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Short duration event related cerebellar TDCS enhances visuomotor adaptation

Matthew Weightman [a, b], Neeraj Lalji [b], Chin-Hsuan Sophie Lin [c], Joseph M. Galea [b], Ned Jenkinson [a], R. Chris Miall [b, *]

[a] School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, UK
[b] School of Psychology, University of Birmingham, UK
[c] Cognitive Neuroscience and Computational Psychiatry Lab, University of Melbourne, Australia

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ABSTRACT

Background: Transcranial direct current stimulation (TDCS) is typically applied before or during a task, for periods ranging from 5 to 30 min.
Hypothesis: We hypothesise that briefer stimulation epochs synchronous with individual task actions may be more effective.
Methods: In two separate experiments, we applied brief bursts of event-related anodal stimulation (erTDCS) to the cerebellum during a visuomotor adaptation task.
Results: The first study demonstrated that 1 s duration erTDCS time-locked to the participants' reaching actions enhanced adaptation significantly better than sham. A close replication in the second study demonstrated 0.5 s erTDCS synchronous with the reaching actions again resulted in better adaptation than standard TDCS, significantly better than sham. Stimulation either during the inter-trial intervals between movements or after movement, during assessment of visual feedback, had no significant effect. Because short duration stimulation with rapid onset and offset is more readily perceived by the participants, we additionally show that a non-electrical vibrotactile stimulation of the scalp, presented with the same timing as the erTDCS, had no significant effect.
Conclusions: We conclude that short duration, event related, anodal TDCS targeting the cerebellum enhances motor adaptation compared to the standard model. We discuss possible mechanisms of action and speculate on neural learning processes that may be involved.

1. Introduction

Transcranial direct current stimulation (TDCS) of the brain is increasingly used as an experimental intervention across a wide range of different cognitive, emotional, sensory, and motor domains [1–4]. TDCS applied over the cerebellum has been reported to enhance motor adaptation [5–7], in line with evidence from imaging, clinical studies and transcranial magnetic stimulation research suggesting the cerebellum has a critical role in motor learning [8,9]. But the behavioural effects of most cerebellar TDCS interventions are modest, and many null results have also been reported [10,11].

The null results are not well understood. The electrical currents used in TDCS (typically 1 or 2 mA applied at the scalp) are small, and some reports suggest that much stronger electric fields are needed to be effective [12]. In contrast, electrophysiological and imaging studies have shown that TDCS at these strengths does have reliable effects on neural excitability, almost certainly by altering the probability of neural firing rather than by causing the neurons to fire directly [13–15]. However, these neural changes do not always evoke measurable behavioural changes [16]. In addition, there is considerable variability in the responses to TDCS [17] in part due to differences in brain folding, cerebrospinal fluid volume, and skull thickness [18] and other physiological variables [19]. On top, many behavioural tasks have variability in performance [20]. Thus, the difficulty for researchers is to design their behavioural tasks to maximize sensitivity to small changes in neural processing. A task too easy (or too difficult) may not be sensitive to the modest changes in neural performance that are possible under the

* Corresponding author. School of Psychology, The University of Birmingham Edgbaston Birmingham, B15 2TT, UK.
E-mail address: r.c.miall@bham.ac.uk (R.C. Miall).

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influence of TDCS [21]. There is therefore a strong drive to increase the efficacy of TDCS protocols, for example by using multiple electrode arrays [22], different electrode montages [23,24], and tuning alternating current (TACS) frequencies to be task-specific [25,26].

We have recently shown that short duration (3 s) episodes of anodal TDCS during one of two motor adaptation conditions (velocity dependent 'curl fields' of opposing sign) can selectively enhance learning: movements timed to occur during stimulation were adapted more effectively than movements made during sham stimulation, despite the two movement contexts being interleaved on a trial-by trial basis [27]. We argued that the enhanced adaptation in the stimulated context was due to the temporal contiguity between cerebellar stimulation and action. Traditionally TDCS protocols bear no temporal relationship to the task, and a typical protocol uses a stimulation duration of 20–30 min, applied either prior to or throughout an experimental task. Thus, there is only very loose contiguity between stimulation and the task being measured and all behaviours occurring during that period (that are influenced by the targeted neural structure [28]) might be affected.

Given our prior result, we sought further evidence that short duration TDCS can enhance motor performance. We examined adaptation to a visuomotor perturbation, a well-documented task that allows us to apply brief pulses of TDCS in an event-related manner, synchronous with the movement being adapted. Hence, we hypothesized stronger adaptation and reduced error for participants stimulated synchronously with each target reaching movement compared to a standard TDCS protocol, while the standard TDCS would have a smaller but still noticeable effect compared to sham. In contrast, event related TDCS delivered outside the period of active task performance might be ineffective, or even interfering.

2. Methods

2.1. Participants

The experiments were approved by the University of Birmingham Research Ethics Committee and conformed to the research ethics principles of the Declaration of Helsinki. Participants were awarded course credits or were paid £10 for their time.

2.2. Visuomotor adaptation task

Participants sat in front of a sloped table. A mirror blocked direct vision of the table and reflected a large flat-screen monitor, such that the virtual image appeared on the occluded table surface (Fig. 1A). The participants held in their preferred hand a small motion tracker whose position was shown by a cursor on screen. They slid the tracker across the table surface to move the cursor towards a home position and then towards one of 8 targets regularly spaced around an invisible semi-circle of 8 cm radius (Fig. 1B). The targets were surrounded by grey semi-circle of 10 cm radius, and participants were instructed to "shoot through" the target, reaching at least as far as the outer grey semi-circle. Targets were presented in pseudorandom order, randomly shuffled in epochs of eight (i.e. an epoch is 8 consecutive trials, one to each target).

After initial practise, participants performed 40 baseline trials (5 epochs). Then a visuomotor rotated was applied to the cursor (Fig. 1B). This was maintained for the 240-trial adaptation phase (two blocks of 120 trials, separated by a brief rest of ~1 min). A de-adaptation or wash-out phase (40 trials, 5 epochs) followed.

