Original Article

Online polarity-dependent effects of cerebellar transcranial direct current stimulation on motor speed and fine manual dexterity

A randomized controlled trial

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ABSTRACT

الأهداف: استكشاف دورالتحفيز بالتيارالمباشر للمخيخ عبر الجمجمة (ctDCS) في تعديل وظائف المخيخ في المجالات الحركية الدقيقة من البراعة وسرعة الحركة.

المنهجية: أجريت دراسة عشوائية أحادي التعمية –زائف– السيطره عليها بين يناير ويوليو 2018 في مختبر علم الأعصاب بجامعة الإمام عبد الرحمن بن فيصل. تم تقييم ما مجموعه 63 من المشاركين الأصحاء للأهلية. استوفى ستون منهم معايير الدراسة وتم تقسيمهم بشكل عشوائي إلى ثلاث مجموعات يتلقون ctDCS التيار المصعدي، والتيارالمهبطي والتيار الزائف. أجرى الأشخاص امتحانين – حيث أن اختبار(GPT) Pegboard Pegboard خاص بتقييم البراعة اليدوية الدقيقة، اختبار(FTT) Finger Tapping Task خاص بتقييم سرعة مهمة أداء الأصابع. جميع المشاركين قامو بأداء الامتحانين في جلسة واحدة أثناء تعرضهم للتحفيزبالتيارالمباشر للمخيخ عبر الجمجمة(ctDCS) لمدة 20 دقيقة بقوة 2mA. كذلك تم استخدام النسخة المختصره لمقياس أدنبره لتقييم اليدوية، ثم تنفيذ كلا الامتحانين أولاً باليد المهيمنة ثم اليد غير المهيمنة. تتضمن مقاييس النتائج الأولية وقت الانتهاء من الامتحانين كل من البراعة اليدوية الدقيقة وتقييم سرعة مهمة أداء الأصابع لكل يد.

النتائج: كشف تحليل التباين(ANOVA) تفاعل مهم للغاية يعتمد على قطبية المجموعة (p<0.01) لدرجات تقييم سرعة مهمة أداء الأصابع (FTT). كشف تحليل التباين (ANOVA) أيضًا عن تفاعل غير مهم للمجموعة لدرجات بتقييم البراعة اليدوية الدقيقة (GPT).

الخلاصة: تشير النتائج إلى أن (ctDCS) له تأثير معياري على سرعة الحركة وقد يكون تدخلاً علاجياً واعداً لعلاج الحالات العصبية مع العجز الحركي.

Objectives: To investigate the role of cerebellar transcranial direct current stimulation (ctDCS) in modulating cerebellar functions in the motor domains of fine motor dexterity and motor speed.

Methods: A single-blind, randomized sham-controlled study was conducted between January and July 2018 at the neuroscience laboratory of Imam Abdulrahman Bin Faisal University. A total of 63 healthy participants were assessed for eligibility. Sixty subjects met the criteria of the study and were randomly divided into 3 groups that received anodal, cathodal or sham ctDCS. Subjects performed 2 motor tasks, The Grooved Pegboard test (GPT) assessed fine manual dexterity and the Finger Tapping Task (FTT) assessed motor speed. Subjects undertook the 2 tasks in a single intervention session while 20 minutes of 2mA ctDCS was administered online. The short form of the Edinburgh Handedness Inventory was used to assess handedness and both tasks were performed first with the dominant and then the non-dominant hand. The primary outcome measures included the time of completion of GPT for fine manual dexterity and the mean number of finger-taps for motor speed of each hand.

Results: ANOVA revealed a highly significant polarity dependent Group*Task interaction (p<0.01) for FTT scores. ANOVA also revealed a non-significant Group*Task interaction for GPT scores.

Conclusion: Findings indicate that ctDCS has a modulatory effect on motor speed and could be a promising therapeutic intervention for treatment of neurological conditions with motor deficits.

