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Timing is everything: event-related transcranial direct current stimulation improves motor adaptation

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Abstract

There is a fundamental discord between the foundational theories underpinning motor learning and how we currently apply transcranial direct current stimulation (TDCS). The former is dependent on tight coupling of events; the latter is conducted with very low temporal resolution, typically being applied for 10-20 minutes, prior to or during performance of a particular motor or cognitive task. Here we show that when short duration stimulation epochs (< 3 seconds) are yoked to movement, only the reaching movements repeatedly performed simultaneously with stimulation are selectively enhanced. We propose that mechanisms of Hebbian-like learning are potentiated within neural circuits that are active during movement and concurrently stimulated, thus driving improved adaptation.

Introduction

Coincident, time-dependent mechanisms of synaptic plasticity are the canonical basis of theories of motor learning (Hebb, 1949; Kandel & Hawkins, 1992). These 'Hebbian' mechanisms are ubiquitous throughout the mammalian brain, having been described in the hippocampus, cerebellum, and sensory-motor cortices (Shatz, 1992; Ito, 2001; Malenka & Bear, 2004), and are believed to underpin all forms of learning and memory. Yet, protocols for non-invasive brain stimulation intended to promote motor learning and rehabilitation - particularly transcranial direct current stimulation (TDCS) - largely ignore timing-dependent mechanisms. TDCS is a non-invasive form of brain stimulation often used to induce plasticity in the motor system by modulating neural excitability. Changes in neuronal excitation have been shown to be almost instantaneous in terms of increased firing rates (Bindman, Lippold,

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& Redfearn, 1964; Landau, Bishop, & Clare, 1964; Purpura & McMurtry, 1965) and motor evoked potentials (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998; Nitsche & Paulus, 2000) following the application of TDCS and other forms of polarising currents. Despite this, most conventional studies apply TDCS for 15-20 minutes in a continuous stimulation period, prior to and/or during a motor task. If TDCS can instantaneously modulate neural activity, applying short duration epochs of TDCS temporally aligned with movement has the potential to specifically and selectively enhance learning, by driving coincident mechanisms of plasticity in the circuits of the brain that are active during the movement. Here we demonstrate (and replicate) that brief epochs of stimulation, applied in synchrony with movement, selectively enhanced motor adaptation whilst, importantly, having no effect on the adaptation of the non-stimulated (yet interleaved) movements. We believe this novel stimulation protocol harnesses mechanisms of Hebbian plasticity, resulting in the selective, transient, potentiation of those neurobehavioural circuits that are active concomitant with stimulation.

Results & Discussion

We designed a context-dependent force-field adaptation task, in which we applied short epochs of TDCS coincident with reaching movements performed through one of two opposite force-fields in the same session - a stimulation protocol we termed event-related TDCS (er-TDCS). Healthy young participants (Total: n = 78, Main experiment: n = 60, 3 groups of 20; Secondary experiment: n = 18) learned to reach through two opposing velocity-dependent force- fields, applied on interleaved trials in a pseudorandomised order (Howard, Wolpert, & Franklin, 2013). The two force-fields were contextually distinguished by a leftward or rightward shift in the visual display, although the movement was always

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performed in the midline (see Figure. 1 and Methods for more detail). During adaptation a leftward shift in visual task display was associated with a clockwise (CW) curl-field and a rightward shift in display was associated with a counter-clockwise (CCW) curl-field. During baseline and washout, trials were still distinguished by workspace shifts but were performed without any forces applied (null-field). In the main experiment, er-TDCS was applied over the cerebellum or M1 in brief (< 3 second) bouts, but only during movements through the CCW force-field and associated rightward shift in visual task display. For the secondary experimental group, er-TDCS was again applied over the cerebellum, but now during movements through the CW force-field and leftward shift in task display; this additional group controlled for any directionally specific adaptation-stimulation interactions. Consequently, in all groups, only one of the two learning contexts was performed with simultaneous stimulation, while the other context provided a within-subject non-stimulation control.

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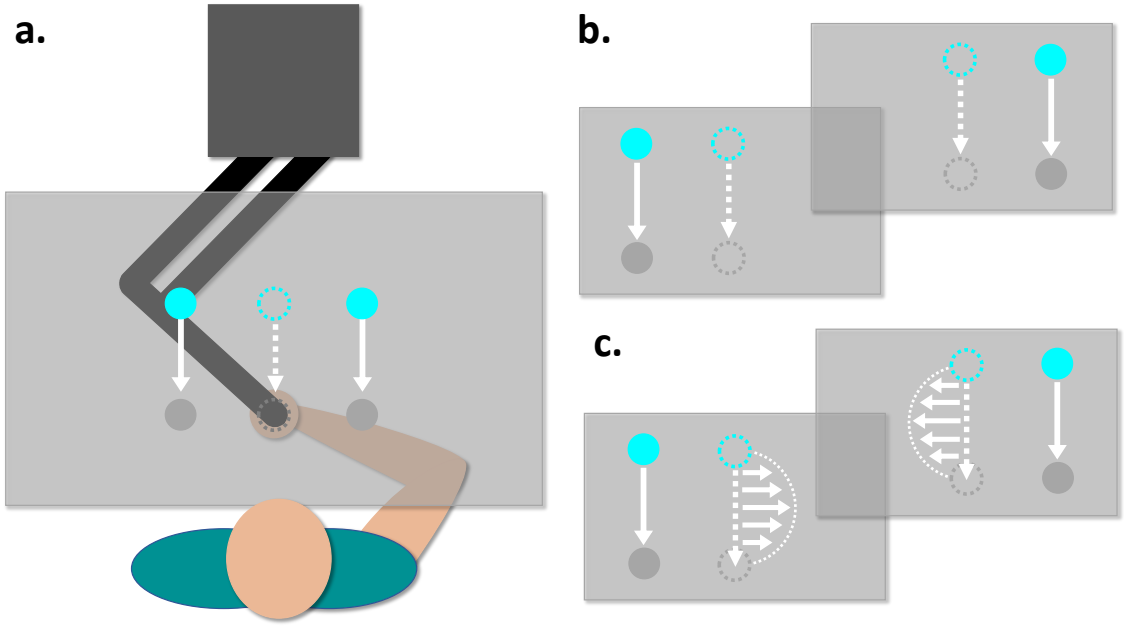

Figure. 1: Experimental design and set-up.
a. *A schematic of the task set-up, with an example screen display. Movements were always made in the midline position, but the cursor, home and target markers would be shifted either 10cm to the right or left. The order of the contextual shift in the task display was pseudorandomised, with an equal number in each task phase and runs of no more than three trials of the same contextual shift. Examples of the task display during null field* ***(b)*** *and context-dependent force-field* ***(c)*** *trials for both trial types.*

Our results from the main experiment show that event-related stimulation of the cerebellum selectively improved force-field adaptation, by driving a larger reduction of error during stimulated trials compared to unstimulated trials. We measured the area under the learning curve (calculated from lateral deviation of movements from the target midline; see methods for further details) in order to compare adaptation performance on trials performed with simultaneous stimulation and those without, using a 3x2x3 mixed-design ANOVA. The ANOVA contained within-subject factors of adaptation phase (baseline, adaptation, washout) and trial context (CW (left-shift), CCW (right-shift)) and the between-subject factor of stimulation group (M1 er-TDCS, cerebellar er-TDCS, sham). There was a significant three-way interaction between group, phase and trial context: $F(4, 342) = 3.62$, p

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= 0.007, ηp^2 = 0.04, Figure. 2 – figure supplement 1). Participants in the cerebellar stimulation group made significantly less error, and thus adapted better, on stimulated CCW trials compared to unstimulated CW trials, $p < 0.001$ (following Bonferroni corrected multiple comparisons). In contrast, there was no evidence of enhanced adaptation following M1 er-TDCS, as participants made similar levels of error on both stimulated and unstimulated trials ($p = 0.9$). Participants who received sham stimulation adapted comparably during CW and CCW ($p = 0.76$), suggesting there was no in-built task bias (Figure. 2 – figure supplement 1).