Angular error was measured as the cursor crossed the target circle (8 cm). Trials with errors >60° were removed; the remaining trials in each epoch were averaged. The mean error of the last 3 baseline epochs were subtracted from all epochs. A small number of participants showed either no reduction in error, very sudden switches in performance during adaptation, or no aftereffects in the de-adaptation phase. We assume these participants had adopted a strategic solution to the task, reducing the amount of implicit adaptation [29,30] for which the cerebellum is critical (eg. Refs. [31,32]), and hence we removed them from further analysis.

2.3. General TDCS details

All participants were screened for TDCS suitability and safety and reported to have no history of any neurological condition or brain trauma. They were blinded to the stimulation conditions (see Supplementary Tables 1 and 2 for subjective reports) but the experimenters were unblinded. TDCS (active or sham stimulation, as well as all forms of event-related stimulation – see below) was applied during the two adaptation blocks, and not in the ~1 min rest period, nor in the baseline or the de-adaptation blocks.

Anodal 2 mA TDCS was applied to the lateral cerebellum ipsilateral to the hand, centred 1 cm below and 3 cm lateral to the inion [33]. The cathodal electrode was strapped to the ipsilateral upper arm over the deltoid muscle. The Neuroconn DC-stimulator Plus was controlled in real-time by a remote voltage signal provided by the experimental computer. Conductive rubber electrodes in saline-soaked sponges, 5 × 5cm, were held in place with rubber straps. For standard TDCS, current was ramped up over 10 s at the start of each adaptation block and ramped down over 5s at the end of the block. For the standard sham, the current was ramped up to 2 mA over 10 s, held for 10 s and then ramped down to zero over 5 s, after which brief 15 ms pulses of 0.1 mA were applied every 500 ms until the end of the block. For all groups, a 12 s delay before and 10 s delay after each adaptation block was imposed to allow ramping of the standard TDCS/sham conditions.

The total duration of the standard TDCS/sham was determined by the participants' speed in completing the 240 adaptation trials, in the range of 15–22 min. Afterwards, participants completed a debrief questionnaire.

2.4. Data analysis

We compared average errors between groups at four periods: first, all 30 epochs of the adaptation phase; second, epochs 2–15 of that phase, to capture early adaptation; third, epochs 17–30 to capture late adaptation; fourth, epochs 2–5 of the de-adaptation phase. In the latter 3 cases we excluded the first epoch of the block [10]: in early adaptation the epoch average error was dominated by the initial perturbation onset and thus consistent across all groups [34]; in late adaptation it was influenced by the resumption of the task after the short break between the two blocks; and in de-adaptation it was dominated by the sudden removal of the perturbation.

2.5. State-space modelling

We fitted the whole session epoch-averaged error datasets with a single-state learning model with 2 free parameters: retention rate (RR) and learning rate (LR). The model estimated the epoch-averaged error data with a state-update equation [35]:

$x(n+1) = RR*x(n) + LR*error(n)$.

and a predicted error term:

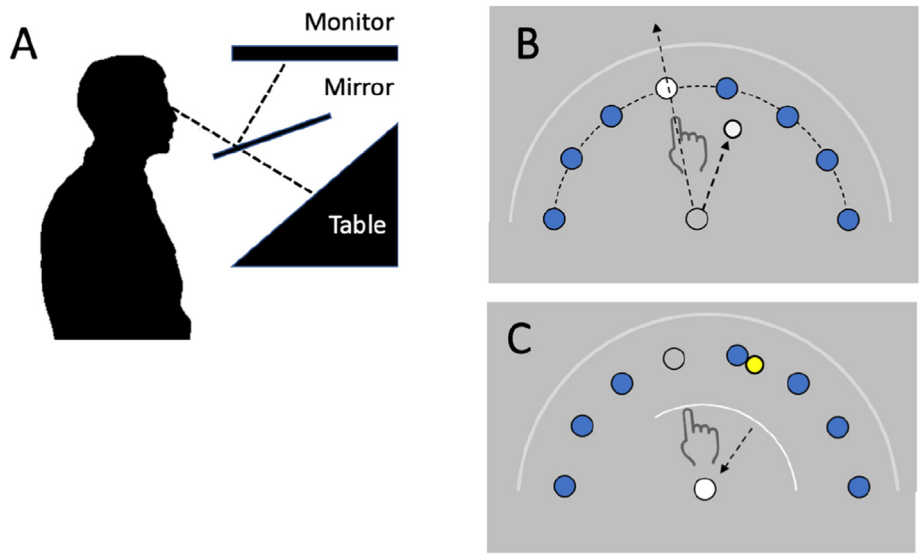

Fig. 1. Experimental set up. Participants moved a hand-held motion tracker across a sloped tabletop (A); they viewed a monitor screen reflected in a mirror, such that the display appeared co-planar with the table surface. The hand was unseen, below the mirror, throughout the experiment; its position was recorded by a hand-held electromagnetic motion tracker (Polhemus Fastrak, Experiment 1) or Liberty (Experiment 2). The display (B, C) had a dark background, a semi-circle of 8 targets, and an outer grey arc. One target turned white (B), and the central home position darkened as a cue to reach through the target to the arc; during adaptation, the cursor was rotated with respect to the hand. On reaching the target distance, the cursor was replaced by a static yellow feedback dot (C). An on-screen message informed the participant if the movement was too slow or fast (see main text) and instructed them to wait for 1 s before the feedback cursor disappeared. On return to the home position the participant was guided home by a 120-degree arc that provided distance feedback but no accurate angular information (C). The experiment was coded using PsychToolBox 3 and ran under Matlab version 2017a. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

error(n) = VMR(n)- x(n).

where n is the trial number, x is the estimated state and VMR is the applied visuo-motor rotation. RR and LR were estimated for each participant using the Matlab (version R2022b) function *nlinfit.* For display purposes we generated 50 error datasets per group, using the recorded group means and SEMs, and fitted the model to each dataset.

2.6. Statistics

Data were tested for normality using the Anderson–Darling test via the Matlab R2022b *adtest* function. Most data-sets proved to have a least one group with non-normal distribution, and so Matlab's *kruskalwallis* function was used to run non-parametric statistics, followed, where appropriate, by pair-wise comparisons via the *multcompare* function. For experiment 1 we test three stimulus conditions vs the sham, and so scale the *multcompare* lsd probabilities by 3 (i.e., Bonferroni correction). For experiment 2, to test the core hypothesis, we compare the synchronous stimulation condition against standard TDCS, and then perform four planned comparisons between each stimulus conditions and their associated sham, scaling the *multcompare* lsd probabilities by 4 to achieve Bonferroni correction. Comparison of group demographics and participant responses to questionnaires was with either one-way ANOVA or chi-squared, as appropriate (see Supplementary Materials).

