

# Modality-specific Changes in Motor Cortex Excitability After Visuo-proprioceptive Realignment

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## Abstract

■ Spatial realignment of visual and proprioceptive estimates of hand position is necessary both to keep the estimates in register over time and to compensate for sensory perturbations. Such realignment affects perceived hand position, which the brain must use to plan hand movements. We would therefore expect visuo-proprioceptive realignment to affect the motor system at some level, but the physiological basis of this interaction is unknown. Here, we asked whether activity in primary motor cortex (M1), a well-known substrate of motor control, shows evidence of change after visuo-proprioceptive realignment. In two sessions each, 32 healthy adults experienced spatially misaligned or veridical visual and proprioceptive information about their static left index finger. Participants indicated perceived finger position with no performance feedback or knowledge of

results. Using TMS over the M1 representation of the misaligned finger, we found no average difference between sessions. However, regression analysis indicated that, in the misaligned session only, proprioceptive realignment was linked with a decrease in M1 activity and visual realignment was linked with an increase in M1 activity. Proprioceptive and visual realignment were inversely related to each other. These results suggest that visuo-proprioceptive realignment does indeed have a physiological impact on the motor system. The lack of a between-session mean difference in M1 activity suggests that the basis of the effect is not the multisensory realignment computation itself, independent of modality. Rather, the changes in M1 are consistent with a modality-specific neural mechanism, such as modulation of somatosensory cortex or dorsal stream visual areas that impact M1. ■

## INTRODUCTION

Human perception is multisensory. For example, the brain can estimate hand position ( $Y$ ) using vision, from an image on the retina ( $\hat{Y}_V$ ), and proprioception, from sensors in the joints and muscles ( $\hat{Y}_P$ ).  $\hat{Y}_V$  and  $\hat{Y}_P$  are likely to differ in both variance and bias because of independent processing (Smeets, van den Dobbelaert, de Grave, van Beers, & Brenner, 2006). In addition, neither perception is constant, being subject to changes in lighting, movement history, and other factors (Proske & Gandevia, 2012; Mon-Williams, Wann, Jenkinson, & Rushton, 1997). The brain is thought to make the best use of available sensory estimates by weighting and combining them to form an integrated estimate  $\hat{Y}_{VP}$  (Ernst & Banks, 2002; Ghahramani, Wolpert, & Jordan, 1997):

$$\hat{Y}_{VP} = W_V \hat{Y}_V + (1 - W_V) \hat{Y}_P \quad (1)$$

where  $W_V$  is the weight of vision versus proprioception ( $W_V > 0.5$  implies greater reliance on vision). Multisensory integration gives us the flexibility to cope with the frequent sensory perturbations we experience. For example, up-weighting proprioception when lighting is low (Mon-Williams et al., 1997) or realigning one or both

sensory estimates when they become spatially misaligned (Sober & Sabes, 2003, 2005; van Beers, Wolpert, & Haggard, 2002; Bedford, 1999; Redding & Wallace, 1988; Baily, 1972; Welch, 1969; Hay & Pick, 1966), as when washing dishes with the hands immersed in water, which refracts light (Figure 1A). Complete compensation for a misalignment is unlikely (Smeets et al., 2006), but in general, both modalities undergo some realignment. The minimum variance model predicts that each modality will realign in proportion to the variance in that sensory input and in inverse proportion to the weighting of that modality (Ernst & Banks, 2002; van Beers et al., 2002; van Beers, Sittig, & Denier van der Gon, 1999; Ghahramani et al., 1997). Thus, a participant who relies more on vision will likely realign proprioception more than vision (Block & Bastian, 2011).

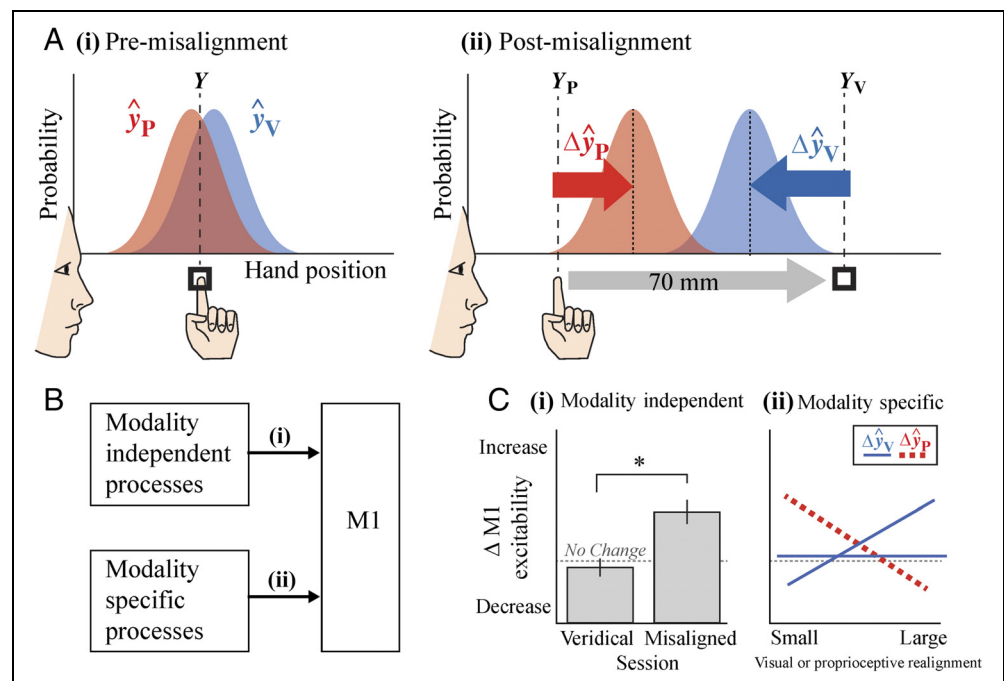
Any change in the brain's estimate of hand position will influence all movements planned with that hand, meaning that multisensory and motor processing are inextricably linked in a functional sense. For basic and clinical fields such as systems neuroscience and motor rehabilitation, as well as applications like brain-machine interface design, it is crucial to understand how multisensory and motor processes interact. For example, recent studies have found that motor adaptation, a process of modifying internal models to correct for movement errors, is associated with proprioceptive realignment, whether proprioception is misaligned from vision (Cressman

& Henriques, 2009, 2015; Mostafa, Kamran-Disfani, Bahari-Kashani, Cressman, & Henriques, 2015; Nourouzpour, Salomonczyk, Cressman, & Henriques, 2015; Henriques & Cressman, 2012) or not (Ostry & Gribble, 2016; Bernardi, Darainy, & Ostry, 2015; Vahdat, Darainy, & Ostry, 2014; Ito, Darainy, Sasaki, & Ostry, 2013; Mattar, Darainy, & Ostry, 2013; Ostry, Darainy, Mattar, Wong, & Gribble, 2010). A number of studies of proprioceptive training or stimulation suggest some effect of perceptual change on the motor system (Ostry & Gribble, 2016), but it is difficult to draw conclusions about multisensory processing if only proprioception is examined. Furthermore, it is difficult to investigate the connection between multisensory integration and the motor system using tasks that involve motor as well as perceptual learning, as the motor learning itself is expected to involve physiological changes in the motor system.

