Somatosensory cortex and body representation: Updating the motor system during a visuo-proprioceptive cue conflict

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Data Availability

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ABSTRACT

The brain's representation of hand position is critical for voluntary movement. Representation is multisensory, relying on both visual and proprioceptive cues. When these cues conflict, the brain recalibrates its unimodal estimates, shifting them closer together to compensate. Converging lines of evidence from research in perception, behavior, and neurophysiology suggest that such updates to body representation must be communicated to the motor system to keep hand movements accurate. We hypothesized that primary somatosensory cortex (S1) plays a crucial role in conveying the proprioceptive aspects of the updated body representation to the motor system. We tested this hypothesis in two experiments. We predicted that proprioceptive, but not visual, recalibration would be associated with change in short latency afferent inhibition (SAI), a measure of sensorimotor integration (influence of sensory input on motor output) (Expt. 1). We further predicted that modulating S1 activity with repetitive transcranial magnetic stimulation (TMS) should affect variance and recalibration associated with the proprioceptive estimate of hand position, but have no effect on the visual estimate (Expt. 2). Our results are consistent with these predictions, supporting the idea that (1) S1 is indeed a key region in facilitating motor system updates based on changes in body representation, and (2) this function is mediated by unisensory (proprioceptive) processing, upstream of multisensory visuo-proprioceptive computations. Other aspects of the body representation (visual and multisensory) may be conveyed to the motor system via separate pathways, e.g. from posterior parietal regions to motor cortex.

Significance Statement

Representation of the hand, which is critical for accurate control of movement, comes from weighting and combining available proprioceptive and visual cues. Our results suggest that when the hand representation is modified, the motor system receives updates directly from the primary somatosensory cortex (S1). These updates are proprioceptive, having not yet been integrated with visual cues through interaction with high-level posterior parietal regions. This might provide advantages in terms of faster updates, for example, because multisensory integration likely adds processing time. Research seeking to manipulate motor control via multisensory perception (e.g., virtual reality or mirror training for motor rehabilitation) should therefore consider the parallel unisensory and multisensory pathways that affect the motor system.

INTRODUCTION

Performing complex movements with the hands is a universal human experience. By adulthood we have learned countless such motor skills: tying our shoes, controlling a computer mouse, etc. Understanding how the brain learns in these situations is complicated by the involvement of multiple motor, sensory, and multisensory processes. “Learning” likely entails not only improving the speed-accuracy tradeoff (motor skill) and adjusting motor commands to compensate for any systematic movement errors (motor adaptation), but also fine-tuning perception of the hand itself. The brain may adjust how it interprets proprioceptive (position sense) cues from the muscles and skin, recalibrating its proprioceptive estimate of hand position in response to sensory prediction errors[1]. Importantly, if we can see our hands, then our brain’s estimate of hand position is likely multisensory, arising from a weighted average of both visual and proprioceptive cues[2,3]. If visual and proprioceptive cues conflict but are still interpreted as arising from the same source (the hand), the brain is expected to recalibrate each unimodal estimate of hand position in proportion to its relative variance (Fig. 1A), updating the integrated multisensory estimate of hand position[2].

Visuo-proprioceptive recalibration in hand perception is an example of the brain's ability to update body representation. Converging lines of evidence from research in perception[4,5], behavior[6–8], and neurophysiology[9,10] suggest that such updates to body representation must be communicated to the motor system to keep hand movements accurate. For example, even in the absence of motor learning, recalibration resulting from visuo-proprioceptive cue conflict altered movements of the hand that experienced cue conflict[11]. Perceptual recalibration has also been associated with changes in primary motor cortex (M1) excitability. We previously used transcranial magnetic stimulation (TMS) to test M1 excitability before and after participants experienced mismatched or veridical visuo-proprioceptive information about index finger position[9]. No performance feedback was available, and participants recalibrated both proprioceptive and visual estimates of the index finger as expected[12–15]. Results indicated that M1 excitability decreased in association with proprioceptive recalibration, but increased in association with visual recalibration[9]. These M1 changes were somatotopically focal, affecting only the index finger representation and not forearm or biceps representations[10].

The observed modality-specific changes in M1 excitability could suggest that the neural mechanism conveying body representation updates to the motor system involves plasticity in areas traditionally considered unisensory, such as primary somatosensory cortex (S1)[16,17] or early visual areas that have indirect connectivity with M1[18]. S1 is an intriguing candidate region, being linked both with (1) parietal regions likely involved in multisensory visuo-proprioceptive perception[19–24], and (2) frontal motor regions, including M1 (Fig. 1A). The degree to which somatosensory input affects motor output, termed sensorimotor integration, can be measured neurophysiologically: Short latency afferent inhibition (SAI) describes the inhibitory effect of a peripheral electrical stimulus delivered before a motor response evoked by transcranial magnetic stimulation (TMS)[25]. The exact neuronal pathway is not known, but thought be mediated at the level of cortex, by projections from S1 pyramidal cells to M1 interneurons[26,27].

Here we asked two questions about the function of S1: (1) Is S1 important for conveying hand representation updates to the motor system, and (2) If so, is the involvement of S1 multisensory, involving both visual and proprioceptive updates (downstream of multisensory computations), or unisensory (related to proprioception only)? In Experiment 1 we assessed SAI before and after 22 participants estimated the position of a series of veridical or conflicting visual and proprioceptive cues about their left index finger (Fig. 1B-D). Each participant experienced both behavioral conditions, in two sessions on different days, with order randomized. In Experiment 2, three groups of 27 participants received continuous theta burst TMS (cTBS) over the S1 or M1 representation of their left index finger, or sham (Fig. 1E). cTBS is thought to reduce cortical activity for up to an hour[28]. All participants estimated the position of a series of veridical visuo-proprioceptive cues about their left index finger before and after cTBS, followed by a block of trials in which a visuo-proprioceptive conflict was gradually introduced.