2.7. Experiment 1 specific details

2.7.1. Task

The visuomotor rotation was 10-degrees clockwise. All participants used their right-hand. Terminal error feedback was displayed for 500 ms immediately after the cursor reached the outer circle (10 cm from home position), and on-screen text informed the participant if the movement was "Too slow" (>300 ms) or "Too fast" (<100 ms) and instructed them to "Wait" for 1.5 s before returning to the home position. The next target appeared 2.0 s after the cursor first entered the home position.

2.7.2. Participants

123 participants were pseudo-randomly allocated to four stimulation conditions. After exclusion of 12 participants who showed very erratic performance or no aftereffects, the groups were: '*standard*' (n = 26; 21.9±4.2 years), '*sham*' (n = 35; 21.7±4.5 years), '*synch*' (n = 25; 23.3±9 years) and '*asynch*' (n = 25; 19.1 = /-1.1 years). The number of participants excluded across these groups was 1, 6, 2 and 3, respectively.

2.7.3. TDCS conditions

The '*standard*' and '*sham*' groups received stimulation during the two adaptation blocks (see "**General TDCS details**" above for details). The '*synch* 'and '*asynch*' groups received short duration (1000 ms) erTDCS time-locked to each trial during the adaptation phase, ramped up over 100 ms to 2 mA, held constant for 800 ms and ramped down over 100 ms. Synchronous erTDCS ('*synch*') was triggered at the onset of the target reaching action but overlapped both the end of each reaching action and the onset of visual feedback. Asynchronous erTDCS ('*asynch*') started as soon as the participant first entered the home position and finished before the onset of target presentation for the subsequent trial; because some participants took time to settle in the home position, the stimulation may have been active during the small corrective movements at or near the home position.

2.8. Experiment 2 specific details

2.8.1. Task

The visuomotor perturbation was 33-degrees clockwise for right-handed participants, 33-degrees anticlockwise for left-handers; data for left handers were subsequently mirror reversed.

To accentuate terminal feedback, the on-line cursor was reduced in size and contrast, while the static visual feedback dot was increased in size and shown in bright yellow. It was displayed for 1500 ms starting 500 ms after the cursor reached the outer circle, and on-screen text informed the participant if the movement was "Too slow" (>400 ms after onset), "Too fast" (<250 ms) or "Good". Other details as in Experiment 1.

2.8.2. Participants

139 participants were pseudo-randomly allocated to eight stimulation or sham conditions (see **TDCS** section below for details). After exclusion of 5 participants who showed no aftereffects, the first 5 groups were: '*standard*' (n = 15, 23.7 ±4.8 years [mean age ± 1SD]), '*sham*' (n = 18, 23.1 ±3.3 years), '*synch*' (n = 15, 24.4 ± 4.4 years), '*asynch*' (n = 15, 20.6 ± 2.8 years) and '*feedback*' (n = 19, 23.6 ± 3.2 years). The number of participants excluded across these five groups was 2, 2, 0, 0 and 1, respectively. Another three groups are identified as '*synch-vib*' (n = 17, 24.9 ± 3.9 years), '*asynch-vib*' (n = 15, 21.3 ± 3.4 years) and '*feedback-vib*' (n = 20, 23.5 ± 2.3 years). No participants were excluded from these three groups.

2.8.3. TDCS

The '*standard*' and '*sham*' groups received stimulation as in Experiment 1. The '*synch*', '*asynch*' and '*feedback*' groups received 500 ms erTDCS time-locked to each trial during the adaptation phase.

erTDCS was ramped up to 2 mA over 50 ms, held constant for 400 ms and ramped down over 50 ms. *Synchronous* erTDCS started at the onset of the target reaching action; the buffering delay was eliminated for Experiment 2. Stimulation typically outlasted the movement by 150–200 ms (average reach duration for all participants: 325±18 ms) but terminated before delivery of visual feedback. *Asynchronous* erTDCS started after the participant remained stationary at the home position for 200 ms, it finished 1.0 s before the next target presentation. *Feedback* erTDCS started 500 ms after the end of a target reaching action, simultaneous with visual feedback presentation; it terminated before the start of the return movement towards the home position.

Short duration erTDCS requires rapid onset and offset and is thus more readily perceived. To control for possible perceptual cueing, 3 groups received vibrotactile stimulation of the same scalp location, without active TDCS. We placed a small vibrator (Coin Micro Vibration Motor, 200 Hz, 10 mm × 2.7 mm encased in a resin cube, 2x2x2 cm) against the scalp at the same location as the anodal electrode used for TDCS and drove the vibrator with a waveform ramping up from 0 to 2 V over 50 ms, 400 ms constant at 2v, and down to zero again over 50 ms. The onset timing was identical to that of the corresponding erTDCS groups, and we term these groups '*synch-vib*', '*asynch-vib*', and '*feedback-vib*'.

3. Results

3.1. Experiment 1

3.1.1. Baseline

We first compared average error across the three epochs of baseline (the epochs used to normalise all data). There was no significant difference between the groups (Kruskal-Wallis ANOVA test, chi-sq(3,107) = 2.11, p = 0.104).

3.1.2. Adaptation

Participants showed clear adaptation to the visuomotor perturbation, with a gradual decline in error after the 10-degree rotation was applied, and then a smaller but still noticeable affect effect upon rotation removal (Fig. 2).