One approach to clarifying the basis of interactions between multisensory and motor processing would be to examine motor system physiology in the context of visuo-proprioceptive realignment, without motor learning. For example, activity in M1, a well-known substrate of motor control and execution (Kakei, Hoffman, & Strick, 1999), may show evidence of change after visuo-proprioceptive realignment, even with no change in motor performance. If so, it would suggest multisensory interactions with the

motor system at the physiological level. Changes in M1 could conceivably reflect the multisensory realignment computation itself, independent of which modality is being realigned (Figure 1B(i)). In that case, we would expect M1 excitability to change after a session in which participants experienced visuo-proprioceptive misalignment, compared with a session of veridical visuo-proprioceptive information (Figure 1C(i)). In addition or alternatively, M1 activity could reflect the specific modality being realigned (Figure 1B(ii)). When faced with a spatial misalignment between vision and proprioception, some participants realign proprioception more and vision less, whereas others do the opposite (Block & Bastian, 2011); thus, it is possible that the magnitude or sign of change in M1 activity could reflect the ratio of proprioceptive versus visual realignment that a participant uses to compensate for the mismatch (Figure 1C(ii)). These outcomes would have different implications for a neurological model of multisensory–motor interaction. Modality-independent changes in M1 activity would suggest plasticity in M1 inputs from multisensory regions, such as areas of posterior parietal cortex (PPC; Block, Bastian, & Celnik, 2013; Lewis & van Essen, 2000; Andersen, Snyder, Bradley, & Xing, 1997; Blatt, Andersen, & Stoner, 1990). Modality-specific changes in M1 activity would suggest plasticity in inputs from areas traditionally considered unisensory, such as

**Figure 1.** Theoretical considerations of visuo-proprioceptive realignment. (A) Visual and proprioceptive estimates ( $\hat{y}_V$ ,  $\hat{y}_P$ ) of true hand position ( $Y$ ), with the participant observing his or her hand from the origin of the  $x$  axis (face). (i) When visual and proprioceptive stimuli (black square and cartoon hand, respectively) are aligned with each other,  $\hat{y}_V$  and  $\hat{y}_P$  are aligned to some degree as well, although not perfectly (Smeets et al., 2006). (ii) After a 70-mm misalignment between visual and proprioceptive stimuli has been imposed,  $\hat{y}_V$  and  $\hat{y}_P$  are each likely to shift in the other's direction by some amount ( $\Delta\hat{y}_V$  and  $\Delta\hat{y}_P$ ). If the participant is seated at the origin of the  $x$  axis (face), we would expect him or her to overestimate  $Y_P$  and underestimate  $Y_V$  when using only proprioception or vision, respectively. (B–C) If a change in multisensory integration, such as visuo-proprioceptive realignment, has a physiological impact on the motor system, we might expect to detect an associated change in M1. If so, this could take two different forms: (i) The realignment computation itself is somehow linked to M1. More realignment, whether in vision or proprioception (modality independent), should result in more change in M1 activity. In this case, we would predict that, on average, M1 activity should change more in the misaligned session than in the veridical session. This would be consistent with realignment-associated changes in a multisensory region in PPC with direct connections to M1. (ii) In addition or alternatively, M1 activity could reflect realignment in specific sensory modalities. M1 activity might change only in relation to proprioceptive realignment and not visual realignment, or vice versa. This would be consistent with changes in areas traditionally considered unisensory (or perhaps interactions between such areas), such as SI, which also has direct connections to M1.



somatosensory cortex (SI; Ostry & Gribble, 2016; Krubitzer & Kaas, 1990) or dorsal stream visual areas.

In this study, we asked whether visuo-proprioceptive realignment ( $\Delta\hat{Y}_P$ ,  $\Delta\hat{Y}_V$ ), triggered by spatial misalignment between the senses (Figure 1A), is associated with changes in M1 activity outside the context of motor adaptation or learning. In contrast with a visuomotor adaptation task, the visuo-proprioceptive misalignment task used here did not include performance feedback or knowledge of results. The absence of information about movement errors precludes the motor adaptive processes we would see in a visuomotor shift or rotation task, for example (Block & Bastian, 2012), allowing us to elicit perceptual rather than motor learning (Bedford, 1999). We used TMS to assess the input/output (I/O) curve for the M1 representation of a left index finger muscle, first dorsal interosseous (FDI), before and after participants experienced visuo-proprioceptive misalignment in their perception of target fingertip position (Block & Bastian, 2011). To control for any motor effects of the behavioral task itself, participants also performed a session with veridically aligned visual and proprioceptive information throughout. Because the index finger of interest performed the same action—touching a stationary tactile marker—in both sessions, any between-session differences in outcome measures can be attributed to factors relating to the misaligned versus veridical visuo-proprioceptive information.

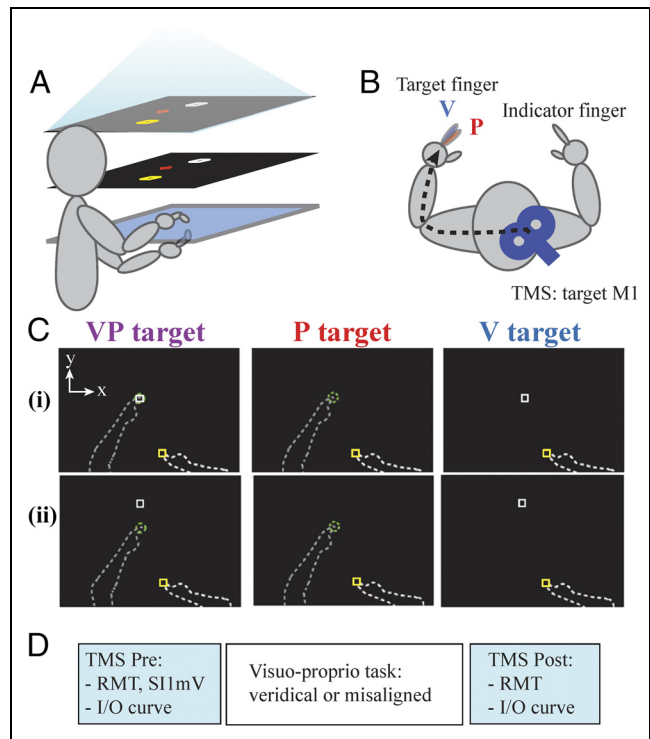
## METHODS

### Participants

Thirty-two participants (20 women) aged 18–36 years participated in the study. All participants reported themselves to be right-handed and neurologically healthy, with normal or corrected-to-normal vision. Each participant gave written informed consent. All procedures were approved by the Indiana University institutional review board. All participants completed both a misaligned session and a veridical session. Sessions were separated by a minimum of 5 days to minimize any carry-over effects. On average, there were  $16 \pm 8$  (mean  $\pm$  standard error [SE]) days between sessions. Session order was counter-balanced across participants so that order could be excluded as a potential confound in any group level differences between sessions.

### Visuo-proprioceptive Perceptual Alignment Task

Participants were seated at a custom 2-D virtual reality apparatus (Figure 2A) with a two-sided touchscreen consisting of two touch overlays (PQLabs) with a 3-mm-thick pane of glass sandwiched between. Overlays use IR beams to detect touch on either side of the glass with  $<0.5$ -mm resolution. The two-sided touchscreen was positioned in the horizontal plane beneath the mirror, where visual feedback appeared. Visuo-proprioceptive



**Figure 2.** Visuo-proprioceptive perceptual alignment task. Not to scale. (A) Participants viewed a virtual reality (reflected rear projection) display where images seen in the mirror (middle layer) appeared to be in the plane of the touchscreens (bottom layer). Drape blocking vision of shoulders and arms not shown for clarity. (B) Measurements with TMS were made over the right motor cortex, which primarily controls the left target finger, which experienced the perceptual misalignment. (C(i)) Participants moved their unseen indicator finger on top of the glass from one of five start positions (yellow box) to targets perceived either proprioceptively (P target: target index fingertip placed on tactile marker beneath glass, green dashed circle), visually (V target: white box in the display), or both (VP target: target finger placed beneath the white box). (ii) In the misaligned session, the white box moved gradually away from the target finger without the participant's awareness, resulting in a 70-mm misalignment. In the control session, VP targets remained veridical. Fixation cross (Block & Bastian, 2011) not shown for clarity. Dashed lines not visible to participant. No performance feedback or knowledge of results was available to the participant. (D) Single-session design. We used TMS to measure M1 excitability in an index finger muscle representation (FDI) before and after participants performed a perceptual alignment task with misaligned or veridical visuo-proprioceptive information about the target index finger.

