Behavioral/Cognitive

Cerebellar–M1 Connectivity Changes Associated with Motor Learning Are Somatotopic Specific

Danny A. Spampinato,[1,3,4] Hannah J. Block,[5,6] and Pablo A. Celnik[2,3,4]

Departments of [1]Biomedical Engineering, and [2]Neuroscience, Johns Hopkins University, Baltimore, Maryland 21205, Departments of [3]Physical Medicine and Rehabilitation, and [4]Neurology, Johns Hopkins University, Baltimore, Maryland 21281, and [5]Department of Kinesiology and [6]Program in Neuroscience, Indiana University, Bloomington, Indiana 47405

One of the functions of the cerebellum in motor learning is to predict and account for systematic changes to the body or environment. This form of adaptive learning is mediated by plastic changes occurring within the cerebellar cortex. The strength of cerebellar-to-cerebral pathways for a given muscle may reflect aspects of cerebellum-dependent motor adaptation. These connections with motor cortex (M1) can be estimated as cerebellar inhibition (CBI): a conditioning pulse of transcranial magnetic stimulation delivered to the cerebellum before a test pulse over motor cortex. Previously, we have demonstrated that changes in CBI for a given muscle representation correlate with learning a motor adaptation task with the involved limb. However, the specificity of these effects is unknown. Here, we investigated whether CBI changes in humans are somatotopy specific and how they relate to motor adaptation. We found that learning a visuomotor rotation task with the right hand changed CBI, not only for the involved first dorsal interosseous of the right hand, but also for an uninvolved right leg muscle, the tibialis anterior, likely related to inter-effector transfer of learning. In two follow-up experiments, we investigated whether the preparation of a simple hand or leg movement would produce a somatotopy-specific modulation of CBI. We found that CBI changes only for the effector involved in the movement. These results indicate that learning-related changes in cerebellar–M1 connectivity reflect a somatotopy-specific interaction. Modulation of this pathway is also present in the context of interlimb transfer of learning.

Key words: adaptation; cerebellum; connectivity; somatotopy; transcranial magnetic stimulation

Significance Statement

Connectivity between the cerebellum and motor cortex is a critical pathway for the integrity of everyday movements and understanding the somatotopic specificity of this pathway in the context of motor learning is critical to advancing the efficacy of neurorehabilitation. We found that adaptive learning with the hand affects cerebellar–motor cortex connectivity, not only for the trained hand, but also for an untrained leg muscle, an effect likely related to intereffector transfer of learning. Furthermore, we introduce a novel method to measure cerebellar–motor cortex connectivity during movement preparation. With this technique, we show that, outside the context of learning, modulation of cerebellar–motor cortex connectivity is somatotopically specific to the effector being moved.

Introduction

The cerebellum is known to play an important role in adaptive motor learning, an error-based process in which the brain learns to compensate for systematic movement errors. For example, in a visuomotor rotation, a cursor is rotated relative to hand movement such that the cursor's movement direction no longer matches that of the hand. This creates a mismatch between the predicted and actual sensory outcome of a movement, which drives error reduction in healthy individuals (Tseng et al., 2007; Shadmehr et al., 2010). The cerebellum is thought to be critical for learning error-based adaptation tasks (Martin et al., 1996; Diedrichsen et al., 2005; Chen et al., 2006) because patients with cerebellar degeneration show a marked impairment in such learning (Weiner et al., 1983; Martin et al., 1996; Smith and Shadmehr, 2005). In addition, acquisition of a visuomotor adaptation is enhanced when anodal transcranial direct current stimulation, a form of noninvasive excitatory stimulation, is applied over the

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Correspondence should be addressed to Pablo Celnik, M.D., Johns Hopkins School of Medicine, 600 North Wolfe St., Phipps 160, Baltimore, MD 21287. E-mail: pcelnik@jhmi.edu.

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cerebellum during training (Galea et al., 2011; Block and Celnik, 2013).

Although it is recognized that the cerebellum is crucial for adaptation, possible physiological mechanisms have only recently been explored (Medina and Lisberger, 2008; Carey, 2011; Schonewille et al., 2011; Gao et al., 2012; Yang and Lisberger, 2014). Transcranial magnetic stimulation (TMS) has been used to assess these neurophysiological responses in humans: a paired-pulsed TMS technique is used to stimulate the cerebellum just before stimulating the contralateral motor cortex (M1) (Ugawa et al., 1995; Pinto and Chen, 2001; Daskalakis et al., 2004). It is well established that dentate nucleus of the cerebellum projects to M1 (Allen and Tsukahara, 1974; Hoover and Strick, 1999) in a disynaptic excitatory pathway via the ventrolateral thalamus (Shinoda et al., 1985; Dum and Strick, 2003; Evrard and Craig, 2008). Therefore, this TMS technique is thought to measure the inhibitory projection from the cerebellar cortex to the dentate, which reduces M1 activity via the dentate-thalamus-cortical pathway (cerebellar inhibition; CBI). We have shown recently that the level of CBI to a leg muscle, the tibialis anterior (TA), decreases when healthy subjects learn a cerebellum-dependent locomotor adaptation task (Jayaram et al., 2011). Interestingly, those participants experiencing a larger magnitude of adaptation (i.e., greater degree of learning) expressed greater reduction in CBI. A similar reduction of CBI has also been observed in a hand muscle, the first dorsal interosseous (FDI), in subjects learning a visuomotor adaptation hand task (Schlerf et al., 2012) and in response to observing or performing a finger sequence task (Torriero et al., 2011). These findings suggest a change in cerebellar excitability associated with learning. However, it is not known whether these learning-associated changes are somatotopically specific to the trained effector.

To determine whether motor learning-related changes in cerebellar–M1 connectivity are somatotopy specific or global enough to affect untrained effectors, we examined CBI in both a hand and leg muscle (FDI and TA, respectively) before, during, and after participants learned a visuomotor rotation with the hand. Because this type of learning can transfer to untrained limbs (Sainburg and Wang, 2002; Criscimagna-Hemminger et al., 2003; Wang and Sainburg, 2004; Morton and Bastian, 2006; Savin and Morton, 2008; Balitsky Thompson and Henriques, 2010; Joiner et al., 2013), modulation of CBI in an untrained limb could be related to interlimb transfer (i.e., reflecting a somatotopy-specific plastic mechanism) or it could be a nonspecific response. Therefore, we also investigated CBI in the context of movement preparation in the absence of motor learning. We predicted that modulation of CBI would be somatotopy specific in both situations, meaning that, in the motor learning task, any CBI changes in the untrained effector could be related to transfer of learning.

