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ABSTRACT

Background: The cerebellum and primary motor cortex (M1) are crucial to coordinated and accurate movements of the upper limbs. There is also appreciable evidence that these two structures exert somewhat divergent influences upon proximal versus distal upper limb control. Here, we aimed to differentially regulate the contribution of the cerebellum and M1 to proximal and distal effectors during motor adaptation, with transcranial direct current stimulation (tDCS). For this, we employed tasks that promote similar motor demands, but isolate whole arm from hand/finger movements, in order to functionally segregate the hierarchy of upper limb control.
Methods: Both young and older adults took part in a visuomotor rotation task; where they adapted to a 60° visuomotor rotation using either a hand-held joystick (requiring finger/hand movements) or a 2D robotic manipulandum (requiring whole-arm reaching movements), while M1, cerebellar or sham tDCS was applied.
Results: We found that cerebellar stimulation improved adaptation performance when arm movements were required to complete the task, while in contrast stimulation of M1 enhanced adaptation during hand and finger movements only. This double-dissociation was replicated in an independent group of older adults, demonstrating that the behaviour remains intact in ageing.
Conclusions: These results suggest that stimulation of distinct motor areas can selectively improve motor adaptation in the proximal and distal upper limb. This also highlights new ways in which tDCS might be best applied to achieve reliable rehabilitation of upper limb motor deficits.
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Introduction

Good control of the upper limb is vital to carrying out even the most basic activities of daily living: eating, bathing, dressing etc. The subtle, but gradual decline in motor performance associated with increasing age can restrict the ability of older adults from safely carrying out these activities, having considerable consequences on their independence and well-being [1,2]. In addition, upper limb motor deficits linked to age-related diseases such as stroke and Parkinson's Disease (PD) place further burdens on the quality of life of these older adults.

Normally, we smoothly integrate control of the arm and hand. However, the proximal and distal portions of the upper limb appear to be subserved by somewhat distinct neural substrates. The primary motor cortex (M1) seems to have a particularly important role in hand and finger movements. In primates, including humans, direct corticomotoneuronal (CM) projections from M1 to spinal motor neurones are thought to be key [3–6]. Additionally, the large neural representations in M1 that code for hand and finger movements support its role in distal upper limb control [7]. M1 however, is only one of several nodes in the central nervous system, such as the basal ganglia, cerebellum and spinal cord, that contribute to accurate and coordinated movements of the upper limbs. Of these, the cerebellum has a particularly strong influence

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over movements of the proximal upper limb. The human cerebellar cortex contains motor representations of all four limbs, with prominent representations of the arms and hands [8], while cells in the monkey cerebellar cortex and nuclei fire with proximal arm movements [9]. Additionally, the cerebellum has major connections to nuclei in the brainstem that are the origin of descending pathways controlling the proximal musculature and send prominent outputs to important parietal reach-related areas [10,11].

The differential control of the proximal versus the distal upper limb was highlighted by Don Lawrence and Hans Kuypers in the late 1960s [12,13]. Their studies culminated in an experiment that lesioned the corticospinal tract in monkeys at the level of the pyramids. This left the motor cortex intact, but removed its direct influence on the spinal cord. Although initially severe motor impairments were observed, the animals recovered rapidly and after a short period of time were able to walk, run, climb, and importantly use their arms to reach and grasp for food. However, they never recovered the ability to independently move their digits, always using all their fingers in concert. The dissociated recovery of the proximal and distal upper limb has also been displayed in humans post-stroke [14] and following surgical extirpation of the motor cortex that was used as an early surgical intervention for epilepsy [15–17]. These findings show that recovery of hand muscles is more dependent on corticospinal tract integrity compared to arm muscles. Finally, there are age-related changes in the density and composition of the corticospinal tract [18,19] and suggestions of differential changes in cortical grey matter [20,21] that imply the relative contribution of M1 and the cerebellum to different aspects of motor control might shift with advancing age.

With this background in mind, we turn to the recent literature on transcranial direct current stimulation (tDCS). Due to its capacity to modulate the excitability of different parts of the brain [22–24], tDCS had become a popular research tool, with potential clinical translation. Behavioural studies have shown that the application of tDCS can improve various aspects of upper limb motor function and learning in healthy young adults [25,26], older adults [27,28] and patient populations [29,30]. However, studies using tDCS have shown inconsistent effect sizes, both in the normal brain and in rehabilitation [31,32]. One possible reason for this is the lack of spatial specificity of tDCS. Unlike transcranial magnetic stimulation (TMS), there is little evidence that tDCS can be used to accurately modulate specific brain areas. It is also not clear that the behavioural tasks used have been chosen to highlight the contribution of the brain areas targeted.

We therefore sought to combine targeted stimulation of the cerebellum and M1 with tasks that share similar motor control characteristics but isolate whole arm movements from hand/finger movements. Given the differing levels of control exerted by the cerebellum and M1 over proximal and distal muscles, we hypothesised that cerebellar but not M1 stimulation would improve performance in the arm movement task in healthy young adults. Conversely, M1 but not cerebellar stimulation would improve performance in the task requiring hand and finger movements. As there is evidence for age-related change in these two motor regions, we also examined if this double dissociation was seen in older adults.

Materials & methods

Participants

Ninety healthy younger adults (46 females; aged 18–29 years, mean 19.5 ± 1.4 (standard deviation) years) and seventy-two healthy older adults (41 females; aged 66–84 years, mean

74.9 ± 4.1 years) gave written consent to take part in this study (approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at The University of Birmingham). Older adults were offered travel expenses for taking part and younger adults (all undergraduate students at the University of Birmingham) received research credits that counted towards their degree mark. Participants were all right-handed (self-report) and had normal or corrected to normal vison. Safety screening questionnaires for TMS and tDCS were completed prior to the experiment and no participants were taking centrally acting drugs.