estimates of hand position were assessed with a bi-manual task, using an “indicator” (right) hand to indicate the participant's perception of the “target” (left) hand's position (Figure 2B and C) when visual (V), proprioceptive (P), or both types of information about the target (VP) were available (Block et al., 2013; Block & Bastian, 2011, 2012; Smeets et al., 2006; van Beers et al., 1999, 2002; van Beers, Sittig, & Denier van der Gon, 1996, 1998). V targets consisted of a 1-cm white square; P targets consisted of the target index fingertip placed on one of two tactile markers on the lower surface of the glass, with no white square; and VP targets were a combination of the

two, with the white square projected directly on top of the target finger except during misalignment. During V target trials, participants were instructed to lower their target hand to rest in their lap. For P and VP trials, the target finger was actively positioned by the participant on the tactile marker to increase the likelihood of a mixture of visual and proprioceptive realignment in the perceptual learning response (Welch & Warren, 1980; Welch, Widawski, Harrington, & Warren, 1979) and to make participants more likely to perceive the visual target as representing their own finger (Balslev, Nielsen, Lund, Law, & Paulson, 2006). Participants were explicitly told that the white square was directly above the target finger on VP trials and that they should “aim for that location.” The indicator hand remained above the glass at all times, and participants indicated their perception by placing the indicator fingertip on the upper surface of the glass over where they felt the target was located.

Because it was a perceptual rather than a motor learning task, participants were told to move at a comfortable speed and not to rush. No direct vision of the hands was possible, and no feedback about performance or knowledge of results was provided. At the beginning of each trial, the participant was aided in positioning his or her indicator finger in the desired start position (a yellow square) by a cursor representing indicator finger position (an 8-mm blue disc). The blue disc was removed as soon as the indicator finger was correctly positioned, to avoid giving the participant feedback about the indicator finger’s movements during the trial. As we have done previously, start positions could appear in any of five positions, and targets could appear in either of two positions, to vary the required movement direction and extent (Block et al., 2013; Block & Bastian, 2011, 2012). In addition, participants were asked to fixate a red cross throughout each trial, so that we could attribute changes in performance on V targets to changes in visual perception, as opposed to changes in eye position. The red cross could appear anywhere within an invisible 10-cm zone surrounding the target. Participants have occasionally been confused about the task instructions and consciously attempted to point to the red cross rather than the target, especially on P targets where no other visual information is presented. Although gaze direction is known to have some effect on reaching performance (Henriques, Medendorp, Gielen, & Crawford, 2003), we wanted to check that participants were not pointing to the red cross on purpose. To assess this, after each session, we calculated a regression between red cross and indicator finger end points on P targets. For the  $x$  dimension, the  $R^2$  in this study was  $.059 \pm .013$  (mean  $\pm$  SE) in the misaligned session and  $.056 \pm .011$  in the veridical session. For the  $y$  dimension, the  $R^2$  was  $.089 \pm .019$  in the misaligned session and  $.090 \pm .021$  in the veridical session. These values are consistent with previous studies (Block & Bastian, 2011, 2012).

After a baseline of 69 veridical V, P, and VP trials to become accustomed to the task, participants performed a

set of 84 trials (42 VP, 21 V, and 21 P). Order was mixed (VP, V, VP, P, ... [Block & Bastian, 2011]) to reduce proprioceptive drift in the target hand (Wann & Ibrahim, 1992). VP trials were presented more frequently because they were used to gradually impose the perceptual misalignment; the V and P trials served as outcome measures and were only needed to compute the change in perception from early to late in the task. In the veridical session, the white square was displayed veridically above the target finger throughout. In the misaligned session, the white square’s position was gradually shifted away from the target finger in the positive  $y$  direction, creating a misalignment of 70 mm by the end of the 84 trials (Figure 2C(ii)). Because the shift was gradual, 1.67 mm per VP trial, participants did not typically notice this perturbation (Block & Bastian, 2011). When questioned at the end of the session about the perceived position of the white box in relation to their left finger, 2 of the 19 participants reported a forward displacement in both sessions, one participant reported a forward displacement in the veridical session only, and two participants reported a forward displacement in the misaligned session only. Because this perception did not appear related to the presence of the forward visuo-proprioceptive perturbation in the misaligned session, these participants were included.

Indicator finger end points on unimodal (V or P) targets were used to assess visuo-proprioceptive realignment. If the proprioceptive estimate of the target finger moved forward to close the visuo-proprioceptive gap (proprioceptive realignment), then we would expect to observe overshoot of the indicator finger when pointing to P targets (Figure 2C(ii), center). Similarly, if the perceived position of the white box moved closer to the target finger (visual realignment), then we would expect to observe undershoot of the indicator finger on V targets (Figure 2C(ii), right). We therefore quantified visual and proprioceptive realignment ( $\Delta\hat{y}_V$  and  $\Delta\hat{y}_P$ ) by calculating the average indicator finger end point positions in the dimension of the perturbation ( $y$  coordinates) on the first and last four V and P trials, respectively, in the 84-trial sequence (Block et al., 2013; Block & Bastian, 2011, 2012). We then computed the difference relative to actual target position, which does not change for P targets but shifts 70 mm for V targets during the misaligned session:

$$\Delta\hat{y}_P = \text{last 4 P end points} - \text{first 4 P end points} \quad (2)$$

$$\Delta\hat{y}_V = 70 - (\text{last 4 V end points} - \text{first 4 V end points}) \quad (3)$$

Thus, for both modalities, realignment in the expected direction comes out positive. We also computed an experimental estimate of participants’ weight of vision relative to proprioception ( $w_V$ ) when both modalities were available (VP targets):

$$w_V = \frac{\hat{y}_P - \hat{y}_{VP}}{(\hat{y}_P - \hat{y}_{VP}) + (\hat{y}_V - \hat{y}_{VP})} \quad (4)$$

where  $\hat{y}_P - \hat{y}_{VP}$  and  $\hat{y}_V - \hat{y}_{VP}$  are the  $y$ -dimensional distances between the mean end point position of the indicator finger on P or V targets, respectively, and the mean end point position on VP targets (Block et al., 2013; Block & Bastian, 2010, 2011, 2012). For example, if VP end point positions are closer to P than V positions, this is interpreted as relying more on proprioception than vision ( $w_V < 0.5$ ). This method takes advantage of the naturally different spatial biases inherent in the alignment of vision and proprioception (Crowe, Keessen, Kuus, van Vliet, & Zegeling, 1987; Foley & Held, 1972), even with no perturbation (Smeets et al., 2006). Because  $w_V$  is known to fluctuate over time, we computed a separate value for each VP trial, using the average of the four V and four P trials that occurred closest in time to the VP trial of interest (Block & Bastian, 2010, 2011). To estimate how much participants were relying on vision versus proprioception in the  $y$  dimension during the misalignment phase of the task, the 42  $w_V$  values computed for that phase (one for each VP trial) were averaged for both the misaligned and veridical sessions.

## M1 I/O Curve

### *Stimulation and Recording*

TMS was used to assess motor corticospinal excitability for the left (target) finger before and after the visuo-proprioceptive perceptual alignment task in each session (Figure 2D). The target finger experienced visuo-proprioceptive misalignment (Figure 2B) but did not perform any motor task other than touching fixed tactile markers beneath the touchscreen glass. Although other muscles (e.g., biceps) were undoubtedly involved in holding the target index finger up to the tactile marker, we chose to assess the cortical representation of an index finger muscle, FDI. Spatially and somatotopically, this muscle is more proximal to the fingertip, which was the point participants were asked to focus on and indicate their perceptions about.