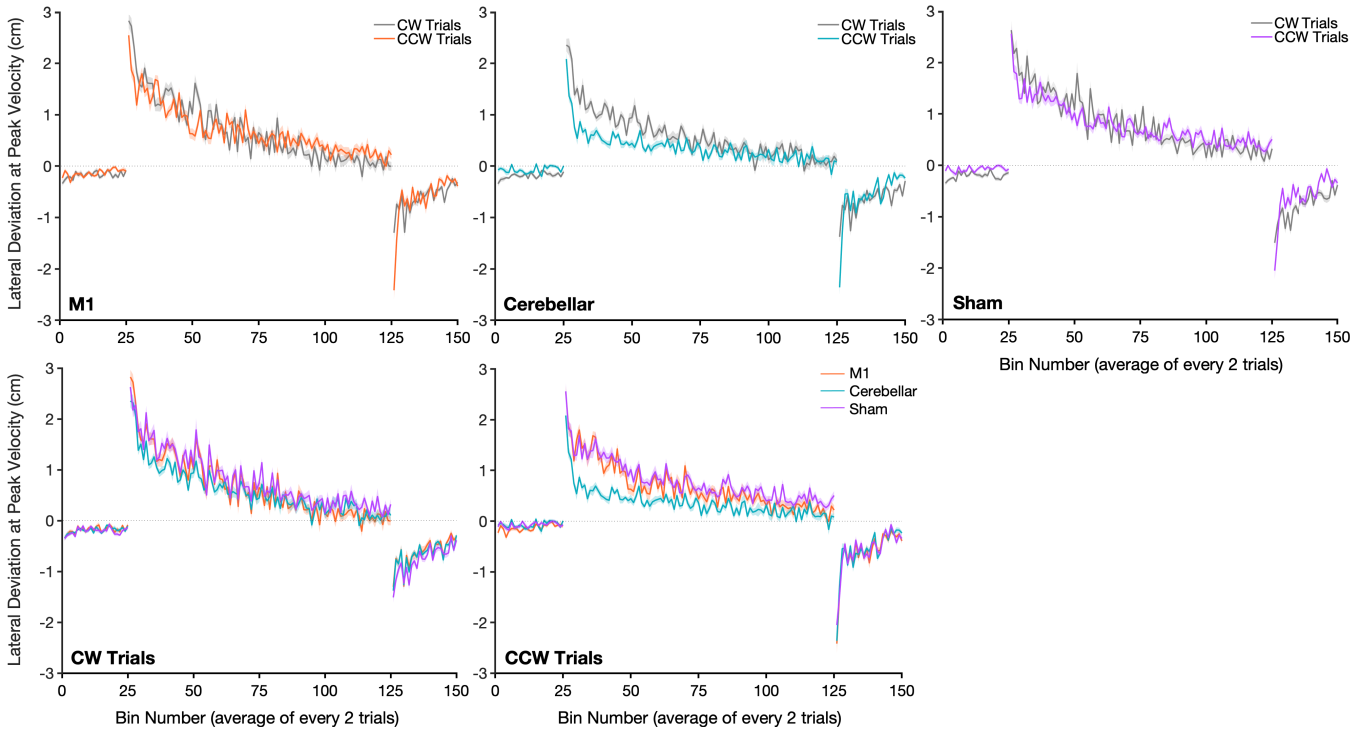

Figure. 2: Cerebellar er-TDCS selectively improves context-dependent force-field adaptation.
Top panel: *Mean lateral deviation for CW (left-shift) and CCW (right-shift) trials (± standard error, shaded regions), averaged into bins of two trials for the M1 er-TDCS, cerebellar er-TDCS and sham stimulation groups. The M1 and cerebellar groups received er-TDCS on CCW trials during the adaptation phase.* ***Lower panel:*** *mean LD (bins of two trials) for all three stimulation groups during either CW or CCW contextual trials.*

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Testing the robustness of these effects using estimation statistics (Ho, Tumkaya, Aryal, Choi, & Claridge-Chang, 2019), confirmed that er-TDCS applied to the cerebellum selectively improved the adaptation on CCW trials, while CW trials were unaffected. The effect size for this comparison was substantial (paired Cohen's d = -1.3) with 95.0% confidence intervals (CI) that did not overlap zero ([-2.05, -0.53]; Figure. 3). Conversely, the paired Cohen's d between CW and CCW trials for the M1 er-TDCS group was close to zero, which fell well within the CI (d = -0.0059, 95.0% CI = [-0.66, 0.64]); for the sham group d = -0.061 and 95.0% CI = [-0.69, 0.57].

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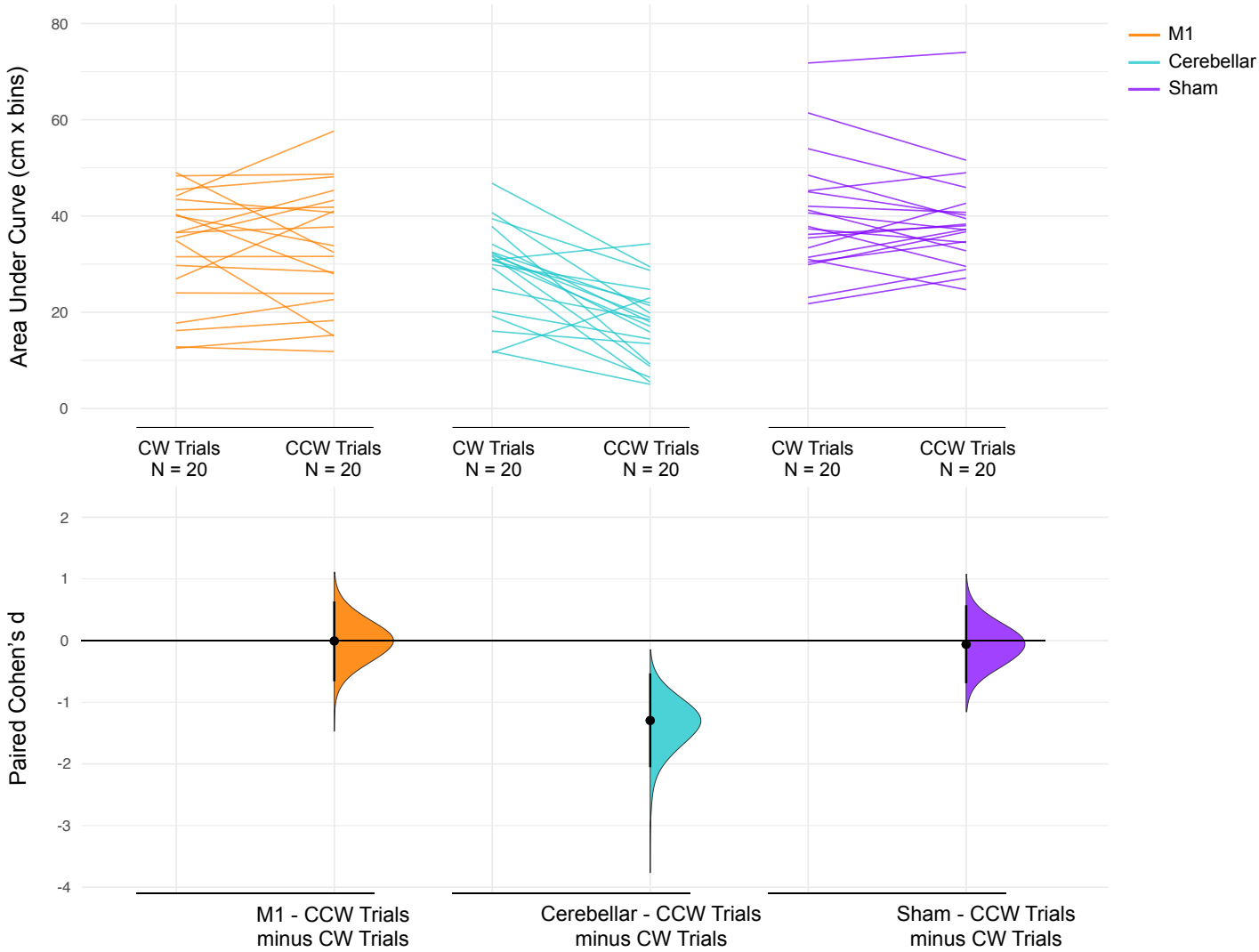

Figure. 3: Direct comparisons of adaptation during CW and CCW force-fields. ***Top panel:*** *area under the curve (cm x bins) for CW vs CCW trials for each participant during the adaptation phase, with each participant's data connected by a line.* ***Lower panel:*** *paired Cohen's d plotted as a bootstrap sampling distribution. Mean differences are depicted as dots, with 95.0% CIs indicated by black vertical bars.*

Results from our secondary experimental group helped confirm the findings from our main experiment. We again found that er-TDCS over the cerebellum enhanced adaptation of movements through the stimulated context (now CW, unlike the CCW context in the main experiment) compared to the unstimulated control (Figure. 4a and Figure. 2 - supplement 1) – a replication of the selective adaptation effect initially found (Figure 2). Area under the learning curve was compared in a 3x2 way ANOVA (Task Phase: baseline,

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adaptation, washout; Trial Context: CW (left-shift), CCW (right-shift)), and revealed significant main effects of task phase ($F(2, 102) = 248.23$, $p < 0.001$, $\eta p^2 = 0.83$), trial context ($F(1, 102) = 12.49$, $p < 0.001$, $\eta p^2 = 0.11$) and a significant interaction ($F(2, 102) = 6.05$, $p = 0.003$, $\eta p^2 = 0.11$). Bonferroni corrected multiple comparisons showed that during the adaptation phase participants made significantly less error on stimulated CW trials, compared to CCW trials ($p < 0.001$). Estimation statistics affirmed this result and revealed a large effect size (paired Cohen's d = 0.82, 95% CI = [0.095, 1.43]), with zero falling outside the 95% CI range (see figure 4b).

As expected, we found no evidence to suggest performance during the two trial contexts were different during baseline or washout phases (both $p > 0.53$).