All participants were pseudo randomly assigned to either the joystick or vBOT task and then again into one of three stimulation groups (M1, Cerebellar or Sham):

- vBOT Task:
  o M1 Stimulation: 15 young (7 females) and 12 older adults (6 females).
  o Cerebellar Stimulation: 15 young (8 females) and 12 older adults (7 females).
  o Sham Stimulation: 15 young (9 females) and 12 older adults (7 females).
- Joystick Task:
  o M1 Stimulation: 15 young (8 females) and 12 older adults (7 females).
  o Cerebellar Stimulation: 15 young (7 females) and 12 older adults (7 females).
  o Sham Stimulation: 15 young (7 females) and 12 older adults (7 females).

Experimental design

vBOT task

Participants sat comfortably in an armless chair and used their right hand to grasp the handle of a custom-built two-dimensional planar robotic manipulandum [33] which allows movement in the horizontal plane (Fig. 1a). The vBOT measured and stored the position and velocity of the handle at 1000 Hz. The task display was reflected onto a horizontal 'semi silver' screen (60 cm × 76 cm) in front of the participants from a computer monitor (Mac Cinema HD Display) located directly above. The screen displayed a white outlined circle (diameter: 12 cm) and a red cursor (diameter: 0.5 cm), which was controlled by movement of the vBOT handle (Fig. 1c). At rest the cursor would be located in the centre of the circle. During the task a green target (diameter: 0.5 cm) would alternate between the centre position and one of eight equidistant target locations around the circle perimeter, with a dwell time of 1 s in each position. Participants were instructed to make straight, fast movements with the vBOT handle towards and through the target and then return to the centre position, without making corrective adjustments. The point where participants' movement crossed the perimeter circle (i.e. their final angle), would be displayed by an open red circle, remaining on screen until the target returned to the centre. The room was darkened prior to the start of the task to block vision of the hand/arm underneath the screen. In addition, a 'curtain' was attached to the vBOT frame and prevented participants viewing their upper arm. The vBOT handle was grasped with a power grip, and the 10–15 cm motion of the vBOT was achieved mainly with shoulder and elbow motion, and with only limited wrist flexion/extension.

Joystick Task

Participants were seated at a comfortable distance away from a vertical computer screen (22.5 cm × 30.5 cm), so that they could reach and manipulate a small, sprung joystick (APEM 9000 Series,
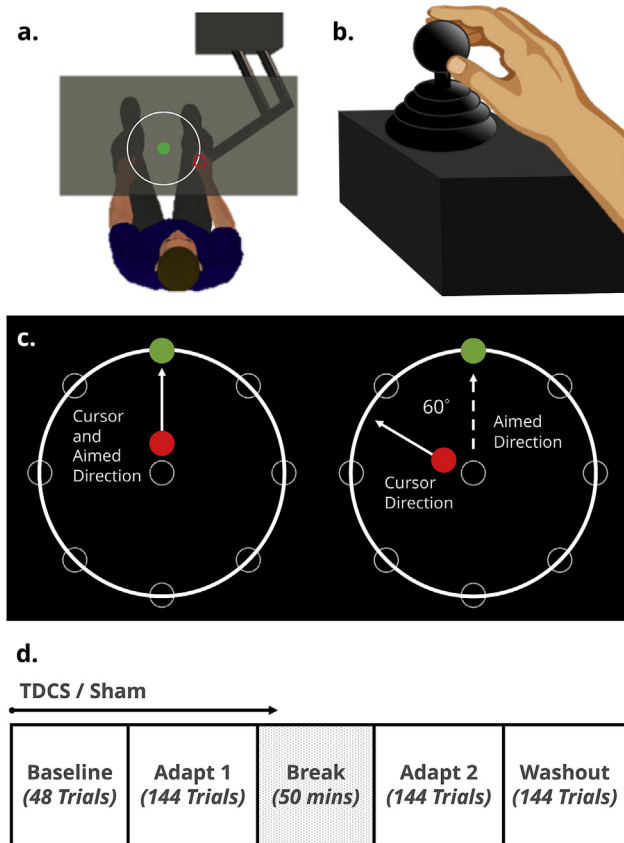
Fig. 1. Schematic diagrams of the vBOT (**a**) and Joystick (**b**) experimental set up. (**c**) An example of the display for both tasks during baseline/washout trials (left), where the aimed and cursor direction are matched and rotational perturbation trials (right), where a 60-degree counter-clockwise rotation is added to the vBOT handle/joystick. (**d**) A time course of the study protocol. Each trial was to one of 8 targets, in pseudorandom order. In Adapt 1 and Adapt 2, a 60-degree rotation between movement of the vBOT/joystick and the displayed cursor was imposed. tDCS started at baseline (1.75 min), continued throughout Adapt 1 (5.25 min) and then was turned off 10 min into the break. After the break period, participants performed Adapt 2 and Washout blocks (5.25 min each).

75 Hz sampling rate) with their right hand (Fig. 1b). The joystick was 6.5 cm in height, 2 cm in width and fixed to the desk next to the computer screen with a clamp. The task display, paradigm and timings were exactly the same as for the vBOT task to allow between group comparisons. Participants were asked to make single, rapid and uncorrected movements with the joystick towards and through the target, then back to the centre. Vision of the hand was blocked during the task using an opaque box and participants were asked to refrain from moving their arm/shoulder. 2–3 cm motion of the joystick was typically achieved by index finger and thumb movement and wrist abduction/adduction.