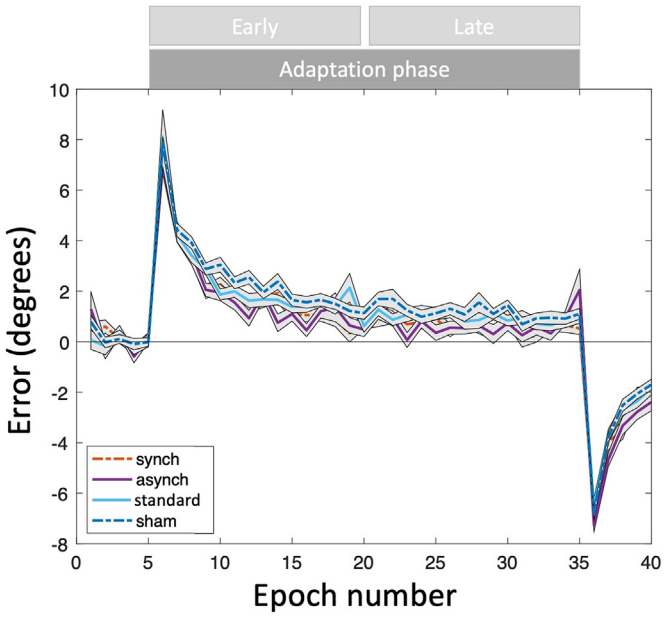

Fig. 2. Average error for each of the 4 groups in Experiment 1. A rapid reduction in mean error can be seen for all groups, with slower decline for the sham group (dashed orange line). The '*synch*' and '*asynch*' group data largely overlap, indicating equivalent adaptation performance. Thick lines (dashed or solid) are the group means of the individual epoch-averaged errors; grey zones are ± 1 SEM around the group mean. An epoch is 8 trials, one to each target position. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

To test for group differences, we first compared the whole of the adaptation phase with the Kruskal-Wallis test, as 2 groups had non-normal data. There was a significant difference between the groups (chi-sq(3,107) = 10.37, p = 0.015; Supplementary Fig. S1). Pairwise multiple comparisons with Bonferroni-corrected p-values indicated that '*synch*' and '*asynch*' had smaller error than sham (p = 0.044 and p = 0.033); the difference between standard and sham was not significant. Mean '*synch*' error was 71% of the sham group; mean '*asynch*' error was 68% of sham.

There was a very similar group difference in early adaptation (epochs 2–15; chi-sq(3,107) = 9.77, p = 0.021, Fig. 3A). Post-hoc comparisons suggested that '*synch*' group had smaller error than sham although just outside significance (74%, p = 0.056, Bonferroni-corrected). The standard TDCS group was not statistically different from '*sham*' (p = 0.50). Surprisingly, the '*asynch*' group showed the smallest errors, significantly smaller than '*sham*' (68%, p = 0.026).

In late adaptation (epochs 17–30), across-group differences diminished and but remained significant (chi-sq(3,107) = 8.08, p = 0.044, Fig. 3B). While '*synch*' and '*asynch*' both showed low errors, post-hoc comparison with '*sham*' (p = 0.031 and p = 0.044) did not survive Bonferroni correction (p = 0.09 and p = 0.13).

At all three stages (early, late and de-adaptation), the '*standard*' mean group error was intermediate between the two erTDCS groups and the sham group (Fig. 3).

3.1.3. De-adaptation

Mean error in epochs 2–5 of the de-adaptation phase (Fig. 3C) showed a group difference just outside significance (chi-sq(3,107) = 7.67,p = 0.053). However, post-hoc comparisons showed the '*asynch*' group had a significant greater after-effect compared to sham (p = 0.023, Bonferroni corrected). Although mean after-effects were larger for '*synch*' and '*standard*' groups than sham, these differences were not significant.

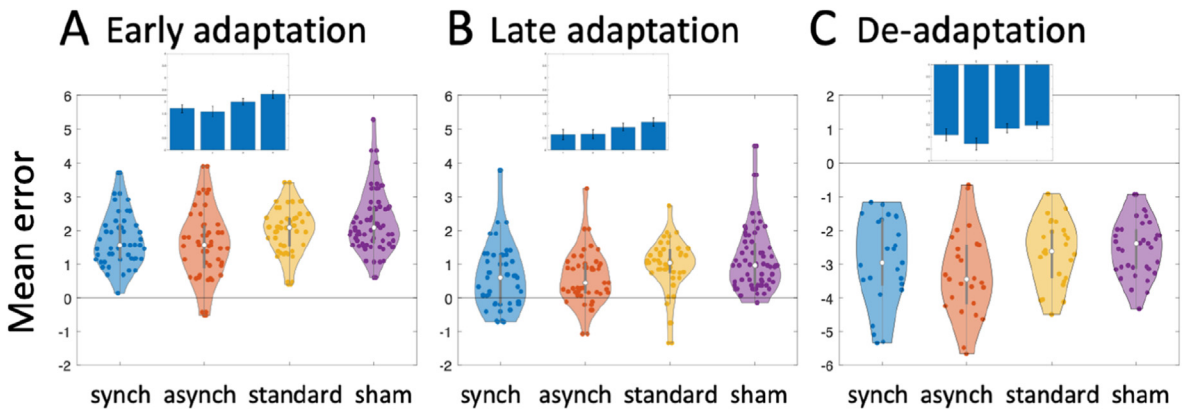

Fig. 3. The distribution of mean error in the adaptation (A, B) and de-adaptation phases (C) for each stimulation group. The violin-plots show the mean error for each participant (filled dots) and the group median (white dot); the central thick vertical bars within the violins span the second and third quartiles. The small inset bar-graphs show the group means ± 1 SEM for easier comparison of the group differences. All bar-graphs the same vertical axis. The 240-trial adaptation phase has been analysed separately for early (A) and late (B) halves. The magnitude of the average de-adaptation error is higher than in the early and late adaptation phases as the experiment only allowed partial wash-out.

3.1.4. State-space modelling

The retention rate estimates had significant differences across the four groups (Fig. 4A; chi-sq(3,107) = 11.41, p = 0.01). The '*synch*' and '*asynch*' groups had the highest retention, and '*sham*' had the lowest. Post-hoc comparison showed significantly greater retention for the '*asynch*' group compared to sham (p = 0.012, Bonferroni corrected); the comparison for the '*synch*' group (p = 0.04) did not survive Bonferroni correction (p = 0.11). The learning rate parameter estimates (Fig. 4B) did not differ (chi-sq(3,107) = 2.2, p = 0.53).

3.2. Experiment 2

3.2.1. Baseline

Comparing the 3 epochs used to normalise all data, there was no significant difference between the groups (Kruskal-Wallis ANOVA test, chi-sq(7,126) = 1.45, p = 0.191).