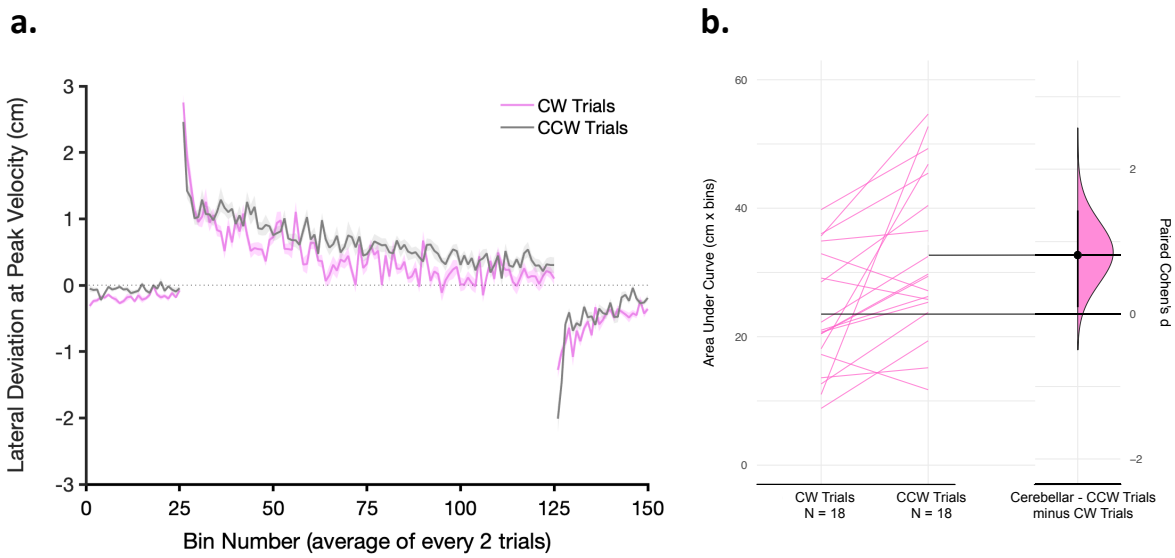

Figure. 4: Adaptation performance and context selectivity for the secondary experimental group receiving er-TDCS during CW trials

a: *Mean lateral deviation for CW (left-shift) and CCW (right-shift) trials (± standard error, shaded regions), averaged into bins of two trials for the secondary experimental group. Participants in this group received er-TDCS over the cerebellum during CW adaptation trials. Panel* ***(b.)*** *depicts the area under the curve (cm x bins) for CW vs CCW trials for each participant during the adaptation phase, with each participant's data connected by a line in a Paired Gardner-Altman plot, with the paired Cohen's d plotted as a bootstrap sampling distribution alongside. The mean difference is shown as a dot, with 95.0% CIs indicated by black vertical bars.*

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One concern was that short epochs of TDCS, with rapid onset/offset, might be perceived by the participant and act as a form of attentional cue. However, we found no significant differences between their self-reported Confidence in Stimulation ($F(3,74) = 0.078$, $p = 0.97$, $\eta p^2 = 0.003$, see methods for more detail), suggesting successful blinding to the stimulation condition was achieved. Given that this er-TDCS protocol is relatively novel, it is also pleasing that the short bouts of TDCS did not cause excessive discomfort (Perceived Comfort: $F(3,74) = 2.31$, $p = 0.084$, $\eta p^2 = 0.085$), with all groups reporting low levels of discomfort. Notably, comfort levels were similar to those reported after 17 minutes of continuous TDCS (Weightman, Brittain, Punt, Miall, & Jenkinson, 2020). Crucially, only one participant (in the M1 er-TDCS group) noticed that the stimulation only occurred on CCW force-field trials with a corresponding right-shift in task display. The lack of that awareness of stimulation timing in the cerebellar group suggests enhanced adaptation cannot be due to explicit cueing or other explicit mechanism such as increased attention towards CCW (right-shift) trials.

These results suggest that brief periods of TDCS applied in synchrony with movement can selectively and specifically improve motor adaptation of that movement, while leaving adaptation of interleaved movements unaffected. Although many studies have reported positive effects of TDCS on motor learning and rehabilitation, when applied continuously for 10-20 minutes (Hummel et al., 2005; Fregni et al., 2006; Galea, Vazquez, Pasricha, Orban de Xivry, & Celnik, 2010; Hardwick & Celnik, 2014; Allman et al., 2016; Benussi et al., 2017; Chiou, Morris, Gou, Alexander, & Gay, 2020; Weightman et al., 2020), there are a growing number of studies reporting null or mixed effects (Jalali, Miall, & Galea, 2017; Hulst et al., 2017; Mamlins, Hulst, Donchin, Timmann, & Claassen, 2019; Wiltshire & Watkins, 2020), leading to uncertainty around the effectiveness of TDCS (Horvath, Forte, & Carter, 2015).

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During continuous stimulation, for 10-20 minutes, any number of different behaviours may be performed alongside the specific task that is the 'target' of stimulation. The concatenation of all these behaviours under the same stimulation conditions may lead to changes in excitation levels in multiple cortical circuits that confound the results, contributing to some of the conflicting findings (Antal, Terney, Poreisz, & Paulus, 2007). In contrast, event-related TDCS may selectively modulate only those circuits and task-related synapses that are contemporaneously active and undergoing concurrent plasticity. Such mechanisms have been proposed previously and here we add experimental evidence support to the suggestion that TDCS acts as a modulator of activity-related synaptic plasticity (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017; Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Bikson, Paulus, Esmaeilpour, Kronberg, & Nitsche, 2019). As such, er-TDCS could prove beneficial when long experimental or rehabilitative protocols are required, as recent research suggests that long continuous bouts of TDCS may cause the modulatory effects of TDCS to reverse over time, i.e. from excitation to inhibition (Hassanzahraee, Nitsche, Zoghi, & Jaberzadeh, 2020). Neural recording studies have also found that the effects of direct current stimulation may attenuate during long stimulation blocks. Such decreases have been seen in spontaneous neural activity and evoked potentials, due to short-term habituation-like adaptation processes (Creutzfeldt, Fromm, & Kapp, 1962; Kunori & Takashima, 2019; Asan, Lang, & Sahin, 2020).

Therefore, we propose that (1) pulsing TDCS during a movement - in this case reaching movements in a context-dependent force-field adaptation task - enhances plasticity by boosting the neural activity within the circuit associated with and activated by this specific behaviour. This increased activity in turn potentiates the synapses within this circuit that are 'eligible' for Hebbian change during this stimulated behaviour. (2) By providing brief er-

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TDCS, it is more likely that only those circuits involved in the particular (concurrent) behavioural context are the ones that are potentiated. In essence, er-TDCS provides transient heightened potentiation that 'focuses' Hebbian learning onto specific neurobehavioural circuits (Kronberg et al., 2017; Kronberg, Rahman, Sharma, Bikson, & Parra, 2020).

These results open up new possibilities for the use of TDCS in both research and clinical settings, to improve its effectiveness and specificity. They also demonstrate that stimulation can be applied in very short bouts without inducing severe discomfort or side-effects, and without the participants' explicit knowledge of the specific stimulation protocol.

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Materials & Methods

Participant Details

A total of seventy-eight participants (aged 18-32 years, mean = 20.6 ± 3.0 years; 39 male) gave written informed consent to take part in the study (approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham). All participants were right-handed, had normal or corrected to normal vision and completed a safety screening questionnaire for TMS and TDCS prior to beginning the session. For the main experiment sixty participants were pseudo-randomised into one of three experimental groups: M1 er-TDCS group (n = 20; mean age = 19.7 ± 0.8 years, 10 males), Cerebellar er-TDCS group (n = 20; mean age = 19.8 ± 1.9 years, 11 males) or a Sham TDCS group (n = 20; mean age = 19.5 ± 0.8 years, 9 males). A further eighteen naive participants (n = 18, mean age = 23.9 ± 4.7 years, 9 males) were recruited for a secondary experimental group. Participants in this secondary group also received cerebellar er-TDCS. Importantly, data from the secondary group were collected after the conclusion of the main experiment in order to replicate the main experimental finding. No a priori statistical methods were used to determine sample size. Instead, our sample size was chosen to be consistent with, or greater than similar existing literature (Panouillères et al., 2015; Spampinato, Satar, and Rothwell, 2019; Weightman et al., 2020).

Experimental Design

Participants were seated in an armless chair so they could comfortably reach and manipulate the handle of a custom-built robotic manipulandum (vBOT; Howard, Ingram, and Wolpert, 2009) with their right arm. The vBOT measured and stored the position and velocity of the handle at 1000Hz, only allowing movements in the horizontal plane. The

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visual display screen (Mac Cinema HD Display) was reflected in a horizontal mirror (60 x 76 cm) to appear as a virtual image co-planar with the manipulandum. The screen displayed two grey circular markers (2 cm diameter) which represented the home position and the target, located 20 cm and 10 cm away from the edge of the screen respectively. The screen also displayed a white cursor (1 cm diameter) which showed the position of the vBOT handle. The home and target markers were displaced 10cm left or right of the screen midline, depending on the context of the trial, and the cursor was displaced 10cm left or right of the vBOT handle (Figure. 1a).

Participants were told that the aim of the task was to make fast movements from the home marker to the target marker, so that the cursor moved in a straight line between the two (10 cm movement). At the beginning of each trial the participant entered the home position and were held there for 3 seconds by stiff spring forces on the vBOT handle, before being allowed to move. The home marker then changed from grey to blue indicating that participants were allowed to make their movement and the holding forces were released. During the hold period participants were asked to keep relaxed and not to ‘pull’ or ‘lean’ on the handle. To encourage fully completed movements, participants were told that it was acceptable to overshoot the target slightly, but were discouraged from making excessively large movements. If the movement was accurate and hit the target marker it would flash yellow for 1 second indicating a successful trial. If the movement failed to hit the target or deviated ± 2 cm from the midline at any point during the movement path the target would flash red for 1 second, indicating an unsuccessful trial. Once the movement was completed, the vBOT would actively guide the handle back to the home position with a spring force, ready for the next trial to start. Each trial took roughly 5 seconds from start to finish (3

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second hold, 1 second movement, 1 second return). Vision of the upper arm was blocked during the task using a curtain and all lights extinguished prior to starting the task.