Materials and Methods

Subjects

In total, 32 subjects (mean age 23.9 years; 19 men) participated in three experiments (10 in Experiment 1, 10 in Experiment 2, and 12 in Experiment 3). All subjects reported that they did not have conditions that would exclude them from noninvasive brain stimulation, including previous history of migraines, diabetes, seizures, or any brain or peripheral nerve diseases. Exclusion criteria also included the use of nicotine, alcohol, and recreational drugs and the absence of prescribed medication affecting the CNS, all of which may alter plasticity and motor learning. All subjects reported that they were right-handed and neurologically healthy. All subjects gave informed consent approved by the Johns Hopkins Institutional Review Board.

Experiment 1: CBI changes due to visuomotor adaptation

Experimental protocol. Each subject participated in an experiment testing changes in CBI in the right hand (FDI) and right leg (TA) before and during right hand visuomotor adaptation (Fig. 1*A*). The experimental session consisted of five training blocks. The Baseline block consisted of 200 trials with the right hand. After the baseline block, a 30° clockwise perturbation (CW) was applied to the cursor display (Adapt1, 48 trials). To assess how much the individual learned, each participant underwent a quick eight-trial segment with the 30° clockwise perturbation turned off (Catch). Participants then completed another 144 trials with the visuomotor rotation turned back on (Adapt2) to allow them to fully correct for the perturbation. Before Baseline and immediately after Catch and Adapt2, CBI measurements were recorded for right FDI and right TA.

Behavioral tasks. Subjects were seated in front of a vertical computer screen (Fig. 2*A*). A wireless digitizing pen (Wacom) was attached to their dominant index finger with a co-flex bandage. Subjects were instructed to move their finger over a digitizing tablet (Wacom) positioned horizontally at waist level. Subjects viewed feedback of their finger movements as a white dot (2 mm) displayed on the computer screen. Subjects were instructed to move to the starting position, a white square (3 mm) at the center of the screen, and then to "shoot" through one of eight targets that appeared 10 cm radially from the starting position.

The 2D position of the digitizing pen was recorded continuously at 75 Hz using a custom MATLAB program (The MathWorks). All kinematic data were filtered at 10 Hz with a low-pass Butterworth filter and differentiated numerically to calculate velocity. The onset of each movement was determined as the point at which radial velocity crossed 5% of peak velocity. Once subjects had moved 10 cm from the starting position (10 cm circular boundary), their final position was recorded.

To ensure consistency in movement duration, subjects received auditory feedback at the end of each movement: a low-pitched or high-pitched tone if they were too slow (>375 ms) or too fast (<275), respectively. Subjects' vision of their hands or the digitizing tablet was blocked. Targets were displayed pseudorandomly such that every set of eight consecutive trials included one of each of the target positions. For each trial, subjects' performance was quantified as the angular end point error, which was defined as the angle between the starting position to the center of the target and the imaginary line connecting the starting position to the end point (Hadipour-Niktarash et al., 2007; Galea et al., 2011). Epochs were created by binning eight consecutive trials. For each block, the initial amount of error (mean error) was determined by averaging over consecutive epochs (Krakauer et al., 2005).

EMG recordings and TMS protocol. EMG was recorded with Ag/AgCl EMG electrodes placed over the training FDI muscle and ipsilateral TA muscle (Experiment 1: right FDI and TA, Experiment 3: right FDI). EMG data were stored for offline analysis using Signal software (CED). M1 excitability of the right FDI (Experiments 1 and 3) and TA (Experiment 1 only) muscles was assessed using a 70-mm-diameter figure-eight TMS coil (Magstim) over the motor representation of the muscle. To localize the stimulation site and to maintain consistency of responses, we used a Brain Sight neuronavigation system (Rogue Research). After determining the resting motor thresholds for these muscles using standard procedures (Rossini et al., 1994), we determined the stimulator output intensity needed to elicit motor evoked potentials (MEPs) of ~1 mV (SI1 mV) at rest and before movement onset (Experiment 3 only). TMS before movement onset was triggered via a customized MATLAB function using the peri-triggering capability of Signal software.

CBI. We measured the level of cerebellar–M1 connectivity or CBI for right FDI and TA using a standard paired-pulse TMS paradigm (Ugawa et al., 1995; Werhahn et al., 1996; Pinto and Chen, 2001; Daskalakis et al., 2004). First, we determined the brainstem motor threshold using a double cone coil (Magstim) over the inion. This is defined as the minimal intensity (to the nearest 5% of stimulator output) required to elicit five 50 μv MEPs of the target muscle (Rossini et al., 2015). Second, we tested CBI by delivering a conditioning stimulus (CS) 3 cm lateral to the inion and 5 ms before a test stimulus (TS) targeting the contralateral M1 representation of FDI or TA (Galea et al., 2009; Jayaram et al., 2011; Schlerf et al., 2015).

