Somatosensory versus cerebellar contributions to proprioceptive changes associated with motor skill learning: A theta burst stimulation study

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Abstract

Background: It is well established that proprioception (position sense) is important for motor control, yet its role in motor learning and associated plasticity is not well understood. We previously demonstrated that motor skill learning is associated with enhanced proprioception and changes in sensorimotor neurophysiology. However, the neural substrates mediating these effects are unclear.

Objective: To determine whether suppressing activity in the cerebellum and somatosensory cortex (S1) affects proprioceptive changes associated with motor skill learning.

Methods: 54 healthy young adults practiced a skill involving visually-guided 2D reaching movements through an irregular-shaped track using a robotic manipulandum with their right hand. Proprioception was measured using a passive two-alternative choice task before and after motor practice. Continuous theta burst stimulation (cTBS) was delivered over S1 or the cerebellum (CB) at the end of training for two consecutive days. We compared group differences (S1, CB, Sham) in proprioception and motor skill, quantified by a speed-accuracy function, measured on a third consecutive day (retention).

Results: As shown previously, the Sham group demonstrated enhanced proprioceptive sensitivity after training and at retention. The S1 group had impaired proprioceptive function at retention through online changes during practice, whereas the CB group demonstrated offline decrements in proprioceptive function. All groups demonstrated motor skill learning. However, the magnitude of learning differed between the CB and Sham groups, consistent with a role for the cerebellum in motor learning.

Conclusion: Overall, these findings suggest that the cerebellum and S1 are important for distinct aspects of proprioceptive changes during skill learning.

Key Words

Skill learning, proprioception, somatosensory cortex, cerebellum, theta burst stimulation

1. Introduction

Motor learning involves changes in behavior associated with practice. Learning can describe modifications of already-well learned movements (motor adaptation) or the acquisition of new skills (skill learning). Both are associated with changes in motor brain regions, including the motor cortex and cerebellum. These changes can occur during the acquisition phase of learning (i.e., online learning), or between sessions (i.e., offline learning) (Dayan and Cohen, 2011; Kantak and Winstein, 2012).

The extent to which specific brain regions are involved in learning depends on the phase and type of learning. Adaptation involves modification of already well-learned movements to compensate for an external perturbation. This trial-by-trial reduction in errors occurs within minutes (Bastian, 2008; Krakauer and Mazzoni, 2011). Transcranial direct current stimulation (tDCS) research suggests that the cerebellum contributes to the rate of adaptation whereas the primary motor cortex (M1) contributes to retention after the perturbation is removed (Galea et al., 2011).

M1 and the cerebellum likely also contribute to different phases of skill learning (Spampinato and Celnik, 2017). Unlike adaptation, skill learning involves the acquisition of new movement patterns in the absence of a perturbation. There is an improvement in movement quality rather than regaining a baseline performance; this can occur on a longer time scale (i.e., days, weeks, years) (Krakauer and Mazzoni, 2011; Shmuelof et al., 2012). Excitatory cerebellar tDCS facilitated total skill learning through online rather than offline changes (Cantarero et al., 2015). Other studies using the same skill task found that excitatory M1 tDCS enhanced skill retention, without affecting online gains (Reis et al., 2009; Saucedo Marquez et al., 2013). Overall, previous literature suggests a potential dichotomy in the roles of the cerebellum and M1 during adaptation and skill learning, with the cerebellum playing a larger role in online changes and M1 playing a larger role in offline processes.

While the motor brain regions have been investigated frequently in the context of motor learning, sensory functions have received less attention. Given anatomical, functional, and physiological evidence suggesting reciprocal links between sensory and motor processes (Ostry and Gribble, 2016), consolidation of sensory memories may also play a role in motor learning. We and others have shown that motor skill learning is associated with improvements in body position sense (proprioception) that are retained at least 24 hours after practice ends (Cuppone et al., 2018; Mirdamadi and Block, 2020). We also demonstrated changes in somatosensory projections to motor cortex after training (Mirdamadi and Block, 2020). However, the neural substrates driving these sensory changes have not been directly investigated.

Here we consider two possible neural substrates that may be important for proprioceptive changes associated with motor skill learning: the cerebellum and primary somatosensory cortex (S1). Both regions process proprioceptive information from the periphery, and are interconnected with other cortical areas important for sensorimotor integration (Edwards et al., 2019; Gilman, 2002; Ostry and Gribble, 2016; Proske and Gandevia, 2012). Cerebellar involvement in proprioception is thought to be more non-conscious, contributing to online movement corrections (Baumann et al., 2015; Riemann and Lephart, 2002). In contrast, S1 is thought to be involved in higher-order proprioceptive processing and conscious limb detection (Johnson et al., 2008). Here, we applied continuous theta burst stimulation (cTBS), an inhibitory non-invasive brain stimulation paradigm, over S1 or the cerebellum after training. We compared these groups to a Sham group to determine whether S1 and the cerebellum have different roles in proprioceptive changes associated with motor skill learning.

2. Methods

2.1. Participants

54 right-handed healthy young adults (35 female, age 18-33 years), with no known neurological disorders nor contraindications to transcranial magnetic stimulation (TMS), gave written informed consent and participated. The study was approved by the Indiana University Institutional Review Board. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Participants were randomly assigned to one of three stimulation groups: S1, Cerebellum (CB), and Sham (Fig.1A), with 18 participants in each group. This sample size was based on existing literature involving neuromodulation, motor training, and/or somatosensory assessment in a between-groups design. Our motor skill task was adapted from McGrath and Kantak (2016), which found significant between-group differences with 10 participants per group. We recently used TMS to evaluate neurophysiological changes before and after training with 15 participants (Mirdamadi and Block, 2020). Other studies that had stimulation over M1, S1, or the cerebellum paired with motor skill training across days ranged from 10-17 participants per group (Cantarero et al., 2015; Reis et al., 2015, 2009; Vidoni et al., 2010). It could be argued that additional variability may result from comparing groups that received neuromodulation over different brain regions. Therefore, we also considered studies that compared different stimulation targets in the context of learning (i.e., M1 versus S1, M1 versus cerebellum, M1 versus prefrontal cortex), which had between 10-12 participants per group (Galea et al., 2011; Kantak et al., 2010; Kumar et al., 2019). For instance, Kumar et al. (2019) compared S1 versus M1 cTBS with motor adaptation (N= 10 per group), and at a retention test (as done here) detected significant differences between the two groups. To ensure sufficient power to detect between-group differences in the present study, we therefore chose a sample size at the high end of the range of these studies.