Behavioural Protocol

The behavioural task consisted of 600 trials and was split into three phases: Baseline (100 trials), Adaptation (400 trials) and Washout (100 trials). On each trial, in all three phases, the task display would either be presented with a 10 cm leftward or rightward shift from the midline position. The order of this shift was pseudo-randomised, so that there was an equal number of leftward and rightward shift trials in each phase and no more than 3 consecutive trials with the same contextual shift. The trial/shift order was the same for all participants. During baseline trials no forces were imposed on the handle so participants could move between the home marker and the target unperturbed (Figure. 1b). For adaptation trials the leftward or rightward contextual shift in the task display was consistently associated with either a clockwise (CW, for left-shift) or counter-clockwise (CCW, for right-shift) velocity sensitive curl force-field (Figure. 1c) - thus creating two distinct trial contexts. The strength of both imposed force-fields was 12 N/m/s (see equation 1).

$$\begin{bmatrix} Fx \\ Fy \end{bmatrix} = \begin{bmatrix} 0 & -12 \\ 12 & 0 \end{bmatrix} \begin{bmatrix} Vx \\ vy \end{bmatrix} \qquad (1)$$

Washout trials immediately followed the adaptation phase, which were once again performed without any forces i.e. identical to baseline. Participants were not given any explicit information regarding the link between the visual shift and associated direction of force-field.

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In order to measure compensatory forces applied against the curl field, 60 error-clamp trials were pseudorandomly interleaved throughout the task (10% of all trials). These trials were distributed proportionally throughout the three task phases. During error- clamp trials, movements were constrained to a 'virtual channel' between the home position and target marker, so that forces produced against the channel walls could be measured (see Figure. 2 – supplement 2 and Figure. 4 – supplement 1 for data and analysis). Error-clamp trials took place twice every 20 trials and the contextual shift was pseudorandomly ordered so that no more than two successive error-clamp trials were of the same shift. Additionally, error-clamp trials only occurred on trials where there was a switch in context and not after one or two trials of the same shift. To avoid directional feedback, the vBOT position was indicated via an expanding semi-circle representing only the distance from start location (Lago-Rodriguez & Miall, 2016). At the end of the task each participant was asked if they had noticed the relationship between the visuospatial context and direction of the force in order to understand their explicit knowledge during the task.

Transcranial Direct Current Stimulation

Anodal TDCS was delivered via two sponge electrodes (5 x 7 cm) soaked in saline solution, using a nurostym tES device (Neuro Device Group S.A., Poland). For cerebellar stimulation the anodal electrode was placed over the right cerebellar cortex (3 cm lateral to the inion; Galea, Jayaram, Ajagbe, and Celnik, 2009) and the cathode was positioned on the superior aspect of the right trapezius muscle (Panouillères, Joundi, Brittain, & Jenkinson, 2015; Panouillères, Miall, & Jenkinson, 2015; Weightman et al., 2020; Weightman, Brittain, Miall, & Jenkinson, 2021). For M1 stimulation the anodal electrode was positioned over the hand area of the left motor cortex, identified by single pulse TMS (Magstim Rapid2 stimulator;

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Magstim Ltd, UK) delivered at suprathreshold stimulus intensity so as to elicit a visible twitch of the first dorsal interosseous muscle. The cathode electrode was placed on the skin over the contralateral supraorbital ridge (Nitsche & Paulus, 2000). TDCS was only delivered during the adaptation phase, the parameters of which depended on the stimulation group. Once the task had ended, participants rated their perceived comfort and confidence in their belief that they received real stimulation on a 10-point visual analogue scale (VAS). They were also asked if they noticed anything specific regarding the timing of the stimulation, with respect to the task.

In the main experiment, participants in the M1 and cerebellar stimulation groups received brief epochs of TDCS during the adaptation phase, with each epoch, temporally overlapping with movements made through the CCW force-field, when the task display was shifted to the right. Stimulation was ramped up over 1 second during the hold period (1 second prior to the movement cue). It was then held at 2 mA for 1 second during the movement and then ramped down over 1 second as the vBOT returned the participant's hand to the home position. TDCS was applied on both force-field and error-clamp trials. In the secondary experimental group, the er-TDCS protocol was conducted as per the main experiment, however, stimulation was only applied over the cerebellum and concurrently with movements made during the CW force-field and associated left-shift in visual display. Data from this group served as an attempt to replicate the effect found in the main experiment, with stimulation applied during movements through the opposing force-field direction. For the sham group, stimulation was ramped up over 10 seconds at the start of the adaptation phase, held at 2 mA for 10 seconds and then ramped down over a further 10 seconds. The electrode montage was randomly assigned to either M1 or cerebellar prior to starting the session.

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Data & Statistical Analysis

Data collected from the vBOT were analysed offline in MATLAB (The Mathworks, version R2018b). The lateral deviation (LD) of movements at peak velocity was calculated for null and force-field trials and subsequently averaged into bins. For error-clamp trials, a force compensation ratio (FC) was calculated, see equation 2.

$$\frac{\int_{t0}^{t\,end} actual\ force}{\int_{t0}^{t\,end} ideal\ force} \times 100 \qquad (2)$$

Actual force was the forces generated against the channel walls, integrated across the movement; ideal force was the force required to fully compensate for the perturbation in force-field trials (ideal force: velocity x field constant). Any LD or FC values that fell outside ± 2 SD of the mean across the group were excluded prior to averaging and thus removed from further analysis. LD and FC values were analysed separately for the two contexts. Area under the learning curve for LD and FC during each phase of null, force-field and error-clamp trials was calculated to be used for statistical analysis, providing a measure of total error/adaptation during the task.

Statistical analyses were conducted in MATLAB, R (R Core Team, version 3.6.3) and SPSS (IBM, version 26). All ANOVAs were run in general linear model format and followed up with Bonferroni-corrected multiple comparisons, when a significant main effect or interaction was found. The threshold for statistical significance was set at $p < 0.05$ and we report partial eta squared (ηp^2) effect sizes for ANOVAs. Estimation statistics were conducted as per Ho et

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al. (2019), reporting paired Cohen's d effect sizes and bias-corrected and accelerated confidence intervals (following 5000 bootstrap samples).

Data from the secondary experimental group were processed and analysed separately as they were collected after the main experiment and this group was not included in the original study design.

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Author Contributions

MW, JSB, RCM and NJ conceived and designed the study. MW collected the data. MW, JSB, AH, RCM and NJ analysed and interpreted the data. MW wrote the first draft of the paper. JSB, AH, RCM and NJ reviewed and edited the paper and all authors agreed with the final submitted version.

Competing Interests

The authors declare no competing interests exist

Data and Code Availability

Data used in this manuscript to create figures have been deposited to Mendeley Data and are available at:

DOI: 10.17632/2k33svf244.2

For further information and requests for resources please communicate with corresponding author, Matthew Weightman (mcw423@adf.bham.ac.uk).