Visuomotor rotation paradigm

The behavioural task was split up into a baseline phase, two visuomotor adaptation phases (Adapt 1 and Adapt 2), separated by a break period, and a washout phase (Fig. 1d). During baseline trials the on-screen cursor movement would match the movement of the joystick/vBOT handle. Throughout the two rotational phases, a 60° counter-clockwise (CCW) rotation was applied to the cursor with respect to the joystick/vBOT handle (Fig. 1c). The Adapt 1 and 2 phases were separated by a 50-min break period, where the participants sat at rest. The washout phase immediately followed Adapt 2 and returned the cursor rotation to 0°, so that it again

matched the movement of the joystick/vBOT handle. There was no on-screen cue of this condition; prior to the experiment participants were told that a perturbation would be applied to the cursor at some point but were not informed about its nature. They were asked not to use any explicit strategies in order to overcome it, but to try their best to hit or get as close to the target as they could in each trial.

tDCS

tDCS was administered at 2 mA via two saline soaked sponge electrodes measuring 5 × 7 cm, using a DC-Stimulator (neuro-Conn, Ilmenau, Germany). For M1 stimulation the anodal electrode was positioned over the 'hand area' of the left motor cortex, identified for each participant via first dorsal interosseous muscle activation using single pulse TMS (Magstim 200 mono pulse stimulator/Magstim Radpid[2] stimulator; Magstim Ltd, UK) and the cathode electrode was placed over the contralateral supraorbital ridge [22]. For cerebellar stimulation the anode was centred over the right cerebellar cortex, 3 cm lateral to the inion [24] and the cathode was placed on the superior aspect of the right trapezius muscle. This extra-cephalic reference has been found to maximally stimulate the cerebellar hemispheres and avoid unwanted current spread [34,35]. In both stimulation conditions the current was ramped up at the start of baseline trials over 10 s and then held at 2 mA throughout Adapt 1 and 10 min into the break period (totalling 17 min), before being ramped back down over a further 10 s period. For the sham condition, the electrode montage was pseudorandomly assigned to either the M1 or cerebellum arrangement for each participant. The stimulation was ramped up over 30 s, held for 30 s before ramping down over 30 s and then switched off. Longer ramping durations were chosen during the sham condition as they have been found to achieve high levels of blinding [36]. Ten-point visual analogue scale (VAS) questionnaires for perceived comfort and confidence in receiving active stimulation were used to determine whether sufficient blinding was achieved.

Data analysis

The position of the joystick and vBOT handle were tracked trial-by-trial and recorded using custom analysis in MATLAB (version R2018b, Mathworks). Our primary outcome measure was rotational error defined as the angular displacement between the direction of participants' movement at peak velocity and the target location. Trials were rejected and thus removed from subsequent analysis, if a participant failed to make a movement towards the target, peak velocity was ill defined, and/or more than one movement was made (0.12% of trials were rejected for younger adults and 0.26% for older adults). Data from each participant during Baseline, Adapt 1, Adapt 2 and Washout phases was averaged across bins of 4 trials to be used in further analysis. Area under the curve calculations were performed in MATLAB for each participant in each adaptation phase and subsequently averaged across stimulation groups to quantify total rotational error during the tasks and indicate adaptive performance.

Frequentist statistical analyses were carried out in SPSS Statistics (IBM, version 25). ANOVAs were run in general linear model format, with significant main effects and interactions followed up with Bonferroni-adjusted post-hoc tests. Statistical significance was set at $p < 0.05$.

Bayesian ANOVAs were carried out using JASP 0.10.1 (JASP Team, 2019 [37]). Comparisons were made using Bayes Factors (BF), which were assigned descriptive classifications following Lee and

Wagenmakers' [38] modification of Jeffereys' [39] scheme; BF of 1 provides no evidence, 1–3 anecdotal evidence, 3–10 moderate evidence, 10–30 strong evidence, 30–100 very strong evidence, and BF > 100 provides extreme evidence. All Bayesian ANOVAs considered 19 models; these were models admitting combinations of Age Group, Task and Stimulation Group, as well as their second and third-order interactions (Table 1). The null model contains the grand mean only. We report posterior model odds (the change from prior to posterior model odds; BF_M), the Bayes Factor between models (BF), and the Bayes Factor (BF) to provide evidence for inclusion of terms in the chosen model. This latter measurement is the change from prior inclusions odds to posterior inclusion odds for each component, averaged by all models that includes the component [40].

Results

Baseline performance did not differ between stimulation groups

Differences in baseline performance were assessed using a three-way ANOVA (Age Group x Task x Stimulation Group) and revealed no significant main effects of Age Group (F(1,150) = 1.57, p = 0.21) or Stimulation Group (F(2,150) = 1.56, p = 0.21). There was however, a main effect of Task (F(1,150) = 68.83, p < 0.001) and an Age Group*Task interaction (F(1,150) = 13.17, p < 0.001). Post-hoc tests (Bonferroni adjusted) revealed significant differences in performance between the vBOT and joystick tasks for both age groups (Young Adults: p = 0.01, Older Adults; p < 0.001). These differences between tasks likely stem from a slight negative (anti-clockwise) reaching bias in the vBOT task and a slight positive (clockwise) bias in the joystick task across both age groups at the beginning of baseline trials (Fig. 2). A Bayesian ANOVA supported this analysis, with the preferred model including terms for Age Group, Task and the Age Group*Task interaction, BF_M = 36.07 (consistent with the principle of marginality: we do not consider models with interaction terms that do not contain all corresponding main effects [40]). Given the data, this model was 4.89 times more likely than the next best model, which had the additional term for Stimulation Group, and 19.96 times more likely than the model only including the Task main effect.