2.2. Experimental Design

Each group participated in three consecutive sessions that involved motor skill and proprioceptive tasks identical to our previous experiment (Mirdamadi and Block, 2020), with cTBS delivered at the end of day 1 and day 2. On day 3, we assessed retention of proprioceptive function and motor skill in the absence of cTBS. (Fig.1B).

Behavioral tasks were performed using the KINARM Endpoint 2D robotic manipulandum (BKIN). For both the motor skill and proprioceptive task, participants grasped the manipulandum with their right hand and viewed a task display that appeared in the plane of the manipulandum (Fig. 2A). They performed all tasks without direct vision of their arms or the manipulandum (Mirdamadi and Block, 2020).

For the motor skill, participants navigated a visual cursor representing their hand position (white circle, 10mm diameter) through an irregular shaped track (20x20 cm space, 1.5 cm width) (Fig. 2B) as accurately as possible within the desired movement time range. The visual cursor specifically appeared at the center of the manipulandum handle, which was surrounded by the fingers and thumb in a whole-hand grasp. After each movement, participants received feedback on their speed (too slow, too fast, good speed) and accuracy in the form of points. They were instructed to first prioritize speed, and then improve accuracy (McGrath and Kantak, 2016; Mirdamadi and Block, 2020).

The motor skill assessment on day 1 and day 3 (Fig. 1B) assessed a speed-accuracy tradeoff over five movement time (MT) ranges, with 10 trials in each range, randomized across participants (MT1: 300-600 ms; MT2: 600-850 ms; MT3: 850-1100 ms; MT4: 1100-1400 ms: MT5: 1400-1700 ms). During motor training on day 1 and day 2 (Fig. 1B), participants trained at a fixed MT range (MT3) for 120 trials and 150 trials, respectively (Mirdamadi and Block, 2020).

Proprioception was assessed using a passive two-alternative forced choice task that required participants to verbally report where their hand was in relation to a constant 2cm-diameter visual reference marker (Fig. 2D). They were told that the center of the robotic manipulandum handle, which was grasped in the right hand, corresponded to hand position, and that the robotic manipulandum would passively move their hand to different positions in the workspace (Jones et al., 2010; Mirdamadi and Block, 2020; Wilson et al., 2010; Wong et al., 2011). Proprioception was assessed in the horizontal (left/right) and sagittal (up/down) dimensions, with order randomized across participants. After the robotic manipulandum moved the hand to the reference, there was a random distractor movement to minimize learning (Mirdamadi and Block, 2020; Wong et al., 2011), followed by a subsequent movement to a test position where the hand was held until the participants verbally reported where their hand was (i.e. left or right for the horizontal dimension) relative to the center of the visual reference (Mirdamadi and Block, 2020; Wilson et al., 2010). Test positions followed an adaptive staircase algorithm based on the Parameter Estimation by Sequential Testing method (PEST) (Taylor and Creelman, 1967). There was a total of four staircases, beginning 6 cm left/right or up/down of the reference. Subsequent test positions were adjusted depending upon the subject's response. Initial step size was 2 cm, and decreased by half when the subject's response reversed (i.e. from left to right). Each staircase terminated after four reversals (Mirdamadi and Block, 2020).

2.3. Transcranial Magnetic Stimulation (TMS) and Recordings

Participants were seated with their arms relaxed on a pillow. TMS was delivered using a Magstim Super Rapid Plus stimulator with a D70^2 70-mm figure-of-eight coil (Magstim Company LTD, United Kingdom). BrainSight neuronavigation system (Rogue Research, Montreal, Canada) was used for consistent coil positioning. Surface electromyography (EMG) was recorded from the right first dorsal interosseous (FDI) muscle. EMG signals were amplified (AMT-8; Bortec Biomedical, Calgary, Canada), band-pass filtered (10-1000 Hz), sampled at 5000 Hz, and recorded using Signal software (Cambridge Electronic Design Ltd, United Kingdom).

At the beginning of day 1 and day 2, single pulse TMS was delivered over left motor cortex to identify the FDI "hotspot", or optimal scalp position that evoked the largest and most consistent motor evoked potential (MEP) in right FDI muscle. The coil was held tangentially with the handle 45° to the midline to evoke posterior-to-anterior current in the cortex. Next, we found resting motor threshold (RMT), defined as the minimum intensity that evoked an MEP at least 50 microvolts in at least 10 out of 20 trials (Rossini et al., 2015).

cTBS was delivered at the end of day 1 and day 2 (Fig. 1B). Our goal was to assess the effects of cTBS on hand perception changes associated with motor skill learning. Therefore, for S1 cTBS, we targeted the left S1 hand representation. Traditionally, TMS studies targeting the S1 hand representation use a position 2 cm posterior to the M1 hand representation (Conte et al., 2012; Ishikawa et al., 2007; Tsang et al., 2014). However, a recent systematic review and experimental evidence suggest revision of this method is necessary, and that the S1 hand representation is actually more lateral than posterior to the FDI hotspot (Holmes et al., 2019; Holmes and Tamè, 2018). Based on this recent recommendation, the S1 target was defined 1 cm posterior and 2 cm lateral to the left FDI hotspot, with the handle 45° from the midline. The right CB target was 3 cm lateral and 1 cm inferior the inion with the handle pointing superiorly. This particular scalp location has been suggested to target the posterior and lateral lobes of the cerebellum, and has previously been shown to modulate both sensorimotor integration of the hand as well as upper limb motor behaviors (Andrew et al., 2020; Casula et al., 2016; Del Olmo et al., 2007; Harrington and Hammond-Tooke, 2015; Koch et al., 2008; Li Voti et al., 2014). cTBS consisted of three pulses presented at 50 Hz, repeated at 5 Hz for 40s, for a total of 600 stimuli (Huang et al., 2005). The intensity was 70% of RMT (Gentner et al., 2008; Goldsworthy et al., 2014). The Sham group experienced cTBS with the coil tilted 90° away from the CB target with only the coil edge on the scalp (Brusa et al., 2012; Monaco et al., 2014).