If S1 is important for conveying hand representation updates to the motor system (question 1), we predicted that Expt. 1 would show a change in SAI that was related to perceptual recalibration in the cue conflict, and not the veridical, session. If the involvement of S1 is multisensory (question 2), we predicted the SAI change in Expt. 1 would be related to both visual and proprioceptive recalibration, and that modulating S1 with cTBS in Expt. 2 would affect both visual and proprioceptive recalibration. This would suggest that S1's role is downstream of multisensory computations, perhaps reflecting interaction with posterior parietal cortex (PPC), such that S1 transmits both visual and proprioceptive updates to the motor system (Fig. 1A purple dashed arrow). On the other hand, if the involvement of S1 is unisensory, we predicted the SAI change in Expt. 1 would be related only to proprioceptive recalibration, and that cTBS over S1 in Expt. 2 would affect only proprioceptive recalibration. This would suggest that S1's role is upstream of multisensory computations, such that S1 is transmitting proprioceptive

information to the motor system that has not yet been integrated with visual information (Fig. 1A orange arrow).

RESULTS

Experiment 1

Behavior

Twenty-two participants used their unseen right index finger to indicate where they perceived a series of visual (V), proprioceptive (P), and bimodal (VP) targets related to their left index finger (Fig. 1B). There were no speed requirements and participants were asked to be as accurate as possible. To prevent motor learning, no performance feedback was given and target locations and starting positions were varied. Each participant completed both a cue conflict session and a veridical session, on different days in random order (Fig. 1C). In the cue conflict session, the visual cue was gradually shifted forward of the proprioceptive cue over the course of 84 trials, to a max of 70 mm. On average, participants recalibrated vision 34.7 ± 6.9 mm (mean ± 95% CI) and proprioception 11.1 ± 5.3 mm (Fig. 2Ci). Some participants recalibrated proprioception more than vision (Fig. 2A) while others recalibrated vision more than proprioception (Fig. 2B). As shown previously, visual and proprioceptive recalibration were inversely associated ($r = -0.52$, $p = 0.013$) (Fig. 2Ciii)[9].

In the veridical session, there was no cross-sensory mismatch, so the amount of visual and proprioceptive recalibration is expected to be roughly zero on average. In line with previous work, participants recalibrated vision -1.2 ± 5.0 mm and proprioception -2.2 ± 4.9 mm (Fig. 2Cii)[9,10].

Neurophysiology

We found no evidence that baseline neurophysiological measures differed across sessions (Table S1), or that SAI changed from pre-alignment task to post-alignment task timepoint in either session (ANOVA Session x Timepoint: $F_{1,21} = 1.08$, $p = 0.31$; Session: $F_{1,21} = 3.70$, $p = 0.068$; Timepoint: $F_{1,21} = 2.29$, $p = 0.15$) (Fig. 2D). We also found no change over time in unconditioned motor evoked potential (MEP) amplitude (Session x Timepoint: $F_{1,21} = 0.31$, $p = 0.58$; Session: $F_{1,21} = 0.08$, $p = 0.78$; Timepoint: $F_{1,21} = 2.72$, $p = 0.11$), indicating that any associations between SAI and recalibration behavior were not confounded by differences in motor cortex excitability.

Two example participants with different magnitudes of proprioceptive recalibration in the cue conflict session are shown in Figure 2. The individual with relatively larger proprioceptive recalibration had a decrease in SAI post-cue conflict (Fig. 2A), whereas the individual with smaller proprioceptive recalibration had an increase in SAI post-cue conflict (Fig. 2B). Consistent with this pattern, multilevel regression model results suggest that change in SAI from before to after the alignment task (post divided by pre) showed modality-specific recalibration associations with the cue conflict, but not the veridical session (Table S2). These associations are illustrated with predictor residual plots (Fig. 2E), which allows us to show the relationship of one predictor variable with the dependent variable, after statistically controlling for the effect of the other predictor[29]. For either modality, recalibration in the positive direction is beneficial in the cue conflict session (helps compensate for the visuo-proprioceptive mismatch).

After controlling for the effect of visual recalibration, greater positive proprioceptive recalibration was associated with greater decrease in SAI (less inhibition post-alignment task) in the cue conflict session ($\beta = 1.80$, $t_{39} = 3.12$, $p = 0.003$), but not the veridical session ($\beta = 0.28$, $t_{39} =$

0.38, p = 0.704) (Fig. 2Ei). After controlling for the effect of proprioceptive recalibration, change in SAI was not significantly associated with visual recalibration (cue conflict session: β = -0.29, t_{39} = -1.00, p = 0.324; veridical session: β = -0.99, t_{39} = -1.37, p = 0.179; Fig. 2Eii).

In the veridical session, SAI at baseline was negatively correlated with proprioceptive variance (r = -0.45, p = 0.034). Baseline SAI was not significantly correlated with visual variance (r = -0.11, p = 0.64) or with participants' weighting of vision vs. proprioception on bimodal trials (r = 0.18, p = 0.42). In the cue conflict session, SAI at baseline was not significantly correlated with proprioceptive recalibration (r = -0.19, p = 0.40).

Experiment 2

Veridical blocks

Three groups of 27 participants performed a block of V, P, and veridical VP trials before and after cTBS was delivered over their target hand representation in S1, M1, or sham (Fig. 1E). We computed 2D variance of participants' estimation endpoints on unimodal V and P trials in each veridical block to assess whether visual or proprioceptive variance changed after cTBS (Fig. 3Ai-ii). Proprioceptive variance was similar across groups before cTBS (M1: 56.1 ± 16.6; S1: 53.8 ± 12.7; Sham: 60.5 ± 14.4 mm^2) (mean ± 95% CI). Proprioceptive variance changed differently across groups post cTBS relative to pre (ANOVA Group x Timepoint: $F_{2,78}$ = 3.53, p = 0.034). There was no main effect of group or timepoint (p > 0.5). The interaction was driven by an increase in proprioceptive target estimation variance following S1 cTBS (p=0.023), with no change observed following M1 or sham cTBS (p = 0.88, p = 0.16, respectively) (Figure 3Bi). Visual variance was similar across groups before cTBS (M1: 72.2 ± 17.0; S1: 91.6 ± 30.7; Sham: 68.5 ± 28.9 mm^2) (mean ± 95% CI). cTBS had no impact on visual target estimation variance regardless of group (Group x Timepoint: $F_{2,78}$ = 1.60, p = 0.21; Timepoint: $F_{1,78}$ = 0.12, p = 0.7; Group: $F_{2,78}$ = 0.45, p = 0.6) (Figure 3Bii).