Older adults were impaired in motor adaptation compared to younger adults

In order to investigate differences in adaptation between age and stimulation groups, the area under the curve (a measure of total error) for each participant was compared in 3-way ANOVAs (Age Group x Task x Stimulation Group) for the different adaptation phases (Adapt 1, 2 and Washout). During both Adapt 1 and 2 older adults displayed impaired adaptation performance compared to younger adults. In Adapt 1 there was a significant main effect of Age Group (F(1,150) = 80.94, p < 0.001) and a significant Age Group*Task interaction (F(1,150) = 4.85, p = 0.03). Post-hoc tests revealed that older adults made significantly more error in both the vBOT (p < 0.001) and joystick (p < 0.001) tasks. This was confirmed using a Bayesian ANOVA with models containing a main effect of Age Group demonstrating extreme evidence of an effect (BF = 5.2×10^{12}; compared with matched-models without this term), whilst models containing the Age Group*Task interaction showed anecdotal evidence of an effect (BF = 1.896). Similarly during Adapt 2, there was a significant main effect of Age Group (F(1,150) = 165.37, p < 0.001) and a significant Age Group*Task interaction (F(1,150) = 15.38, p < 0.001). Post-hoc tests showed that performance was significantly worse for older adults in both tasks (vBOT: p = 0.004, joystick: p < 0.001). Again, the main effect of Age Group demonstrated extreme evidence in the Bayesian ANOVA (BF = 2.8×10^{20}), with the Age Group*Task interaction now also demonstrating extreme evidence of an effect (BF = 117.7).

Cerebellar tDCS improved adaptation during the vBOT task, whereas M1 tDCS improved adaptation during the joystick task in both age groups

We next sought to investigate the differences in adaptation between the stimulation groups in the different tasks, seen in Fig. 2. In the same 3-way ANOVA as above (Age Group x Task x Stimulation Group), there was a significant main effect of Stimulation Group (F(2,150) = 12.44, p < 0.001) and a significant Task*Stimulation Group interaction (F(2,150) = 13.28, p < 0.001) for Adapt 1. Post-hoc tests showed that for the vBOT task participants in the cerebellar groups displayed significantly less error than the M1 (p = 0.009) and sham groups (p < 0.001), with no differences

Table 1
The 19 models considered in all Bayesian ANOVAs. Models included combinations of the main effects; Age Group, Task and Stimulation Group and their associated second or third-order interactions (interactions could only be included in the model if the corresponding main effects were also present). Note that the dependent variable changed with each separate analysis.

| Bayesian ANOVA Models |
| --- |
| Null Model |
| Age Group |
| Task |
| Stimulation Group |
| Age Group + Task |
| Age Group + Task + Age Group*Task |
| Age Group + Stimulation Group |
| Age Group + Stimulation Group + Age Group*Stimulation Group |
| Age Group + Task + Stimulation Group |
| Age Group + Task + Stimulation Group + Age Group*Task |
| Age Group + Task + Stimulation Group + Age Group*Stimulation Group |
| Age Group + Task + Stimulation Group + Task*Stimulation Group |
| Age Group + Task + Stimulation Group + Age Group*Task + Age Group*Stimulation Group |
| Age Group + Task + Stimulation Group + Age Group*Task + Task*Stimulation Group |
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| Age Group + Task + Stimulation Group + Age Group*Task + Age Group*Stimulation Group + Task*Stimulation Group |
| Age Group + Task + Stimulation Group + Age Group*Task + Age Group*Stimulation Group + Task*Stimulation Group + Age Group*Task*Stimulation Group |
| Task + Stimulation Group |
| Task + Stimulation Group + Task*Stimulation Group |
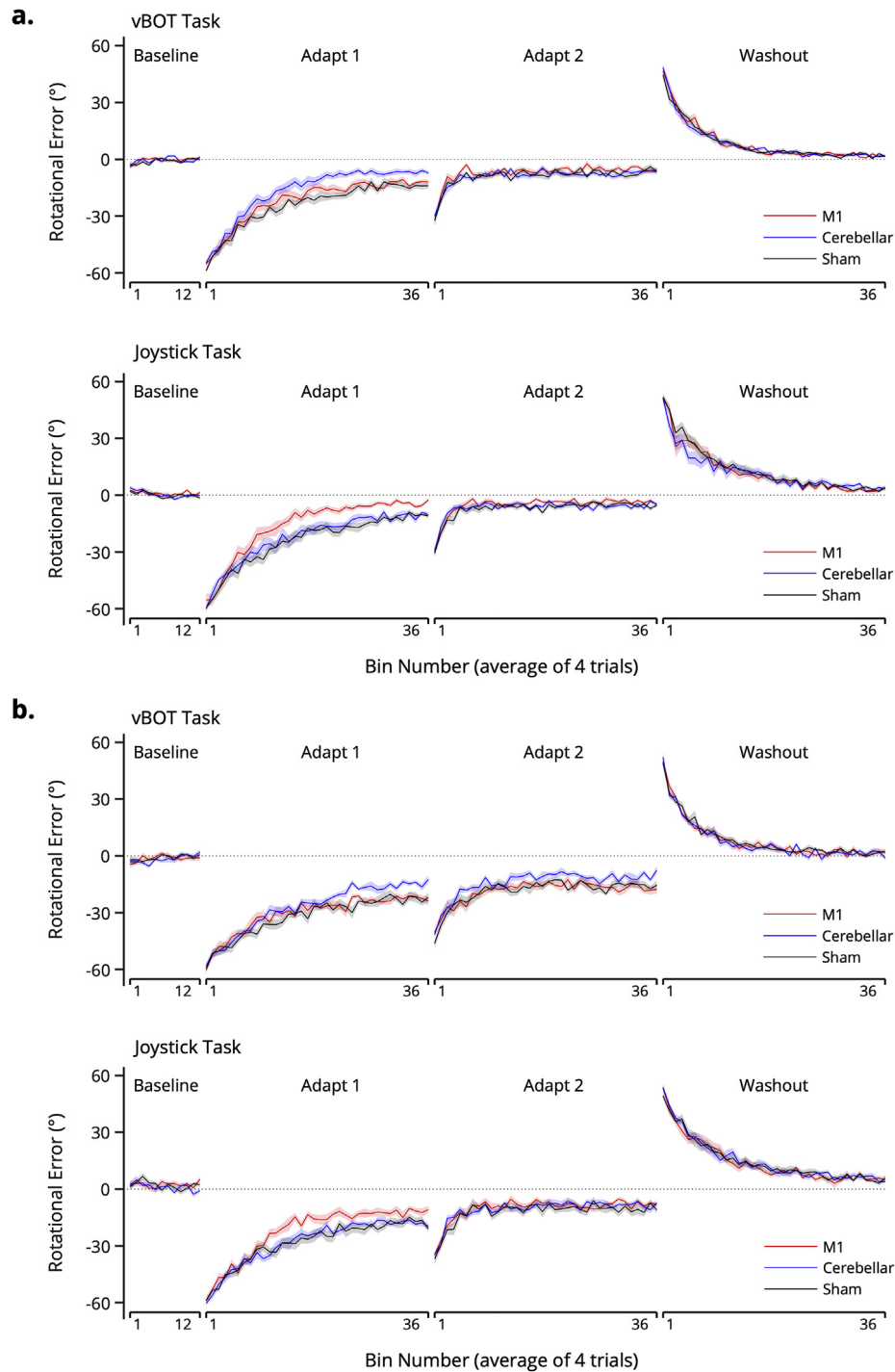
Fig. 2. Mean rotational error (±standard error, shaded region), averaged every four trials into bins, for young (**a**) and older adults (**b**) during Baseline (no rotation), Adapt 1 (60° CCW rotation), Adapt 2 (60° CCW rotation) and Washout trials (no rotation) in all stimulation groups and both tasks.