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Supplementary Information

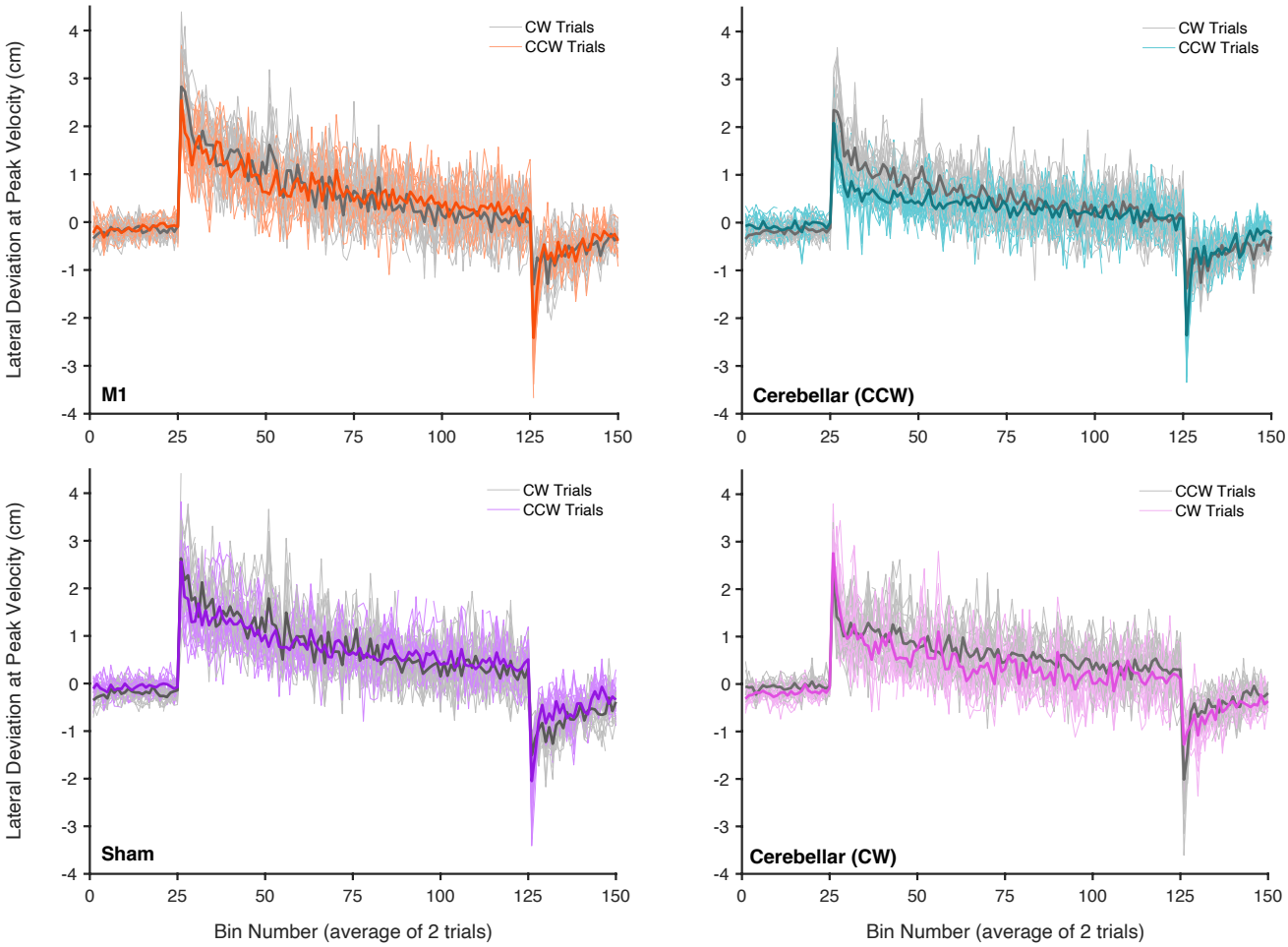

Figure. 2 - supplement 1: Individual data traces for lateral deviation.
Lateral deviation for CW (left-shift) and CCW (right-shift) trials averaged into bins of two trials for the M1 er-TDCS, cerebellar er-TDCS, sham stimulation and the secondary cerebellar er-TDCS groups. The M1 and cerebellar groups received er-TDCS on CCW trials during the adaptation phase and the secondary experimental group (cerebellar (CW)) received er-TDCS during the adaptation phase on CW trials. Individual traces are plotted for each participant for each trial context, with the group mean superimposed in bold on top.

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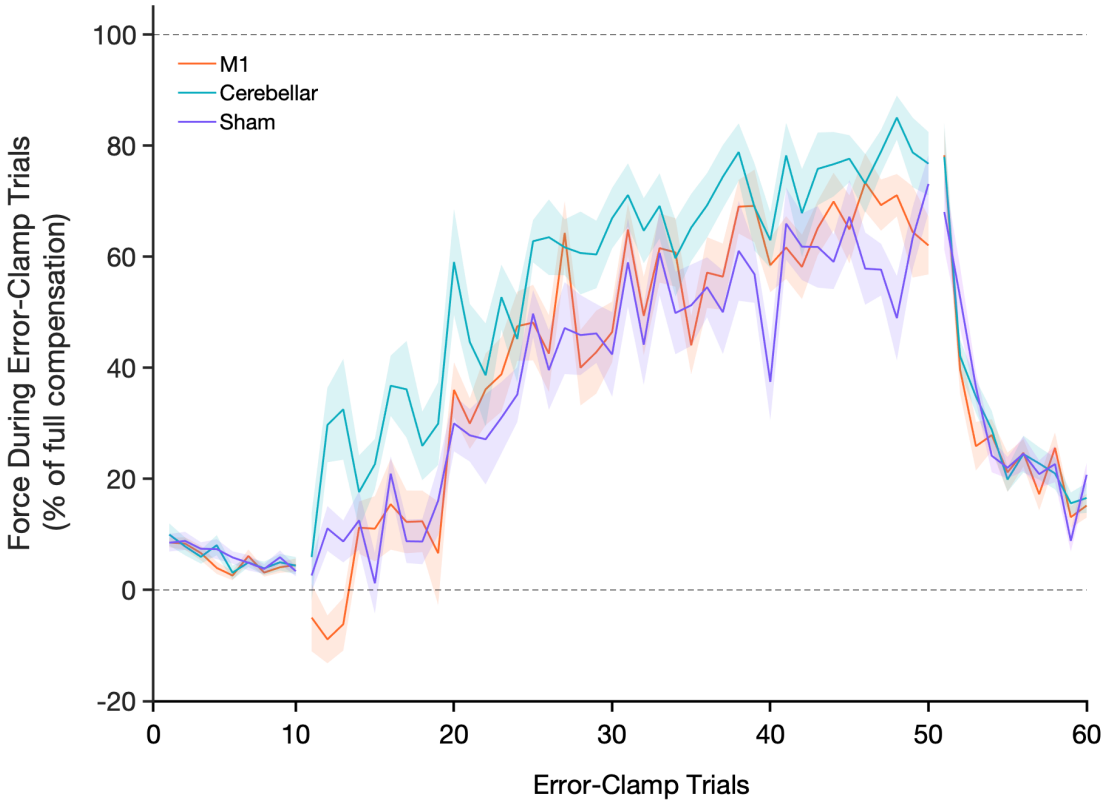

Figure. 2 - supplement 2: Force compensation during error-clamp trials, main experiment. *Average force compensation during error-clamp trials (±standard error, shaded region) in each task phase for all three stimulation groups. Data is sign adjusted to show the percentage of full compensation for both left and right-shift error-clamp trials. Area under the curve was calculated (AUC-compensation) for each participant in each task phase and trial context, in order to compare performance. A 3x3x2 (task phase x stimulation group x contextual shift) mixed-design ANOVA revealed