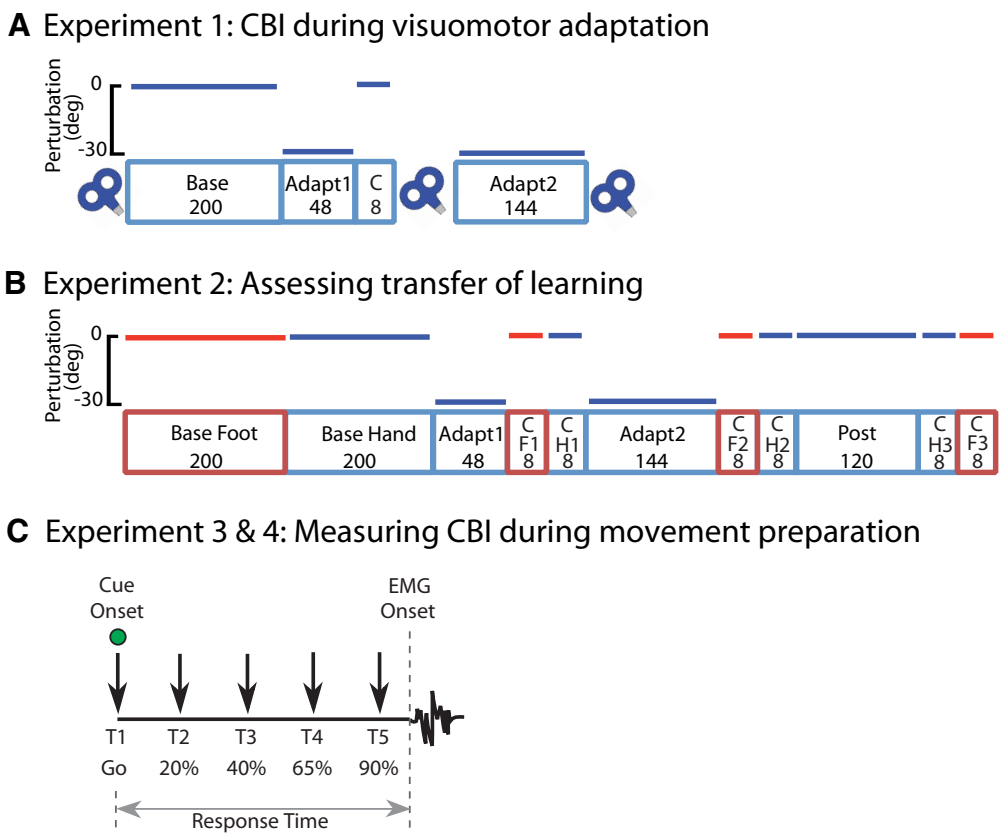

Figure 1. Experimental design. ***A***, Experiment 1 consisted of five behavioral blocks and three physiological measurements. In Adapt1 and Adapt2, subjects were exposed to a 30° CW cursor rotation; cursor movement was veridical in the remaining blocks. Cerebellar-motor cortex connectivity (CBI) was assessed before Base and after Catch and Adapt2. The numbers in each block represent the number of trials. ***B***, Experiment 2 consisted of 11 behavioral blocks. Adapt1 and Adapt2 had a 30° CW rotation; other blocks were veridical. Red, Right foot movements; blue, right hand movements. There were no physiological measurements for this experiment. ***C***, In Experiment 3, premovement CBI for the FDI was assessed at five different timings (T1–T5) before movement initiation with either the index finger or foot, with T1 at cue onset and T5 being the closest to movement onset. Timings were adjusted to individual RTs. Experiment 4 mirrored the setup of Experiment 3, but premovement CBI was assessed for the TA muscle.

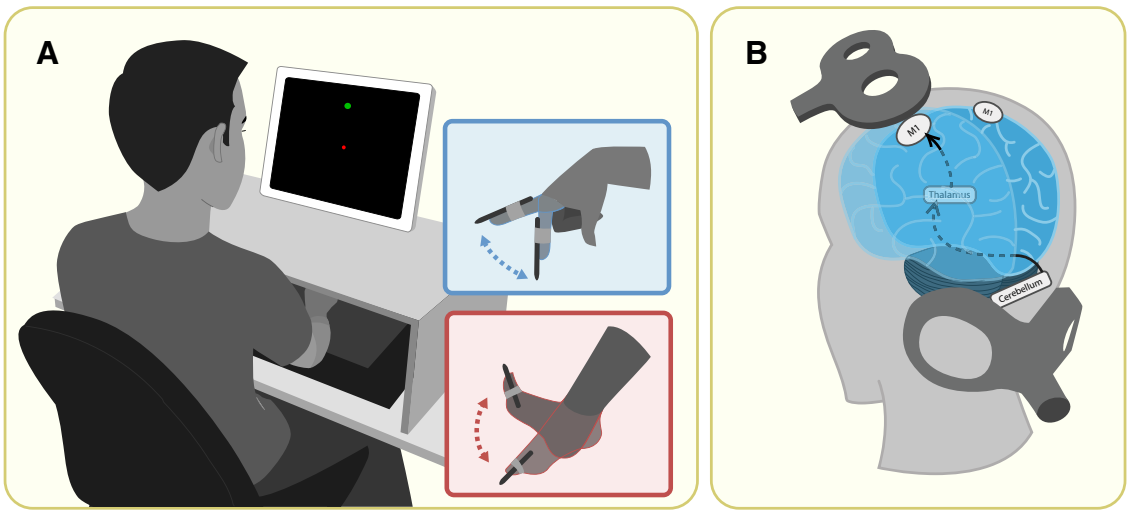

Figure 2. Methods. ***A***, Setup for the behavioral task used in all three experiments. Participants viewed the vertical computer monitor for visual feedback about the task and trained with the right hand before switching to the right foot to assess hand-to-foot transfer. For foot movements, the tablet was placed vertically and the foot was propped up. ***B***, Coil placement to measure CBI. This technique requires paired-pulse stimulation in which one TMS coil is placed over M1 (test) and the other over the cerebellum (condition). To determine CBI for the right hand muscle (FDI), the conditioning pulse was delivered over the right cerebellum 5 ms before the test pulse was applied over the left M1 representation of FDI. The same procedure was followed to determine CBI for the right leg muscle (TA), with the test pulse applied over the left M1 representation of TA.

CS intensity was set at 5% below the brainstem motor threshold to the cerebellum. This elicits maximum recruitment of the cerebellar–M1 connections, whereas lower intensities results in less inhibition of this pathway (Werhahn et al., 1996; Pinto and Chen, 2001; Daskalakis et al., 2004; Galea et al., 2009). Test stimulus over M1 was adjusted to elicit MEPs with average peak-to-peak amplitude of ~1 mV (SI1 mV), which is ideal for CBI assessment (Ugawa et al., 1995; Pinto and Chen, 2001; Daskalakis et al., 2004). Ten paired pulses (cerebellum + M1) and 10 single pulses

(M1 only) were intermixed randomly and delivered at 5 s intervals. CBI is expressed as the average MEP amplitude evoked by the cerebellar-conditioned stimulation relative to the average MEP amplitude evoked by the unconditioned TMS pulses over M1.

Experiment 2: Transfer from right hand to right leg

Experimental protocol. Each subject completed 11 behavioral blocks. No physiological measurements were tested in this experiment. (Fig. 1*B*). A total of 200 trials with the right foot (Baseline Foot) were followed by 200 trials with the right hand (Baseline Hand). As in Experiment 1, a screen–cursor 30° CW transformation was applied during Adapt1 and Adapt2 (48 trials each, right hand) to elicit adaptive learning. Immediately after Adapt1, the transformation was removed and eight trials in the foot (Catch Foot1) and hand (Catch Hand1) were performed to determine the presence of transfer of learning to the foot. Transfer was again assessed after Adapt2 with another nonperturbed eight trials with the foot and hand (Catch Foot2 and Catch Hand2). Participants then completed a final 120 hand movements without perturbation to wash out the learning (Post). Finally, another eight trials with the foot and hand were assessed to determine whether any previously seen transfer would wash out as well (Catch Foot3 and Catch Hand3). No physiological measurements were made.