TMS was delivered over the right-hemisphere M1 representation of target hand FDI using a Magstim 200<sup>2</sup> stimulator (Magstim Company LTD, United Kingdom) with a 70-mm figure-of-eight coil. The coil was positioned tangential to the skull with the handle pointing posteriorly, 45° to the interhemispheric line to evoke posterior-to-anterior current in the cortex (Rossini et al., 2015; Figure 2B). During TMS application, both the participant's arms were relaxed on a pillow. The location and trajectory of the FDI hotspot were registered to a standardized neuroanatomical template using aBrainsight neuro-navigation system (Rogue Research, Montreal, Canada) for consistent coil positioning within and between sessions. Activity in target hand FDI was recorded with surface EMG using a belly-tendon montage, with a single common ground electrode over the ulnar styloid process of the target arm. EMG recordings were amplified (AMT-8; Bortec Biomedical, Calgary, Canada), band-pass filtered

(10–1000 Hz), sampled at 5000 Hz, and recorded on a hard drive for a subsequent analysis using Signal software (Cambridge Electronic Design Ltd, United Kingdom) and MATLAB (The Mathworks, Inc., Natick, MA).

At the beginning of each session, we determined resting motor threshold (RMT) as the minimum stimulator intensity to evoke motor evoked potentials (MEPs) > 50  $\mu$ V in at least 10 of 20 trials (Rossini et al., 2015). We also determined the stimulus intensity that would evoke a 1-mV response on average (SI1mV) in FDI. RMT and the I/O curve were both measured before and after the visuo-proprioceptive perceptual alignment task. Monophasic single pulses were delivered at a range of intensities in a random order with an interpulse interval of 4–6 sec. For 13 of the 32 participants, we recorded 20 trials at each of the following TMS intensities: 90%, 100%, 110%, 120%, and 130% of SI1mV (Rosenkranz, Kacar, & Rothwell, 2007). For the remaining 19 participants, we tested a slightly larger range of intensities with 10 pulses per intensity, either 60–140% of SI1mV (three participants; Avanzino et al., 2015; Rosenkranz et al., 2007) or 90–200% of RMT in 10% increments (16 participants; Carson et al., 2013). All I/O curves included the range 90–130% of SI1mV, which was therefore used in group analysis. Importantly, for a given participant, the same method was used to determine stimulus intensities before and after the perceptual alignment task and in both sessions.

### *TMS Data Processing and Analysis*

Single trials in which root mean square EMG exceeded 15  $\mu$ V in the 100 msec before the TMS pulse were excluded. One participant (not included in the 32) was excluded from analysis because more than 40% of all trials contained baseline muscle activity. For each I/O curve (two per session per participant), MEP amplitude at each stimulus intensity was calculated and ordered by increasing stimulus intensity. When plotted over a range of intensities, these data form a sigmoidal curve.

To quantify changes in corticospinal excitability, we computed area under the 90–130% SI1mV range of the I/O curve using the trapezoidal rule before and after the behavioral task (Carson et al., 2013). For the participants who were stimulated in 10% steps of RMT, we computed the range of tested stimulus intensities that most closely approximated 90–130% of SI1mV. We chose to focus on area under the I/O curve because this method captures changes in slope as well as any changes in excitability that are constant across stimulus intensities. To assess any changes in excitability of the neuron pool activated at threshold, we also compared RMT before and after the behavioral task.

## Statistical Analysis

We investigated whether percent change (post divided by pre) in either RMT or area under the I/O curve was related

to individual responses to misalignment. We did this by computing separate multilevel linear models for each variable in association with session type (misaligned or veridical). We decided to use multilevel models because they have fewer assumptions than repeated-measures ANOVA and because, unlike multiple linear regression, they can account for the repeated-measures structure of the data (Hoffman & Rovine, 2007). We initially developed full models including main effects for Session type (veridical/misaligned) and Realignment type (proprioceptive/visual), together with the corresponding interaction terms. However, when we calculated the variance inflation factor (VIF) values for each predictor, we found that each model had one predictor with VIF values  $> 10$  and three predictors with VIF values  $> 5$ , suggesting the presence of severe multicollinearity. We therefore computed a reduced model for each neurophysiological variable that included only the interaction terms; in other words, the minimum number of predictors needed to answer the question of whether individuals' visual and proprioceptive realignment was related to their change in M1 excitability. For each neurophysiological variable, a  $\chi^2$  test showed no significant differences between the full and reduced models (both  $ps > .71$ ), and no predictors in these reduced models had a VIF value greater than 1.8. The fixed part of each reduced model was composed of interaction terms of Session type with Proprioceptive and Visual realignment. The models also included a random intercept to account for variability among participants, related to the repeated-measures design of the study. We calculated an  $\Omega^2$  for each model to have an indication of effect size (Xu, 2003). We fitted all models using the lmer4 package, Version 1.1.12 (Bates, Machler, Bolker, & Walker, 2015), of the R programming language (R Core Team, 2016).

We also evaluated the presence of potential outliers by calculating the Cook's distance of each data point for each multilevel model (Nieuwenhuis, te Grotenhuis, & Pelzer, 2012). For the model including area under the I/O curve as a dependent variable, no data point showed a  $D$  value  $> 1$  (all  $ps < .26$ ), therefore not suggesting the presence of outliers (Cook & Weisberg, 1982). In contrast, for the model including RMT as a dependent variable, one data point showed a  $D$  value  $> 1$  (1.35) and was therefore excluded from the subsequent analysis.

We also computed correlations between visual and proprioceptive realignment and between  $w_v$  and proprioceptive realignment. To determine whether indicator finger behavior differed between the two sessions, for each participant in each session, we computed the average indicator finger end point  $y$ -coordinate across all trials of the perceptual alignment task. We compared this parameter across sessions with a paired-sample  $t$  test. We also computed a correlation coefficient for proprioceptive realignment versus the difference between mean indicator  $y$ -coordinate in the two sessions, to determine whether the realignment magnitude was related to any between-session difference in indicator finger behavior

at the individual level. Changes in raw area under the I/O curve and RMT were assessed using a Session  $\times$  Time repeated-measures ANOVA. Finally, we checked for significant between-session differences in the initial value of area under the I/O curve or RMT by performing a paired-sample  $t$  test for each variable.