significant main effects of task phase ($F (2, 342) = 873.68$, $p < 0.001$, $\eta p^2 = 0.84$) and stimulation group ($F (2, 343) = 10.78$, $p < 0.001$, $\eta p^2 = 0.06$), but no significant three-way complex interaction ($F (4, 342) = 0.66$, $p = 0.99$, $\eta p2 = 0.001$). There were no differences between force compensation on left vs right-shift trials for any of the stimulation groups, all $p > 0.072$, suggesting er-TDCS had no specific effect on performance during error-clamp trials. The ANOVA, however, did reveal a significant interaction between phase and stimulation group ($F (4, 342) = 9.92$, $p < 0.001$, $\eta p^2 = 0.1$). Multiple comparisons showed that the three stimulation groups performed similarly on error-clamp trials during baseline and washout phases (all $p > 0.99$), yet during the adaptation phase, participants in the cerebellar er-TDCS produced greater levels of force compensation compared to the M1 er-TDCS and sham group, both $p < 0.001$, with no difference between the latter two group ($p = 0.39$). These results may suggest that er-TDCS over the cerebellum had a global effect on force compensation during error-clamp trials, rather than the specific timing-dependent effect observed for lateral deviation error-reduction.*

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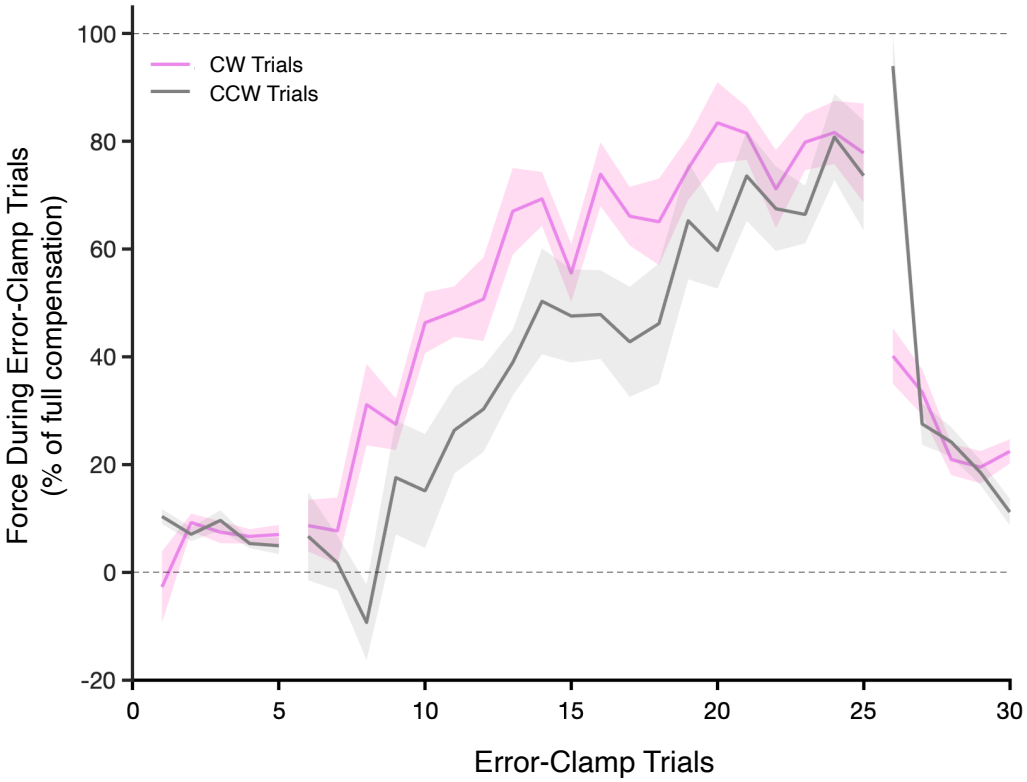
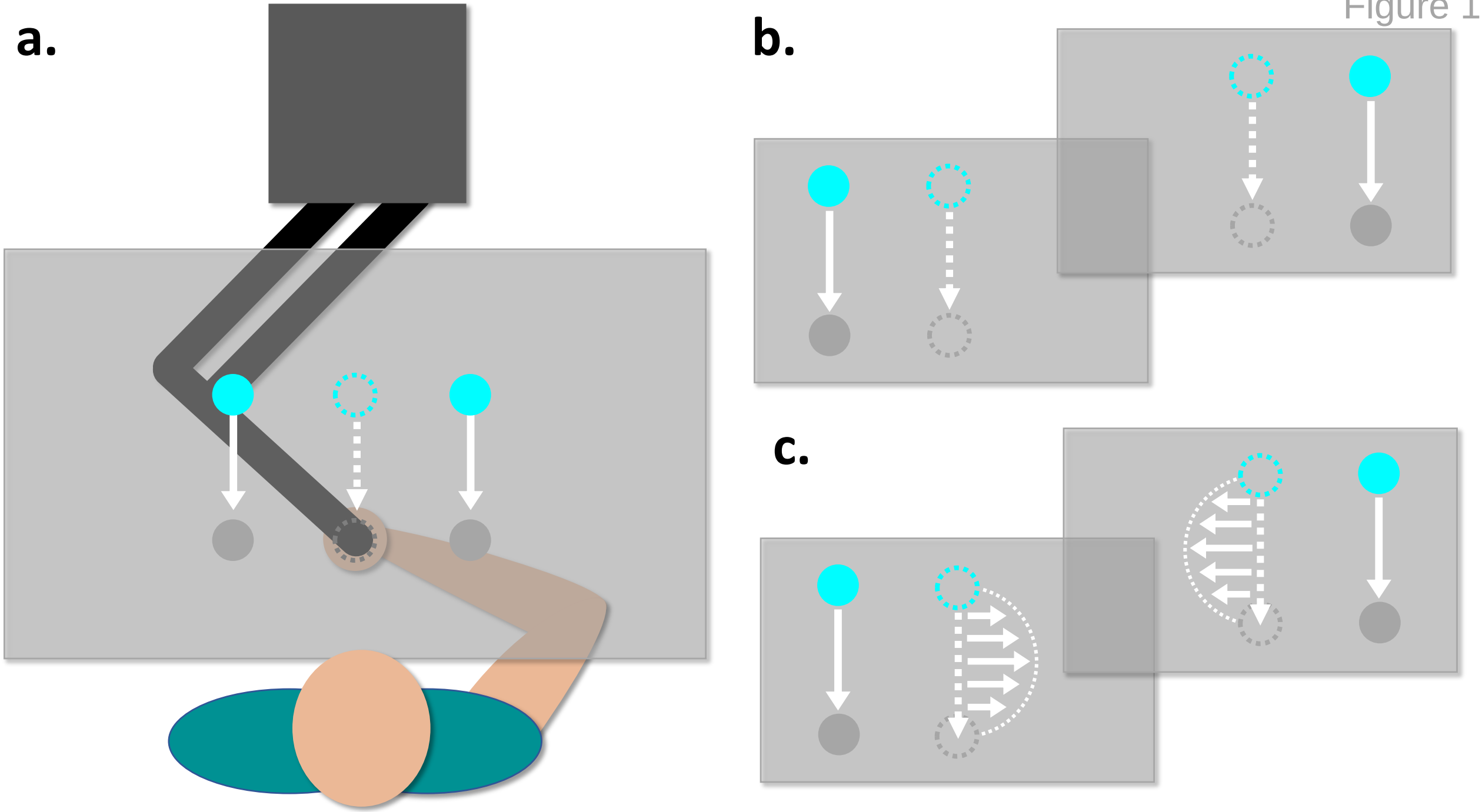


