories subtracted central target (left) and right target (right).



Throwing task: transfer

Models showed no significant effect of TIME, GROUP or GROUP*TIME when considering the 20 throwing post-tests trials. However, we found moderate but significant effects of GROUP ($\beta = -4.13$, SE = 2.03, $t(239) = -2.03$, $p = .04$) and GROUP*TIME ($\beta = .26$, SE = .13, $t(222) = 2.03$, $p = .04$) when considering trials 11 to 20 and pooling the two targets. These effects may indicate that transfer was greater in the Sham group while the evolution of values toward zero was steeper in the C-tDCS group than across post-tests trial repetition.

Analyses also revealed significant effects of TIME ($\beta = -.66$, SE = .21, $t(99) = -3.06$, $p < 10^{-2}$), GROUP ($\beta = -5.65$, SE = 2.44, $t(120) = -2.32$, $p = .02$), and GROUP*TIME ($\beta = .68$, SE = .32, $t(99) = 2.09$, $p = .04$) for trials 6 to 10 toward the right target (see Supplementary materials; **Table 2** for all values). After-effect transfer tended to increase across these five trials on the right target in both groups. This evolution was more marked in the C-tDCS group. However, mean terminal errors were larger in the Sham group, suggesting a stronger after-effect transfer as compared to C-tDCS group.

Discussion

The aim of the study was to explore the effect of cathodal cerebellar tDCS on the transfer of prism-acquired after-effects from pointing to throwing. Results revealed that participants in the C-tDCS group showed (1) altered error reduction and pointing trajectories during exposure, mainly during the first trials; (2) increased magnitude but reduced robustness of pointing after-effects; and crucially, (3) slightly altered transfer of after-effects to the throwing task. These results will be discussed in the light of former neuro-stimulation studies to highlight the possible role of the cerebellum in prism adaptation mechanisms.

Cerebellar C-tDCS interferes with pointing deviations and trajectories during exposure.

C-tDCS interferes with pointing terminal errors during exposure.

During early exposure (10 first trials), error reduction (i.e., correction of the terminal error induced by the optical shift) was greater for the Sham group. This effect was visible from the very first pointing trial under prism deviation, which shows that error correction was also faster. As there was no difference in movement durations and movements velocities between groups, a slower movement execution cannot explain differences in error reduction during exposure. Moreover, trajectories during the first trials and the overall terminal errors reliably

showed larger errors in the C-tDCS group. Therefore, it is unlikely that a transient change in speed-accuracy trade-off in the Sham group might explain these differences.

Findings on early exposure might suggest that C-tDCS impaired fast strategic adjustment (i.e. recalibration) in accordance with previous evidence (Küper et al., 2014; Panico et al., 2016; Panico, Sagliano, Nozzolillo, et al., 2018). As far as data on the very first pointing trial are concerned, a possible interpretation is that the cerebellum plays a role in online control (Panico et al., 2018). In Panico et al. (2018), authors provided three measures of pointing deviations during exposure: initial, early, and late components, which reflected respectively online control, recalibration, and realignment. Interference of C-tDCS on the initial component (average of the 2 first trials and not only the first trial) was interpreted as a sign of impaired online control, which seems to be in line with the present results. Another possible explanation is that C-tDCS impaired feedforward control of pointing movements under exposure. This is compatible with recent evidence indicating that the cerebellum plays a major role in predictive (feedforward) control of movement and in adaptive mechanisms of sensory predictions needed to adjust movement commands based on previous experience (Bastian, 2006; Therrien & Bastian, 2019). Nonetheless, the present study is the first in showing C-tDCS influence on the very first trial of exposure.

Surprisingly, the significant difference between groups in term of terminal errors was found only during early exposure (10 first trials) while in Panico et al.'s studies (2018, 2016), differences were found across the entire exposure phase. Importantly, the number of trials during exposure was smaller in our study compared to Panico et al.'s studies. Noticeably, our analysis did reveal a significant effect of the Group*Time interaction term suggesting that performance evolved differently from trial 11 to trial 60 during exposure according to the stimulation condition: the slope of the reduction curve was steeper in the C-tDCS group as compared to the Sham group. This may be simply due to the fact that errors were more stable in the Sham group : their performance accuracy was regained after a dozen of trials in these subjects. This was not observed in the C-tDCS group. A closer look at kinematics of pointing movements during exposure revealed differences in movements' orientations at intermediate direction during late exposure.

C-tDCS interferes with initial direction of pointing movements during early exposure and with intermediate direction during late exposure.