3.2.2. Adaptation

The overall profile of error across the session showed obvious differences between the groups (Fig. 5) with, the '*synch*' group showed a rapid reduction in error (Fig. 5A). The other stimulated groups showed similar behaviour to the sham group, with markedly slower error reduction than '*synch*'.

Average errors across the entire adaptation phase significantly differed (chi-sq(1,126) = 18.64, p = 0.009) with smaller errors seen for the stimulation groups overall compared to the sham groups (Supplementary Figs. S3A and B). Post-hoc comparisons showed that '*synch*' group error was significantly smaller than that its control group, '*synch-vib*' (p = 0.006, Bonferroni corrected) and compared to the standard TDCS group (p = 0.042). The '*synch*' group average error was just 79% of that of '*sham*', and 66% lower than the '*standard*' group.

These group differences were pronounced in early adaptation, epochs 2–15, (chi-sq(3,126) = 19.52, p = 0.007). Most '*synch*' participants reached a very low error (Fig. 6A; group mean 60% of '*sham*', and 55% of '*standard*'). Errors in the '*synch*' group were smaller than '*synch-vib*' (p = 0.004, Bonferroni corrected) and smaller than '*standard*' (p = 0.018, uncorrected). No other effects were significant.

Late adaptation errors also differed across the groups (Fig. 7; chi-sq(7,126) = 22.93, p = 0.002). The '*synch*' and '*feedback*' groups both differed from their vibrotactile shams (p = 0.036 and

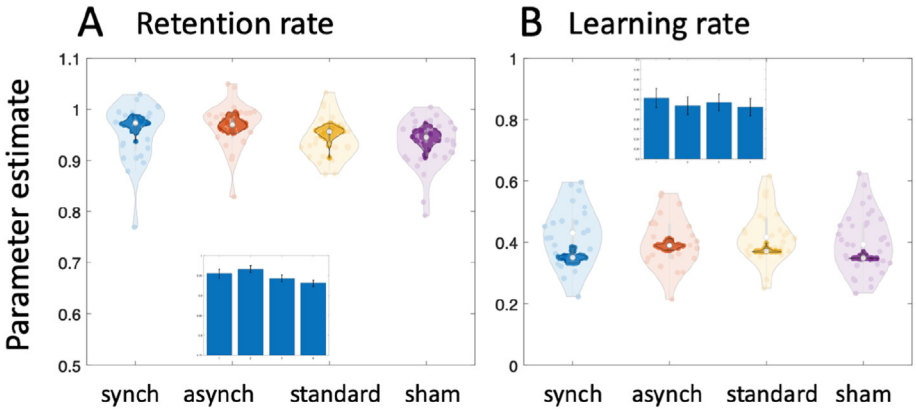

Fig. 4. A, B. Parameter estimates for a single state-space model fitted to the epoch-averaged errors for each participant. The retention (A) and learning rate estimates (B) are plotted by stimulation group. The pale violin plots show the distribution of individual parameter estimates for the four groups; the darker superimposed violin plots are from 50 datasets simulated to have the group mean and SEM of the originals, for visualization. The median r-sq for the model fits to simulated datasets was 0.89 (range 0.71–0.93); for the original data the median was 0.81, range 0.36–0.97.

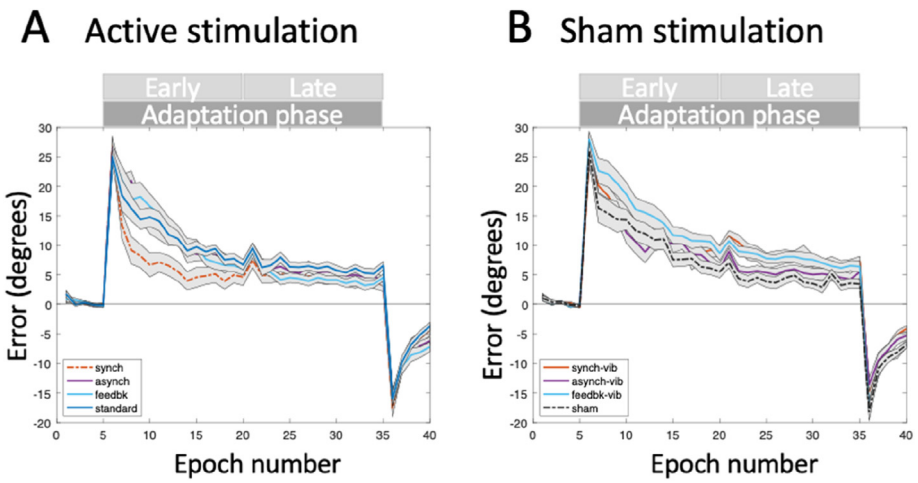

Fig. 5. Average error for each of the 8 groups in Experiment 2. (A) the 4 active stimulation groups; (B) the 4 sham groups. The rapid reduction in mean error can be seen for the synchronous stimulation group (A, dashed red line) relative to the other stimulation groups (A) and the sham group (B, dashed black line). Thick lines (dashed or solid) are group means; grey zones are ± 1 SEM around the mean. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

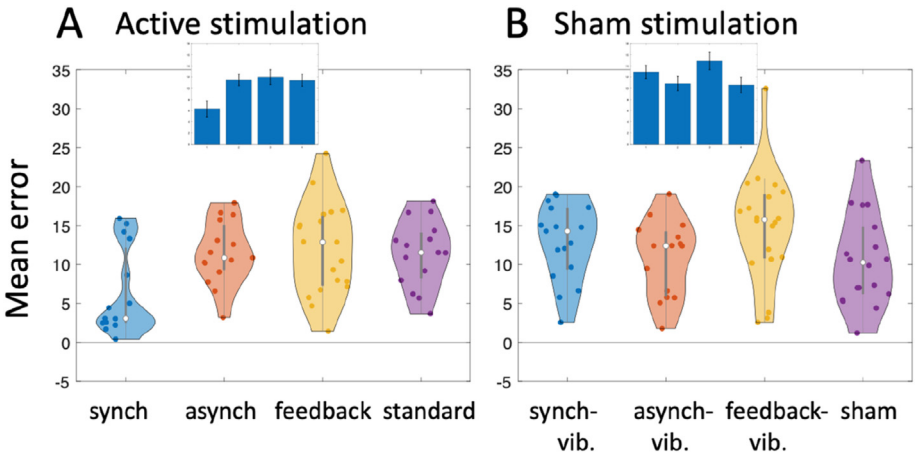

Fig. 6. Violin plots show the distribution of mean error during early adaptation (epochs 2–15, i.e., the first half of the adaptation phase) for Experiment 2. The group median is shown by the white dots. The inset bar graphs show the group mean±1 SEM for ease of comparison of group differences.