## RESULTS

### Behavioral Responses to Visuo-proprioceptive Misalignment

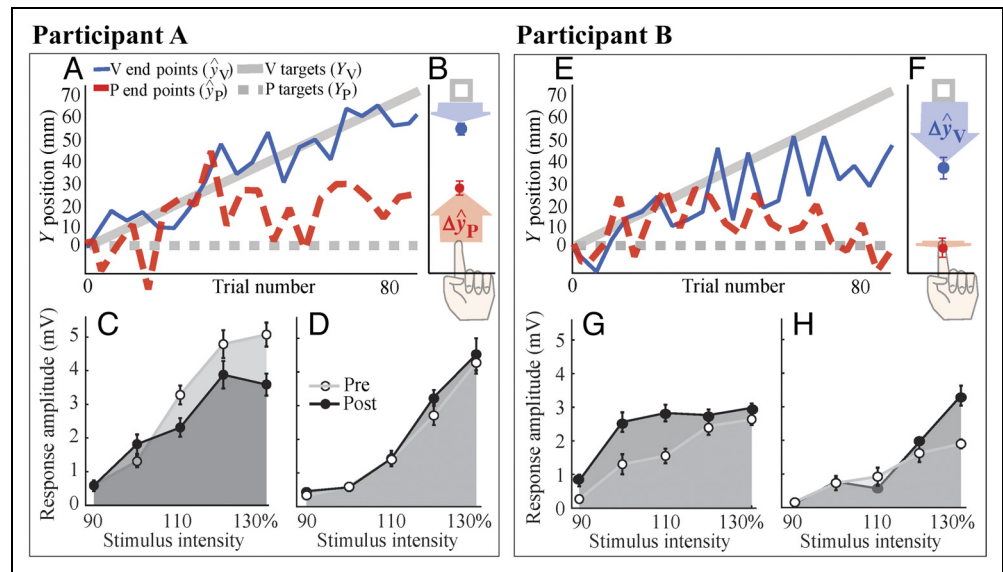
All participants compensated for some amount of the 70-mm misalignment between visual and proprioceptive estimates of target finger position by some combination of visual and proprioceptive realignment. Some participants realigned proprioception more than vision; in other words, their indicator finger end points on P targets gradually shifted forward, although the P target was stationary, but indicator finger end points on V targets largely followed the position of the V target (Figure 3A and B). Other participants realigned vision more than proprioception; clear undershoot of the indicator finger was observable on V targets, but indicator finger end points on P targets did not shift substantially in the dimension of the perturbation (Figure 3E and F). Thus, in the misaligned session, proprioceptive and visual realignment (Equations 2 and 3) were negatively correlated with each other ( $r = -.53$ ,  $p = .002$ ; Figure 4A). As we have found previously (Block & Bastian, 2011), these individual differences in realignment were related to individual differences in the weighting of vision versus proprioception, which was positively correlated with proprioceptive realignment ( $r = .36$ ,  $p = .045$ ; Figure 4B). This is consistent with minimum variance model predictions: Lower-weighted (presumably higher-variance) modalities were realigned more (Ghahramani et al., 1997). On average, participants realigned proprioception  $15.81 \pm 3.98$  mm (range =  $-4.25$  to  $37.10$  mm) and vision  $31.52 \pm 5.64$  mm (range =  $0.05$  to  $62.05$  mm) in the misaligned session, with mean total realignment coming to  $47.34 \pm 2.51$  mm (mean  $\pm$  95% confidence interval [CI]).

In the veridical session, conversely, visual and proprioceptive realignment were positively correlated ( $r = .57$ ,  $p < .001$ ), meaning that any change in indicated visual estimate of hand position was matched by a similar change in indicated proprioceptive estimate of hand position. This could reflect motor or perceptual drift in the indicator hand or perceptual drift in the target hand. Group averages for these parameters were quite small, however, with participants shifting their indicated target position  $2.84 \pm 5.06$  mm (range =  $-35.28$  to  $37.74$  mm) for proprioceptive targets and  $-0.04 \pm 5.27$  mm (range =  $-32.02$  to  $24.51$  mm) for visual targets in the veridical session (mean  $\pm$  95% CI).

We computed an estimated weight of vision versus proprioception ( $w_v$ ) for the baseline alignment trials, which were veridical in both sessions. These averaged



**Figure 3.** Example individual data. Participant A: (A) Over the course of 84 trials, visual targets (solid gray line) were gradually shifted away from proprioceptive targets (dashed gray line) in the positive  $y$  direction. (B) Any overshooting of the indicator finger on P targets (cartoon target hand) reflects proprioceptive realignment ( $\Delta\hat{y}_P$ ), whereas undershooting of the indicator finger on V targets (gray square) reflects visual realignment ( $\Delta\hat{y}_V$ ). Filled circles represent this participant's realignment magnitudes computed with Equations 2 and 3:  $\Delta\hat{y}_P = 27.9$  mm and  $\Delta\hat{y}_V = 21.9$  mm. (C) This participant had more proprioceptive than visual



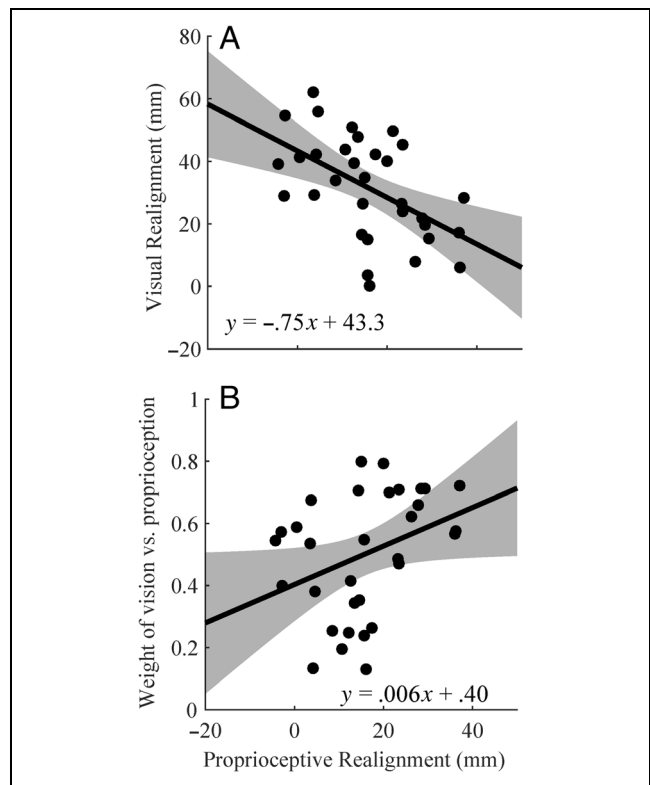
realignment, after which area under the I/O curve decreased (77% of baseline value). Error bars represent mean  $\pm$  SE. (D) In contrast, area under the I/O curve did not change as much after the veridical session (88% of baseline value). Participant B: (E–F) Undershooting on V targets reflects visual realignment ( $\Delta\hat{y}_V$ ), which was dominant in this participant:  $\Delta\hat{y}_V = 35.3$  mm and  $\Delta\hat{y}_P = -2.9$  mm. (G–H) Area under the I/O curve increased after the misaligned session (128% of baseline value), but not after the veridical session (83% of baseline value). Stimulus intensity given as percentages of S11mV.

0.395 and 0.398 in the misaligned and veridical sessions, respectively, which were not statistically different ( $t(31) = -0.46$ ,  $p = .64$ ). We also computed  $w_v$  for the main 84 alignment trials, during which a visuo-proprioceptive mismatch was imposed during the misaligned but not the veridical session. These averaged 0.50 and 0.36, respectively, with participants relying significantly more on vision during the misaligned session compared with the veridical session ( $t(31) = 3.91$ ,  $p < .001$ ).