Figure. 4 - supplement 1: Force compensation during error-clamp trials, secondary experimental group.

Average force compensation during CW and CCW error-clamp trials (± standard error, shaded region) for data from the secondary experimental group. For this group, cerebellar er-TDCS was applied on CW (right- shift) error-clamp trials (trials 6-25 on figure). Data is sign adjusted to show the percentage of full compensation for both left and right-shift error-clamp trials.

Specific enhancement in force compensation was found during error-clamp trials in the stimulated context (CW). Thus, participants applied more force against the channel wall during expected CW adaptation trials than CCW trials. Area under the curve during error-clamp trials were compared in a 3x2 way ANOVA (Task Phase x Trial Context) and revealed significant main effects for Phase ($F(2, 102) = 192.26$, $p < 0.001$, $\eta p^2 = 0.79$), Context ($F(1, 102) = 4.24$, $p = 0.042$, $\eta p^2 = 0.04$) and a significant interaction between trial phase and context ($F(2, 102) = 5.7$, $p = 0.005$, $\eta p^2 = 0.1$). Comparisons from this interaction showed greater compensation on stimulated CW compared to CCW trials ($p < 0.001$) during the adaptation phase, with no differences for baseline and washout trials (all $p > 0.83$).

Figure 1



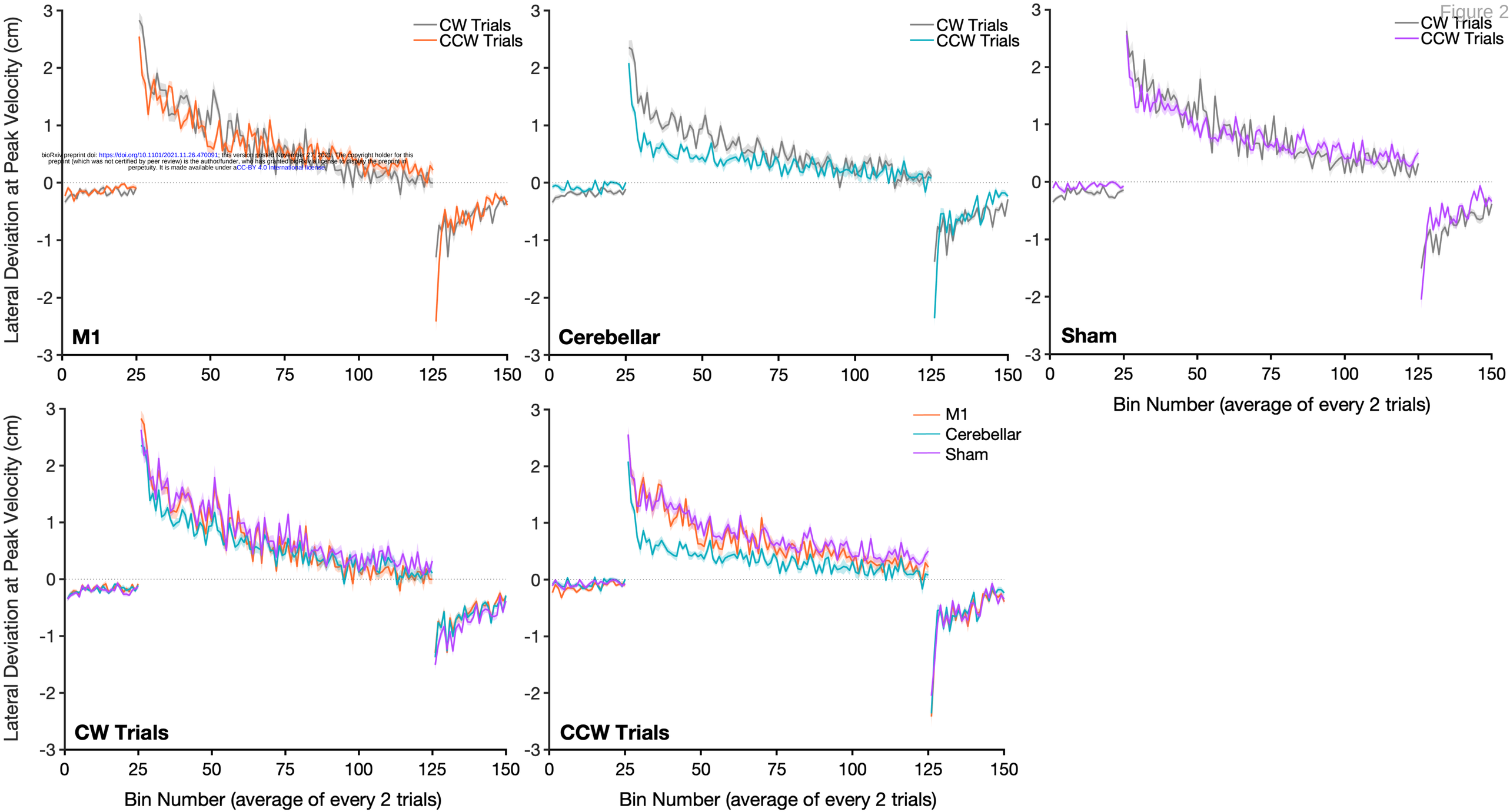


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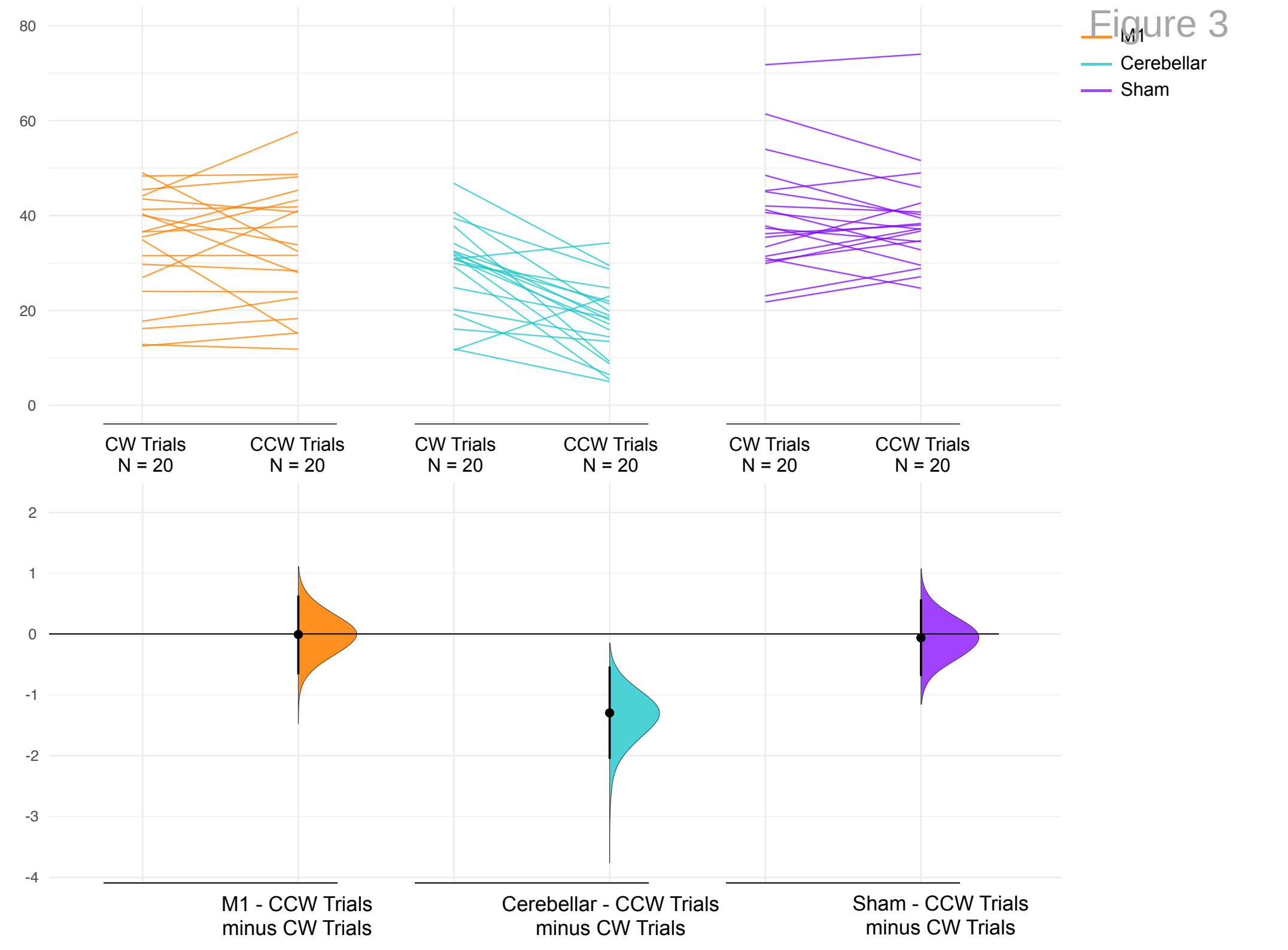
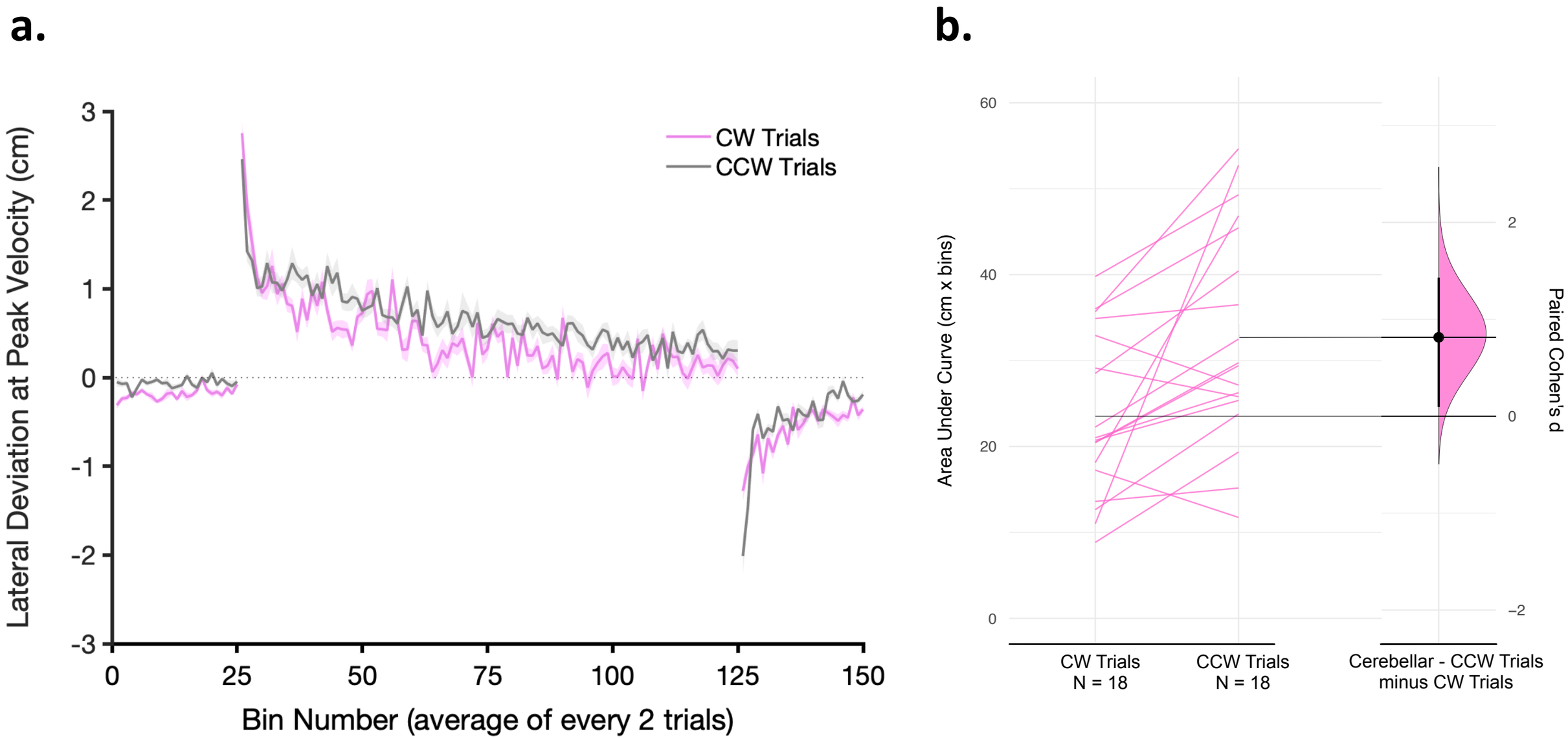
Figure 3


M1
Cerebellar
Sham
80
60
40
20
0
CW Trials
N = 20
CCW Trials
N = 20
CW Trials
N = 20
CCW Trials
N = 20
CW Trials
N = 20
CCW Trials
N = 20
2
1
0
-1
-2
-3
-4
M1 - CCW Trials
minus CW Trials
Cerebellar - CCW Trials
minus CW Trials
Sham - CCW Trials
minus CW Trials


a.
Lateral Deviation at Peak Velocity (cm)
3
2
1
0
-1
-2
-3
0
25
50
75
100
125
150
Bin Number (average of every 2 trials)
CW Trials
CCW Trials
b.
Area Under Curve (cm x bins)
60
40
20
0
CW Trials
N = 18
CCW Trials
N = 18
Cerebellar - CCW Trials
minus CW Trials
Paired Cohen's d
2
0
−2