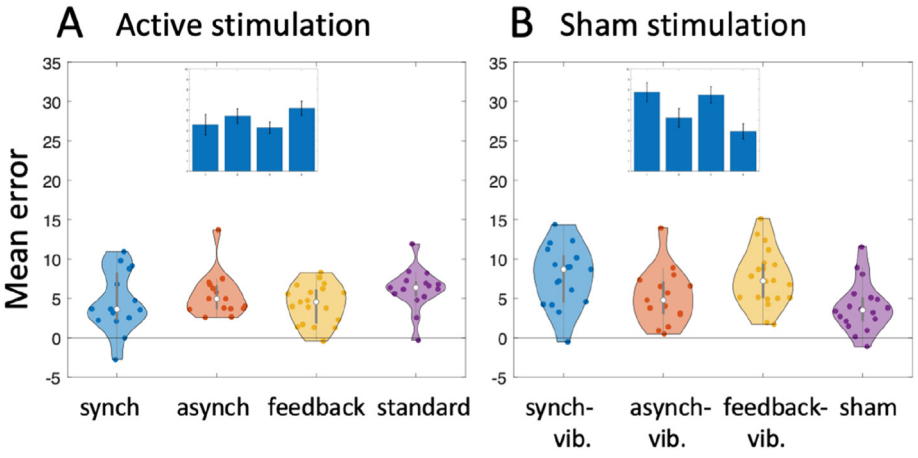

Fig. 7. Average error during late adaptation (epochs 17–30, i.e., the second half of the adaptation phase) for Experiment 2. The format is the same as in Fig. 6 and the vertical axes are also equal to those in Fig. 6.

p = 0.018, Bonferroni corrected). But differences between '*synch*' and '*standard*' had dropped out of significance (p = 0.11).

3.2.3. De-adaptation

The mean errors in the de-adaptation period showed no significant differences (chi-sq(3,126) = 12.97, p = 0.07), although the '*synch*' group participants again showed relatively small de-adaptation errors (Fig. 8) and the group median was smaller than all the other groups.

3.2.4. State-space modelling

There was a significant difference in retention rate between the groups (Fig. 9; chi-sq(7,126) = 23.75, p = 0.0013) with lower retention in the '*standard*' group than '*sham*' (p = 0.006, Bonferroni corrected). Simulations matching the group mean and SEM suggest that the retention rate was particularly high in the '*feedback*' stimulated group (Fig. 9A).

The learning rate parameter estimates were variable (Fig. 10, faint violin plots), but showed a significant difference across groups (chi-sq(7,126) = 15.84, p = 0.027). '*Synch*' showed a higher median learning rate than all other groups, although none of the planned stimulation/sham pairwise comparisons reached significance. The simulations suggest that the learning rate was particularly high in the '*synch* stimulated group, and low in '*feedback*' and '*feedback-vib*' groups.

4. Discussion

We have previously shown that event-related TDCS (erTDCS, duration 3 s) selectively enhances adaptation of one set of movements to dynamic force fields, while not affecting another, interleaved set [27]. We hypothesized in the current study that short duration TDCS would also enhance visuomotor adaptation and be more effective than standard, tonic TDCS. We proposed greater efficacy because event-related TDCS might act more selectively on active neural circuits, undiluted by effects on other circuits [13,36].

Experiment 1 demonstrated that anodal erTDCS of the ipsilateral cerebellum significantly enhanced adaptation compared to sham. The 1 s event-related stimulation was synchronous with the centre-outward target reaches, temporally aligned with activity in cerebellar motor circuits. However, it also overlapped with presentation of visual feedback of error, and hence might have enhanced error-processing; enhanced error correction would neatly explain the improvement in performance. Unexpectedly, asynchronous TDCS also caused significant enhancement. One possible explanation is that both synchronous and asynchronous erTDCS enhanced adaptation because they were perceptible and acted as attentional or motivational cues to the participants. These open questions were addressed by Experiment 2, which also served as a replication study.

In Experiment 2 stimulation duration was reduced to 500 ms to allow more selective targeting of relevant parts of each trial, to separate effects that were not cleanly separated in Experiment 1. The results were clear cut: synchronous stimulation during movement to the target elevated adaptation performance across the whole adaptation period (Supplementary Fig. S2) and especially during the first half of the adaptation phase (Fig. 5). The mean '*synch*' errors were significantly reduced, reaching just 55% of '*standard*' error in the early adaptation period, thus supporting our hypothesis of enhanced efficacy for erTDCS.

A vibrotactile stimulus applied with the same 'synchronous' timing did not enhance learning; if anything, it had a detrimental effect late in the adaptation period (Fig. 5B). Compared with equivalently timed erTDCS, vibration did not appear to distract the '*asynch-vib*' group but did negatively affect the '*feedback-vib*' group, leading to relatively large errors in late adaptation. One suggestion is that the 'asynchronous' delivery of vibration between trials is sufficiently distinct from the task that it caused little disruption, unlike for '*feedback-vib*', when participants were still actively engaged in the task. Thus, there is evidence for some behavioural effect of the perceptual cues, but this cannot account for the enhanced adaption seen with synchronous erTDCS.