Keywords: cerebellar transcranial direct current stimulation, cerebellar modulation, fine manual dexterity, motor speed

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The cerebellum is involved in a wide variety of functions through dense connections to different areas of the cerebral cortex.[1,2] These functions lie under a broad spectrum, ranging from simple motor to complex cognitive processes.[3,4] The cerebellum imposes its effect on motor domains by influencing the cerebral cortex through cerebello-cortical pathways.[5] The facilitation of Purkinje cells inhibits the deeply situated cerebellar dentate nucleus and this inhibition leads to disfacilitation of the primary motor cortex (M1). This inhibitory effect of the cerebellum on M1 was previously termed as cerebellar brain inhibition (CBI).[6] Taking CBI into consideration, several studies have employed non-invasive brain stimulation techniques to investigate the effects of cerebellar modulation on different functional domains.[7-9]

Cerebellar transcranial direct current stimulation (ctDCS) is a safe non-invasive method of brain stimulation where in a small amplitude of current (1-2 mA) is induced into the cerebellum through electrodes placed on the skull.[10] Cerebellar transcranial direct current stimulation can be administered by using 2 types of current polarities (cathode and anode) that continuously activate action potentials in the pre-synaptic neuron through a process known as long term potentiation (LTP).[11] Anodal stimulation is believed to facilitate the inhibitory Purkinje cells thereby inhibiting M1 functions; while cathodal stimulation facilitates M1 by suppressing the inhibitory functions of Purkinje cells.[11] During stimulation, glutamate is released from its vesicles and binds to receptors on the post-synaptic cell membrane. This leads to the activation of N-Methyl-D-Aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors thereby modulating neuronal circuits and strengthening synaptic connectivity.[12] This strengthening of synaptic connections has been proven to modulate cerebellar functions by inducing plastic changes in the cerebellar structure.[13]

McCreery et al[14] found that there was no neuronal harm to the brain below a current density of 25 mA/ cm^2. In terms of cerebellar stimulation, a previous modelling study observed that a current intensity of 2mA produced a current density between 0.021 and 0.013 mA/cm^2 in the cerebellum.[15] Thus, a current intensity of 2 mA does not impose any danger to the brain tissues as it does not exceed a current density of 25 mA/ cm^2. Moreover, damage to brain tissue occurs when the accumulative charge of current crosses a threshold of 216 C/cm^2.[2] Because the maximum total charge attained with an intensity of 2 mA is 1.14 C/ cm^2, no neuronal harm is possible.

In terms of motor functions, blood oxygen dependent level (BOLD) signals were detected in the cerebellum during the performance of a finger tapping task where clusters of activity were observed in the ipsilateral IV-VI cerebellar lobules.[16] Other neuroimaging studies identified motor activations along the cortex and dentate nuclei of the cerebellum.[17] Interestingly, contradictory to the lower limb, face and mouth cerebellar motor representations, the upper limbs were observed to have a more scattered activation pattern.[18] This indicated that the modulation of cerebellum using ctDCS is more likely to improve upper limb functions. A vast body of evidence has focused on the role of modulation of M1 with tDCS to improve motor skills.[19] However, despite evidences highlighting the role of anterior lobe of cerebellum in motor functions[20] and deficits in motor functions with cerebellar dysfunctions,[21] the role of the cerebellum in fine manual dexterity was not investigated. Previous studies that aimed to identify the role of M1 on fine manual dexterity were highly controversial.[22-24] Similarly, few studies have investigated the role of ctDCS on motor speed and the obtained results revealed that the polarity of current affected modulation differently.[25,26] Thus, in this study the effect of ctDCS on fine manual dexterity and motor speed was investigated. Based on the principle of CBI, it was hypothesized that anodal stimulation deteriorates the performance of fine manual dexterity and motor speed while cathodal stimulation improves the same variables. Moreover, it was hypothesized that sham stimulation had no effect on the outcome variables of fine manual dexterity and motor speed.

Methods. PubMed, the Cochrane Library and Imam Abdulrahman Bin Faisal University (IAU) database (Summon) were used to search and extract research articles published in the field of ctDCS. Keywords such as cerebellar modulation, cerebellar transcranial direct current stimulation, motor functions, upper limb motor functions, dexterity, fine manual dexterity, and motor speed were used in the search.

A randomized single-blind sham-controlled study conducted between January and July 2018 at the Neuroscience Laboratory of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. Subjects were divided into 3 homogenous groups with 10

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females and 10 males in each group. The groups were then randomly allocated into 3 ctDCS interventions: anode, cathode, and sham based on a randomized draw (**Figure 1**). Subjects were blind to the type of stimulation group they were assigned to. The sample size was calculated using a sample size calculator (https://www.ai-therapy.com/psychology-statistics/sample-size-calculator). The effect size was determined as large (Cohen's d- 0.8) and the total number of participants was hence calculated as 20 in each group.