We also computed an estimate of how much people were relying on vision vs. proprioception when both were available (weighting), taking advantage of subjects' naturally different spatial biases when estimating V, P, and VP targets[30,31], even with no cue conflict[32]. As computed, this parameter ranges from 0 (only proprioception) to 1 (only vision), with 0.5 indicating equal reliance on vision and proprioception. Weighting was similar across groups before cTBS, with values in line with past work (M1: 0.39 ± 0.07; S1: 0.46 ± 0.09; Sham: 0.41 ± 0.09) (mean ± 95% CI). cTBS had no impact on weighting regardless of group (Group x Timepoint: $F_{2,76}$ = 1.60, p = 0.21; Timepoint: $F_{1,76}$ = 0.12, p = 0.7; Group: $F_{2,76}$ = 0.45, p = 0.6).

Cue conflict block

Visual recalibration was 36.8 ± 7.2 mm for M1, 38.8 ± 7.7 mm for S1, and 32.7 ± 8.4 mm for Sham (mean ± 95% CI). Proprioceptive recalibration was 6.5 ± 6.0 cm for M1, 18.1 ± 7.0 cm for S1, and 9.6 ± 4.5 cm for Sham (Fig. 4A-B). Proprioceptive and visual recalibration were negatively associated for all groups; individuals with larger proprioceptive recalibration had smaller visual recalibration and vice versa (M1: r = -0.57, p = 0.002, S1: r = -0.65, p < 0.001, Sham: r = -0.40, p = 0.04) (Figure 4C).

While visual recalibration was similar across groups ($F_{2,78}$=0.68, p=0.51, η_P^2 = 0.017) (Figure 4Bi), the magnitude of proprioceptive recalibration (Figure 4Bii) and total recalibration (Figure 4Biii) differed across groups ($F_{2,78}$=4.35, p=0.016, η_P^2 = 0.100; $F_{2,78}$=6.18, p=0.003, η_P^2 = 0.137). Proprioceptive recalibration was larger following S1 cTBS relative to M1 cTBS (p=0.015) and tended to be larger relative to Sham, but did not reach statistical significance (p=0.09). In contrast, proprioceptive recalibration was similar between M1 and Sham (p=0.83). Total

recalibration was larger in S1 cTBS compared to M1 or Sham (p=0.012, p=0.006, respectively). However, there was no difference in total recalibration between M1 and Sham (p=0.97).

Subjective ratings and tactile sensitivity

Subjective ratings of pain, sleep quality, attention, and fatigue were similar across groups, as was baseline neurophysiology (Table S3).

An adapted grating orientation test (GOT) was used as a rough estimate of tactile sensitivity in the target index finger before and after cTBS. Immediately after cTBS, the M1 and S1 groups showed a change in GOT threshold of -0.04 ± 0.26 and 0.12 ± 0.27, respectively (mean ± 95% CI). The sham group change in GOT threshold was 0.004 ± 0.24. Change in GOT after cTBS did not differ significantly across groups (χ^2 = 0.33, p = 0.85). Bayes Factor was calculated as 0.148, denoting substantial evidence for equivalence among the groups. This is not consistent with S1 cTBS affecting tactile sensitivity differently than the other interventions.

DISCUSSION

We began with two questions: (1) Does S1 convey hand representation updates to the motor system? (2) Is this involvement multisensory or proprioception-specific? Experiment 1 showed that SAI, a measure of somatosensory-motor integration, changed with proprioceptive, but not visual, recalibration. Experiment 2 found that modulating S1, but not M1, with cTBS increased proprioceptive variance and recalibration, without affecting visual responses. These findings suggest S1 specifically conveys proprioceptive hand representation updates to M1, indicating its role is upstream of multisensory integration (Fig. 1A orange arrow).

Plasticity in S1 projections to M1 reflects proprioceptive recalibration

In Experiment 1, changes in SAI were associated with proprioceptive recalibration in the cue conflict session but not the veridical session. We previously found that individuals who recalibrated proprioception more had larger decreases in M1 excitability, while individual who recalibrated vision more had larger increases in M1 excitability[9,33]. Since the magnitude of SAI is proportional to the magnitude of somatosensory afference to S1[34], decreased SAI likely reflects decreased S1 excitability, which may have driven the previously observed decreases in M1 excitability in individuals who recalibrated proprioception to a greater extent[9,10]. In contrast, the lack of association between SAI changes and visual recalibration suggests that changes in M1 excitability that we previously associated with visual recalibration are likely mediated by areas outside of S1, such as multisensory posterior parietal areas[22,24].

Decreased somatosensory projections to motor cortex may reflect somatosensory gating to help resolve a multisensory conflict. Indeed, decreased SAI and decreased M1 excitability have also been reported after the rubber hand illusion (RHI), another multisensory cue conflict paradigm[19]. Contrary to the RHI, we found no average difference in SAI after the visuo-proprioceptive cue mismatch relative to veridical session. Similarly, the lack of between-session differences in SAI is consistent with the lack of between-session differences in M1 excitability in our visuo-proprioceptive paradigm[9], unlike the RHI which has been shown to modulate M1 excitability. While our visuo-proprioceptive task and RHI both involve a multisensory conflict, there are several differences between the two paradigms that may explain the discrepant neurophysiological changes. The RHI involves inducing a visual-proprioceptive conflict by synchronous stroking of a seen fake arm and felt real arm, which requires additional mechanisms of cognition and body ownership for resolving the multisensory conflict. In contrast,

participants are mostly unaware of the visuo-proprioceptive conflict in the present study[35], and there is extensive variability in how individuals compensate for the multisensory cue conflict[11,15,36,37].