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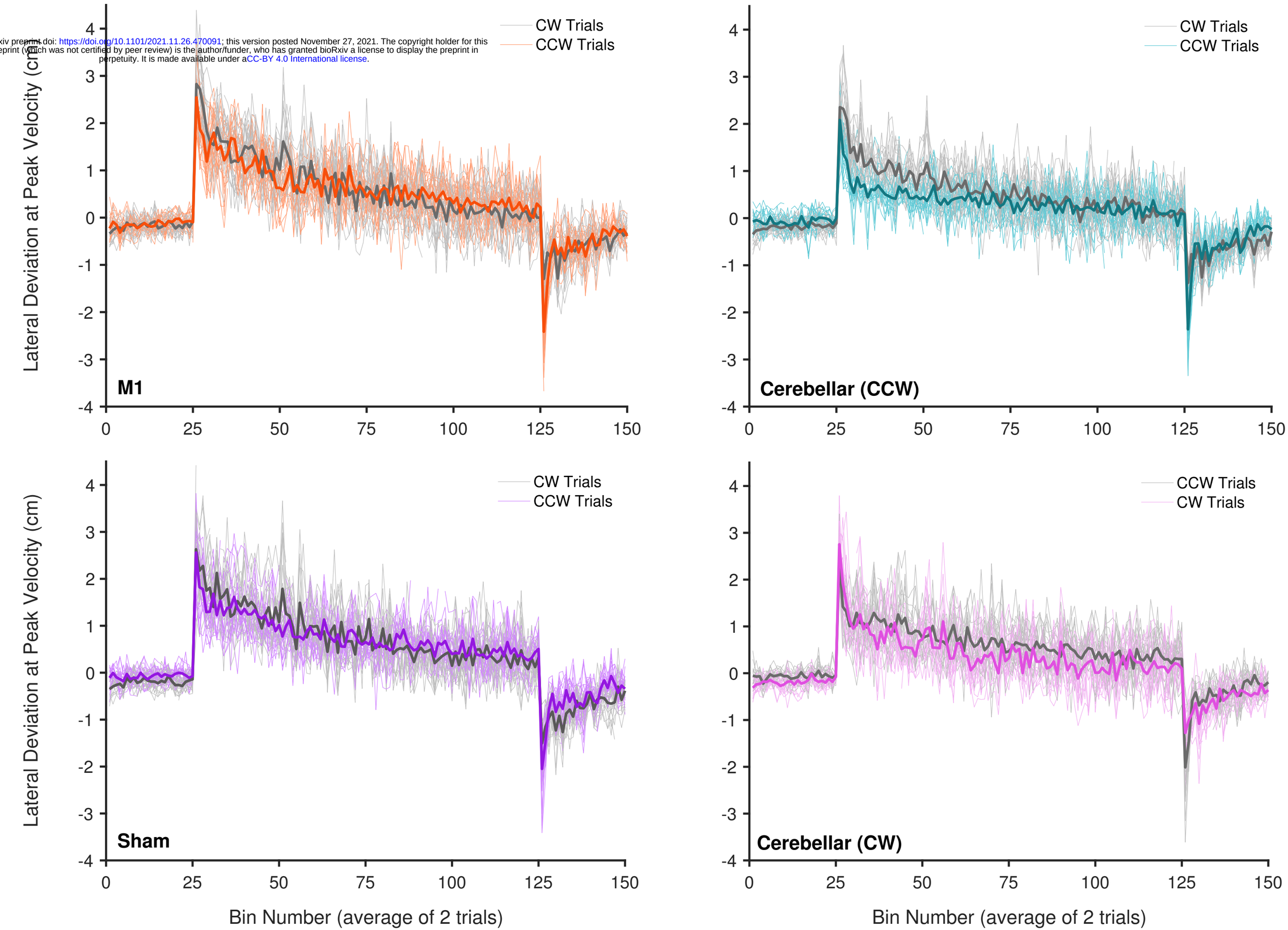
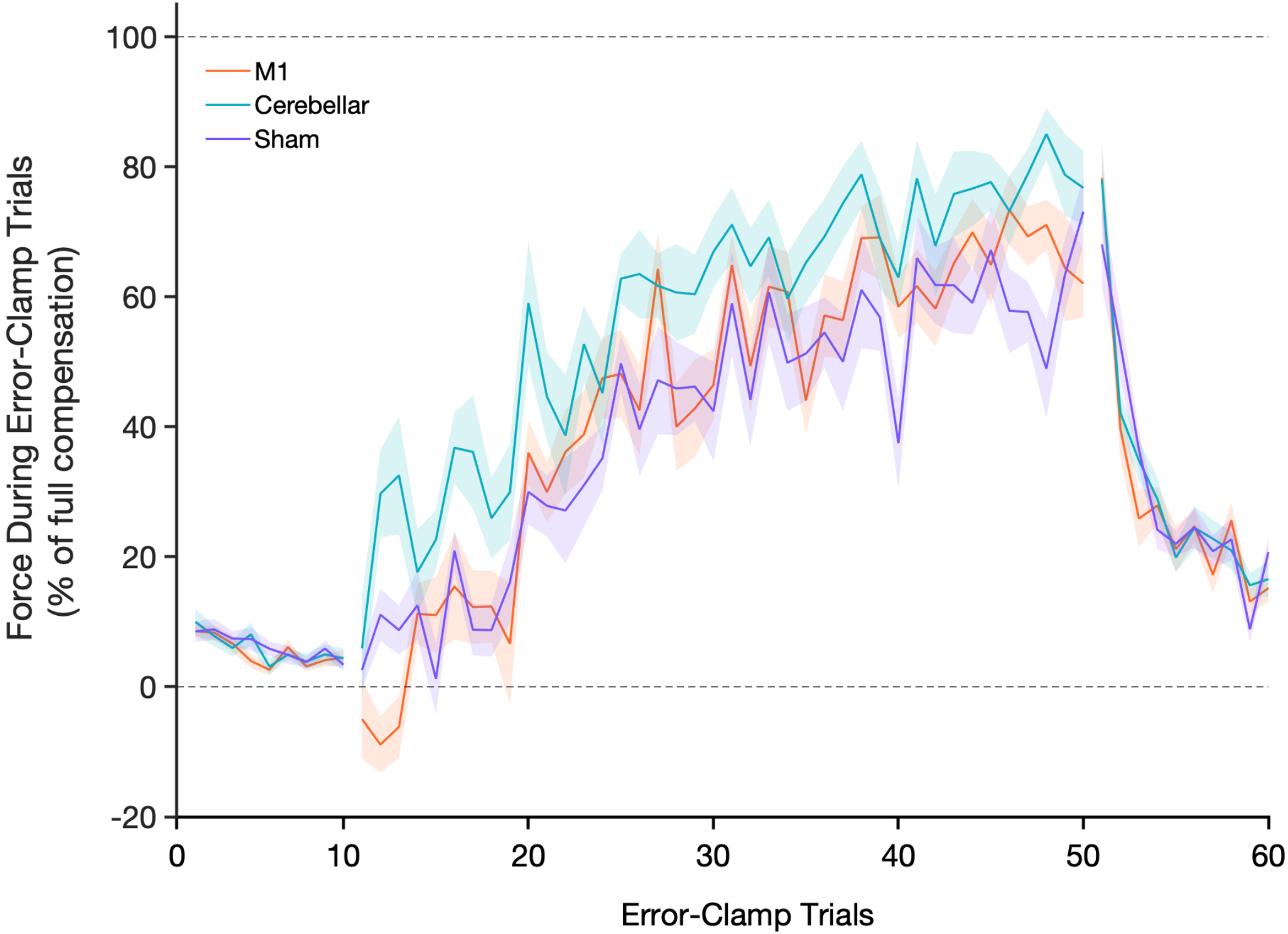
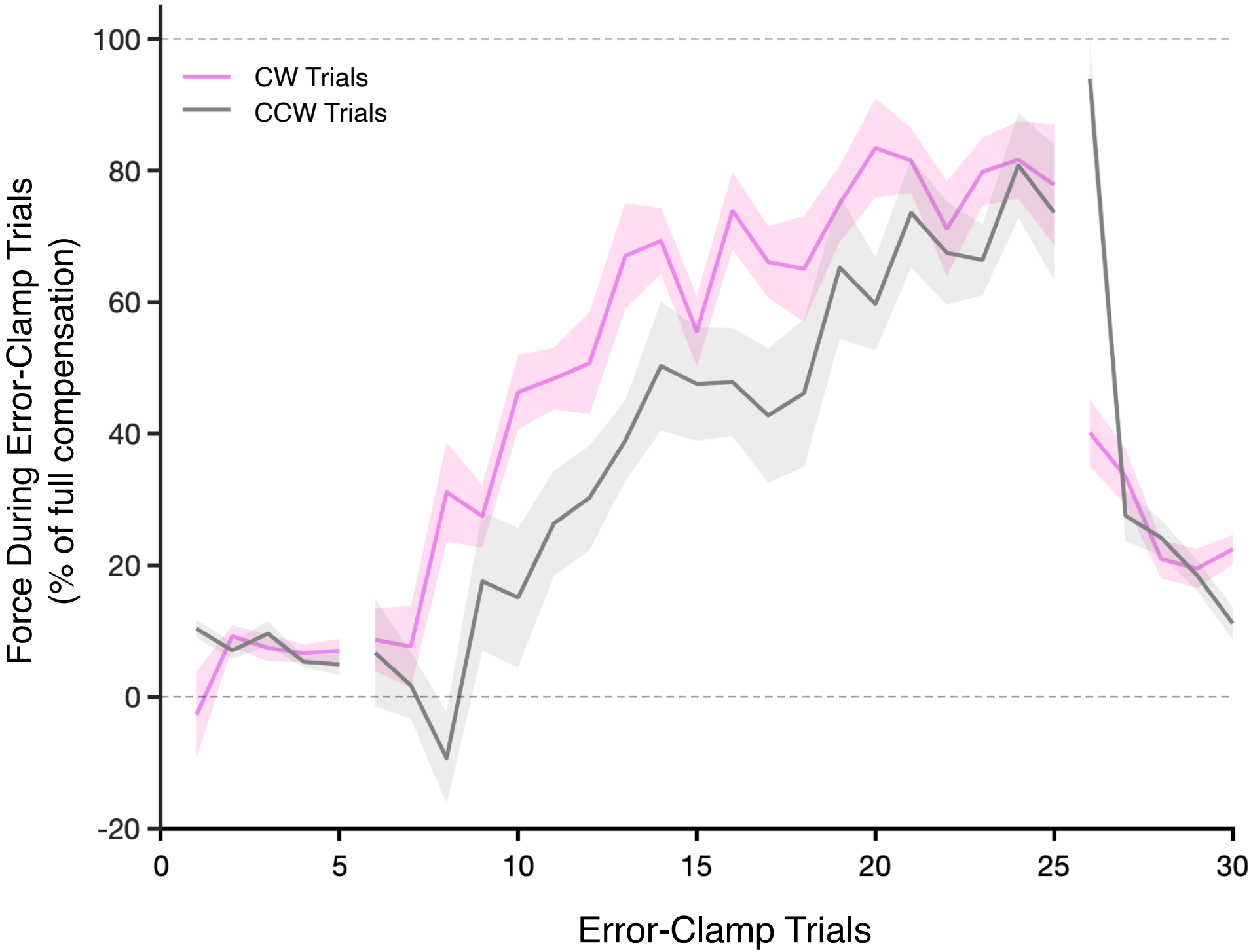



M1
Cerebellar
Sham
Force During Error-Clamp Trials
(% of full compensation)
100
80
60
40
20
0
-20
0
10
20
30
40
50
60
Error-Clamp Trials


CW Trials
CCW Trials
Force During Error-Clamp Trials
(% of full compensation)
100
80
60
40
20
0
-20
0
5
10
15
20
25
30
Error-Clamp Trials