A total of 60 subjects (sample of convenience) were included in the study (30 men and 30 women; mean±SD: 28.35 ± 6.62 years). Inclusion criteria included healthy subjects between the ages of 18 and 40 years. Subjects were excluded if they had a history of central or peripheral nervous system disease, psychiatric disorders, diabetes, pregnant during the time of the study, or if they had previously participated in a non-invasive brain stimulation technique. All subjects signed an informed consent before commencement of the experiment which was approved by the Institute Review Board (IRB) at Imam Abdulrahman bin Faisal University. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Cerebellar transcranial direct current stimulation was administered using a direct current stimulator (The Magstim Co., Whitland, UK) with saline soaked (7x5 cm) rectangular electrodes. Electrode placement was based on the 10-20 EEG system[27] with the active electrode centrally placed 2 cm below the inion and the reference electrode placed on the dominant deltoid muscle.[28] For the sham group, current was ramped up

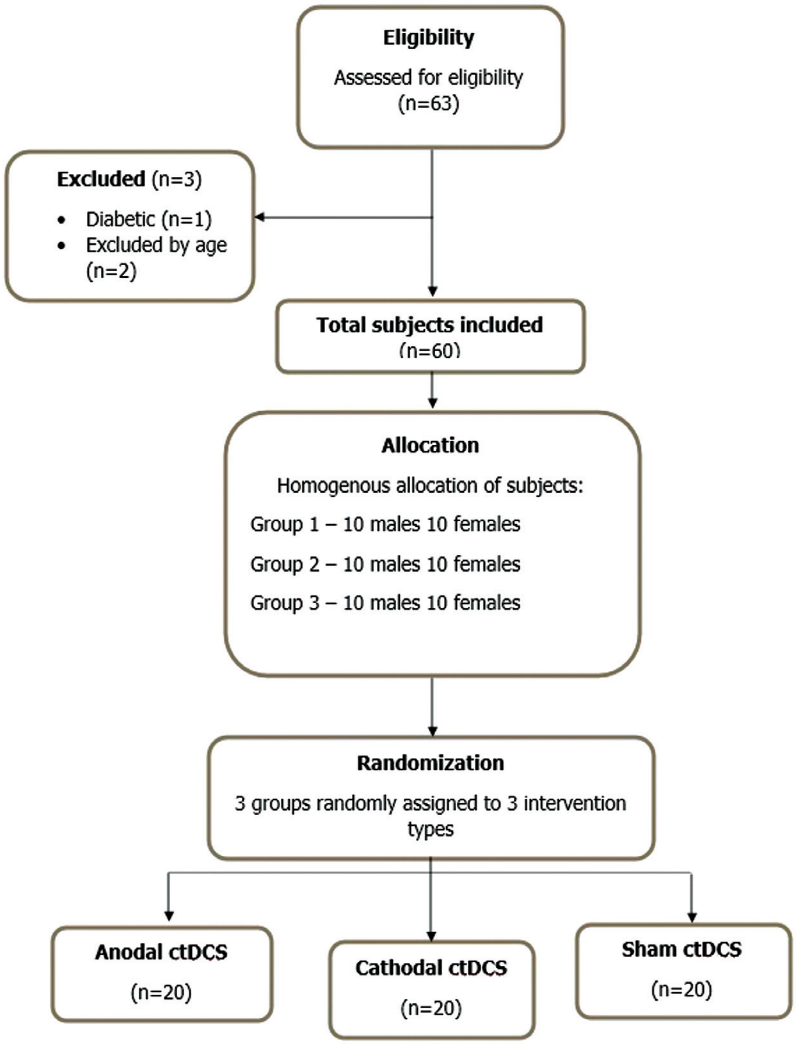

Figure 1 - Flow chart illustrating inclusion, exclusion, allocation and randomization of subjects.

for the first 30 seconds to ensure blinding, after which the current was ramped down to 0. This montage prevents interference created by the placement of both the electrodes on the skull. Direct current of an intensity of 2 mA was induced for 20 minutes, leading to a current density of 0.057 mA/cm^2 and a total charge of 1.14 C/cm^2.[28]

Upon inclusion into the study, subjects were asked a set of questions based on the Edinburgh handedness inventory-short form to decide hand dominance.[29] Out of the 60 subjects, 53 were right dominant, 6 were left dominant, and one was ambidextrous. Mental fatigue level using the visual analogue scale (VAS) was utilized to rate the subject's fatigue level from 0-10. Any subject reporting a mental fatigue of more than 5/10 was given a break before the onset of the next task. In this study, no subjects exceeded the fatigue level of 5 and thus, no rest was needed between tasks. Safety of the subjects was also assessed verbally wherein instructions were given to report itchiness, burning or pain sensation at any time during the course of the study.