Besides using SAI to explore plasticity in somatosensory projections to M1 in response to a visuo-proprioceptive cue conflict, baseline SAI may have functional relevance that predicts how individuals respond during the visuo-proprioceptive task. We found that baseline SAI was associated with proprioceptive variance, but not visual variance, weighting, or recalibration, suggesting that baseline SAI may reflect a more low-level proprioceptive computation rather than a visual computation or those involved in multisensory integration during a cue mismatch. The lack of association between baseline SAI and recalibration is similar to that observed with the RHI[19]. Instead, baseline long latency afferent inhibition was associated with the strength of the illusion, suggesting that processing in other areas like premotor and parietal cortices[26] may be important in understanding mechanisms of multisensory integration.

S1 activity is important for proprioceptive variance and recalibration

If previously reported modality-specific associations between recalibration and M1 excitability[9,10] were driven by somatosensory projections to M1, then one would predict dissociable effects of M1 and S1 neuromodulation on visuo-proprioceptive recalibration. To test this, in Experiment 2 we delivered cTBS over M1 or S1, in comparison to sham stimulation, and quantified changes in veridical task performance and on recalibration in response to a cue conflict. S1, but not M1, cTBS affected proprioceptive variance and proprioceptive recalibration, supporting the role of S1 in proprioceptive processing for guiding action.

Multisensory processes such as weighting and integrating visual and proprioceptive cues may rely on higher-order cortical mechanisms, as neither S1 nor M1 cTBS affected weighting of vision vs. proprioception. The finding that S1 cTBS increased proprioceptive variance without a corresponding decrease in proprioceptive weighting suggests that the relationship between variance and weighting is complex. Proprioceptive variance may reflect a more low-level parameter of proprioceptive processing in S1, while weighting may reflect a high-level multisensory phenomenon that relies on additional circuits outside of S1 such as parietal[14,24,38] or prefrontal cortices[39,40], or the cerebellum[41]. It is interesting to note that while S1 cTBS increased proprioceptive recalibration, it did not affect the inverse relationship between proprioceptive and visual recalibration[2,12–14]. This is consistent with S1's role in proprioceptive recalibration occurring upstream of other multisensory computations that mediate this relationship, such as posterior parietal cortex. In other words, disrupting S1 did not evidently disrupt the coordination of the visual vs. proprioception relationship.

Integrating proprioceptive signals with visual cues about the hand likely involves additional processing time compared to proprioceptive processing alone, due to the additional circuits involved. The neural bases of visuo-proprioceptive recalibration and associated multisensory processes in real life behavior are poorly understood, but may involve interactions among a distributed system of regions such as S1, visual cortex, and multisensory regions of PPC[19–24]. Even theoretically "unisensory" areas such as S1 are involved in cross-sensory interactions[42], and our results do not rule out the idea of S1 being involved in, or having access to, integrated multisensory information about the hand. However, having S1 convey updates about hand representation to M1 that are purely proprioceptive likely has timing advantages, if the motor system receives information that has not been slowed down by additional multisensory processing.

The increase in proprioceptive variance and recalibration with S1 cTBS raises the question of whether the effect was mediated by changes in tactile function, as these proprioceptive estimates required participants to feel a smooth or rough marker. Contrary to prior work, we found no effect of S1 cTBS on the grating orientation test (GOT), suggesting that S1 cTBS effects on proprioceptive perception were not confounded by decreased tactile function. Given that S1 processes tactile information and prior reports of S1 cTBS impairing tactile perception[43–45], at first glance, the null results on GOT may be surprising. However, prior reports were in relatively small sample sizes (n=10-15) and assessed tactile perception using other methods and at different time points. The effects of cTBS are known to be transient, with peak effects occurring at different time scales[28]. For instance, Rai et al. found that cTBS affected temporal discrimination thresholds from 3-6 min and 15-18 min but not in between. It is possible that GOT would have been altered had we examined multiple time points post-cTBS, or it could be that the abbreviated GOT method used here was not sensitive enough to detect small changes. Importantly, the effects of S1 and M1 cTBS were dissociable on a multisensory perceptual task that guided action, the main focus of this study.

Motor system considerations

Proprioception plays an integral role in motor control, and M1, the cortical region most associated with movement execution, is closely interconnected with S1, which processes proprioception. The neural basis of these reciprocal connections has been supported behaviorally; a visuo-proprioceptive cue conflict in the absence of motor adaptation not only affects perception, but also subsequent reaching movements, suggesting a common sensorimotor map for perception and action in this paradigm[11]. In other words, any changes in perceived hand position need to be considered when planning movements in order to maintain accuracy, which presumably reflects a change in S1, M1, or both. It is therefore interesting to note that SAI changed in association with proprioceptive recalibration, and S1 but not M1 cTBS disrupted proprioceptive recalibration; this is consistent with the idea that motor effects of proprioceptive recalibration may be mediated by the S1-to-M1 pathway, although not directly controlled by M1 itself.

Given that S1 activity and SAI changes with motor planning[46] and skill learning[47], it is important to consider whether our findings may reflect motor processing rather than proprioceptive recalibration. Proprioceptive recalibration is often studied in the context of visuomotor adaptation, a form of motor learning where a cursor is rotated from the hand's true trajectory in a target-directed reaching task, prompting participants to adjust their motor commands to compensate for the perturbation. This results in two potential drivers of proprioceptive recalibration: sensory prediction errors and, the focus of the present study, visuo-proprioceptive cue conflict[1]. Visuomotor adaptation is unlikely in our study, as participants received no online or endpoint feedback about their movements. While it is possible that seeing an offset visual cue after placing the target finger on an unseen tactile marker could be interpreted as a sensory prediction error, this is unlikely since (1) the tactile marker itself was the explicit movement goal, and (2) participants had low certainty about the visuo-proprioceptive offset[35].

Our results align with motor learning research that suggests S1 and M1 play distinct roles in motor adaptation and retention[48,49]. Suppressing S1, but not M1, has been shown to impair adaptation without affecting movement kinematics, indicating S1's specific role in learning mechanisms[48]. S1 is thought to contribute to the encoding and retention of learned movements[48–50], motor learning by observation[51,52], and changes in proprioception accompanying motor learning[17]. If what is learned in such tasks is partly an updating of the hand representation, our findings could clarify S1's contribution to learning. Our findings that S1 cTBS affected proprioceptive variance and recalibration are consistent with the idea that previously

reported effects of S1 on motor adaptation may be related to changes in limb representation that then interacted with motor learning.