2.4. Data Analysis

For each trial of motor skill (Fig. 2C), we calculated movement time (MT) and percentage of movement trajectory inside the track (in-track accuracy). Only trials of the correct MT were analyzed. For each proprioception assessment, we calculated the proportion of trials that a participant responded left (horizontal dimension) or down (sagittal dimension) across different test positions. Data were fitted with a logistic function upon which bias and sensitivity were calculated. Bias (perceptual boundary) was defined as the 50% point of the fitted function. Since we were interested in detecting improvements in bias independent of direction, we used the absolute bias value in group analyses. Sensitivity (uncertainty) was defined as the distance between the 25% and 75% points of the fitted function (Mirdamadi and Block, 2020; Wilson et al., 2010; Wong et al., 2011) (Fig. 2E).

Since total change in proprioceptive function between baseline and retention (proprioception day 3 – pre day 1) can be manifested through online changes, offline changes, or a combination, we also calculated online and offline changes in bias and sensitivity. Online change was calculated by: (proprioception post day 1 – pre day 1) + (post day 2 – pre day 2). Offline change was calculated by: (proprioception pre day 2 – post day 1) + (day 3 – post day 2).

2.5. Statistical Analysis

To determine the effect of cTBS on proprioceptive changes associated with training, we performed a 3-way mixed measures ANOVA with within-subject factors Training Day (day 1, day 2) and Time (pre-training, post-training), and between-subject factor Group (S1, CB, Sham). We ran a one-way ANOVA on each of online changes, offline changes, and total changes. Horizontal and sagittal dimensions were analyzed separately.

To determine the effect of cTBS on motor skill learning, we performed a mixed measures ANOVA with within-subject factors Session (baseline, retention) and MT Bin (MT1, MT2, MT3, MT4, MT5) and between-subject factor Group (S1, CB, Sham) on in-track accuracy.

To assess whether the three groups were similar at baseline, we performed one-way ANOVAs with between-subject factor Group (S1, CB, Sham) on proprioceptive bias and sensitivity. A two-way ANOVA with between-subject factor Group and within-subject factor MT Bin (MT1, MT2, MT3, MT4, MT5) on in-track accuracy was performed to determine baseline skill. Finally, to see if RMT differed across groups or days, we performed a two-way ANOVA with between-subject factor Group and within-subject factor Training Day (day 1, day 2).

Statistical analysis was performed using the R computing language. For all ANOVAs (R package “afex”), assumptions for normality and homogeneity of variance were checked using the Shapiro-Wilk test and Levene’s test, respectively, and log-transformed if necessary. However, all data is plotted using the non-transformed values for clarity. Results were Greenhouse-Geisser corrected if the assumption of sphericity was violated. Generalized eta squared (η_G^2) is reported for effect sizes (Bakeman, 2005; Lakens, 2013). Values of 0.02, 0.13, and 0.26 can be considered small, medium, and large effects, respectively (Bakeman 2005). Significant effects were followed by posthoc contrasts and corrected for multiple comparisons using Tukey’s HSD method (R package “emmeans”).

2.6. Data and code availability

De-identified data and analysis code are available at https://osf.io/kpqta/. We are unable to share task programs for the Kinarm (BKIN Technologies Ltd.) as these are subject to the company’s end user license agreement. No part of the study procedures or analyses was pre-registered prior to the research being conducted.

3. Results

3.1. Proprioceptive sensitivity - horizontal dimension

In the horizontal dimension, proprioceptive sensitivity changed differently between timepoints across the three groups, as indicated by a Group x Time interaction [$F(2,51) = 4.11$, $p = 0.022$, $\eta_G^2 = 0.019$]. No other effects or interactions were significant. The Group x Time interaction reflects a trend for the S1 group having worse, and the CB group better, sensitivity post-training compared to pre-training (S1: $p = 0.053$; CB: $p = 0.078$). Sham did not show significant changes across time ($p > 0.8$) (Fig. 3A). After collapsing across Training Day, Sham did not differ significantly from CB or S1, but CB and S1 differed from each other [Group x Time interaction: $F(1,34) = 9.76$, $p = 0.0036$, $\eta_G^2 = 0.060$], with the S1 group having worse sensitivity after training compared to the CB group.

Total change in horizontal sensitivity, from baseline to retention, differed across groups ($F(2,51) = 5.94$, $p = 0.0048$, $\eta_G^2 = 0.189$). This reflected worsening for the S1 group compared to Sham ($p = 0.003$; Fig. 3B), while the CB group did not differ significantly from Sham or S1 ($p > 0.16$). Group differences in online proprioceptive changes ($F(2,51) = 4.11$, $p = 0.022$, $\eta_G^2 = 0.139$) were driven by a difference between the S1 and CB groups ($p = 0.017$), with the S1 group getting relatively worse. Sham did not differ significantly from either S1 or CB ($p > 0.2$). Finally, group differences in offline proprioceptive changes ($F(2,51) = 3.68$, $p = 0.032$, $\eta_G^2 = 0.126$) were driven by the CB group having worsened offline compared to Sham ($p = 0.024$). The S1 group did not differ from the CB or Sham groups ($p > 0.3$) (Fig. 3B). In summary, the S1 group had worsened total sensitivity in the horizontal dimension relative to Sham, primarily driven by online changes. In contrast, the CB group demonstrated offline decrements compared to Sham.

3.2. Proprioceptive sensitivity – sagittal dimension.

In the sagittal dimension, sensitivity changed after training similarly across groups, as indicated by a main effect of Time [$F(1,51) = 5.33$, $p = 0.025$, $\eta_G^2 = 0.020$]. This reflects a lower (better) sensitivity after training compared to before training regardless of Group or Training Day. There was also a trend for a main effect of Training Day [$F(1,51) = 3.89$, $p = 0.054$, $\eta_G^2 = 0.011$]. This reflects lower (better) sensitivity on day 2 compared to day 1 (Fig. 3C). No other effects or interactions were significant.

Total change in sagittal sensitivity from baseline to retention tended to differ among the three groups ($F(2,51) = 3.17$, $p = 0.0504$, $\eta_G^2 = 0.111$). Improvement was smallest for the CB group and largest for the Sham group. Neither online nor offline changes in sagittal sensitivity differed across groups ($p > 0.6$) (Fig. 3D).

3.3. *Proprioceptive bias*

Neither horizontal nor sagittal bias was modulated across training days or at retention, nor was it affected by stimulation site. Horizontal bias across training days was not normally distributed and therefore log-transformed. There were no significant interactions or main effects, suggesting that horizontal bias was similar across training days and between groups (all $p>0.11$, Fig. 4A). At retention, total change in horizontal bias was not different across groups ($p>0.5$). There were no between-group differences in online or offline changes in horizontal bias ($p > 0.2$, Fig. 4B).