between the M1 and sham groups (p = 0.4). For the joystick task, post-hoc tests revealed that M1 stimulation significantly improved adaptive performance compared to cerebellar (p < 0.001) and sham (p < 0.001) stimulation, with no difference between cerebellar and sham (p > 0.05). There was a non-significant interaction of Age Group*Stimulation Group (F(2,150) = 0.54, p = 0.58), suggesting that the stimulation effects were consistent regardless of age (Figs. 3 and 4). In the Bayesian ANOVA, there was an extreme influence of Task*Stimulation Group (BF = 5917.1). Indeed, the winning model across all 19 models (see Methods) included the three

main effects of Age Group, Task, and Stimulation Group, as-well as Age Group*Task, and Task*Stimulation Group interactions ($BF_M = 24.2$); it did not include the Age Group*Stimulation Group interaction, or the three-way interaction (the full model was 31.3 times less likely, given the data). To understand the specific effect of the Task*Stimulation Group interaction, we compared the winning model to the analogous model lacking only the Task*Stimulation Group term; the winning model proved 6468.3 times more likely given the data, and thus provides extremely strong evidence that Stimulation imposes a Task-specific effect.
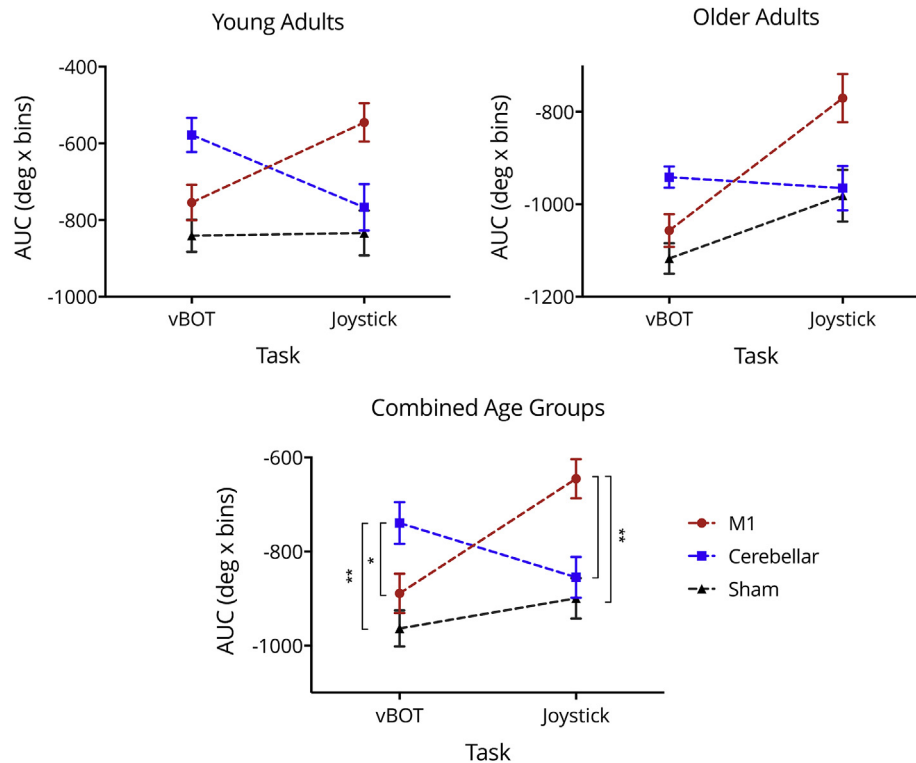
Fig. 3. Area under the curve (mean AUC ± standard error) for each stimulation group in both tasks during Adapt 1. Initially separated by Age Group (upper row) and then combined with significance displayed (* = p < 0.05, ** = p < 0.001) following 3-way ANOVA post-hoc tests.