Behavioral tasks. Participants were seated in front of a computer screen as in Experiment 1. In addition, a bench was placed between the computer station and chair. The right leg was supported comfortably such that the foot was lifted a few inches of the floor, with the leg remaining parallel to the floor. For experimental blocks using the leg, the digitizing tablet was clamped vertically in front of the right foot. The digitizing pen was attached with a co-flex as an extension to the inner side of the bare foot. Feedback (both visual and auditory) of foot movements was the same as described for hand movements. To reduce the complexity of the performance with the foot, only four targets (up, down, left and right from the center) of the possible eight were presented; the order of appearance of these targets was random. The hand was exposed to the eight different target locations as described in Experiment 1.

Experiments 3 and 4: Premovement CBI changes due to simple reaction time task

Experimental protocol. Each subject participated in two sessions testing CBI in the right hand (FDI; Experiment 3) or the right leg (TA; Experiment 4) during a simple reaction time task. In Experiment 3 only, a CBI recruitment curve for the FDI muscle was assessed at rest. In Experiment 4, a double-cone coil was used over M1 to elicit MEPs at rest for the TA muscle. For each experiment, subjects performed abduction of the right index finger in one session and dorsiflexion of the right foot in the other session, with session order counterbalanced across subjects. Paired- and single-pulse TMS was applied at intervals during movement preparation.

Behavioral tasks. Subjects were seated in front of a computer monitor and instructed to respond to a visual (green circle) go signal by lifting either the right index finger or lifting the right foot in separate sessions. The go signal appeared at random intervals (5–7 s). Before the appearance of the go signal, subjects were instructed to remain relaxed and avoid anticipation of the cue. Response Time (RT) was defined as the interval between the go signal and the onset of the EMG burst in FDI or TA (Fig. 1*C*). At the beginning of each session, subjects were familiarized with the simple reaction time paradigm and 30 trials were performed to characterize each subject's individual RT to the go signal in the absence of TMS. A total of 120 trials were completed per session. Trials in which background EMG was detected before TMS onset were excluded from analysis.

EMG recordings and TMS protocol were identical to those in Experiment 1, with the following exceptions. EMG was recorded from either the right FDI in Experiment 3 or the right TA in Experiment 4 and TMS measures were made for the M1 representation of right FDI (Experiment 3) or right TA (Experiment 4). In addition, the stimulator output intensity needed to elicit MEPs of ~1 mV (SI1 mV) both at rest and before movement onset was calculated. TMS before movement onset was triggered via a customized MATLAB function using the peri-triggering capability of Signal software.

The CBI protocol was identical to that in Experiment 1 except that the level of cerebellar–M1 connectivity for right FDI in Experiment 3 and for the right TA in Experiment 4 were measured. In addition, CS intensity for Experiment 3 was based on a CBI recruitment curve (RC_{CBI}). In Experiment 4, the CS intensity was set at 5% below the brainstem motor threshold to the cerebellum. This intensity was selected because cerebellar–M1 connections for the TA muscle show reduced inhibition compared with the FDI muscle (Jayaram et al., 2011).

RC_{CBI} was computed at rest before beginning the Experiment 3 behavioral session. This was done by decreasing cerebellar CS intensity by −5% steps below brainstem threshold using four different CS intensities (−5%, −10%, −15%, and −20% brainstem threshold). For each subject, the CS intensity inflection point collected from RC_{CBI} was used for premovement CBI measurements (CBI_{move}) to evaluate whether movement preparation elicits further inhibition or disinhibition.

For both Experiments 3 and 4, CBI_{move} was measured at five different time intervals throughout the course of the simple reaction time paradigm in a pseudorandomized order (Fig. 1*C*; T1–T5). To do this, 12 paired pulses (cerebellum + M1) and 12 single pulses (M1 only) were measured for each time interval. As described previously, the different time intervals were tuned to each subject's RT of the task (Murase et al., 2004; Duque et al., 2005; Hummel et al., 2009), where T1 corresponded to cue onset and T2–T5 reflects 20%, 40%, 65%, and 90% of subject RT, respectively.

Statistical analysis

Statistical analysis was performed using SPSS software. For each block in Experiments 1 and 2, apart from catch trial blocks, initial error (mean error) was determined by averaging across epochs (Krakauer et al., 2005). Repeated-measures ANOVA ($ANOVA_{RM}$) was used to compare changes in CBI across time points (Baseline, Adapt1, and Adapt2) and muscles (Right FDI vs Right TA), and separately to compare mean movement error across time points (Baseline and Catch epochs) and limbs (hand vs foot in Experiment 2).

In Experiments 3 and 4, each participant's RTs were averaged in bins of 30 trials and a paired-sample *t* test was used to compare the first 30 RT trials to the last 30 trials to determine whether participants were improving their performance throughout the task. The magnitude of CBI_{move} at T1–T5 was expressed relative to CBI recorded at rest [e.g., CBI_{move} T5 modulation = (CBI at T5)/(CBI at rest) × 100%] to better characterize changes in CBI relative to rest. Subsequently, to compare changes in CBI_{move} across sessions (finger-movements, foot-movements), $ANOVA_{RM}$ with premovement timing (T1–T5) was used as a within-subjects factor. For Experiment 3, $ANOVA_{RM}$ was also used to compare the effect of changing CS intensity (−5%, −10%, −15%, and −20% below brainstem threshold) on CBI (RC_{CBI}).

For all experiments, when ANOVAs yielded significant results, *post hoc* analyses were conducted using Tukey's HSD tests.

Results

Experiment 1: CBI decreases after visuomotor adaptation

When the 30° CW visuomotor transformation was applied in Adapt1, large initial errors were observed (first epoch mean ± SE was −26.45 ± 2.24°; Fig. 3*A*). When the visuomotor transformation was removed for a Catch epoch after 48 movements, subjects displayed partial learning of the rotation, as indicated by counter-CW errors (11.08 ± 0.97°). When the perturbation resumed at the beginning of Adapt2, error reduction continued and, by the end of Adapt2, subjects had compensated for 25.92 ± 1.03° of the original 30° perturbation.

The magnitude of CBI for both the FDI and TA muscles (hand and leg) was reduced after adaptation with the right hand, indicating disinhibition (Fig. 3*B*). An $ANOVA_{RM}$ on CBI ratio values revealed a time effect ($F_{(2,36)} = 9.785$; $p < 0.01$), but no effect on muscle group ($F_{(1,18)} = 2.74$; $p = 0.12$) and, importantly, no interaction ($F_{(2,36)} = 0.16$; $p = 0.90$). *Post hoc* tests revealed that CBI after Catch and after Adapt2 was significantly different from baseline CBI ($p < 0.01$; $p = 0.01$, respectively), suggesting that visuomotor adaptation with the hand results in a significant reduction in CBI for both FDI and TA muscles.