Motor speed was assessed using a neuropsychological task known as the finger tapping task (FTT) which examines motor functioning and integrity of the neuromuscular system.[30] It involves assessing the tapping speed of dominant and non-dominant hands. This task was completed using the PEBL Psychological test battery.[31] Instructions were provided to press a key as fast as possible using the index finger within a time interval of 10 seconds (s). The subjects performed a total of 5 blocks of 10 s trials for each hand. The mean of 5 blocks (for each hand) was recorded as the mean number of finger taps. Moreover, the total number of finger-taps per block were recorded as D1, D2, D3, D4, and D5 for the dominant hand and ND1, ND2, ND3, ND4, and ND5 for the non-dominant hand. The grooved pegboard test (GPT) (Lafayette Instrument, Model 32025) was used to assess fine manual dexterity.[32] Subjects were instructed to manipulate and insert 25 pegs into holes as fast as possible. The task was performed first with the dominant and then the non-dominant hand. The time of completion was recorded in milliseconds (ms) as an outcome of the task. Two scores were recorded for analysis: dominant and non-dominant scores.

Statistical analysis. All statistical tests were conducted using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc., Chicago, III., USA). One-way analysis of variance (ANOVA) assessed the *Group*Task* interactions for between-subject comparison between the dominant and non-dominant hands of GPT ($p<0.05$). Similarly, *Group*Task* interactions (one-way ANOVA) assessed the between-subjects factor for dominant and non-dominant hands of FTT. A repeated measures (RM) Spilt-plot ANOVA was conducted to analyze the within-subject factor for the 5 blocks of dominant (D1, D2, D3, D4, D5) and 5 blocks of non-dominant hands (ND1, ND2, ND3, ND4, ND5) for FTT. Further multiple group comparisons were assessed using post-hoc Tukey test.

Results. Demographic characteristics such as gender, age, and hand dominance are presented in **Table 1**. Finger tapping task: Dominant FTT scores: *Group*Task* interaction revealed highly significant difference in dominant hand scores [$F(2, 57) = 6.97$; $p=0.002$]. Post-hoc Tukey test revealed a significant difference between anode (mean±SD: 62.10 ± 7.57) and sham (mean±SD: 52.65 ± 7.61) ($p=0.001$) scores. However, cathode (mean±SD: 58.62 ± 9.00) showed no significant difference in anode and sham groups (**Figure 2**). Repeated measures (RM) ANOVA for the five blocks (D1, D2, D3, D4, D5) of dominant hand revealed a highly significant between-subjects FTT dominant *Group*Task* effect ($p=0.003$) (**Figure 3**). However, within-subjects Block effect was not significant ($p=0.47$) with a partial eta-squared value of 0.031.

Table 1 - Demographic characteristics of subjects in the anode (a-ctDCS), cathode (c-ctDCS), and sham (s-ctDCS) groups.

Demographic characteristics	a-ctDCS (n=20)	c-ctDCS (n=20)	s-ctDCS (n=20)
Age (mean±SD, years)	28.3 ± 6.1	29.1 ± 7.3	27.6 ± 6.6
Gender (woman, %)	10 (50)	10 (50)	10 (50)
Laterality (right-handed, %)	17 (85)	18 (90)	18 (90)

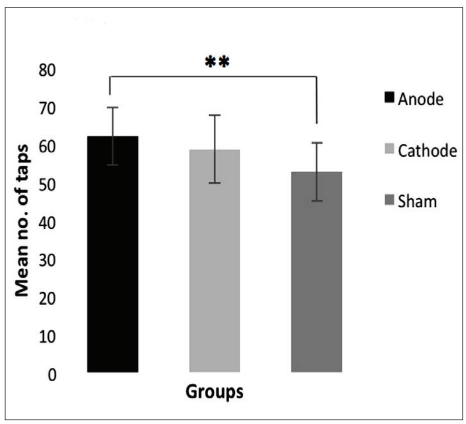

Figure 2 - Graphical representation of mean finger tapping task dominant scores of the anode, cathode, and sham groups; **significant $p<0.01$; *significant $p<0.05$