Conclusions

Representation of the hand is critical for accurate control of movement, and our results suggest S1 plays a key role in updating the motor system about changes in this representation. When hand representation is modified via recalibration in response to a visuo-proprioceptive cue conflict, the motor system receives updates directly from S1 that are proprioceptive, having not yet been integrated with visual cues through interaction with posterior parietal regions. These findings add to our understanding of the interaction of multisensory body representation with control of movement.

METHODS

Participants

A total of 103 self-reported right-handed healthy young adults participated in the study. All participants had normal or corrected-to-normal vision, and no contraindications to TMS [53]. Procedures were approved by the Indiana University Institutional Review Board. All participants provided written informed consent before participating in the study.

Perceptual alignment task general methods

The two experiments used variations of the same behavioral task to examine participants' perceived hand position using visual, proprioceptive, or bimodal cues. The apparatus, targets, and trial sequence shared by both experiments are outlined here. In addition, participants in both experiments were asked to rate their level of attention, fatigue, and pain from TMS at the conclusion of each session to evaluate whether different sessions or groups had similar subjective experiences. Details of the session and trial block design, which differ between experiments, are explained in their respective sections.

Apparatus. Participants were seated in front of a custom 2-D virtual reality apparatus with a two-sided touchscreen and a mirror positioned at eye level (Fig. 1A). The touchscreen was positioned beneath the mirror such that visual information appeared in the plane of the touchscreen. A fabric drape attached to the apparatus was fastened around their neck, preventing vision of their limbs or surrounding environment. The participants always kept their right hand above the touchscreen and their left hand below the touchscreen.

Target types. Participants were asked to use their unseen right index fingertip (indicator finger) to indicate the position of one of three target types (Fig. 1B): a visual only target (V), a proprioceptive only target (P), and a visuo-proprioceptive target (VP). For the V target, participants were asked to indicate their perceived position of a projected visual white square (1 cm). For the P target, participants were asked to indicate their perceived position of their left index fingertip, which was placed on one of two tactile markers below the touchscreen. For the VP target, participants were asked to indicate their perceived position of the white box projected on top of their left index fingertip. All subjects were told explicitly that the white box would always be right on top of their target fingertip on VP target trials. For V target trials, participants rested their left hand in their lap.

Single trial procedure. Each trial began with the participant placing their indicator fingertip in a yellow square that served as the starting position. A blue cursor representing their indicator fingertip was initially shown to help position their fingertip in the starting square, which then disappeared to avoid any feedback cues. Next, participants were instructed where to place their target hand (in lap for V targets, on one of the tactile markers for P and VP targets). When both hands were correctly positioned, participants heard a go signal and, at their own pace, lifted their indicator finger off the touchscreen and placed it down where they perceived the target to be. There was no speed requirement or knowledge of performance or results. Adjustments were permitted, and the trial terminated after the indicator fingertip remained still on the touchscreen for 2 seconds. The x-y coordinates of the indicator finger endpoint served as a proxy for where the participant perceived the target to be.

The starting position was presented at one of five locations. The tactile marker (1 cm) used in the P and VP targets was one of two positions (3 cm apart), resulting in 10 combinations. Throughout each trial, participants were also instructed to focus on a red cross. The red cross was positioned at random coordinates within 10cm of the target to minimize any strategies tied to different gaze directions.

Experiment 1 design

Participants

Twenty-two adults (12 male, 21.6 ± 3.68 years, mean ± SD) participated in Experiment 1. Participants completed 2 sessions each. In the Cue conflict session, a 70 mm mismatch between visual and proprioceptive cues about the left index fingertip was gradually imposed. In the Veridical session, visual and proprioceptive information remained veridical. The sessions were separated by at least 5 days, with order randomized, to minimize carry-over effects. On average there were 16 ± 14 days (mean ± SD) between sessions. TMS measurements were performed pre- and post- perceptual alignment task in each session (Fig. 1C).

Behavior

Perceptual alignment task blocks. There were two blocks of trials in each session. The first block was identical between sessions and consisted of a baseline block with 15 V, 15 P, and 10 VP trials that were pseudorandomized. The second block comprised 84 trials (42 VP, 21 V, and 21 P, alternating order). In the Cue conflict session, the white box was gradually shifted forward from the target index fingertip on VP trials. The offset increased by 1.67 mm per VP trial. By the end of the block, the visual cue was displaced 70 mm forward of the proprioceptive cue, in the sagittal plane. Participants rarely become aware of this manipulation [35]. In the Veridical session, there was no offset and VP targets remained veridical throughout.

Visual and proprioceptive recalibration. Figure 2 shows indicator finger estimates relative to the true positions of V and P targets for two exemplar participants across trials in the cue conflict block. Similar to past work, the magnitude of visual and proprioceptive recalibration was calculated using indicator fingertip endpoints of the V and P targets, respectively, by the average y-estimate of the last four trials relative to the average of the first four trials of the cue conflict block.

$$(1)\ \Delta\hat{Y}_P = \text{last 4 P endpoints} - \text{first 4 P endpoints}$$

$$(2)\ \Delta\hat{Y}_V = 70 - (\text{last 4 V endpoints} - \text{first 4 V endpoints})$$

Recalibration was expressed relative to the true y-position of the target (70 mm for V targets, 0 mm for P targets at the end of the block). Therefore, for both modalities, a positive recalibration value indicates recalibration in the expected direction (i.e., undershooting for V targets and overshooting for P targets).

Weighting. Weighting was calculated using the 2D estimated indicator fingertip position in VP targets relative to the unimodal targets during the first block of each session (veridical targets). For instance, a person that relies more on vision would be expected to have their mean estimate of VP targets closer to the mean estimate of V targets compared to P targets. Based on formula (3) a weighting value greater than 0.5 indicates greater reliance on vision whereas a value less than 0.5 indicates greater reliance on proprioception.

$$(3)\ Wv = \frac{\hat{Y}P - \hat{Y}VP}{(\hat{Y}P - \hat{Y}VP) + (\hat{Y}V - \hat{Y}VP)}$$

Consistent with previous work [54], we computed a separate Wv for each VP trial, comparing the VP trial endpoint with the 4 closest V and 4 closest P trials in the sequence. If the V and P trial endpoints were too closely overlapping (less than 0.5 SD apart), no Wv was computed for that VP trial.