Another observation from Experiment 2 is that erTDCS during feedback processing ('*feedback*') or when at the home position ('*asynch*') was ineffective early in adaptation. This observation is important, as it implies that the temporal effects of the stimulation are tightly specific: the neural effects of stimulation synchronous with the action did not "bleed over" into other periods, and vice versa – the effects of stimulation just before or just after movement did not affect adaptation of the reaching actions performed a second or two later. This implies that the brief stimulation bursts did not induce longer lasting aftereffects, as are found with the typical stimulation periods of 5–20 min [37], although more direct electrophysiological measures of excitability are needed to clarify this. Further, it suggests that the effects observed in the '*synch*' group in Experiment 1 were not due to the overlap of erTDCS with the feedback processing stage. However, the '*asynch*' group in Experiment 1 did show strong effects, somewhat larger than the '*synch*'

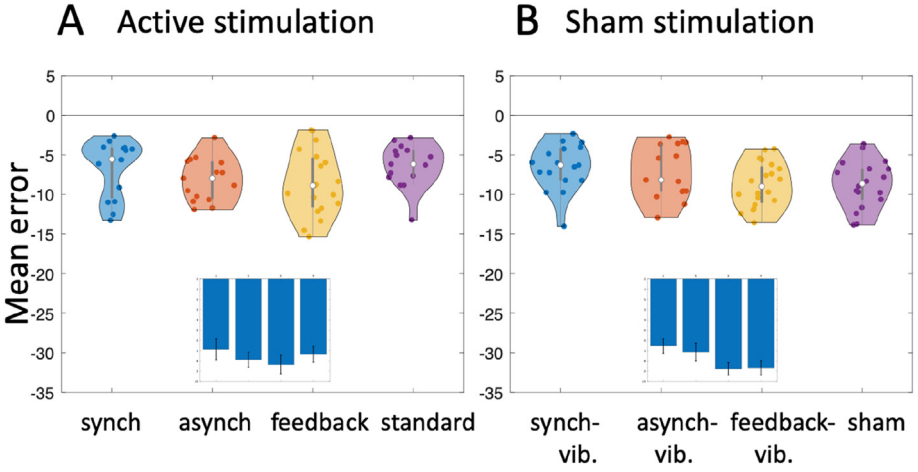

Fig. 8. Average error during epoch 2–5 of the de-adaption phase for Experiment 2. The format and the vertical axes are the same as those in Fig. 7.

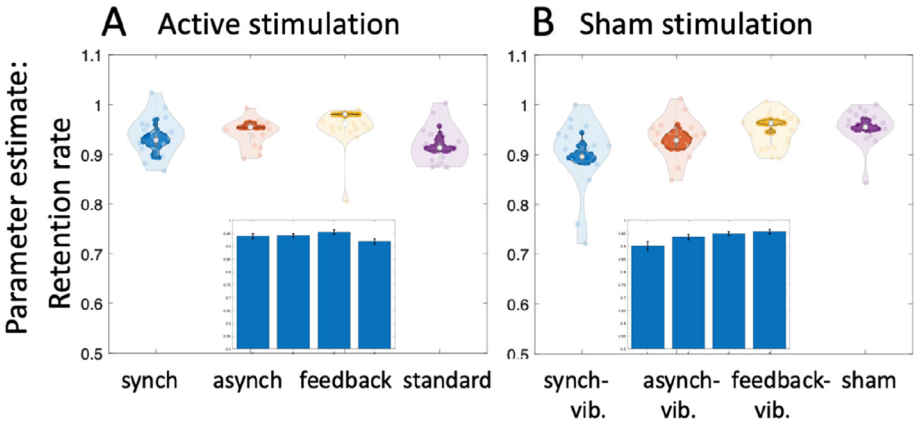

Fig. 9. Average retention rate estimates from single-state modelling of epoch-averaged errors, Experiment 2. The pale violin plots are the parameter estimates for the original datasets (i.e., per participant); the small inset bar-graphs show the group means ± 1 SEM for easier comparison of the group differences. The darker superimposed violin plots are from 50 datasets simulated to have the group mean and SEM of the originals, for visualization. The median r-sq for the fits to simulated data was 0.86 (range 0.68–0.94); for the original data the median was 0.87, range 0.31–0.98.

group. This was not replicated in Experiment 2 and remains to be explained. There are three possibilities, all related to the timing in Experiment 1. One is that the stimulation occurred during the process of settling the cursor into the home location, which often entailed a corrective movement or two. Why this might enhance adaptation for the outward reaching actions is not clear. The second possibility is that the '*asynch*' stimulus ended just before target presentation, and if there are any brief after-effects of stimulation, potentially the planning of the next trial would be influenced. The first two possibilities were eliminated in Experiment 2, where we ensured the '*asynch*' pulse only started once a stable home position was achieved, and the pulse ended well before the next trial started. The third possibility is that because of its duration and timing, asynchronous stimulation was detected by Experiment 1 participants and acted as a cue to enhance attention or motivation. Twice as many '*asynch*' participants (60%) stated that they noticed a relationship between stimulation and the task timing compared to '*synch*' *(30%)*. In Experiment 2 no groups differed in their reported perception of stimulus or sham and '*asynch*' erTDCS was ineffective. Thus, the difference in '*asynch*' group responses in the two experiments requires further study. It would be particularly useful to explore possible planning- and movement-preparation related effects.

There was weak effect of the standard, tonic, TDCS effect in both experiments: a reduction in early and late error compared to sham in Experiment 1, and a small increase in retention and learning rates; none of these effects reached statistical significance. In Experiment 2 the effects were even smaller – and there was no adaptation advantage. This emphasises the often-modest effect of the standard protocol on visuomotor adaptation [10].

Awareness of stimulation seems not to affect the results. The participants in both experiments were poor at judging if they received active or sham TDCS. In Experiment 2 they were generally unaware of a specific relationship between erTDCS or vibrotactile stimulation and the task timing; in fact, as many reported being aware of a relationship when there was none (in '*standard* 'and in '*sham*') as when there was a genuine link (see Supplementary Materials). This suggests enhanced adaptation in the '*synch*' group cannot be due to explicit cueing or other explicit mechanism, such as increased attention, and thus must be due to neural activation.