The three groups were similar across training in sagittal bias, as indicated by the absence of any interactions or main effects (all $p>0.1$, Fig. 4C). There were no group differences in total sagittal bias change nor in online or offline changes (all $p > 0.3$, Fig. 4D).

3.4. *Motor Skill Learning*

All groups were able to learn the motor skill, as indicated by a main effect of Session ($F(1,51) = 48.55$, $p < 0.0001$, $\eta_G^2 = 0.064$). There was a Session x MT Bin interaction [$F(3.15,160.85) = 7.52$, $p<0.0001$, Greenhouse-Geisser corrected, $\eta_G^2 = 0.024$], with higher accuracy at retention compared to baseline for all MT bins except MT5 (MT1: $p = 0.0001$; MT2: $p<0.0001$; MT3: $p=0.0001$; MT4: $p=0.011$; MT5: $p=0.43$) (Fig. 5A). However, a significant Group x Session interaction [$F(2,51) = 3.27$, $p = 0.046$,

$\eta_G^2 = 0.009$] suggests differences in learning across the three groups. The CB group learned significantly less than Sham ($p = 0.041$). The Sham group learned the most (6.89% gain, $p = 0.0001$) whereas the CB group learned the least (2.85% gain, $p = 0.016$). The S1 group gained 4.08% ($p = 0.0008$). No other group differences were noted ($p>0.2$) (Fig. 5B).

3.5. Baseline performance and neurophysiology measures

Proprioceptive bias and sensitivity at baseline did not differ between groups in either dimension (all $p>0.35$). For baseline motor skill, the absence of any effect or interaction involving Group suggests the groups had a similar level of skill before training. A main effect of MT bin [$F(4,204) = 282.89$, $p<0.0001$, $\eta_G^2 = 0.758$] reflects greater accuracy at slower speeds, as expected. Finally, RMT analysis revealed no significant effects or interactions (all $p>0.16$).

4. Discussion

We compared cerebellar versus S1 contributions to proprioceptive changes associated with motor skill learning. Consistent with previous findings, the Sham group demonstrated motor skill learning and improvements in proprioceptive sensitivity after training, which persisted at retention (Mirdamadi and Block, 2020). cTBS over the cerebellum and S1 impaired proprioceptive sensitivity in the horizontal dimension, though during different phases of the learning process: the cerebellum contributed to offline proprioceptive decrements while S1 contributed to online proprioceptive decrements that persisted at retention.

4.1. Cerebellar versus somatosensory involvement in proprioceptive function

Proprioceptive information from the periphery ascends along two routes: the dorsal column-medial-lemniscal pathway, which terminates in S1, and the spinocerebellar pathway, which terminates in the spinocerebellum (Proske and Gandevia, 2012). The cerebellum also has extensive parallel loops with cortical areas for additional sensory inputs and motor commands (Wolpert et al., 1998). Patient studies demonstrate the cerebellum contributes to proprioceptive function (Bhanpuri et al., 2013; Weeks et al., 2017). Individuals with cerebellar damage perform similar to controls in passive proprioceptive tasks, but are impaired in active proprioceptive tasks (Bhanpuri et al., 2013). These findings suggest that the cerebellum may be particularly important for sensory prediction of motor commands. In the horizontal dimension, CB cTBS led to offline decrements in proprioceptive sensitivity. In the sagittal dimension, there was a trend for attenuated sensitivity improvements compared to Sham. Overall, these findings support the role of the cerebellum in proprioception. Given that the cerebellum plays more of a role in proprioception for active movements (Bhanpuri et al., 2013), it would be interesting to test whether other group differences would be observed with an active proprioceptive test.

Neuroimaging studies in patients and non-invasive brain stimulation studies in healthy young adults suggest S1 contributes to proprioceptive function (Ben-Shabat et al., 2015; Findlater et al., 2018; Ingemanson et al., 2019; Kumar et al., 2019; Vidoni et al., 2010). Proprioceptive deficits of the finger post-stroke were best predicted by total sensory system injury (S1, secondary somatosensory cortex, and thalamocortical sensory tract) and functional connectivity between secondary somatosensory cortex and M1 (Ingemanson et al., 2019). Similarly, residual sensory function in chronic stroke was related to functional connectivity in sensorimotor networks, specifically between S1, M1, and supplementary motor area (Vahdat et al., 2019). In neurologically-intact individuals, Kumar et al. observed that S1 cTBS impaired proprioceptive sensitivity immediately after stimulation (Kumar et al., 2019). Our findings suggest S1 has more than transient impact, playing a role in consolidation of proprioceptive changes. Like the CB group, the S1 group seemed to have attenuated improvements in sensitivity in the sagittal dimension. More pronounced was that compared to baseline, sensitivity in the horizontal dimension was worse at retention, primarily due to online decrements. This suggests that the cerebellum and S1 may have different contributions (offline versus online) to proprioceptive changes associated with skill learning. These findings may be analogous to previous research suggesting a dichotomy in cerebellar versus M1 contributions to different phases of motor learning (Galea et al., 2011; Spampinato and Celnik, 2017).

To our knowledge, only one other study has directly compared the effects of S1 and cerebellar stimulation on sensory function. Conte et al. found that S1 but not cerebellar TBS affected somatosensory temporal discrimination (Conte et al., 2012). At first glance, if we simply looked at total changes in proprioceptive function, our results would be consistent with Conte et al.'s findings. However, the current study suggests the cerebellum also contributes to proprioceptive function through offline mechanisms.

Regardless of group or day, we did not detect changes in proprioceptive bias. Several studies have observed changes in bias after motor adaptation (Henriques and Cressman, 2012; Ostry et al., 2010; Vahdat et al., 2011). However, there are mixed reports on whether bias changes after learning without a perturbation (Cuppone et al., 2018; Mirdamadi and Block, 2020; Wong et al., 2011), which may be related to differences at baseline (Mirdamadi & Block, 2020). Further research is needed to elucidate which aspects of learning contribute to changes in proprioceptive bias.

Since both proximal and distal joints are involved in the task, we might wonder whether targeting a more proximal limb muscle representation in S1 would similarly influence changes in hand position sense as assessed in the present study. While this is an interesting question, we targeted the S1 hand representation because proprioception is thought to be most salient when the endpoint effector (hand) is estimated rather than focusing on proximal joint angles such as elbow (Fuentes and Bastian 2010). We therefore previously targeted S1 hand representation to assess the influence of hand proprioception on motor cortex in the same whole-arm maze task used in the present study (Mirdamadi and Block, 2020), and others have targeted S1 hand representation to successfully disrupt hand proprioception in a whole-arm reaching task in the context of prism adaptation (Yoon et al., 2014).