In Adapt 2 there remained a main effect of Stimulation Group (F(2,150) = 3.92, p = 0.02) but there was no Task*Stimulation Group interaction (F(2,150) = 1.59, p = 0.21). Post-hoc tests showed that cerebellar groups displayed significantly less error than sham groups (p = 0.04), with no further significant differences between M1 and cerebellar groups or M1 and sham groups (all p > 0.05). The differences between Stimulation Groups may be anecdotally ascribed to reduced error for older adults receiving cerebellar stimulation in the vBOT task (Fig. 4b). Bayesian analysis supported a winning model containing the three main effects (Age Group, Task and Stimulation Group), as well as Age Group*Task, and Age Group*Stimulation Group interactions (BF$_M$ = 10.945). This proved 4.5 times more likely than the full model, and 2.2 times more likely than the same model containing a Task*Stimulation Group interaction.

For Washout trials there was no significant main effect of Stimulation Group (F(2,150) = 0.23, p = 0.79) and no Task*-Stimulation Group interaction (F(2,150) = 0.19, p = 0.83), suggesting that tDCS had no effect on de-adaptation during the tasks (Fig. 4). Again, the Bayesian ANOVA supports this with extreme evidence of a Task effect (BF = 7.7 × 10^{12}), and the winning model contained Task as the only term (BF$_M$ = 14.1). The Task*Stimulation Group interaction demonstrated moderate evidence *against* its inclusion (BF = 0.121).

Adaptation performance differed between the two tasks for both older and younger adults

During Adapt 1 there were significant differences in performance between the two tasks for older adults, but not for the younger adults. The 3-way ANOVA revealed a significant main effect of Task (F(1,150) = 6.38, p = 0.01) and a significant Age Group*Task interaction (F(1,150) = 4.85, p = 0.029). Post-hoc

testing showed that older adults made significantly greater errors during the vBOT task (arm movements) compared to the joystick task (hand movements): p = 0.002, with no differences for younger adults (p = 0.81). Models containing an Age Group*Task interaction demonstrated anecdotal evidence of an effect (BF = 1.8), with the winning model also proving 1.8 times more likely than the analogous model with the interaction excluded. For Adapt 2 there was again a main effect of Task (F(1,150) = 61.16, p < 0.001) and an Age Group* Task interaction (F(1,150) = 15.38, p < 0.001). Post-hoc tests revealed that both older and younger adults made significantly more error during the vBOT task (p = 0.004 and p < 0.001 respectively). Models containing an Age Group*Task interaction demonstrated extreme evidence for inclusion (BF = 115.2), with the winning model proving 17.9 times more likely than the analogous model with this term excluded. During Washout trials, there was also a main effect for Task (F(1,150) = 82.81, p < 0.001) and an Age Group*Task interaction (F(1,150) = 4.25, p = 0.04). Post-hoc tests revealed that less error was made during the vBOT task compared to the joystick task for both age groups (both p < 0.001), suggesting that adaptation in the joystick task caused greater after-effects. During Washout, there was anecdotal evidence for inclusions of the Age Group*Task interaction (BF = 1.5), with the winning model (Task term only) proving 1.5 times more likely than the analogous model with Age Group and Age Group*Task Interaction.

No differences in perceived comfort or perceived stimulation

To ensure sufficient blinding to the stimulation type received (active or sham), all participants rated their perceived comfort and their confidence in receiving active stimulation on a 10-point visual analogue scale (VAS), shown in Table 2. A 3-way ANOVA (Age Group x Task x Stimulation Group) showed that all participants reported similarly high levels of comfort with no main effect of Stimulation
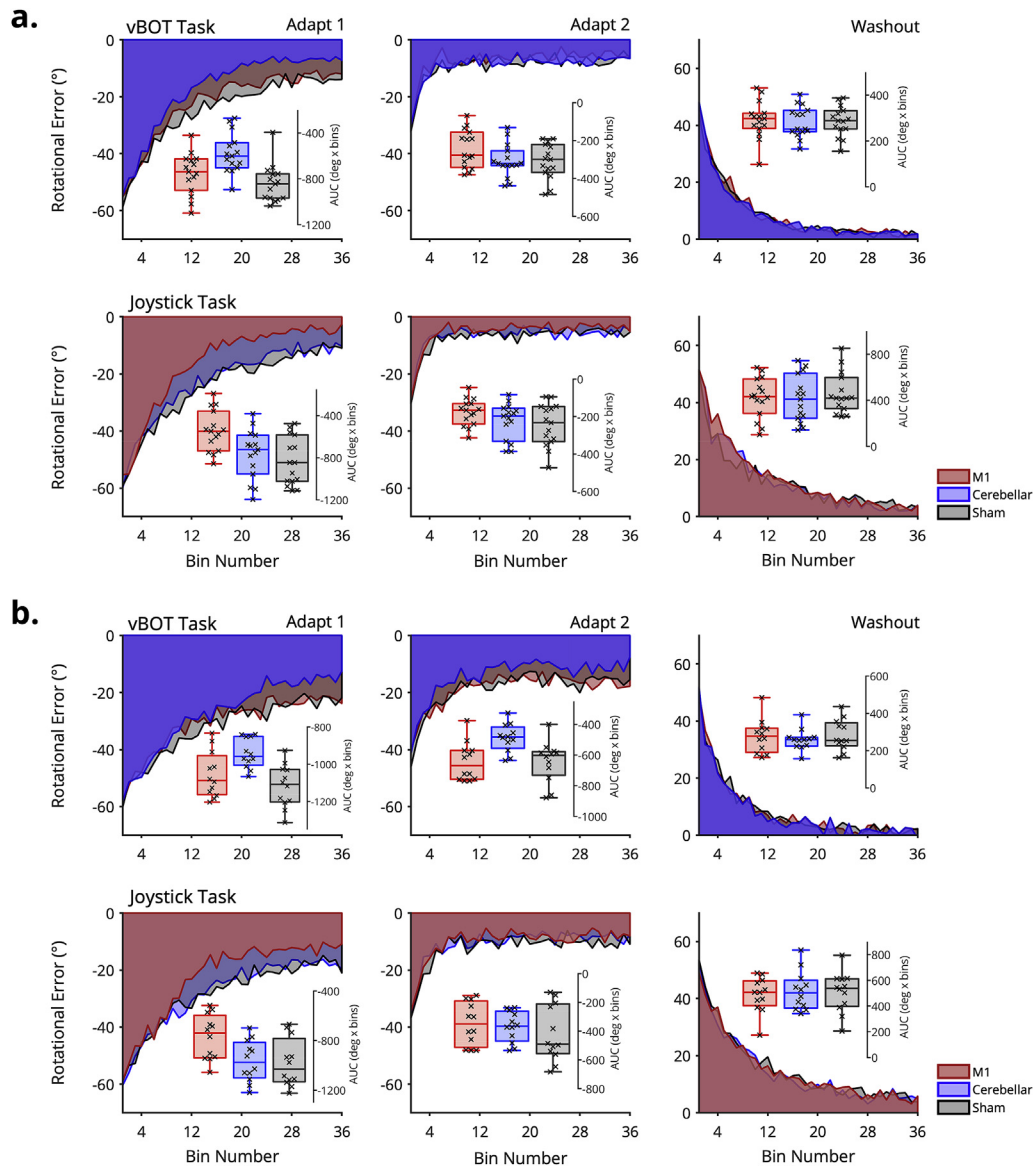
Fig. 4. Visualisations of the area under the curve (AUC) for younger adults (**a**) and older adults (**b**) in all stimulation groups for both the vBOT and joystick tasks. Box plot inserts represent the area under the curve for each stimulation group during the different phases of the tasks (with the box indicating mean, upper and lower quartiles; the range shown by the error bars; and individual participant values in each group marked by an 'x').