Non-dominant FTT scores. *Group*Task* interaction showed a significant difference in non-dominant hand scores [F(2, 57)=5.05; *p*=0.01]. Post-hoc Tukey test revealed a significant difference between anode (mean±SD: 54.75 ± 6.51) and sham (mean±SD: 47.92 ± 5.65) scores (*p*=0.02). Similarly, cathode (mean±SD: 54.67 ± 10.38) and sham (mean±SD: 47.92 ± 5.65) showed a significant difference in mean task scores (*p*=0.02). However, cathode and anode showed no significant difference in scores (**Figure 4**). Repeated measures split-plot ANOVA of within-subjects factor for the 5 blocks (ND1, ND2, ND3, ND4, ND5) of FTT non-dominant *Block*Group* revealed non-significant effect (*p*=0.22) with a partial eta-squared value of 0.045 (**Figure 5**).

Grooved pegboard test. i) Dominant GPT scores: For the dominant hand, mean±SDs were 62.85 ± 8.22 for anode, 61.35 ± 9.36 for cathode, and 62.15 ± 10.49 for sham. One-way ANOVA revealed a non-significant *Group*Task* effect on GPT dominant scores [F(2, 57) = 0.12; *p*=0.881]. ii) Non-dominant GPT scores: In terms of non-dominant hand scores, mean±SDs were 69 ± 7.90 for anode, 67.70 ± 8.83 for cathode, and 66.55±9.45 for sham. Concurrent with the findings above, one-way ANOVA revealed a non-significant *Group*Task* effect on GPT non-dominant hand scores [F(2, 57) = 0.39; *p*=0.67].

Discussion. The observations from this study revealed a polarity dependent *Group*Task* effect of cerebellar modulation, where a significant difference was observed between anodal and sham ctDCS for the dominant and non-dominant hands. These results were precisely concurrent with previous studies that investigated the effect of cerebellar modulation on motor speed. While cathodal stimulation showed no effect on the performance of FTT,[25] anodal stimulation was found to enhance the performance of the task.[24] The fact that no difference was noted between anode-cathode or cathode-sham groups proves that the effect of cathodal stimulation is not necessarily an inverse of anodal stimulation.[5] Cantarero et al[9] have previously raised the prospect that cathodal stimulation might not have a strong influence on cerebellar processes. In this study, the dominant hand showed a significantly higher motor speed than the non-dominant hand. As the non-dominant hand has a relatively slower performance than the dominant hand, there is a higher potential for improvement in performance. This has been previously explained as the "ceiling effect", where the performance

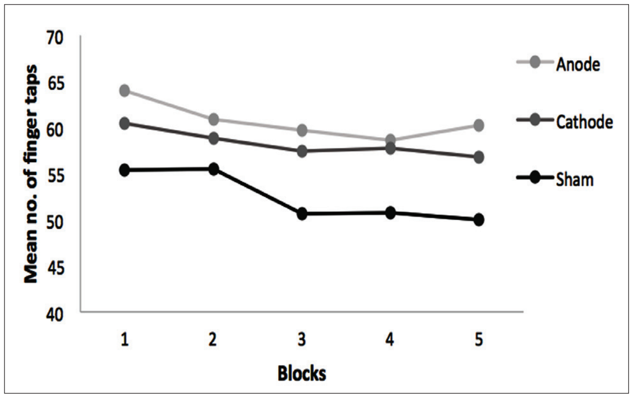

Figure 3 - Graphical representation of finger tapping task scores for the five dominant hand blocks in the anode, cathode, and sham groups.

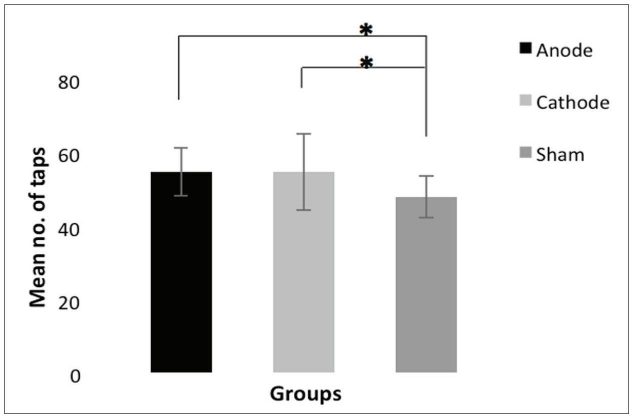

Figure 4 - Graphical representation of mean finger tapping task of non-dominant scores in the anode, cathode, and sham groups; ** Significant p<0.01; * Significant p<0.05