In the present study, participants were instructed to use the center of the manipulandum handle, which was surrounded by their fingers and thumb, as the proprioceptive focal point to compare with the center of the visual reference. Proprioceptive information about the posture and shaping of hand and fingers was thus involved in fine-tuning any rough proprioceptive estimate of whole-hand position that could be obtained from the proximal limb segments. In the area of cortex we stimulated, proprioceptive neurons are known to code for the posture and shaping of the whole hand (Goodman et al., 2019). This is in contrast to cutaneous neurons in SI, which code for small regions of skin on individual hand/finger segments (Goodman et al., 2019). Therefore, while determining the role of S1 proximal vs. distal representations is outside the scope of the present study, we can be confident that the stimulated S1 hand representation was pertinent to the present task.

A similar question could be raised for the target site of cerebellar cTBS. The scalp location of 1 cm inferior and 3 cm lateral to the inion is consistent with the majority of cerebellar rTMS literature targeting the lateral hemisphere in the absence of individual neuroanatomical scans. Neuroimaging studies have shown that this location corresponds to the posterior and superior lobules of the lateral cerebellum, activated during upper limb tasks and tactile stimulation of the hand (Bushara et al., 2001; Stoodley and Schmahmann, 2010). Cerebellar network-guided rTMS, based upon functional magnetic resonance imaging, is needed to further elucidate the role of the cerebellum in proprioceptive function and motor learning. However, based on what is currently known, the chosen cerebellar target is appropriate for tasks involving hand, fingers, and arm (Andrew et al., 2020; Del Olmo et al., 2007; Koch et al., 2020, 2007; Li Voti et al., 2014; Torriero et al., 2004).

4.2. Cerebellar versus somatosensory role in motor skill learning

Cerebellar contributions to motor learning are well documented for adaptation paradigms (Bastian, 2008; Martin et al., 1996; Shadmehr and Mussa-Ivaldi, 1994; Tseng et al., 2007). Recent evidence suggests the cerebellum is also involved in skill learning. Shmuelof et al. observed increases in functional connectivity between the cerebellum and motor cortex that were associated with reduced movement variability after three days of practicing an arc-tracing task (Shmuelof et al., 2014). Further, Spampinanto et al. found changes in cerebellar-motor inhibition early in skill learning on a visuomotor pinch force task, but not later phases of learning (Spampinato and Celnik, 2017). Using the same task, excitatory cerebellar tDCS applied during training enhanced total learning through online improvements in accuracy rather than offline learning (Cantarero et al., 2015). The present study had a similar design to Cantarero et al., except we stimulated at the end of practice to interfere with consolidation. Although the CB group still demonstrated skill learning at retention, individuals learned significantly less than Sham, suggesting that the cerebellum contributes to skill learning. Since we did not measure neurophysiology pre and post cTBS, it is difficult to speculate on the underlying mechanisms. However, other reports of cerebellar TBS have observed changes in cerebellar-motor excitability (Popa et al., 2013), motor cortical inhibition (Harrington and Hammond-Tooke, 2015; Koch et al., 2008), and TMS-evoked activity in M1 and posterior parietal cortex (Casula et al., 2016; Harrington and Hammond-Tooke, 2015). Therefore, disrupting the cerebellum likely influenced skill learning via alterations in interconnected cortical areas through dentato-thalamo connections.

One concern with cerebellar stimulation is the potential for stimulating cervical neck roots that in turn drive changes in performance. Our stimulation intensity of 70% RMT is in alignment with other cerebellar TBS studies using 80% of active motor threshold (Casula et al., 2016; Harrington and Hammond-Tooke, 2015; Koch et al., 2008; Popa et al., 2013, 2010), and lower than studies that used 1 Hz repetitive TMS (Del Olmo et al., 2007; Popa et al., 2010). Further, others have performed control experiments stimulating the nerve roots directly, and found cerebellar but not cervical neck muscle stimulation affected cerebellar-motor connectivity and behavior on a tapping task (Del Olmo et al., 2007; Popa et al., 2010). Thus, it is unlikely that our results are due to neck muscle stimulation.

Although most literature has focused on motor contributions to learning, reciprocal connections between motor and somatosensory cortices provide a framework for motor learning to also involve somatosensory plasticity (Ostry and Gribble, 2016). At the behavioral level, proprioception changes after motor adaptation and visuomotor skill learning (Henriques and Cressman, 2012; Mirdamadi and Block, 2020; Ostry et al., 2010; Wong et al., 2011). There is also evidence from somatosensory evoked potentials and resting state functional connectivity to suggest plasticity involving sensory areas following motor adaptation (Nasir et al., 2013; Ostry and Gribble, 2016; Vahdat et al., 2011). Further, inhibitory repetitive TMS over S1 prior to training on a visuomotor tracking task impaired the magnitude of learning compared to Sham (Vidoni et al., 2010). In the present study, the S1 group learned less than Sham, but the difference was not significant. An important distinction between the two studies is the time at which stimulation was delivered. Stimulation before training may have affected proprioception, motor control, or both. In contrast, since we delivered stimulation after training, we rule out any stimulation-induced differences in training performance that may have otherwise affected learning (Kumar et al., 2019).

Kumar et al. (2019) demonstrated that S1 cTBS delivered after force-field learning with a gradual load onset blocked motor memory consolidation (Kumar et al., 2019). At first, our findings seem discrepant with Kumar et al.’s findings, but it is difficult to make direct comparisons given the different learning paradigms. Adaptation involves overcoming a perturbation to an already well-learned behavior, with learning indicated by a reduction in systematic errors. In contrast, skill learning involves acquiring new movement patterns without a perturbation, with learning indicated by a shift in the speed-accuracy tradeoff (Krakauer and Mazzoni, 2011; Shmuelof et al., 2012). However, it is important to consider that when learning a new skill, elements of adaptation (i.e. learning the dynamics of a tennis racket) and their associated neural mechanisms may contribute. For instance, cerebellar-motor networks changed during both the early phases of skill learning (i.e. the first training day), as well as following adaptation (Galea et al., 2011; Spampinato and Celnik, 2018, 2017). It is unclear why S1 cTBS abolished retention after adaptation with a gradual load onset but not skill learning as in the present study. One possibility is that skill learning involves a more distributed network compared to adaptation. This hypothesis is consistent with Kumar's findings that demonstrated partial retention when S1 was suppressed after adaptation with an abrupt load onset. The authors suggested that with an abrupt load, explicit strategies likely require areas other than S1 for learning. Similarly, with skill learning, explicit processes may be involved when subjects explore different strategies to find the optimal movement patterns for completing the maze.