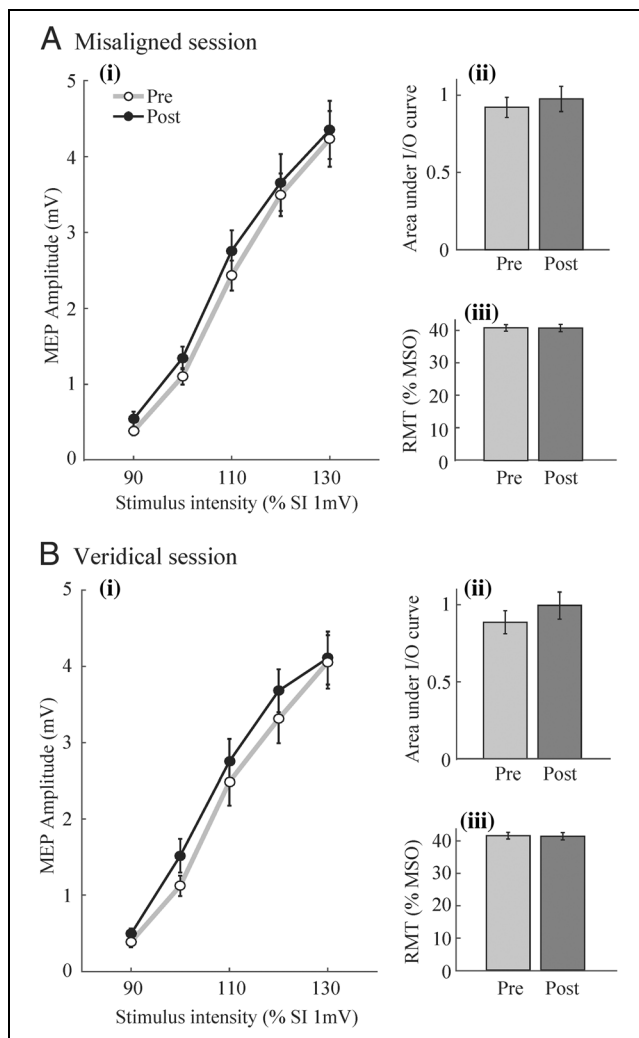
Although the variety of start and target positions in the perceptual alignment task was meant to prevent participants from making any particular stereotyped movement with their indicator finger, we wondered whether the visuo-proprioceptive mismatch in the  $y$  dimension might cause the indicator finger to reach further, on average, in the misaligned session than the veridical session. However, the mean indicator finger end point position in the  $y$  dimension did not differ significantly across sessions ( $p > .9$ ). In addition, participants' between-session differences in average indicator finger end point  $y$ -coordinate were not significantly correlated with proprioceptive realignment in the misaligned session ( $r = -.24$ ,  $p = .19$ ), which is inconsistent with a relationship between perceptual realignment and indicator finger behavior.

### Physiological Responses to Visuo-proprioceptive Misalignment

The Session  $\times$  Time repeated-measures ANOVA on area under the I/O curve resulted in a main effect of Time ( $F(1, 31) = 4.32$ ,  $p = .05$ ; Figure 5A(i–ii) and B(i–ii)), suggesting that M1 excitability increased from before to after the



**Figure 4.** Group behavior. (A) Visual versus proprioceptive realignment in the misaligned session, showing a significant negative correlation ( $r = -.53$ ,  $p = .002$ ). (B) Weight of vision relative to proprioception ( $w_v$ ) plotted against proprioceptive realignment in the misaligned session, showing a significant positive correlation ( $r = .36$ ,  $p = .045$ ).



**Figure 5.** Group physiology in the misaligned (A) and veridical (B) sessions. (i) Mean group I/O curves before and after the perceptual alignment task. Error bars represent *SEM*, which is equivalent to a 68% CI. (ii) Mean  $\pm$  *SE* of area under the I/O curve before and after the perceptual alignment task. (iii) RMT as percentage of maximum stimulator output before and after the perceptual alignment task. There was no significant interaction between session type and time point for either RMT or area under the I/O curve.

perceptual alignment task, independent of session. The effect of Session ( $F(1, 31) = 0.03, p = .86$ ) and the interaction ( $F(1, 31) = 0.53, p = .47$ ) were not significant. The Session  $\times$  Time repeated-measures ANOVA on RMT showed no significant effects (Figure 6A(iii) and B(iii)). RMT did not change across Time ( $F(1, 26) = 1.01, p = .32$ ) or Session ( $F(1, 26) = 0.84, p = .37$ ). The Session  $\times$  Time interaction was not significant ( $F(1, 26) = 0.13, p = .72$ ).

The multilevel model of the association between percent change in area under the I/O curve and session type had an  $\Omega^2$  of 0.56, denoting a strong effect size (Xu, 2003). Results suggest a negative association between the misaligned session and proprioceptive realignment as computed with Equation 2 ( $\beta = -1.50, t(49.52) =$

$-3.54, p < .001$ ) and a positive association between the misaligned session and visual realignment as computed with Equation 3 ( $\beta = 0.49, t(49.08) = 2.00, p = .05$ ). To illustrate these relationships, we used predictor residual plots (Figure 6), which allow us to display the relationship of one predictor variable with the dependent variable, after having statistically controlled for the effect of other predictors (McElreath, 2016). Lines of best fit and the corresponding 95% CIs are also included (Figure 6). Stated another way, after statistically controlling for the effect of visual realignment, the greater the proprioceptive realignment exhibited during the misaligned session, the greater the decrease in area under the I/O curve. Conversely, after statistically controlling for the effect of proprioceptive realignment, the greater the visual realignment during the misaligned session, the greater the increase in area under the I/O curve. Importantly, this was only observed during the misaligned session as no statistically significant interaction was observed during the veridical session for either proprioceptive or visual realignment (all  $ps > .19$ ; Table 1).

At the individual level, participants who realigned proprioception ( $\Delta\hat{y}_P$ , Equation 2) more than vision ( $\Delta\hat{y}_V$ , Equation 3) tended to have a decrease in area under the I/O curve, reflecting decreased excitability of the M1 representation of FDI (Figure 3C). In contrast, participants who realigned proprioception very little, compensating for the perturbation largely by realigning vision ( $\Delta\hat{y}_V$ ), had an increase in area under the I/O curve (Figure 3G). These patterns were absent from participants' veridical sessions (Figure 3D and H).

To assess whether changes in excitability of the neuron pool activated at threshold were associated with perceptual changes, we computed a multilevel linear regression model for the association of percent change in RMT with session type. This model had an  $\Omega^2$  of 0.42, indicating a moderate effect size (Xu, 2003). However, no predictor exhibited a statistically significant association with this outcome variable (Table 1).

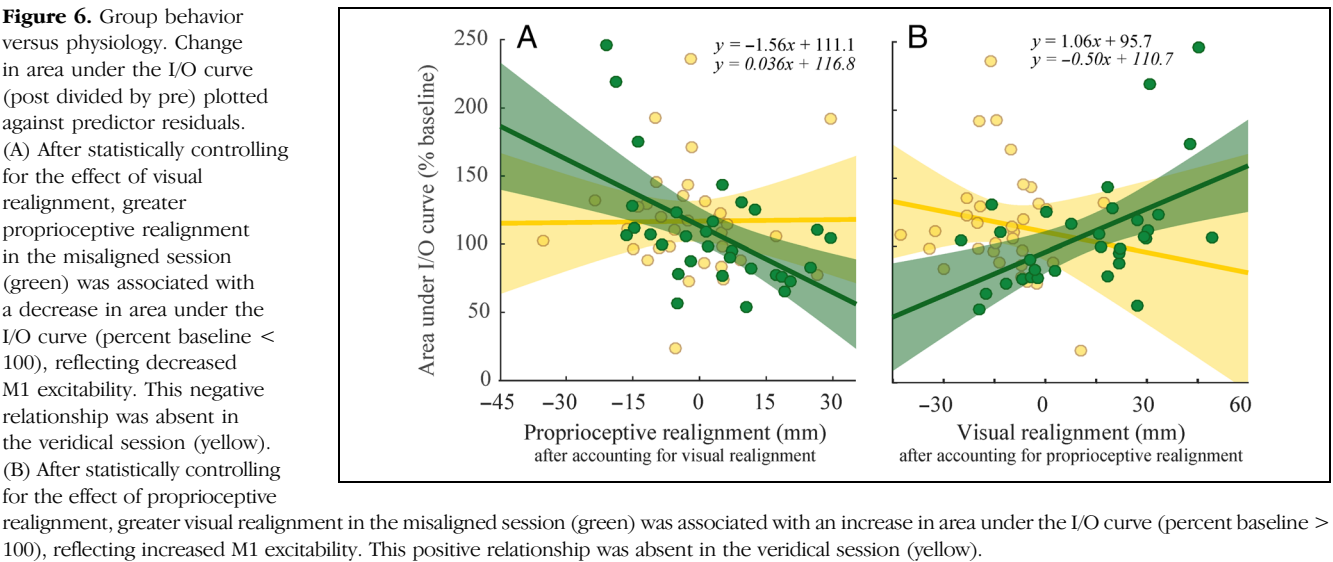
## Baseline Measures

To confirm that participants had similar M1 excitability at the beginning of each session, we used paired-sample *t* tests to compare pre-alignment task RMT and area under I/O curve in the misaligned versus veridical sessions. Neither comparison was statistically significant ( $p > .21$ ), suggesting that M1 was in an equivalent state at the start of the two sessions.