We cannot yet be certain about the neural mechanism that links (proposed) enhanced activity in the cerebellum and enhanced learning and retention. As mentioned, we do not think it is due to higher level, cognitive, motivational, or perceptual cueing. The montage places the anodal electrode over the lateral cerebellum, and simulations suggest the electric field is stronger in this area than in occipital or brainstem regions [38]. The scalp-to-lateral cerebellum distance is also advantageous at this location [39]. Considerable evidence indicates that the cerebellum is critical for visuomotor adaptation [6–9]. Thus the behavioural effect might be

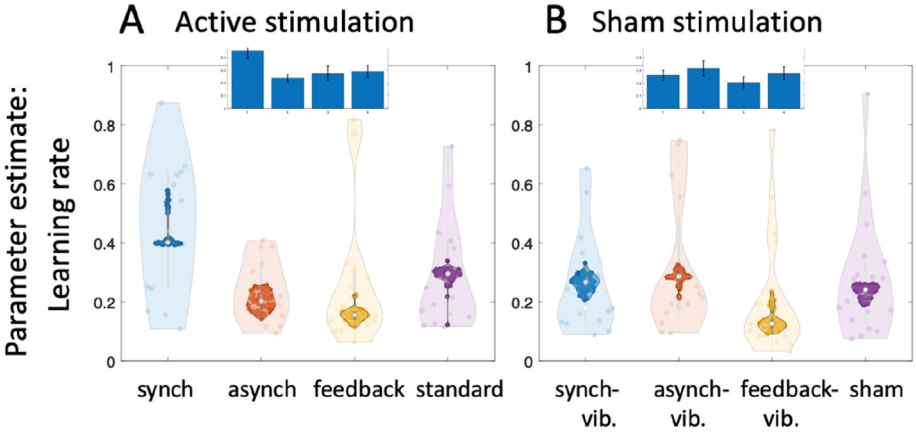

Fig. 10. Average learning rate estimates from single-state modelling of epoch-averaged errors, Experiment 2. The format is the same as in Fig. 9.

by enhanced adaptation of cerebellar forward model processes [40,41]. Cerebellar motor learning occurs at different sites and time scales [42]; it could even be that enhanced cerebellar output leads to greater reinforcement of actions elsewhere [9,43,44].

State-space modelling helps determine how these changes in error performance are achieved. In Experiment 1, the main effect driving strong performance was an increase in the retention rates. In Experiment 2, however, this was due to a significant change in learning rate, 48% higher in the '*synch*' groups than '*standard*' and 56% higher than '*sham*'. The only significant retention rate difference in Experiment 2 was a 4% drop from '*sham*' to '*standard*'. In the state-space model, change in error is a balance between retention and learning rates [45]: high retention rates make the state more stable over trials, while a high learning rate favours more dynamic behaviour. Thus, in Experiment 1, higher stability apparently aided good performance, while in Experiment 2, more dynamic learning aided the '*synch*' group and weaker retention disadvantaged the '*standard*' group. It is possible that the difference in visuomotor perturbation (10 vs 33°) is a factor here: the smaller perturbation in Experiment 1 might favour retention over learning rate, while in Experiment 2 the large perturbation might favour the reverse [46,47].

In animal models, the rapid onset of anodal TDCS is known to cause immediate changes in neuronal excitation, with concomitant increase in firing rates (albeit at higher currents than used here [14,15,48]. There is good reason to think that these field effects scale linearly, such that even small currents would have immediate effects. The fields generated in the human brain with 2 mA stimulation are unlikely to directly activate neurons, but would potentiate them, leading to higher average firing rates [15,49]. Potentiation is likely to be greatest at onset, and gradually decline, presumably because of homeostatic or habituating processes [50–52]. Hence brief stimulation might maximize its effect before any decline. In addition, while the duration we used is much greater than the 10–50 ms synchronization window that underlies spike-timing dependent synaptic plasticity, any increase in firing rates in the active circuits responsible for the reaching action would be expected to enhance Hebbian learning [53–55]. Lastly, although all forms of TDCS causes widespread activation, our event-related protocol should ensure that any Hebbian learning would be temporally concentrated on just those task-specific circuits [56]. We have previously shown (both using standard 20 min and 3 s event-related protocols) that cerebellar TDCS is more effective than M1 TDCS in a force adaption task; we expect similar cerebellar selectivity to be true of visuomotor adaptation. The cerebellum is certainly a critical structure in visuomotor adaptation [6–9]. Its learning processes are dominated by the influence on Purkinje cells of complex spikes driven by climbing fibres. Purkinje cells show both variable learning rate (due to changes in climbing fibre probabilities) and retention [42,57].

4.1. Limitations

While our evidence suggests a cerebellar neural mechanism, we must also accept that TDCS targeting the cerebellum may influence other central areas, notably occipital cortex. It is unclear how activation of visual areas would enhance adaptation (rather than potentially interfere, for example, by generating phosphenes). In addition, it is conceivable that the rise and fall of current necessary for brief erTDCS pulses would cue the participants, and lead to greater motivation or attention. Our control for this using vibrotactile stimulation may cause a different percept and lead to alternative effects. The follow-up questionnaires suggest participants were unreliable in their judgement of active or sham conditions, and in judging any relationship between stimulation and task, but we cannot directly compare percepts across groups. Hence, it would be useful to exclude the scalp stimulus in future experiments, e.g. through topical scalp anaesthetic [58]. It is also possible that peripheral or cranial nerve stimulation may contribute [59], and recent evidence [58] suggests stimulation of the greater occipital nerve might enhance memory (albeit not in a motor context). Exclusion of peripheral nerves such as the greater occipital nerve might require nerve block [60].

4.2. Summary

Short duration event related cerebellar TDCS appears to outperform standard on-line TDCS. We have used it here to target periods of action execution and feedback processing and have compared them to stimulation during between-trial pauses, but the technique would allow further dissection of sensorimotor adaptative processes, including target selection, movement planning, error correction and long-term retention, none of which we have yet addressed. It also offers the possibility of enhancing TDCS efficacy in non-motor domains, an area in which the evidence for TDCS effects is still weak [3]. Additional research is required to explore the time course of neural excitation and aftereffect, and to confirm that the enhanced learning is due to cerebellar modulation.

CRediT authorship contribution statement

Matthew Weightman: Conceptualization, Data curation, Investigation, Writing - review & editing. **Neeraj Lalji:** Data curation, Investigation, Methodology. **Chin-Hsuan Sophie Lin:** Data curation, Investigation, Writing - review & editing. **Joseph M. Galea:** Conceptualization, Supervision, Writing - review & editing. **Ned Jenkinson:** Conceptualization, Writing – review & editing. **R Chris Miall:** Conceptualization, Formal analysis, Data curation, Funding acquisition, Methodology, Software, Writing - original draft.

Declaration of competing interest

The authors declare that no competing interests exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.01.1673.

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