Unfortunately, since the speed-accuracy function was only probed at baseline and retention, we cannot infer anything about online versus offline learning. We did not analyze training performance for two reasons; first, there is a learning-performance distinction such that training performance does not necessarily indicate learning (Kantak and Winstein, 2012). More importantly, changes in performance at a fixed speed may be misrepresentative of total learning which is operationalized by a speed-accuracy tradeoff. If performance at a single speed plateaus during training, it says nothing about how performance changes across the entire speed-accuracy function (Wickelgren, 1977). Future studies will be needed to probe the speed-accuracy function within and between training to assess online versus offline skill learning. Given that the cerebellum and S1 had different online and offline contributions to proprioception, it would be interesting to see whether a similar dichotomy would be observed for skill learning.

5. Conclusions

Proprioceptive changes associated with motor skill learning are mediated by both the cerebellum and S1. However, these regions appear to contribute to temporally distinct processes, with cerebellum linked to offline and S1 to online proprioceptive changes. Future research is needed to test whether the cerebellum and somatosensory cortex contribute differently to online versus offline motor skill learning.

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Figure Captions

Figure 1A. Depiction of stimulation targets used for 3 different groups. Continuous theta burst stimulation (cTBS) was delivered over either the left primary somatosensory cortex (S1), right lateral cerebellum (CB), or right lateral cerebellum with coil tilted away (Sham) **B.** Experimental Design. Proprioceptive function was measured before and after motor training on day 1 and day 2, as in our previous experiment *(Mirdamadi and Block, 2020)*. cTBS was delivered after the behavioral tasks on day 1 and day 2. Retention of proprioceptive function and motor learning was evaluated on day 3 in the absence of cTBS. The motor skill was assessed at 5 different speeds on day 1 and day 3 to evaluate a speed-accuracy trade-off. On day 1 and day 2, motor training was performed at a fixed speed.

Figure 2A. Depiction of 2-D virtual reality apparatus used for the proprioception and motor tasks. Subjects performed the motor skill and proprioceptive task with their right hand, grasping a robotic manipulandum between their thumb and fingers, and had no vision of their arms. **B.** Bird's eye view of motor skill task display. Subject was seated in the direction of the negative y-axis, centered with the track. Subjects navigated the white cursor with the robotic manipulandum through the irregular shaped track, moving from the lower green starting square to the upper green end square. **C.** Representative movement trajectory used to compute movement time (MT) and in-track accuracy. Blue dashed line represents parts of the movement path that were inside the track. Magenta line represents parts of the movement path that were outside the track. **D.** Bird's eye view of passive proprioception assessment. The participant's unseen right hand, grasping the robotic manipulandum handle (black circle), was moved by the robot to different positions in the workspace. The participant's hand was moved to a visual reference position (white circle), followed by a distractor movement, and then a movement to the test position. At the test position, participants verbally reported their hand position in relation to a visual reference (white circle), located at the center of the motor skill track. Participants were specifically instructed to use the center of the manipulandum handle, grasped in their right hand, as a representation of hand position to compare with the center of the visual reference. Proprioception was assessed in the horizontal dimension, where participants indicated whether their hand was to the left or right of the reference, and sagittal dimension, where participants indicated whether their hand was up or down from the reference. **E.**

Example subject proprioceptive data fitted with logistic function. Bias was defined as the 50% point of the fitted function. Sensitivity was defined as the difference between the 25% and 75% points of the fitted function. For this subject, the bias, or perceptual boundary, was computed as -13.55 mm and the sensitivity was 23.83 cm.

Figure 3. Proprioceptive sensitivity changes in the horizontal dimension (top row) and sagittal dimension (bottom row). Lower values represent better proprioceptive function. Vertical dashed lines in (A) and (C) delineate pre-training and post-training on Day 1 and Day 2. Dots in (B) and (D) represent each individual's sensitivity, and the bias represent each group mean. Error bars are standard error of the mean. **A.** Proprioceptive sensitivity in the horizontal dimension changed differently across time for the S1 and CB groups**.** **B.** Total changes in proprioceptive function (retention – baseline) broken down into Online and Offline changes. * Tukey pairwise comparison $p < 0.05$. **C.** Proprioceptive sensitivity in the sagittal dimension decreased (improved) after training regardless of Group or Training Day * denotes main effect of Time, $p < 0.05$. **D.** The magnitude of improvement in total proprioceptive sensitivity was less for the CB and S1 groups compared to Sham, though was not statistically significant ($F(2,51) = 3.17$, $p = 0.0504$). There were no group differences in online proprioceptive change or offline proprioceptive change.

Figure 4. Proprioceptive bias changes in the horizontal dimension (top row) and sagittal dimension (bottom row). Lower values represent better proprioceptive function. Vertical dashed lines in (A) and (C) delineate pre-training and post-training on Day 1 and Day 2. Dots in (B) and (D) represent each individual's bias change, and the bars represent each group mean. Error bars are standard error of the mean. **A.** Proprioceptive bias in the horizontal dimension was not modulated differently across groups. **B.** Total, online, and offline changes did not differ across groups. **C.** Proprioceptive bias in the sagittal dimension was not modulated differently across groups. **D.** Total, online, and offline changes did not differ across groups.

Figure 5A. Speed-accuracy function for the motor skill, collapsed across all groups. Higher numbers indicate better performance. The three groups showed evidence of learning at the first four movement time (MT) bins. *p<0.005. **B.** Total skill learning at retention relative to baseline, collapsed across 5 MT bins. Dots represent each individual’s skill learning, and the bars represents each group mean. The CB group learned to a lesser extent than Sham. *p<0.05.