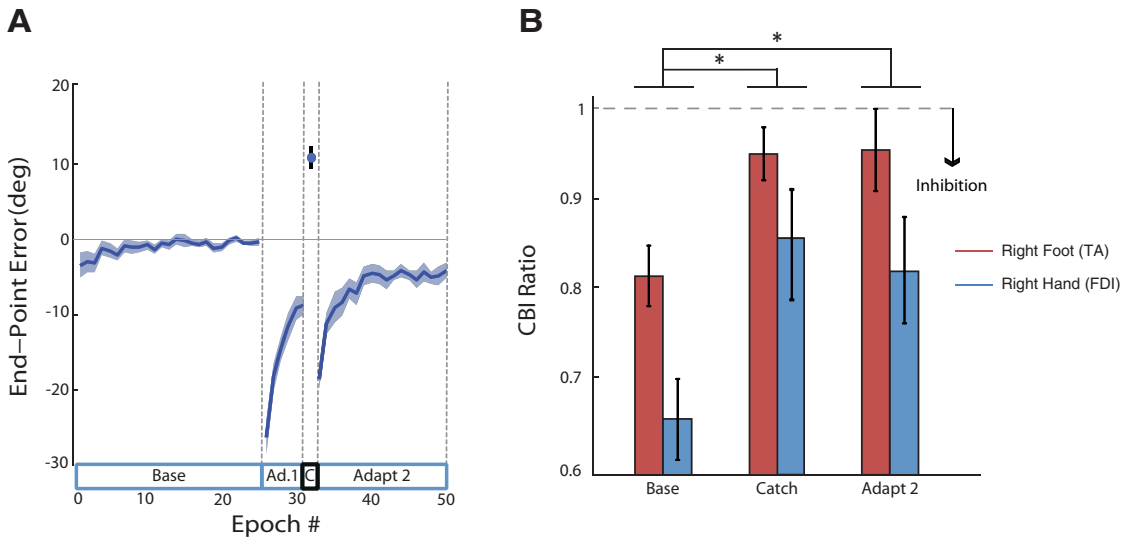

Figure 3. Experiment 1 Results. ***A***, End point error (blue line) with SEs (shaded region) during baseline (Base), adaptation (Adapt1 and Adapt2), and catch trials (C). Negative values indicate clockwise deviations caused by the visuomotor perturbation. ***B***, Physiological measure of CBI for both the right FDI (blue) and TA (red). CBI was recorded before any movements (Base) and immediately after catch trials (Catch) and late adaptation (Adapt2). *CBI decreased significantly for both muscle effectors after early perturbation exposure.

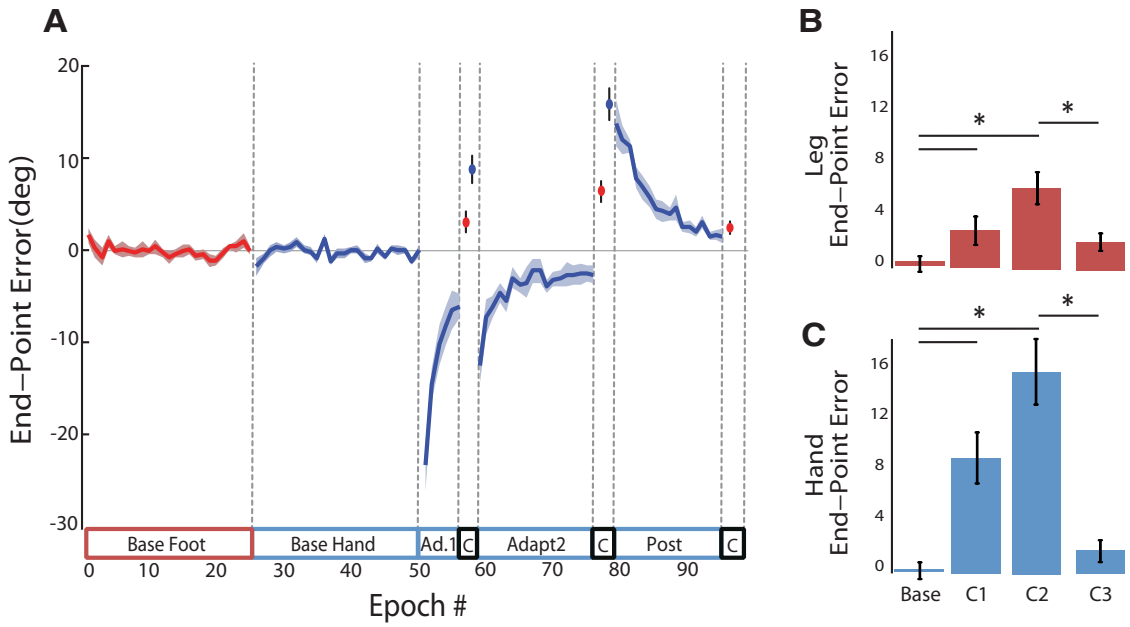

Figure 4. Experiment 2 Results. ***A***, End point error and SEs for right hand (blue) and right leg (red) movements. Negative values indicate clockwise deviation. ***B***, ***C***, Mean end-point errors in degrees (±SEM) for right leg (red) and right hand (blue) for the baseline and three catch trial epochs. *Post hoc* analysis revealed significant changes in error for both effectors, indicating hand-to-foot transfer.

Experiment 2: Right hand learning transfers to right foot movements

As in Experiment 1, subjects in Experiment 2 were able to almost completely adjust their hand movements to the 30° CW visuomotor rotation (mean error of final epoch in Adapt2 was $-2.32 \pm 1.11°$; Fig. 4). When comparing behavioral blocks across right hand and right leg (Baseline, Catch1, Catch2, and Catch3), $ANOVA_{RM}$ revealed a significant effect of time ($F_{(2,36)} = 24.94$; $p < 0.01$), limb ($F_{(1,36)} = 9.44$, $p = 0.01$) and a limb × time interaction effect ($F_{(2,36)} = 5.63$; $p < 0.01$). *Post hoc* analysis revealed that movement error in Catch Foot1 and Catch Foot2 were each different from Base Foot ($p = 0.05, 0.01$), suggesting that the right hand's adaptation transferred to the foot. Critically, *Post hoc* analysis also revealed a difference in Catch Hand1 and Catch Hand2 being different from Base Hand (both $p < 0.01$). A comparison of foot aftereffects (Catch Foot 1–2) with hand aftereffects (Catch Hand 1 and the first epoch of Post 1) indicated that the amount of transfer at Foot Catch1 was 42.3%, and 42.2% at Foot Catch2. *Post hoc* tests also showed that Catch Foot2 and Catch Foot3 were different from each other ($p < 0.01$), suggesting that transfer of learning from hand to foot had degraded after washout of learning from the hand.