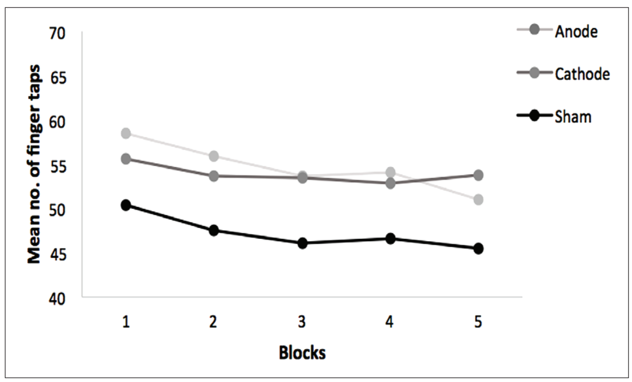

Figure 5 - Graphical representation of finger tapping task scores for the five dominant hand blocks of the anode, cathode, and sham groups.

of a task can improve to a certain extent after which a plateau is reached and further improvement is not possible.[9] If an effect was to be observed, it would have been more probable if the non-dominant FTT scores improved more significantly due to the ceiling effect of the dominant hand.

Further analysis was conducted to scrutinize repeated measures pairwise comparison of scores between the 5 blocks of the dominant (D1-D5) and non-dominant (ND1-ND5) hands. In the dominant hand scores, results revealed no significant increase between the first and the second blocks. However, a highly significant increase was demonstrated in scores of the first and the second blocks in comparison to the third, fourth, and fifth blocks. This suggests that modulation of the cerebellum affected performance during the first 2 blocks where the scores were highest. Subsequently, the scores continued to decrease with no significant increase in the final blocks (D3-D5). This is consistent with a previous study that highlighted that anodal stimulation prompted a hyperpolarization block in descending cortical pathways.[33] Therefore, anodal stimulation imposed maximum modulation of the cerebellum during the first 2 blocks after which the scores reached a plateau. Concurrent with the above findings, the non-dominant within-subjects pairwise comparison revealed a maintenance of high scores during the first 3 blocks (ND1-ND3). This emphasizes that as the non-dominant hand was less proficient in conducting the task, there was a higher potential for improvement with time. Moreover, there was no significant increase between the scores of the third, fourth, and fifth blocks (ND3-ND5). Again, this reveals that anodal stimulation modulated the cerebellum initially before attaining a hyperpolarization block.

In terms of fine manual dexterity, cerebellar modulation using ctDCS failed to show a significant effect on the performance of GPT for the dominant and non-dominant hands. This implies that the cerebellum might not have a significant contribution in modulating fine movements as compared to other cortical areas like M1. Parikh and Cole[34] previously reported that anodal M1-tDCS demonstrated an effect on descending motor pathways by improving the performance of GPT immediately after, and 35 min post stimulation. Similarly, anodal tDCS on M1 demonstrated an online training effect on GPT while cathodal tDCS influenced offline training performance.[22] To delineate the roles of the cerebellum and the cerebral cortex, Galea et al[16] showed that cerebellar modulation using ctDCS improved motor functions.[7] Earlier neuroimaging studies also verified this by illustrating the presence of a mirrored sensorimotor homunculus along the structure of the cerebellum, representing different areas for hand and finger movements.[16] The fact that this study showed no significant effect indicates that the cerebellum might have a role in selective motor functions other than fine manual dexterity.

Study limitations. The data was conducted from a single ctDCS intervention session. It was a single blinded study where only healthy subjects were recruited as a sample of convenience.

In conclusion, based on the findings of this study, cerebellum contributes to motor speed by improving the efficiency of performance. Moreover, the maximum effect observed was during the initial blocks of the task after which the performance deteriorated and reached a plateau. Furthermore, this study failed to demonstrate a modulating effect of the cerebellum on fine manual dexterity in healthy subjects. Collectively, all findings suggest that there is a distinct functional distribution of motor maps and the cerebellum does not necessarily contribute to all motor functions despite its widely scattered motor homunculus.

Future research should attempt to investigate the role of multiple sessions of ctDCS on fine manual dexterity and motor speed in health and disease. Moreover, the long-term effects of ctDCS must be explored to establish ctDCS as a valid treatment for disorders affecting both cerebellar and cortical functions.

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