Group ($F(2,150) = 1.07$, $p = 0.34$) and no interaction with Age Group ($F(2,150) = 1.79$, $p = 0.17$). There was a significant main effect of Age Group ($F(1,150) = 59.37$, $p < 0.001$), and post-hoc comparisons revealed that older adults reported significantly higher levels of comfort during session than younger adults ($p < 0.001$). Bayesian analysis revealed extreme evidence for an effect of Age on comfort ($BF = 6.6 \times 10^9$, with all other terms producing BFs in the range 0.1–0.5). Unsurprisingly, the model with only a single term (Age Group) was preferred ($BF_M = 41.8$, proving 6.9×10^9 times more probable than the null model, given the data). Additionally, all participants reported high levels of confidence that they were in the active stimulation group. There were no main effects of Age Group ($F(1,150) = 0.31$, $p = 0.58$), Task ($F(1,150) = 0.05$, $p = 0.83$) or Stimulation Group ($F(2,150) = 0.54$, $p = 0.59$) and no significant interactions (all $p > 0.05$). In this case, Bayesian analysis supported the null model as the most likely ($BF_M = 32.8$), with all terms producing BFs in the range 0.092 [Stimulation Group] - 0.220 [Age Group*Task].

Discussion

The aim of this study was to investigate whether tDCS targeted at the motor cortex or the cerebellum could specifically improve motor adaptation in tasks dominated by movement of the distal versus proximal upper limb, respectively. In line with our hypothesis, derived from the anatomy and physiology of these motor systems, we demonstrated that stimulation of the cerebellum can selectively improve motor adaptation using arm movements, whereas M1 tDCS selectively improves adaptive performance when using the hand/fingers. This effect was found in two separate age groups.

Both M1 and cerebellar tDCS have previously been shown to improve adaptive motor learning in visuomotor rotation tasks [26–28,41] However, to our knowledge this is the first study to show that selective stimulation of different brain areas can have specific effects on the proximal or distal upper limb. We found that cerebellar tDCS improves adaptation for both younger and older

Table 2
Average ratings (±standard deviation) of perceived comfort (1−10 VAS, 1 = no discomfort, 10 = very high discomfort) and confidence in detecting stimulation (1−10 VAS, 1 = low confidence in receiving real stimulation, 10 = high confidence in receiving real stimulation) for both age group and tasks after the stimulation period. All three younger adult groups contained 15 participants; all three older adult groups contained 12 participants.

Perceived Comfort						Confidence in Stimulation					
Young Adults											
vBOT Task			Joystick Task			vBOT Task			Joystick Task		
M1	Cerebellar	Sham	M1	Cerebellar	Sham	M1	Cerebellar	Sham	M1	Cerebellar	Sham
3.27 (±1.16)	3.07 (±1.16)	3.53 (±1.06)	3.13 (±1.13)	3.33 (±1.11)	3.07 (±1.22)	8.27 (±1.67)	7.6 (±1.18)	7.8 (±1.37)	7.87 (±1.51)	7.93 (±1.91)	7.87 (±1.68)
Older Adults											
	vBOT Task			Joystick Task			vBOT Task			Joystick Task	
M1	Cerebellar	Sham	M1	Cerebellar	Sham	M1	Cerebellar	Sham	M1	Cerebellar	Sham
2.17 (±0.72)	1.92 (±1.68)	1.25 (±0.45)	2.25 (±1.66)	1.67 (±0.89)	1.67 (±1.15)	7.75 (±2.05)	8.17 (±1.8)	7.42 (±3.06)	7.67 (±2.93)	8.08 (±2.5)	7.17 (±2.69)

adults when using reaching movements to complete the task. This finding aligns with evidence that indicates the cerebellum is an important neural substrate in multi-joint upper limb control. Many previous studies have shown that accurate and coordinated whole arm reaching movements are dependent on the cerebellum and deficits in reach behaviour result from cerebellar degeneration [42−45]. The cerebellum is also thought to be heavily involved in the sensorimotor processes that adapt movements of the arm [46,47], although there is current debate as to the effectiveness of cerebellar tDCS on adaptation ([26] vs [32]). We return to this point later.