## DISCUSSION

Because visuo-proprioceptive realignment affects perception of hand position, which is used to plan movements, it is reasonable to expect this process to be associated with physiological changes in the motor system at some level. Here, we asked whether activity in M1 shows





evidence of change after visuo-proprioceptive realignment. Results reflect a modality-specific association, with proprioceptive and visual realignment linked to a decrease or an increase, respectively, in M1 excitability. These findings suggest that changes in multisensory integration are connected to physiological changes in the motor system.

### Neurophysiological and Behavioral Interpretation

In the misaligned session only, proprioceptive realignment was associated with decreased, and visual realignment was associated with increased, M1 excitability as quantified by area under the I/O curve, but not RMT.

The changes in I/O curve but not RMT suggest involvement of the higher-threshold subliminal fringe rather than the core region of neurons (Hallett, 2007; Devanne, Lavoie, & Capaday, 1997). Such an effect could be mediated by changes in recruitment of later indirect waves (i-waves) that arise from activation of corticocortical projections onto corticospinal neurons at higher stimulation intensities (Di Lazzaro & Rothwell, 2014; Ziemann & Rothwell, 2000; Di Lazzaro et al., 1998).

Although little is known about the influence of multisensory processing on the motor system, interactions between the motor and proprioceptive systems have been investigated at length. For example, motor commands have been shown to bias afferent signals from proprioceptors

**Table 1.** Multilevel Regression Model Results Comprising Four Interaction Terms for Session Type (Veridical or Misaligned) and Realignment Type (Proprioceptive or Visual)

	Area Under I/O Curve		RMT	
	$\beta$ (CI)	<i>p</i>	$\beta$ (CI)	<i>p</i>
<i>Fixed parts</i>				
Intercept	116.68 (103.31, 130.05)	<b>&lt;.001</b>	99.53 (98.10, 100.95)	<b>&lt;.001</b>
Veridical session : proprioceptive realignment	0.07 (−1.01, 1.15)	.898	0.06 (−0.09, 0.20)	.454
Misaligned session: proprioceptive realignment	−1.50 (−2.34, −0.67)	<b>.001</b>	0.02 (−0.07, 0.10)	.707
Veridical session: visual realignment	−0.69 (−1.73, 0.34)	.194	−0.09 (−0.21, 0.02)	.116
Misaligned session: visual realignment	0.49 (0.01, 0.98)	<b>.050</b>	−0.01 (−0.06, 0.04)	.619
<i>Random parts</i>				
$N_{ID}$	32		28	
Observations	64		54	

Columns represent percentage of baseline (post divided by pre) in the two neurophysiological outcome variables: area under the I/O curve and RMT.  $\beta$ s are presented with their 95% CIs. **Boldface** identifies statistically significant results.

(Walsh, Proske, Allen, & Gandevia, 2013; Smith, Crawford, Proske, Taylor, & Gandevia, 2009; Gandevia, Smith, Crawford, Proske, & Taylor, 2006). Measurement of proprioception is influenced by the contractile state of the muscle (muscle thixotropy; Proske & Gandevia, 2012) and skin stretch (Edin, 1992, 2001; Grill & Hallett, 1995), both of which change with movement. In other words, proprioception and motor control interact at a very fundamental level. Interestingly, somatosensory responses have been recorded in M1 neurons; the functional meaning of this phenomenon is unclear, but some have speculated a role in predictive signaling related to the future sensory consequences of motor commands (Hatsopoulos & Suminski, 2011).

More complex behaviors, such as reach adaptation in a force field, have been considered recently. In contrast with a visuomotor adaptation paradigm, force perturbation had been thought to elicit movement adaptation only, as visuo-proprioceptive signals remain veridical (Cressman & Henriques, 2009, 2015). Misalignment between senses was thought to be necessary to drive sensory realignment (Sarlegna & Bernier, 2010). However, Ostry et al. (2010) found systematic changes in arm proprioception during force field adaptation, independent of motor adaptation rate (Mattar et al., 2013). Thus, updating the internal models of motor control may have a biasing effect on proprioception.

Our finding of an association between proprioceptive realignment and M1 excitability is consistent with studies of somatosensory plasticity effects on movement (Ostry & Gribble, 2016; Beste & Dinse, 2013). Perceptual learning may influence motor learning (Bernardi et al., 2015), and proprioceptive training can improve movement speed and errors (Wong, Kistemaker, Chin, & Gribble, 2012). Proprioceptive stimulation increases the motor cortex representation of a nearby muscle (Lewis & Byblow, 2004) and affects plasticity throughout the motor network (Carel et al., 2000). However, the natural state of most human behavior is multisensory, and this study is the first, to our knowledge, to examine the effect of a multisensory perturbation on the motor system.

Although we observed clear changes in M1 excitability in relation to visuo-proprioceptive realignment, further studies will be needed to determine the computational specificity of this effect. One possible alternate explanation is that changes in M1 are linked not to realignment itself but to associated differences in weighting of vision versus proprioception, with a high weight of vision versus proprioception associated with proprioceptive realignment (Ghahramani et al., 1997) and thus with decreased M1 excitability. However, although participants relied significantly more on vision in the misaligned than the veridical session, percent change in M1 excitability did not differ across sessions on average, which is inconsistent with this alternate interpretation.

Theoretically (Ghahramani et al., 1997) and empirically (Block et al., 2013; Block & Bastian, 2011, 2012), visual

and proprioceptive realignment are inversely related in a perceptual misalignment task. For example, a participant might close 40 mm of a 70-mm visuo-proprioceptive misalignment by realigning vision 35 mm and proprioception 5 mm. Indeed, visual and proprioceptive realignment were inversely related in the misaligned session of this study. On average, participants only compensated for about two thirds of the 70-mm misalignment. Unlike motor adaptation (Mattar et al., 2013; Hanakawa, Dimyan, & Hallett, 2008), little is known about the time course of visuo-proprioceptive realignment. It is possible that participants would eventually compensate for the full 70 mm, given enough trials, or realignment might level off as the remaining mismatch approaches a level normally tolerated by the system (Smeets et al., 2006).

### Theoretical Implications

If a change in multisensory integration, such as visuo-proprioceptive realignment, has a physiological impact on the motor system, the specific changes we observe in M1 can, to some degree, inform a neurological model of multisensory-motor interaction. A modality-independent change in M1 activity would imply that the multisensory realignment computation itself is somehow linked to M1. More realignment, whether in vision or proprioception (modality independent), should be associated with more change in M1 activity, whether that change is driving, or driven by, the realignment. In this case, we would predict that, on average, M1 activity should change more in the misaligned session than the veridical session. Our results are inconsistent with this idea.