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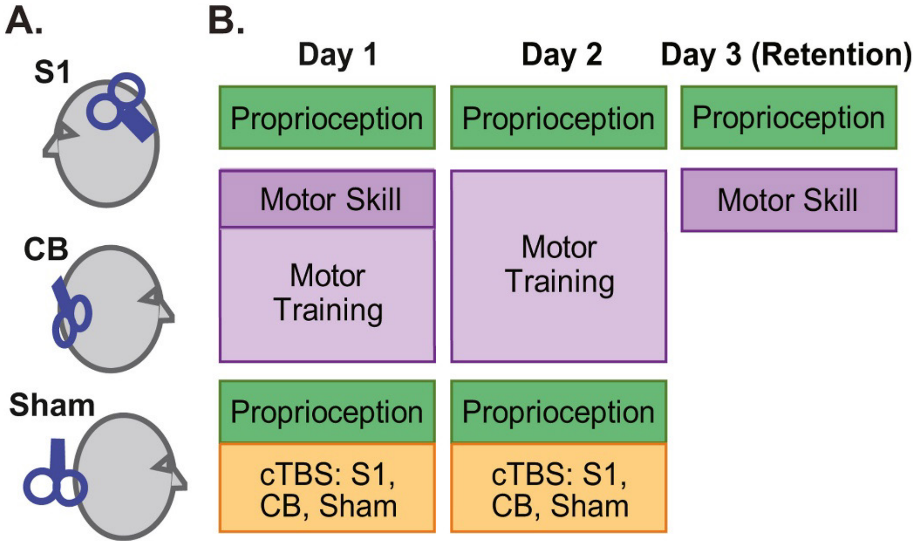
A.
S1
CB
Sham
B.
Day 1
Day 2
Day 3 (Retention)
Proprioception
Proprioception
Proprioception
Motor Skill
Motor Training
Motor Training
Motor Skill
Proprioception
Proprioception
cTBS: S1, CB, Sham
cTBS: S1, CB, Sham

Figure 1

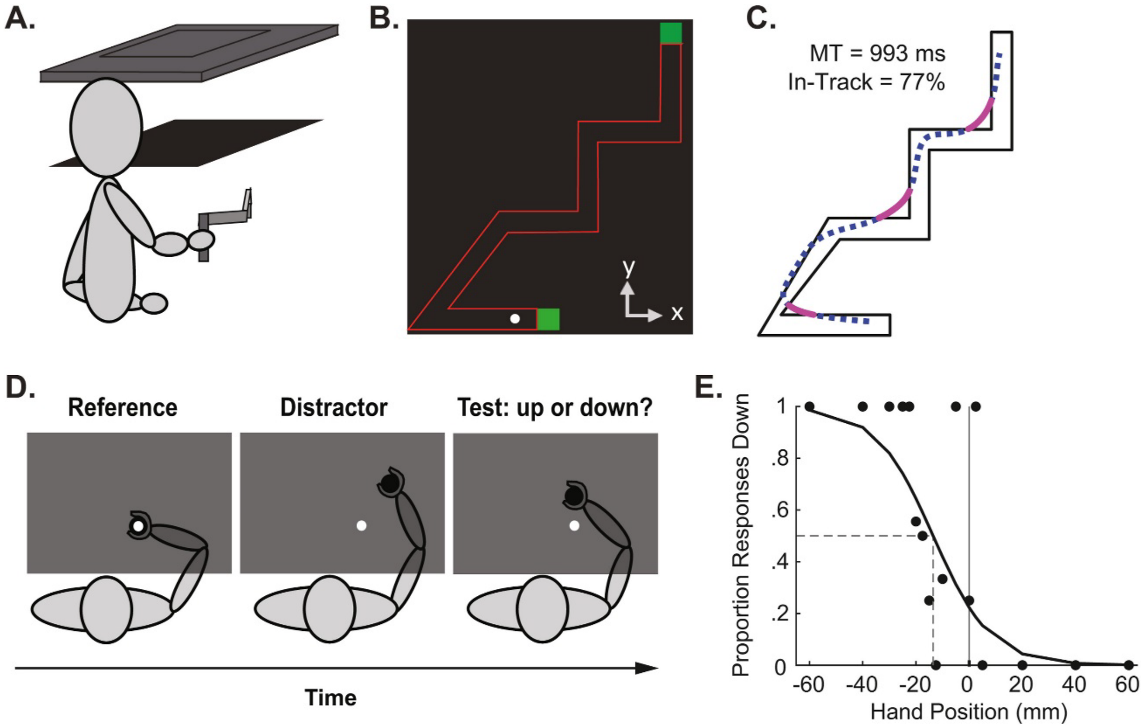
A.
B.
y
x
C.
MT = 993 ms
In-Track = 77%
D.
Reference
Distractor
Test: up or down?
Time
E.
Proportion Responses Down
1
.8
.6
.4
.2
0
-60
-40
-20
0
20
40
60
Hand Position (mm)

Figure 2

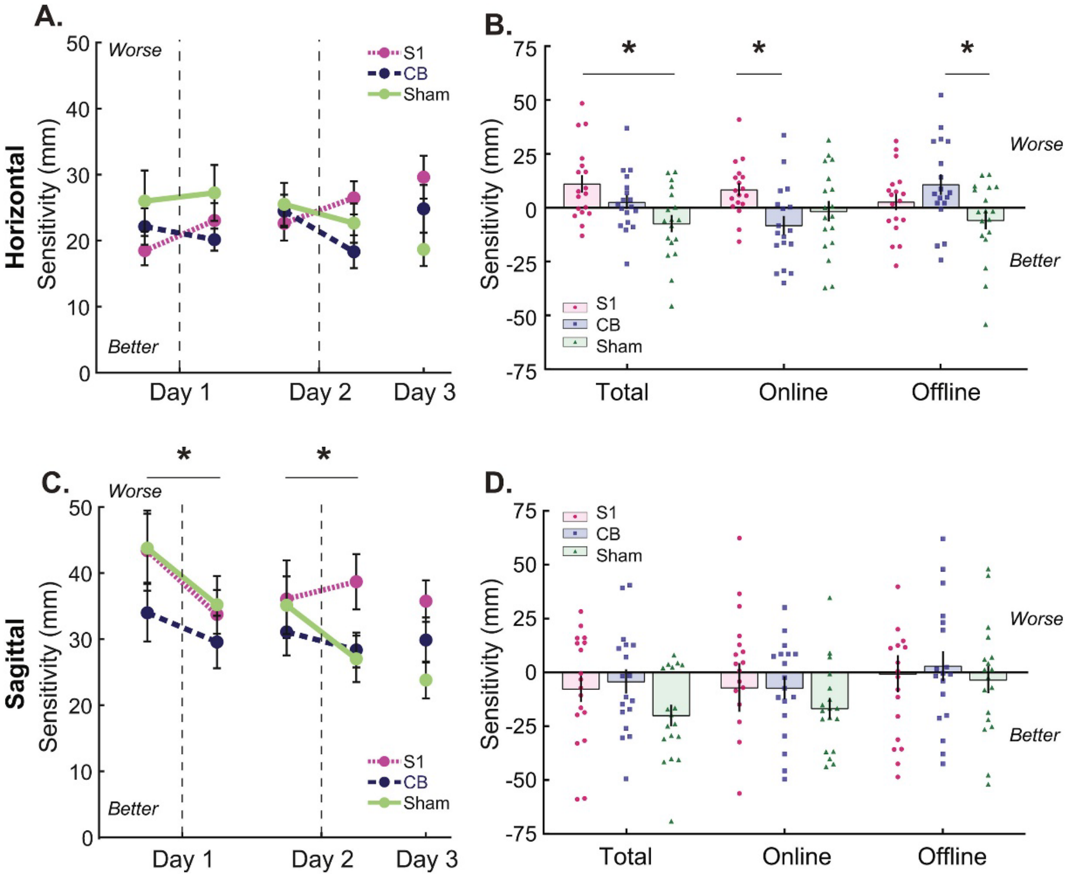
A.
Horizontal
Sensitivity (mm)
Worse
Better
S1
CB
Sham
Day 1
Day 2
Day 3
B.
Sensitivity (mm)
*
*
*
Worse
Better
S1
CB
Sham
Total
Online
Offline
C.
Sagital
Sensitivity (mm)
*
*
Worse
Better
S1
CB
Sham
Day 1
Day 2
Day 3
D.
Sensitivity (mm)
S1
CB
Sham
Worse
Better
Total
Online
Offline