Experiments 3 and 4: CBI changes in a somatotopy-specific manner

RTs

Participants did not improve their RT throughout the experiment. For Experiment 3, the baseline average RT for the hand (176.1 ± 6.2

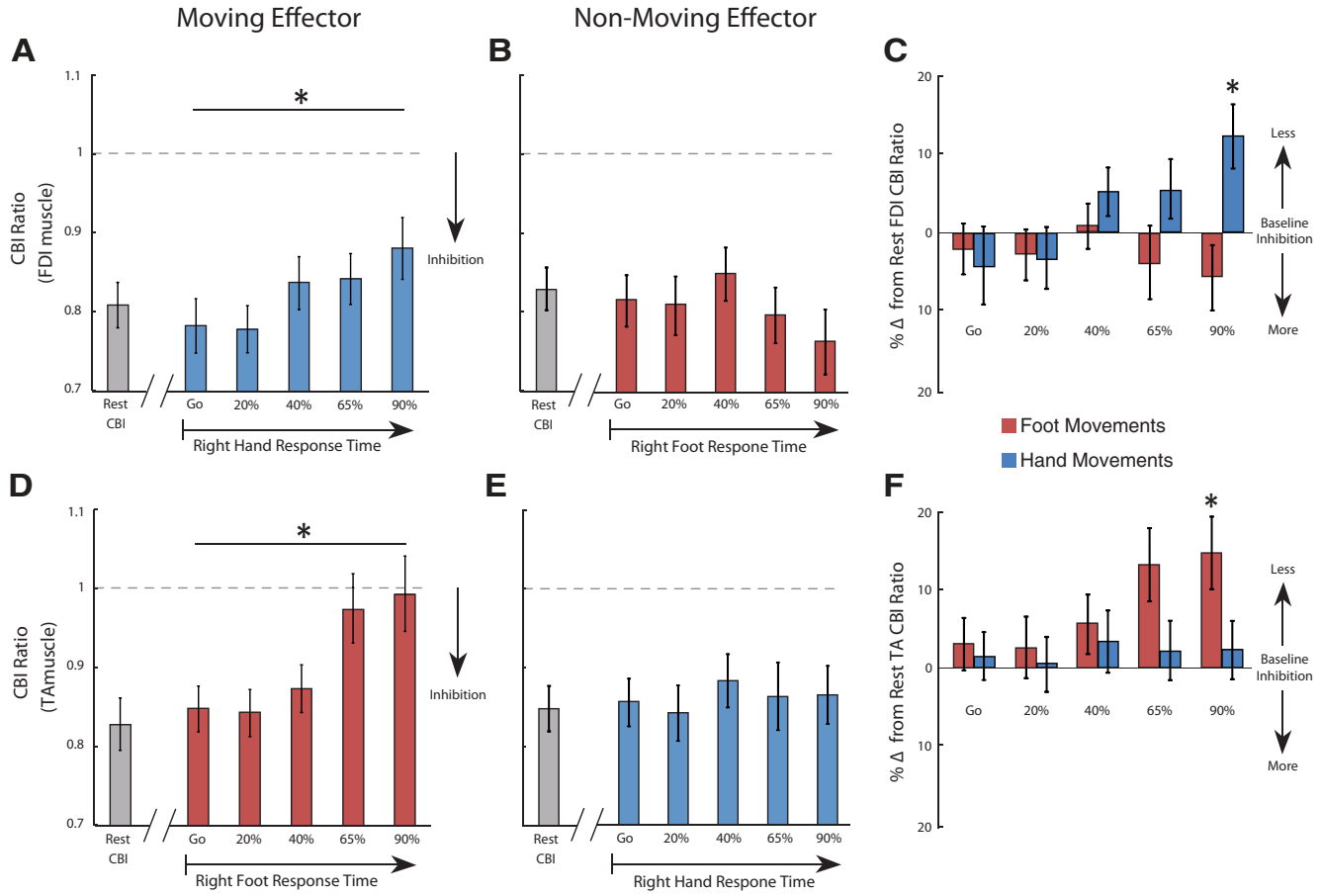

Figure 5. CBI_{move}. ***A***, ***B***, The *x*-axis represents CBI_{move} for the right FDI in preparation to moving the hand (***A***) and foot (***B***). FDI CBI_{move} measured at five timings (T1–T5) with respect to individual mean response times separately for the hand (blue) and foot (red). *CBI was reduced significantly only in preparation of hand movements. ***C***, CBI_{move} was calculated as the percentage difference from FDI CBI obtained at rest. ***D***, ***E***, The *x*-axis represents CBI_{move} for the right TA in preparation to moving the foot (***D***) and hand (***E***). ***F***, Percentage difference from TA CBI obtained at rest. Positive values indicate disinhibition and negative values increased inhibition. *Only hand movements at 90% RT (T5) modulated CBI_{move}. Data are shown as mean ± SEM.

ms) was not significantly different from RT from the last 30 hand trials (174.0 ± 5.6 ms; $t_{(11)} = 1.242$, $p = 0.24$). Baseline foot RT (191.9 ± 8.7 ms) was also not different from the last 30 foot trials (190.3 ± 7.5 ms; $t_{(11)} = 0.8$, $p = 0.44$). Similarly, in Experiment 4, baseline foot RT (196.0 ± 5.7 ms) was not different from the last 30 foot trials (193.3 ± 5.4 ms; $t_{(7)} = 0.971$, $p = 0.36$) and baseline hand RT (181.2 ± 7.3 ms) was not different from the last 30 hand trials (179.9 ± 6.7 ms; $t_{(7)} = 0.759$, $p = 0.47$).

CBI recruitment curve (Experiment 3 only)

$ANOVA_{RM}$ comparing the CBI ratio across CS intensity revealed a significant effect for CS intensity ($F_{(1,11)} = 7.926$, $p < 0.01$). Critically, TS MEP amplitudes were not significantly different across different CS conditions ($F_{(1,11)} = 0.029$, $p = 0.87$), suggesting that the CBI changes were due to changing CS intensities. As a result, the mean CS intensity set for CBI_{move} was 72.9 ± 0.74% of the stimulator output, yielding a rest CBI ratio response of 0.82 ± 0.07.