Visual and proprioceptive endpoint variance. Variance was computed for the 2D indicator finger endpoints on unimodal V and P trials during the first block of each session (veridical). This was accomplished by converting each endpoint to a vector relative to the mean [x,y] coordinates of the cluster of endpoints. Variance was then computed for the vector magnitudes.

Neurophysiology

M1 stimulation. TMS was applied over the M1 hand representation in the right hemisphere, to probe neurophysiology pertaining to the target hand that experiences visuo-proprioceptive misalignment. Single monophasic TMS pulses were delivered using a Magstim 200^2 stimulator (Magstim Company LTD, UK) with a 70 mm figure-of-eight coil. The coil was held tangentially to the scalp with the handle 45 degrees postero-lateral from the midline to elicit posterior-to-anterior current in the right M1. The hotspot was identified by the scalp position that elicited the largest and most consistent response in the left first dorsal interosseous (FDI) muscle. The location and trajectory were registered in BrainSight neuronavigation system (Rogue Research, Montreal, Canada) for consistent coil positioning. Surface electromyography (EMG) was recorded from the left FDI muscle and abductor pollicis brevis (APB) muscle using a belly-tendon montage and a ground electrode over the ulnar styloid process. EMG recordings were amplified (AMT-8; Bortec Biomedical), band-pass filtered (10-1000 Hz), sampled at 5000 Hz, and recorded using Signal software (Cambridge Electronic Design Ltd, UK). At the beginning of each session, we found resting motor threshold, defined as the minimum intensity that elicits a twitch >= 50 μV in at least 10 out of 20 trials. We then found the stimulus intensity that elicited a twitch of 1 mV on average over 10 trials (SI_1mV).

SAI procedure. SAI was assessed before and after the perceptual alignment task in each session (Figure 1C). To elicit SAI, a TMS pulse at SI_1mV was delivered 22 msec after an electrical stimulus at the left median nerve (Figure 1D). Electrical stimuli were delivered with a Grass Instruments S88 stimulator (Astro-Med, West Warwick, RI) with an in-series stimulus isolation unit (SIU-5) and a constant-current unit (CCU-1) (square wave pulse, 0.2-ms duration, cathode proximal). The intensity was set based on the lowest intensity that elicited a slight

thumb twitch and consistent APB M-wave amplitude. The M-wave amplitude was monitored online and kept constant throughout the session [47,55].

20 conditioned pulses (median nerve stimulus + TMS) and 20 unconditioned pulses (TMS alone) were delivered in a random order, with an interstimulus interval of ~ 5 sec, both pre- and post-alignment task. We adjusted the TMS intensity post-alignment task, if needed, to elicit the same size unconditioned MEP response of ~1 mV. Therefore, any changes in SAI reflect changes in somatosensory projections to M1 rather than changes in M1 excitability alone.

SAI magnitude was expressed as a percentage of the average conditioned MEP peak-to-peak amplitude relative to the unconditioned peak-to-peak amplitude (Fig. 1D). Therefore, lower numbers of SAI within a time point (pre or post) indicate greater inhibition by the somatosensory afferent volley. We also calculated the change in SAI (post/pre) for each session. Therefore, smaller delta SAI indicates greater inhibition post relative to pre, while larger delta SAI values indicate less SAI post relative to pre.

Statistical Analysis

Baseline (pre-alignment task) neurophysiology was compared between the veridical and cue conflict sessions using paired t-tests for RMT, SI_1mV, and SAI. To test whether the alignment task influenced SAI differently across sessions, we performed a Session (cue conflict vs. veridical) x Time (pre vs. post) repeated measures ANOVA.

Multi-level hierarchical modeling was used to assess whether an individual's magnitude of proprioceptive or visual recalibration was related to their change in SAI. We first examined a full model that included predictor variables for the interaction between Session and Modality, and their main effects. However, the full model had variance inflation factor (VIF) values that suggested the presence of multicollinearity (VIF value of 6). Therefore, we computed a reduced model that only had the interaction term of Session and Modality, which had VIF values that ranged between 1.04-1.05. Since the reduced model had less multi-collinearity and was not statistically different from the full model (Chi-squared test: $p = 0.7$), the reduced model was used for analysis. Finally, we computed Pearson's correlation coefficients between baseline SAI (pre-alignment task) and 2D Wv in the veridical session, and between baseline SAI and P variance and V variance in the veridical session. The latter were approximated by subtracting ½ P variance from each estimate to remove the proprioceptive variance contributed by the indicator hand [54]. We also computed the correlation between baseline SAI and proprioceptive recalibration in the cue conflict session. Alpha was set at 0.05.

Experiment 2 design

Participants

81 individuals (38 male, 21.68 ± 4.32 years, mean ± SD) participated in Experiment 2. Participants were assigned to one of three stimulation groups: S1, M1, or Sham (N=27 per group). Group assignment was random, following a block randomization table. Group assignment was revealed to the experimenters only when it was time to deliver cTBS, after task training and baseline measures were complete. S1 had 12 male participants (21.44 ± 3.94 years, mean ± SD), M1 had 13 male participants (21.3 ± 4.58 years, mean ± SD), and the Sham group had 13 male participants (22.3 ± 4.28 years, mean ± SD). Sample size was determined *a priori* with a power analysis on pilot data in earlier participants who received S1, M1, or no cTBS (N=8,13,27) with the same session design. We determined a total sample size of 81 would be

needed to have 80% power to detect an effect size f of 0.404 with α of 0.05 with a 1-way ANOVA on 3 groups. The effect size was determined for proprioceptive recalibration in the pilot subjects.

Continuous theta burst stimulation (cTBS) was delivered in between two veridical perceptual alignment blocks (Fig. 1E) to assess any effect of cTBS on baseline behavior. This was followed by a cue conflict block.