In contrast, we found that M1 and not cerebellar tDCS enhanced adaptation for both age groups when the task was executed with the fingers/hand. This result supports findings that M1 stimulation can improve adaptive performance in visuomotor rotation tasks [28] and other forms of motor learning predominantly using distal muscles [25,48−50]. As M1 dominates in control of relatively independent hand and finger movements [5] and projections from M1 terminate more densely among motor neuron pools controlling the hand and digits than any other cortical or sub-cortical region [51,52], we suggest it may play a greater role in the mechanisms that adapt movements of the hand. These effects of M1 and cerebellar tDCS did not consistently continue throughout Adapt 2 for either task or age-group and can likely be attributed to consolidation-mediated ceiling effects. Unlike Galea et al. [24], we found no specific effect of increased retention after M1 stimulation in either task when re-tested during Adapt 2 and washout. It should be noted however, that cursor feedback was present during all phases of the task. Thus, we did not directly investigate the rate of forgetting in the absence of feedback, as Galea and colleagues did [24].

The double dissociation revealed here between the cerebellum/reaching and M1/hand movements is generally consistent within the extant literature on visuomotor adaptation and tDCS use. Galea et al. [26], Block and Celnik [41] and Hardwick and Celnik [27] all found a significant effect of cerebellar stimulation on visuomotor adaptation using reaching tasks (with either whole arm movements of a digitised pen/tablet or robotic manipulandum), whereas Panouillères et al. [28] showed M1 tDCS to enhance adaptation using a hand-held joystick (an effect replicated in the present study). However, the efficacy of tDCS has recently been called into question by some studies that have not found improved adaptation in visuomotor rotation and force-field tasks as a result of tDCS, or have reported inconsistent effects [32,53,54]. These studies also add to the growing body of evidence which suggests that stimulation parameters and study protocols are critical variables in tDCS research [55]. For example, one difference between our study and the studies listed above is the degree of rotational perturbation: 60°

vs 30°. It should be noted that a robust effect of M1 tDCS on this hand/finger 60° visuomotor rotation protocol has been demonstrated by replication in our lab between separate studies and age groups [28], and we conject that the additional difficulty in the task imposed by the greater visual rotation is important. Hence the dissociation we show here between proximal and distal control may help to further clarify the currently confused view of whether tDCS has significant effects in motor adaptation tasks.

It is difficult to speculate on the exact mechanisms in play during the present study, especially as the underlying mechanisms of tDCS induced effects remain relatively unknown. However, stimulation improved performance in the tasks only when applied to structures that are most allied to the control of either arm movements (cerebellum-brainstem) or hand and finger movements (M1-corticospinal tract). Whether the improvement in adaptation is driven indirectly by improved performance of the movements or more directly, by increased plasticity in the stimulated areas cannot be separated by this study and thus remain unknown.

We also acknowledge that, although our rationale for this study has a sound functional foundation, it is reductionist in nature and other factors may have played a part in the results presented here. Despite strong evidence for some segregation in the control of fractionated hand/finger and proximal upper limb movements in lesion studies [12,13,56], we cannot refute that in the intact brain both M1 and the cerebellum will play some part in both proximal and distal motor control. Microstimulation of both the corticospinal and reticulospinal (which receives input from the cerebellum) tracts elicits responses in distal and proximal muscles [57] and as previously stated the cerebellum contains motor representations for both the hands and arms [8]. Additionally, the complex relationship and connectivity between M1 and the cerebellum is known to change during motor skill learning and adaptation [58,59], which may have had some bearing on our results. That being said, a lack of an exact mechanism does not detract from the behavioural data presented which shows a clear and obvious double dissociation between effector and stimulation site.

There is great interest in the therapeutic utility of tDCS for neurorehabilitation. A number of studies have identified tDCS as a potential adjunct therapy after stroke, with some positive results for upper limb deficits [29,60−62]. However, overall results have proven less promising than expected. It should be noted that these studies combined M1 tDCS with clinical tests that measure the functional improvement of the movements of the whole upper limb. Our results raise the possibility that stimulation of M1 may only improve the performance of the distal arm, which may not have been captured by clinical measures of whole arm use. We suggest that M1 and cerebellar tDCS could be directed to specific

subgroups, or potentially used in combination to produce more robust functional improvements of the whole upper limb, especially as proximal and distal upper limb motor recovery post-stroke may be mediated by somewhat functionally dissociated pathways [14]. Additionally, in a recent review Wessel and Hummel [63] introduce the potential benefits of cerebellar tDCS to motor recovery after stroke, where previously only M1 stimulation seems to be considered. The authors suggest that the cerebellum could be an attractive target for tDCS due to its unique plasticity mechanisms, multiple connections to cortical regions and its successful use in the rehabilitation for cerebellar ataxia [64—66] and the motor symptoms of other neurological disorders [67].

In conclusion we have displayed that tDCS over the cerebellum improves motor adaptation using the whole arm, whereas M1 tDCS enhances adaptation using hand and finger movements. These findings suggest that stimulation of different neural substrates - which exert high levels of control over fractionated hand or whole arm reaching movements - drives better adaptation in the respective tasks. They also further highlight the potential for tDCS to be used to ameliorate motor adaptation declines in ageing and present new ideas for more robust upper limb rehabilitation post-stroke.

Author Contributions

MW, JSB, RCM and NJ conceived and designed the study. MW collected the data. MW, JSB, DP, RCM and NJ analysed and interpreted the data and drafted or revised the article.

Declaration of competing interest

The authors declare that no competing interest exist.

CRediT authorship contribution statement

Matthew Weightman: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft. **John-Stuart Brittain:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **David Punt:** Formal analysis, Writing - review & editing. **R. Chris Miall:** Conceptualization, Formal analysis, Writing - review & editing. **Ned Jenkinson:** Conceptualization, Methodology, Formal analysis, Writing - original draft.

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