Premovement CBI_{move}

To assess whether CBI changes are somatotopy specific, we measured CBI_{move} for the FDI (Experiment 3) and TA (Experiment 4) muscle representation when participants were asked to either move the right index finger or right foot. In Experiment 3, when participants made movements with their finger, $ANOVA_{RM}$ revealed an effect of FDI CBI_{move} for RT ($F_{(4,44)} = 8.192$, $p = 0.02$; Fig. 5*A*). Conversely, when FDI CBI_{move} was recorded in preparation of foot movements, $ANOVA_{RM}$ failed to find the same effect ($F_{(4,44)} = 3.214$, $p = 0.22$; Fig. 5*B*). These results indicate that, in the absence of learning, CBI changes of the FDI muscle occurs during the preparation of finger movements, but not the foot. In Experiment 4, when participants made movements with the right foot, $ANOVA_{RM}$ on TA CBI_{move} values revealed a time effect ($F_{(4,28)} = 4.920$; $p < 0.01$; Fig 5*D*). Conversely, when TA CBI_{move} was recorded in preparation of finger movements, $ANOVA_{RM}$ did not reveal the same effect ($F_{(4,28)} = 0.241$, $p > 0.50$; Fig. 5*E*). Together, the results from Experiment 3 and 4 suggest a somatotopic effect of CBI changes during movement preparation.

Furthermore, to compare directly the changes in FDI CBI_{move} between preparation of finger movements and foot movements, we subtracted the amount of CBI measured at rest for each session. Here, $ANOVA_{RM}$ revealed an effect of FDI CBI_{move} for the group (finger, foot; $F_{(1,22)} = 6.214$, $p = 0.02$) and RT (Go, T1, . . ., T5) × group interaction ($F_{(4,88)} = 4.713$, $p = 0.01$; Fig. 5*C*). Specifically, CBI_{move} recorded during movement preparation at 90% RT (T5) was significantly different from CBI assessed at cue representation ($p = 0.03$), indicating that specific FDI CBI changes occur just before movement onset. We performed the same analysis to compare the changes in TA CBI_{move}. Similar to the results of Experiment 3, $ANOVA_{RM}$ showed an effect of TA CBI_{move} for group (foot, finger; $F_{(1,14)} = 7.911$, $p = 0.02$) and the

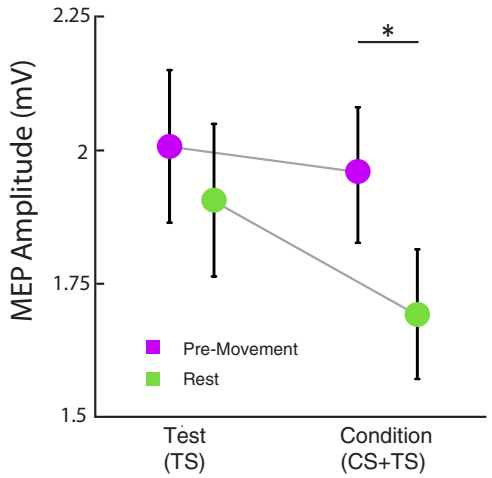

Figure 6. Rest and premovement TS and CS + TS MEP amplitudes. For each participant, we assessed CBI at rest matching the TS MEP amplitudes obtained during CBI_{move} at 90% of RT (TS). CS + TS MEP amplitude (CBI) was only present at rest (green), not when assessed in the context of movement (purple). This indicates that the reduction of CBI_{move} is not due to increased excitability in M1.

RT (Go, T1, . . ., T5) × group interaction ($F_{(4,56)} = 3.210$, $p = 0.02$; Fig. 5*F*).

Importantly, we determined that modulation of CBI were due to changes in conditioned (CS + TS) responses from the cerebellum and not due to changes in TS responses from M1. Although $ANOVA_{RM}$ revealed a significant effect of TS MEP amplitude during finger movement preparation (Go, T1, . . ., T5; $F_{(4,44)} = 14.823$, $p = 0.001$), we controlled for this confound by measuring FDI CBI at rest with a matched TS MEP amplitude observed at the 90% RT of CBI_{move} (TS ~2 mV; Fig. 6). When we compared TS and CS+TS MEP amplitudes between rest and premovement measurements using matched TS responses, two-way $ANOVA_{RM}$ showed a significant interaction of MEP amplitudes for state (rest, premovement) × condition (TS, CS+TS; $F_{(1,22)} = 6.295$, $p = 0.043$). Specifically, CS + TS MEP amplitude for premovement was different from rest ($p = 0.02$) despite having comparable TS MEP amplitude ($p = 0.458$). This indicates that the changes in FDI CBI_{move} observed at 90% RT are due to changes in cerebellar excitability (CS + TS), not to higher M1 excitability.

Discussion

Here, we addressed the question of whether changes in cerebellar–M1 connectivity (CBI) are somatotopy specific in the presence or absence of adaptive motor learning. When individuals learned a visuomotor rotation with the hand, CBI changed for both the involved hand and idle ipsilateral foot. The transfer of learning that we observed between hand and foot could explain why CBI changed in both representations. We disentangled this issue by measuring CBI in the context of movement preparation of a well characterized behavior with no learning. We found that CBI for the hand only changed when participants prepared to make hand movements and not foot movements. Similarly, CBI measured for the foot only changed with preparation of foot movements. This indicates that, in the absence of learning and transfer of learning, CBI only modulates for the effector involved in the movement. These results address an important physiological question, showing that modulation of cerebellar–M1 connectivity responses reflect a somatotopy-specific mechanism.

CBI changes for multiple representations are related to a somatotopy-specific mechanism

Previously, we showed that CBI changes for the trained hand in a visuomotor adaptation task (Schlerf et al., 2012), as well as for the trained leg during locomotor adaptation (Jayaram et al., 2011). The present study extends these findings by showing that adaptive learning with the hand can produce changes in CBI for muscle representations not involved in the task. Interestingly, our second experiment showed transfer of learned movements experienced with the right hand to the right foot, which we would expect to cause CBI changes in both representations. Therefore, the nonspecific changes in cerebellar excitability observed in our first experiment are likely related to a transfer of learning from hand to leg. Results from our final two experiments show that, in the absence of learning, CBI modulates specifically for the muscle involved in movement preparation. Together, these findings indicate that cerebellar–M1 connectivity changes are somatotopy specific.

Premovement CBI Changes versus Learning-Induced CBI changes

We observed CBI changes during both movement preparation and after adaptive learning, but interpret these results to be driven by different mechanisms; premovement CBI is likely due to activity patterns of Purkinje cells (PCs) and deep cerebellar nuclei (DCN), whereas learning-induced changes in CBI reflect cerebellar plastic changes.