Behavior

The apparatus, target types, and task instructions were identical to that of Experiment 1. Each participant performed three blocks of perceptual alignment task trials: Veridical 1, veridical 2, and a cue conflict block, with cTBS delivered after Veridical 1 (Fig. 1E). Each veridical block consisted of 40 trials in repeating order (15 V, 15 P, 10 VP). After the second veridical block, participants completed the same cue conflict block used in Experiment 1. Recalibration, weighting, and endpoint variance were computed as in Experiment 1.

In order to test whether cTBS over S1 had any effect on tactile sensitivity that could interfere with participants' ability to place their target finger on the tactile markers, we performed an abbreviated grating orientation test (GOT) before and after cTBS for all participants. I.e., the first GOT was performed after Veridical 1 and before cTBS, and the second GOT was performed after cTBS and before Veridical 2. We used J.V.P. DOMES for cutaneous spatial resolution measurements. The set consists of domes of 35, 0.5, 0.75, 1.0, 1.2, 1.5, 2, 3, 4, 5 mm grating width. For the assessment, participants had their eyes closed and their left hand resting on the table with the palm facing up. They were tested on their left index fingertip palmar surface. The domes were attached to a force gauge to maintain uniformity in the pressure (0.65N – 0.95N) applied while testing based on an earlier study [56]. The testing started with a 3mm grating width and a random order of orientation (Vertical or Horizontal) was used. No feedback was provided to the participant. If the subject correctly reported six orientations consecutively then a grating of smaller width was used next. If they reported one or more orientations incorrectly then a larger grating was used. This continued until they were unable to report the orientation correctly. The smallest grating width that participants reported correctly was noted as their tactile sensitivity threshold.

Transcranial Magnetic Stimulation

TMS was delivered using a using a Magstim Super Rapid Plus stimulator with a D70^2 70-mm figure-of-eight coil (Magstim Company LTD, United Kingdom). Single pulses were first delivered over right M1 to find the resting motor threshold of the left FDI muscle using identical methods as Experiment 1.

cTBS was delivered over the right M1 or right S1 to modulate the hemisphere that pertains to the left hand (target hand), which experiences the visuo-proprioceptive cue conflict. For the M1 group, cTBS was delivered over the FDI motor hotspot. The S1 stimulation target was defined 2 cm lateral and 1 cm posterior to the M1 target [57–59]. The sham target was the same as the M1 target, but consisted of an unplugged coil placed on the scalp. A second coil, held behind the participant's head out of their view, was plugged in so that the sounds of the cTBS train would be audible.

cTBS was delivered at 70% of RMT [59–61], consisting of triplets of 50 Hz repeated at 5 Hz for 40 seconds [28]. Participants sat quietly for five minutes before and after cTBS to avoid any potential reversal of the after-effects [62].

Statistical Analysis

To determine whether cTBS affected endpoint variance on unimodal P and V targets, we ran a two-way mixed model ANOVA (between-subjects factor group and within-subjects factor block) on 2D endpoint variance for each modality in the two veridical blocks. We analyzed weighting of vision vs. proprioception the same way (Wv). Two participants had closely overlapping distributions of P and V endpoints in one of the veridical blocks and insufficient Wv were calculated to form an estimate for the whole block. These participants were excluded from the Wv analysis.

We tested for group effects on P, V, and total recalibration using separate 1-way ANOVAs, which were followed by Tukey's HSD post-hoc comparisons upon significant result. GOT thresholds pre-cTBS were subtracted from post-cTBS and these changes were compared across groups using the Kruskal-Wallis test. A was defined as 0.05 for all hypothesis tests.

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Figure. 1. Experimental design. A. Multisensory hand representation arises from both visual (V) and proprioceptive (P) cues, leading to recalibration (red and blue arrows) when the cues are in conflict. Such updates in hand representation must be transmitted to frontal motor regions (M1) to keep movement accurate. We hypothesize this process to involve S1, either conveying proprioceptive updates directly to M1 (orange arrow) or conveying multisensory updates to M1 after the proprioceptive information has been integrated with visual information, e.g. in PPC (purple dashed arrow). Expt. 1 assesses the effect of a change in hand representation (recalibration) on the S1-M1 pathway, measured with short latency afferent inhibition (SAI). Expt. 2 modulates activity in S1, M1, or sham with continuous theta burst transcranial magnetic stimulation (cTBS), assessing the impact on hand representation. **B.** Visuo-proprioceptive alignment task. Participants viewed task display in a horizontal mirror (middle layer), making images appear to be in the plane of the touchscreen (bottom layer). Participants used their right index finger on the touchscreen to indicate perceived target positions related to the left (target) index finger below the touchscreen. The three target types, presented in pseudorandom order, were indicated by both visual and proprioceptive cues (VP target), proprioceptive cues only (P target), or visual cues only (V target). Target fingertip on a tactile marker beneath the touchscreen provided proprioceptive cues, and a white box provided visual cues. Not to scale. Dashed lines not visible to subjects. No performance feedback or direct vision of hands. **C.** Experiment 1 design. All participants completed both sessions in random order. SAI was assessed immediately before and after the behavioral portion of each session. **i.** Cue conflict task consisted of V, P, and VP trials, with the visual cue gradually shifted forward relative to the proprioceptive cue on VP trials. **ii.** The Veridical session included the same number of V, P, and VP trials, with cues displayed veridically throughout. **D.** In Expt. 1, SAI was assessed by delivering an electrical stimulus to the left median nerve 22ms prior to a suprathreshold TMS

pulse over right M1. **i.** Schematic unconditioned motor evoked potential (MEP). **ii.** Schematic of MEP conditioned by median nerve stimulus, illustrating inhibition of motor output by somatosensory input. **E.** Experiment 2 design. After a baseline block of V, P, and veridical VP trials, participants received M1, S1, or sham cTBS according to random group assignment. After a second block of veridical trials, participants performed a cue conflict block in which the visual cue gradually shifted forward relative to the proprioceptive cue.