C-tDCS seemed to interfere with initial direction of pointing movements during early exposure (trials 1 to 10), which is in favour of an altered predictive control. However, on the first trial of exposure, initial direction of pointing movement was similar in both groups. Trajectories started to differ from intermediate direction, which is in favour of C-tDCS

influence on online control rather than predictive control. Predictive control of a subsequent pointing movement depends on error feedbacks experienced at the end of the previous trial (Bastian, 2006; Rossetti et al., 1993). Moreover, feedforward control of movement could also be adjusted relatively to online feedback-dependent corrections implemented in the previous trial (Diedrichsen et al., 2005). Therefore, the role of the cerebellum in online versus predictive control under prismatic exposure remains difficult to disentangle. A closer examination of pointing trajectories during early exposure could provide additional information about the possible effects of C-tDCS in early exposure. While initial direction was similar across groups on the very first trials, it appears that feedforward correction of initial direction of subsequent pointing movements differed between groups: participants in the stimulated group implemented a smaller correction compared to the sham group. This observation becomes crucial when one also considers that subjects in the C-tDCS group experienced a larger endpoint error on the first trial. In fact, C-tDCS participants seemed to benefit less from feedback during the first trial (i.e. impaired online control), so they were exposed to a greater amount of errors. However, they still exhibited a minor correction on subsequent trials (i.e. impaired feedforward adjustment), compared to participants of the Sham group. Yet, C-tDCS may interfere with the integration of errors to adjust movements both during pointing movements (online control) and before each subsequent trial (feedforward control). Alternatively, impairment of feedforward control might also be related to difficulties in developing an aiming solution in response to the perturbation during exposure, as suggested by Butcher et al. (2017).

Another interesting finding is that C-tDCS did not interfere with the evolution of terminal direction of pointing movements during exposure (time effect only). However, stimulation altered the evolution of intermediate pointing directions during early exposure (group*time effect) and during late exposure (group effect). As in O'Shea et al. (2014), results suggest that terminal direction of pointing movements during exposure evolved until the end of exposure, while initial and intermediate directions seemed to have reached a plateau. In fact, initial and intermediate deviations showed a quite stable trend following the very first trials but the slope in terminal direction was decreasing from the very first to the very last trials. These findings suggest that the adaptation of the terminal direction of pointing movements has not been completed by the end of exposure (60 trials). Either way, C-tDCS had no influence on this component. However, we may hypothesize that an increased number of trials during exposure would have led to a complete correction of terminal component, and potentially would have revealed an effect of C-tDCS on this very late component. These propositions are in line with Inoue et al.'s findings (Inoue et al., 2015) who suggested the existence of an ultra-slow process in PA.

Altogether, the above findings on deviations and pointing trajectories provide strong evidence of an impaired recalibration in C-tDCS participants compared to participants in the Sham group. The analysis of after-effects described in the next section will enable us to highlight the effects of C-tDCS on the realignment process (Prablanc et al., 2019; Redding et al., 2005).

C-tDCS interferes with magnitude and robustness of pointing after-effects.

C-tDCS participants seem to develop larger but labile after-effects.

A main objective of this study was to investigate the effects of C-tDCS on pointing after-effects and their transfer to throwing. Results showed larger after-effects in the pointing task in the C-tDCS group. Surprisingly, cathodal polarity of the stimulation did not lead to a reduction of after-effects. This finding is compatible with a previous study using similar procedures and reporting larger after-effects though larger errors during exposure (Panico et al., 2016). By contrast, this outcome is not coherent with a more recent study by Panico et al. (2018), in which reduced after-effects were found. However, the latter used a multiple-step prism adaptation procedure and C-tDCS was applied during exposure exclusively. These variations in the experimental procedures may have led to crucial differences in results concerning the observed effects of C-tDCS as previously described by Jalali et al. (2017). Strikingly, while after-effects in the present study were initially larger in the C-tDCS group, it seems that they were less stable and decreased more rapidly across post-tests trials compared to the Sham group. Although it is not straightforward to explain this apparently paradoxical result, we may speculate on several aspects. As suggested in Panico et al. (2016), as C-tDCS interfered with error reduction under prism exposure, it might also have impaired the restoration of non-perturbed motor programs during post-tests, leading to greater after-effects. In addition, as error reduction was impaired in the C-tDCS group, participants were exposed to greater errors under prism deviation and possibly developed greater initial after-effects on the pointing task. Finally, the fact that after-effects looked less stable in the C-tDCS group may be related to a greater cognitive component in after-effects, which is known to be more labile (Redding & Wallace, 2006), and/or to a less robust realignment (Panico et al., 2018). An interesting prospective of this observation will be to prolong the after-effect assessment period to determine whether the weaker stability of the after-effects observed during tDCS would ultimately bring their magnitude below that of the control group.