Although the physiology of cerebellar TMS remains poorly understood, it is possible that stimulation results in the parallel-fiber-mediated activation of PCs, which inhibit the DCN (Celnik, 2015). The reduced CBI closer to movement initiation in this study may therefore represent a decrease of inhibition from hand- or leg-affiliated PCs that activate hand- or leg-affiliated DN cells, respectively. Animal studies have shown burst activity of DCN during preparation of limb movement, in which inactivation of the cerebellum results in delay of M1 activity and delay in the initiation of movements (Brooks, 1975; Miller and Brooks, 1982). In addition, suppression of optogenetically modified PCs in rodents can activate dentate cells (Heiney et al., 2014), suggesting that the onset of activity in DCNs results from disinhibition by PCs. Furthermore, a recent study in monkeys showed that, before wrist movement onset, wrist-affiliated PCs were suppressed whereas wrist-affiliated DN cells showed concurrent burst activity without prior suppression (Ishikawa et al., 2014). Therefore, during the preparation of a specific muscle movement, the cerebellar cortex may reduce its inhibition to M1 via the cerebello-thalamo-M1 pathway, consistent with the results found in this study.

In contrast, we interpret the CBI changes in learning to reflect the plastic changes in cerebellar output that are responsible for changing motor behavior during adaptation. Although the cerebellum contains multiple sites and forms of plasticity (Boyden et al., 2004; Jörntell and Hansel, 2006; Gao et al., 2012), two plasticity sites have been shown to be important for motor learning: long-term potentiation (LTP) of mossy fibers and interneurons in the cerebellar cortex (D'Angelo, 2005; Grasselli and Hansel, 2014) and long-term depression (LTD) of parallel fiber–PC synapses. In particular, animal studies have associated LTD in PCs with adaptive learning, triggered by climbing fiber inputs driven by inaccurate movements (Gilbert and Thach, 1977; Medina and Lisberger, 2008; Yang and Lisberger, 2014). Because errors are prevalent early in adaptive learning, we interpret our CBI changes to reflect reduced PCs activity. Accordingly, if PCs are less excit-

able, then a conditioning stimulus would be less likely to engage the cerebellar-dentate-thalamic pathway, which would result in less M1 inhibition, consistent with the results of this study. However, it is important to consider that LTP of parallel fibers and inhibitory interneurons can result in the same net effect as LTD of parallel fiber–PC synapses (D'Angelo, 2014; Jörntell, 2017). Therefore, it is possible that multiple plasticity mechanisms throughout the cerebellum operate in learning a new behavior (Medina and Mauk, 2000; Jörntell and Ekerot, 2003; Yang and Lisberger, 2014; Mapelli et al., 2015).

The novel finding of this study is that learning-related changes in CBI are somatotopic specific. As described previously (Morton and Bastian, 2004; Savin and Morton, 2008), we found that adaptive learning transfers between the arm and leg. In addition to this behavioral finding, we show a similar effect using a cerebellar physiological measure. Therefore, the transfer in CBI changes found in Experiment 2 appears related to the transfer of learning because CBI follows a somatotopy-specific pattern when assessed in the context of movement preparation.

Hand-to-leg transfer may be mediated by interactions between overlapping cerebellar representations

Several neuroimaging studies have demonstrated gross motor somatotopy for upper and lower limb representations within the cerebellar cortex (Nitschke et al., 1996; Rijntjes et al., 1999; Grodd et al., 2001; Stoodley and Schmahmann, 2009; Schlerf et al., 2010; Buckner et al., 2011) and the dentate nucleus (Dimitrova et al., 2006; Küper et al., 2012). In addition, studies in nonhuman primates have reported that dentate nucleus somatotopic representation of the lower limb is located more rostrally compared with the upper limb (Allen et al., 1978; Rispal-Padel et al., 1982; van Kan et al., 1994). Indeed, retrograde axonal transport of neurotropic viruses injected in different body representations of M1 demonstrated a rostral–caudal output organization of leg, arm, and face representations in the dentate nucleus (Dum and Strick, 2003; Lu et al., 2007). However, there is also evidence of anatomical overlap for these representations. For example, electrical stimulation of the cerebellar nuclei can cause concurrent movement of lower and upper limbs (Rispal-Padel et al., 1982) and, in some cases, dentate neurons reacted to both lower and upper limb movements (van Kan et al., 1994). In humans, fMRI studies have suggested that there is extensive overlap between finger and foot movement activation when looking at group analysis of cerebellar cortex (Rijntjes et al., 1999) and dentate nucleus (Küper et al., 2012) activation.

It is not known to what extent the overlapping arm and leg representations can interact with each other, but the microarchitecture of the cerebellar cortex raises the possibility that such interactions may occur within the cerebellum and serve as a substrate of ipsilateral transfer. A single mossy fiber may have synaptic contacts with 448 cerebellar granule cells (Ito, 1984) and the parallel fibers of each granule cell branch and excite hundreds of Purkinje cells up to several millimeters from the branch point (Fox and Barnard, 1957). Climbing fibers also branch and, although each Purkinje cell receives only one climbing fiber input, each climbing fiber may synapse with 10 Purkinje cells (Eccles et al., 1966). Therefore, it is possible that some Purkinje cells that stimulate the leg representation receive both parallel fiber and climbing fiber inputs from the arm and are therefore able to undergo plastic modifications in response to visuomotor learning with the ipsilateral arm, leading to transfer. An alternative possibility is that, within a cerebellar hemisphere, arm and leg representations interact with each other through the large network of inhibitory interneurons present throughout cerebellar cortex (Ito, 1984). For example, a single Golgi cell receives ~228 mossy fiber and ~4788 parallel fiber inputs, in addition to inputs from climbing fibers, Purkinje collaterals, and other interneurons, and inhibits up to 5700 granule cells (Ito, 1984). Golgi cells and other cerebellar interneurons are thought to be involved in the specificity and modulation of cerebellar cortical computations (Ito, 1984).

Future directions

In addition to demonstrating that cerebellar–M1 connectivity is organized somatotopically, we describe a novel method to measure cerebellar–M1 connectivity physiology during movement preparation. This is important because previous investigations have only provided evidence that the cerebellum exerts an influence on M1 at rest or in an indirect manner. For example, premovement facilitation of MEPs normally observed in response to M1 TMS is reduced in patients with spinocerebellar degeneration (Nomura et al., 2001) and unilateral cerebellar stroke (Battaglia et al., 2006) and this has been linked with deficits in motor preparation and motor imagery in these populations. Therefore, the paradigm used in this study could be used in future research to assess context-dependent (premovement) physiological changes in patients to further understand the role of the cerebellum in movement preparation. Furthermore, future investigations will need to address what aspects of behavioral transfer are associated with changes in cerebellar–M1 connectivity.

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