Figure 3

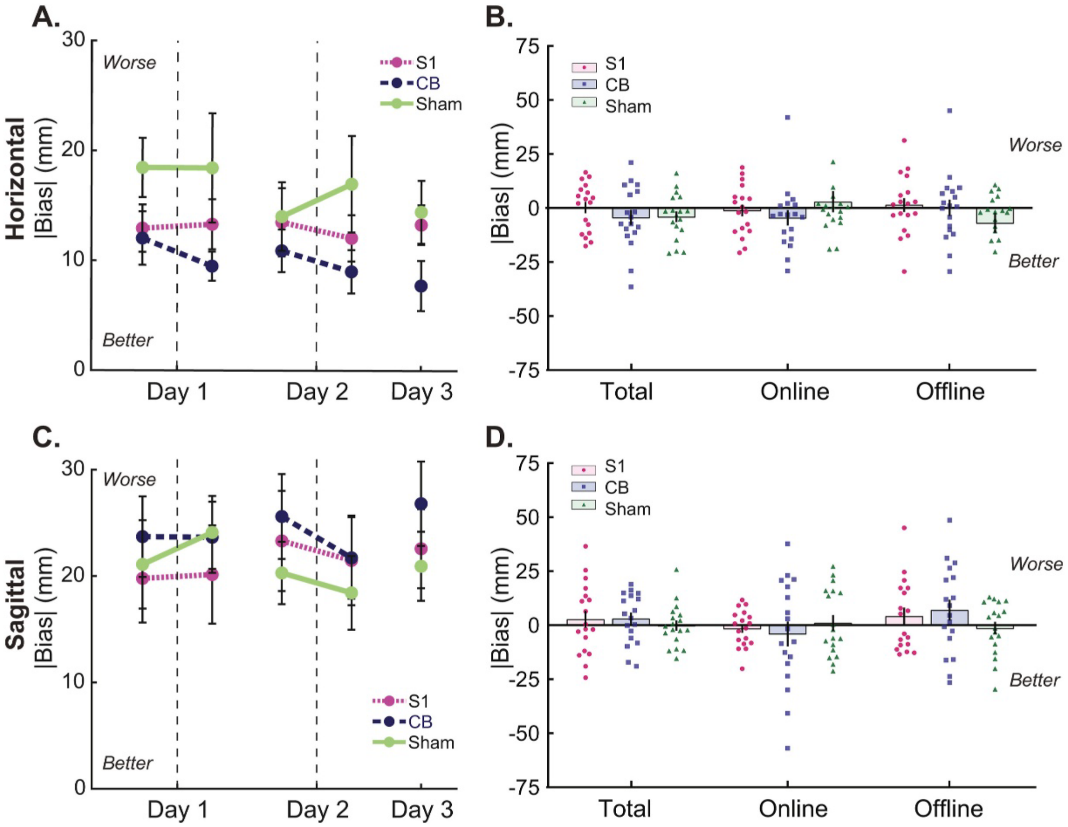
A.
Horizontal
|Bias| (mm)
30
20
10
0
Worse
Better
S1
CB
Sham
Day 1
Day 2
Day 3
B.
75
50
25
0
-25
-50
-75
|Bias| (mm)
S1
CB
Sham
Worse
Better
Total
Online
Offline
C.
Sagittal
|Bias| (mm)
30
20
10
0
Worse
Better
S1
CB
Sham
Day 1
Day 2
Day 3
D.
75
50
25
0
-25
-50
-75
|Bias| (mm)
S1
CB
Sham
Worse
Better
Total
Online
Offline

Figure 4

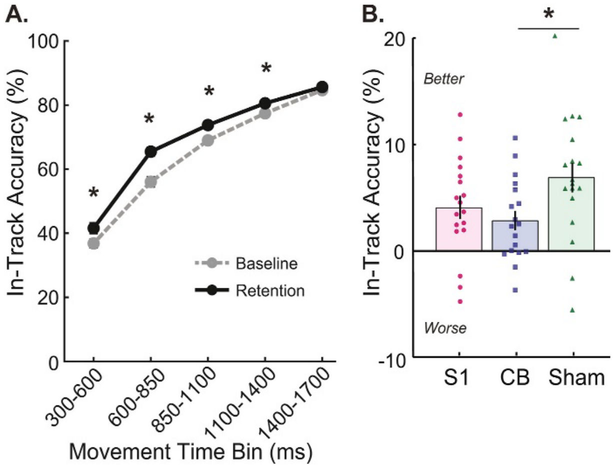
A.
100
80
60
40
20
0
In-Track Accuracy (%)
*
*
*
*
Baseline
Retention
300-600
600-850
850-1100
1100-1400
1400-1700
Movement Time Bin (ms)
B.
*
20
10
0
-10
In-Track Accuracy (%)
Better
Worse
S1
CB
Sham

Figure 5