Another possibility is that visuo-proprioceptive realignment is accompanied by changes in areas traditionally considered unisensory and that the observed changes in M1 are related to the activity in these unisensory areas (modality specific). SI is involved in proprioceptive processing and is reciprocally connected with M1 (Krubitzer & Kaas, 1990). Indeed, somatosensory plasticity has been observed in association with force adaptation-related proprioceptive realignment (Ostry & Gribble, 2016). Given that somatosensory inputs to M1 are predominantly inhibitory (Widener & Cheney, 1997), proprioceptive realignment, if associated with increased SI excitability (Lebar, Danna, Moré, Mouchnino, & Blouin, 2017; Bernier, Burle, Vidal, Hasbroucq, & Blouin, 2009), could then inhibit M1, which would be consistent with our findings. Although early visual areas are not known to have direct connections with M1, visual realignment could be associated with plasticity in these areas, which is transmitted to M1 via the dorsal pathway. However, because visual and proprioceptive realignment were inversely related in the misaligned session, the positive relationship between visual realignment and M1 excitability could also be a consequence of the fact that participants who realigned proprioception more (perhaps activating inhibitory SI-M1 connections) were the same participants who realigned

vision less, and vice versa. It is important to note that our data suggest that proprioceptive and visual realignment are each linked to M1, but the experimental design limits the conclusions that may be drawn. To determine causation, future studies would need to hold one type of realignment constant and vary the other. On the basis of the current data, we cannot discard the possibility that visual realignment drives change in M1. We also cannot discard the possibility that the M1 effect is driven by proprioceptive realignment, and visual realignment only appears linked to M1 because visual and proprioceptive realignment are inversely related.

Overall, these results are consistent with a neurological model in which changes in multisensory integration are reflected in the motor system via altered excitability in regions traditionally considered unisensory. This does not preclude the involvement of multisensory regions in multisensory computations such as realignment. Although the magnitude of visual versus proprioceptive realignment must involve multisensory comparisons at some stage, the comparison could occur at the level of areas traditionally considered unisensory, such as SI and early visual cortices, which are known to interact with each other (Yau, DeAngelis, & Angelaki, 2015). The multisensory comparison could also involve multisensory areas such as PPC, with multisensory regions incorporating somatosensory, visual, and other modalities (Block et al., 2013; Lewis & van Essen, 2000; Andersen et al., 1997; Blatt et al., 1990). In other words, realignment could involve plasticity in PPC–SI and PPC–V1 connections in addition to SI–M1 or dorsal-visual-stream–M1 connections.

The somatotopic specificity of the observed changes in M1 is unknown. Further studies will be needed to determine if visuo-proprioceptive realignment is associated with changes in M1 representations of other muscles in the target arm. We would expect other target index finger muscles to show similar results to FDI, as they are somatotopically proximal to the portion of the body the participant is given explicit information about and asked to focus on (the fingertip). If M1 changes are limited to muscles that are part of the index finger representation, it might suggest a role for the participant's locus of attention or task or context specificity. Alternatively, if M1 representations of the entire effector (including biceps and forearm muscles) are affected, it might suggest that the brain generalizes misaligned finger position information to any motor representation that might be involved in positioning or determining the position of the finger, that is, the whole arm. In either case, we would not predict M1 changes for the nontarget hand, leg muscles, and so forth.

Although we have demonstrated a change in M1 processing after visuo-proprioceptive realignment, any specific function or purpose of this effect is beyond the scope of this study. It is possible that the M1 changes serve no functional purpose and are simply a side effect of changes in regions with anatomical connections to M1. It is also possible that the modulation of M1 activity

reflects some mechanism underlying the effect of a change in perception on motor planning. Future studies could clarify this question by experimentally modulating activity in M1 or other nodes in the multisensory–motor network, perhaps with repetitive TMS, and assessing the effect. Although much progress has been made in understanding the neural mechanisms of multisensory processing (Yau et al., 2015; Eck, Kaas, & Goebel, 2013), substantial further investigation is needed to fully elucidate how these processes are realized in the brain. It may ultimately be possible to assess the effect of specific multisensory computations on specific levels of motor processing and specific components of motor control models, perhaps by systematically varying perceptual and motor parameters and measuring movement kinematics and perceptual changes independently of any motor or perceptual perturbation.

### Potential Confounds

These results cannot be explained by between-session differences in starting M1 excitability, as initial I/O curve area and RMT were consistent across sessions. An order effect is also unlikely, as sessions took place 16 days apart on average, in counterbalanced order, with no performance feedback or knowledge of results. Importantly, the task used here separates perceptual misalignment from motor performance. The target finger, to which visuo-proprioceptive misalignment was applied, performed the same actions throughout both sessions: touching the stationary tactile marker or resting in the participant's lap. Active movement of the target hand means that efferent outflow could contribute to some degree to participants' perception of target hand position, but this would presumably be equal in both sessions, as the target finger always had to be placed on the same static tactile marker.

It should be noted that realignment of perceptual estimates related to the target hand could potentially affect the indicator hand's movements (e.g., increasing overshoot on proprioceptive targets). There is evidence that performance of a unimanual motor task is associated with changes in both ipsilateral and contralateral motor cortices (Perez & Cohen, 2008), so we must consider the possibility that between-session differences in indicator hand movements could explain between-session differences in the M1 excitability of either hemisphere. However, we consider this unlikely for several reasons. First, participants' between-session differences in indicator finger position were not related to their magnitude of proprioceptive realignment. Second, M1 changes in the misaligned session were modality specific but not different on average. Third, the indicator finger had to remain nearly vertical to register on the IR touchscreen, constraining movement changes to the elbow or shoulder.

The active movement of both hands in the alignment task raises the question of motor adaptation. Without

online or end point feedback about indicator finger position, participants had no error information to drive trial-and-error-based motor adaptation in the indicator hand. The possibility cannot be completely excluded for the target hand, however; as visuo-proprioceptive realignment progressed in the misalignment session, perceived target hand location could shift, conceivably resulting in systematic movement errors when the participants raised their hand to touch the tactile marker and thus motor adaptation. It is not clear what effect such a process would have on the target muscle M1 representation; like the indicator finger, the target finger had to be held nearly vertical to register correctly in the touchscreen, constraining movement changes to the wrist or elbow. Nonetheless, target finger positioning would need to be passive to completely exclude this possibility.

Despite the close proximity of SI and M1, any changes in the former are unlikely to confound TMS measurements over the latter. Corticospinal neurons in SI generally terminate in the dorsal horn (Groos, Ewing, Carter, & Coulter, 1978; Coulter & Jones, 1977) and so would not contribute to the MEP. Regardless, single-pulse TMS over M1 is considered sufficiently focal to assess changes in M1 itself. Ninety percent of TMS current intensity is focused within a 1-cm<sup>2</sup> area (Rossini et al., 1994), making it necessary to move the coil several centimeters posterior from the M1 hotspot to efficiently stimulate SI (Song, Sandrini, & Cohen, 2011). In addition, posterior–anterior TMS current primarily causes MEPs through early i-waves, that is, monosynaptic connections to corticospinal neurons that originate from within M1 (Di Lazzaro & Rothwell, 2014). Depending on current intensity, these monosynaptic connections can come from outside M1, but sources are largely premotor rather than somatosensory (Di Lazzaro & Rothwell, 2014).

## Conclusions

We have demonstrated altered M1 activity after visuo-proprioceptive realignment, suggesting a potential mechanism for multisensory–motor interaction. Proprioceptive realignment was associated with a decrease and visual realignment with an increase, in M1 excitability. Although it cannot be concluded from this experimental design whether realignment in one or both modalities is responsible for the changes in M1, these findings are consistent with a modality-specific neurological model of multisensory–motor interaction. Changes in M1 may be driven by areas considered unisensory, such as SI or dorsal stream visual areas. Visuo-proprioceptive realignment may arise from altered cross-modal interactions between SI and V1, perhaps mediated by multisensory PPC. There was no mean difference in M1 between sessions; this is inconsistent with a modality-independent mechanism, as might be expected if PPC–M1 connectivity changed after the realignment computation. Further studies are needed to investigate the specific effects of changes in multi-

sensory integration on higher-level motor areas as well as on motor function and behavior.

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