C-tDCS interferes with intermediate direction of pointing trajectories during post-tests.

Results showed no difference between groups in initial direction of post-tests pointing trajectories. Trajectories started to differ from intermediate direction, thus leading to

differences in endpoint terminal errors, and on the magnitude of after-effects. A possible explanation is that tDCS interfered with the processing of proprioceptive feedbacks during pointing movements. Participants in the Sham group applied a greater online proprioceptive correction as compared to participants in the C-tDCS group. These results may be in favour of an influence of C-tDCS on online control. Another possible explanation is that C-tDCS during exposure led to a different alteration of the proprioceptive modality. As suggested in a previous study (Fleury et al., 2020), reduced after-effects might be related to proprioceptive online corrections during post-tests. We may speculate that sham stimulation left proprioception modality largely unaffected in the present study, thus resulting in reduced after-effects in the Sham group as compared to C-tDCS group.

Does C-tDCS reduce transfer of after-effects to the throwing task?

A main purpose of this study was to test whether C-tDCS altered transfer of prism-acquired after-effects from pointing to throwing. Results showed a moderate but significant effect of C-tDCS on the magnitude of transfer for trials 11 to 20 and trials 6 to 10 toward the right target, suggesting a larger transfer in the Sham group.

The present results raise the possibility that cerebellar C-tDCS impaired transfer of prism acquired after-effects from pointing to throwing. Therefore, cerebellum might play a role in transferring visuo-motor transformations acquired in one context to another. A possible mechanism underlying this effect may be related to the role of the cerebellum in the development of realignment during exposure. In this light, C-tDCS may have impaired the development of true adaptation, thereby leading to a reduced transfer on the non-exposed task (Fleury et al., 2020). This is in line with the fact that after-effects looked less stable in the C-tDCS group, probably indicating a less robust realignment.

Although these findings provide the first evidence on the neural correlates of the transfer, they need to be interpreted with caution. Data showed a strong heterogeneity within both groups, and particularly in the C-tDCS group. Individual responsiveness to C-tDCS may vary among participants as reported by previous studies (Chew et al., 2015; Wiethoff et al., 2014). This may account for a potential higher variability in the effects of active stimulation as compared to sham stimulation in the present results. In addition, rate of adaptation and transfer could also be initially variable within groups (Renault et al., 2018; Stark-Inbar et al., 2017).

Concluding remarks, limitations, and perspectives

In conclusion, the present study demonstrates that C-tDCS interferes with PA from the very beginning of prism exposure until the full deployment of after-effects. These data are

compatible with a possible role of the cerebellum in online control, recalibration (feedforward control) and realignment (after-effects), and are in line with previous neuro-stimulation studies (Panico et al., 2016; Panico, et al., 2018). Our novel result is that the cerebellum appears to be involved in after-effect transfer, thus paving the way for more specific investigations. In fact, stimulation altered multiple PA components, i.e. error reduction during exposure, after-effects and crucially their transfer to another task. This suggests the likely existence of common mechanisms between several aspects of PA and transfer mechanisms, which probably reflects the involvement of true adaptation.

Some limitations of the present experiment must be underlined together with future directions. First, a greater number of trials during exposure may have led to stronger differences in after-effects and possibly to more robust findings on transfer. Second, a larger sample of participants and the use of high-definition tDCS protocols with computational modelling of brain's impedance would improve the reliability and the robustness of the tDCS effects (Jalali et al., 2017). Third, although the cerebellum was a key candidate for transfer, the possibility that transfer properties are undertaken by brain circuits linking the cerebellum with other areas involved in PA (Panico, Sagliano, Grossi, et al., 2018) has to be addressed in further studies. In the same line, further investigation should also test a possible role of the primary motor cortex in transfer, as this area seem to be involved in the storage of motor memories (O'Shea et al., 2017; Panico et al., 2017; review in Panico et al., 2021). Fourth, the present study did not investigate whether cerebellar contribution in transfer occurred during exposure or during after-effects testing. This should be clarified by modulating the timing of C-tDCS application. Finally, the use of additional methods such as electroencephalography (EEG) and ecological neuroimaging methods (functional Near Infrared Spectroscopy, fNIRS) during tDCS administration could help monitoring the effect of stimulation during the task and check for individual variability in C-tDCS effects.

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Authors' contribution

LF, FP and YR designed the study, LF, FP, PR and LD conducted data collection, LD developed custom software for analysis, LF processed and analysed data, AF substantively helped with the statistical analysis, LF, FP and YR interpreted data, LF drafted the manuscript, YR, FP, AF, SJC and CC substantively revised it.

Competing interests

The authors declare no competing interests.