Figure 2. A-B. Expt. 1 example participants' performance on P and V targets in the cue conflict block (i) and their corresponding changes in SAI in the cue conflict session (ii). Undershooting the visual target on V trials represents visual recalibration (blue arrow) and overshooting the proprioceptive target on P trials represents proprioceptive recalibration (red arrow) (i). **A.** Participant with relatively high proprioceptive recalibration (i) demonstrated a decrease in SAI (larger ratio of conditioned relative to unconditioned MEP) post -task relative to pre (ii). **B.** Participant with relatively larger visual recalibration demonstrated an increase in SAI (smaller ratio of conditioned relative to unconditioned MEP) post-task compared to pre. **C.** Group means on unimodal P and V trials (red and blue) during the cue conflict session (i) and veridical session (ii). Shaded regions represent SEM. iii. In the cue conflict session, individuals who recalibrated proprioception to a greater extent recalibrated vision to a lesser extent ($r = -0.52$, $p = 0.013$). **D.** Expt. 1 group mean SAI pre- and post-alignment task for the cue conflict and veridical sessions. SAI was expressed as the conditioned MEP amplitude relative to the unconditioned MEP amplitude (test stimulus alone). Values < 100 indicate inhibition, with smaller values denoting greater inhibition. Error bars are standard error of the mean. **E.i-ii**: Change in SAI (post divided by pre) plotted against predictor residuals, with lines of best fit and corresponding 95% CIs. In the cue conflict session, recalibration of either modality in the positive direction is beneficial (helps compensate for the visuo-proprioceptive mismatch). **i:** After statistically controlling for the effect of visual recalibration, large proprioceptive recalibration in the cue conflict session (green) was significantly associated with reduced SAI (disinhibition). There were no associations between proprioceptive recalibration in the veridical session (yellow) and SAI. **ii:** After controlling for the effect of proprioceptive recalibration, there were no significant associations between visual recalibration and change in SAI for either session.

Figure. 3. Experiment 2 individual (A) and group (B) unimodal target estimation variance before and after cTBS. **A i-iii.** Example participants' indicator finger endpoints in 2D on P (red) and V (blue) unimodal trials before and after cTBS (veridical 1 and 2) for M1, S1, and sham groups, respectively. Data plotted with target always at the origin. Participant was seated in the direction of the negative y-axis. **B.** Group means and standard errors on unimodal P (i) and V trials (ii) before and after cTBS. S1 cTBS increased proprioceptive variance relative to sham cTBS. Visual variance was not different after cTBS for any group.

Figure. 4. Experiment 2 group behavior during the cue conflict block. **A.i-iii.** Mean performance on P and V targets in the cue conflict block after M1, S1, and Sham cTBS, respectively. Undershooting the visual target on V trials represents visual recalibration (blue arrow) and overshooting the proprioceptive target on P trials represents proprioceptive recalibration (red arrow). S1 participants recalibrated proprioception noticeably more than the other groups. **B**. Comparing recalibration across groups. **i.** Visual recalibration did not differ significantly across groups **ii.** Proprioceptive recalibration was larger in the S1 group compared to the M1 group. **iii.** Total recalibration for S1 was greater than M1 or Sham groups. **C. i-iii**. Across all groups, proprioceptive recalibration was negatively associated with visual recalibration.

SUPPLEMENTARY MATERIAL

Table S1. Experiment 1 summary of neurophysiological measures recorded at baseline in each session and subjective ratings recorded at the end of each session. None differed across sessions (all p > 0.2).

	Cue Conflict Session (mean ± 95% CI)	**Veridical Session** (mean ± 95% CI)
RMT (% MSO)	38.5 ± 2.5%	38.5 ± 3.0%
SI_1mV (MEP in mV)	1.0 ± 0.2 mV	1.0 ± 0.1 mV
SAI (% of unconditioned MEP)	58.5 ± 10.4%	50.0 ± 11.3%
Attention rating	7.5 ± 0.4	8.0 ± 0.3
Fatigue rating	4.4 ± 0.7	3.4 ± 0.8
Sleep rating	7.7 ± 0.5	7.4 ± 0.5
Pain rating	2.6 ± 0.8	2.8 ± 0.7

RMT: Resting motor threshold. MSO: Maximum stimulator output. SI_1mV: motor evoked potential (MEP) achieved at a stimulus intensity intended to elicit a 1mV MEP. SAI: Short latency afferent inhibition. All ratings were on a scale from 1-10, reported verbally, with 10 being the best attention and sleep and the worst fatigue and pain.

Table S2. Experiment 1 multilevel regression results for short latency afferent inhibition (SAI), comprising four interaction terms for session type (Veridical or Cue conflict) and recalibration modality (proprioceptive or visual).

Predictors	*β (CI)*	t_{39}	*p*
Fixed parts			
Intercept	105.94 (89.63, 122.25)	13.14	**<0.001**
Veridical session : Proprioceptive recalibration	0.28 (-1.20, 1.75)	0.38	0.704
Cue conflict session : Proprioceptive recalibration	1.80 (0.63, 2.96)	3.12	**0.003**
Veridical session : Visual recalibration	-0.99 (-2.46, 0.47)	-1.37	0.179
Cue conflict session : Visual recalibration	-0.29 (-0.87, 0.30)	-1.00	0.324
NID	22		
Observations	44		

Columns represent percentage of baseline (post divided by pre) in SAI. βs are presented with their 95% CIs. The test statistic (t) is calculated from the parameter estimate divided by SE, and p-values are calculated based on the t-statistic with corresponding degrees of freedom. Boldface identifies statistically significant results.

Table S3. Experiment 2 summary of neurophysiology and subjective ratings across groups.

	M1 (mean ± 95% CI)	**S1** (mean ± 95% CI)	**Sham** (mean ± 95% CI)
RMT (% MSO)	54.6 ± 3.4%	52.2 ± 3.4%	53.2 ± 3.2%
Attention rating	7.39 ± 0.52	7.18 ± 0.50	7.62 ± 0.51
Fatigue rating	4.07 ± 0.78	3.96 ± 0.84	3.53 ± 0.77
Sleep rating	6.78 ± 0.66	7.44 ± 0.47	6.89 ± 0.79
Pain rating	1.82 ± 0.43	1.85 ± 0.49	1.54 ± 0.33

RMT: Resting motor threshold. MSO: Maximum stimulator output. All ratings were on a scale from 1-10, reported verbally, with 10 being the best attention and sleep and the worst fatigue and pain.