Virtual Lesion of Angular Gyrus Disrupts the Relationship between Visuoproprioceptive Weighting and Realignment

Hannah Block[1], Amy Bastian[1,2], and Pablo Celnik[1]

Abstract

■ Posterior parietal cortex is thought to be involved in multisensory processes such as sensory weighting (how much different modalities are represented in sensory integration) and realignment (recalibrating the estimates given by unisensory inputs relative to each other, e.g., when viewing the hand through prisms). Sensory weighting and realignment are biologically independent but can be correlated such that the lowest-weighted modality realigns most. This is important for movement precision because it results in the brain's estimate of hand position favoring the more reliable (higher-weighted) modality. It is unknown if this interaction is an emergent property of separate neural pathways for weighting and realignment or if it is actively mediated by a common substrate. We applied disruptive TMS to the angular gyrus near the intraparietal sulcus (PGa) before participants performed a task with misaligned visual and proprioceptive information about hand position. Visuoproprioceptive weighting and realignment were unaffected. However, the relationship between weighting and realignment, found in control conditions, was absent after TMS in the angular gyrus location. This suggests that a specific region in the angular gyrus actively mediates the interaction between visuoproprioceptive weighting and realignment and may thus play a role in the decreased movement precision associated with posterior parietal lesions. ■

INTRODUCTION

The posterior parietal cortex (PPC) is a large, heterogeneous area of the brain, with many regions that respond to more than one sensory modality. For instance, the macaque ventral intraparietal cortex responds to visual, tactile, vestibular, and auditory stimuli (Klam & Graf, 2003; Duhamel, Colby, & Goldberg, 1998; Bremmer, Duhamel, Ben Hamed, & Graf, 1997; Colby, Duhamel, & Goldberg, 1993). The human homologue has similar properties (Grefkes & Fink, 2005). For instance, Bremmer et al. found in a human fMRI study that visual, tactile, and auditory stimuli caused overlapping bilateral activations in the fundus of the intraparietal sulcus (IPS), similar to macaque (Bremmer et al., 2001). Additionally, patients with lesions in PPC may experience complex multisensory deficits, such as neglect (lack of awareness of contralesional space) and optic ataxia (impairment in visually directed arm movements).

The multimodal quality of PPC is an intriguing feature and is widely thought to be the basis for sensory integration (e.g., Grefkes & Fink, 2005). Sensory integration can be thought of as the weighting and combining of unimodal estimates, such as visual ($\hat{Y}_V$) and proprioceptive ($\hat{Y}_P$) estimates of hand position (Y), to form a single integrated estimate ($\hat{Y}_{VP}$) with which to control movement (e.g., Ghahramani, Wolpert, & Jordan, 1997). If W_V is the weight of vision versus proprioception (i.e., W_V of 0.5 implies equal reliance on vision and proprioception),

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

The neural basis of multisensory computations in the brain are poorly understood. For instance, when faced with a discrepancy between vision and proprioception (e.g., viewing the hand underwater or through prisms shifts $\hat{Y}_V$ away from $\hat{Y}_P$), the brain can compensate by increasing the contribution of one modality relative to the other, for example, up-weighting vision while down-weighting proprioception (changing W_V, a weighting strategy). Alternatively, the brain can realign the inputs, for example, bring $\hat{Y}_P$ closer to $\hat{Y}_V$ (a realignment strategy).

Block and Bastian (2011) suggested that sensory weighting and realignment are biologically independent processes; although a robust correlation between the two occurred when participants compensated for a visuoproprioceptive misalignment without any explicit error feedback (with the lower-weighted modality realigning more), the relationship was absent when participants received feedback encouraging them to rely on vision. Instead, some participants compensated for the misalignment

---

[1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Kennedy Krieger Institute, Baltimore, MD

with a weighting strategy, whereas others relied primarily on realignment, and some did both, demonstrating that these processes can operate independently (Block & Bastian, 2011). However, the existence of a correlation between weighting and realignment is thought to be the most usual mechanism of multisensory calibration (van Beers, Wolpert, & Haggard, 2002; Ghahramani et al., 1997) and is likely important for precision in motor control. Specifically, because the modality that is trusted the least changes the most, and vice versa, the final estimate of the body's spatial position favors the more reliable (higher-weighted) modality. For example, if a person attempts to retrieve a fallen spoon from a sink full of water, his view of his underwater hand will be misaligned from his proprioceptive sense of the hand's position, because of the refraction of light by water. He will be most precise if he integrates the visual and proprioceptive information (Ernst & Banks, 2002; van Beers, Sittig, & Denier van der Gon, 1998; Ghahramani et al., 1997), which necessitates weighting and, if the misalignment is substantial, realigning the unimodal estimates to more closely match each other (Equation 1; Ghahramani et al., 1997). Which sensory modality prevails will depend on the circumstances. For instance, if the room is dimly lit, proprioception may be more reliable than vision (van Beers et al., 2002; Mon-Williams, Wann, Jenkinson, & Rushton, 1997), in which case the brain should realign vision to match proprioception.

The neural basis of this interaction is unknown, however. It may be a simple emergent property of separate neural pathways, in which case disrupting an area important for realignment should also disrupt the correlation between weighting and realignment (Figure 1A(1)). Alternatively, it may depend on the active participation of a common neural substrate, in which case disrupting the neural substrate of the weighting–realignment interaction should leave both weighting and realignment intact but disrupt their correlation (Figure 1A(2)).

Several studies have found PPC activation related to visuomotor adaptation (e.g., Newport, Brown, Husain, Mort, & Jackson, 2006; Krakauer et al., 2004; Inoue et al., 1997), and this activation has been attributed specifically to visuoproprioceptive remapping (Inoue et al., 1997; Clower et al., 1996). For instance, Clower et al. (1996), in a PET study of prism adaptation, found activity in a region along the IPS in the angular gyrus while participants wearing prism goggles reached to visual targets on a touchsreen. Although imaging alone could not determine whether the activation was functionally relevant, they speculated it could represent proprioceptive realignment in response to the prismatic perturbation. Here we used continuous theta burst TMS (cTBS) to noninvasively create a "virtual lesion" (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) in the PPC. Specifically, we chose the coordinates identified by Clower et al. (1996) because
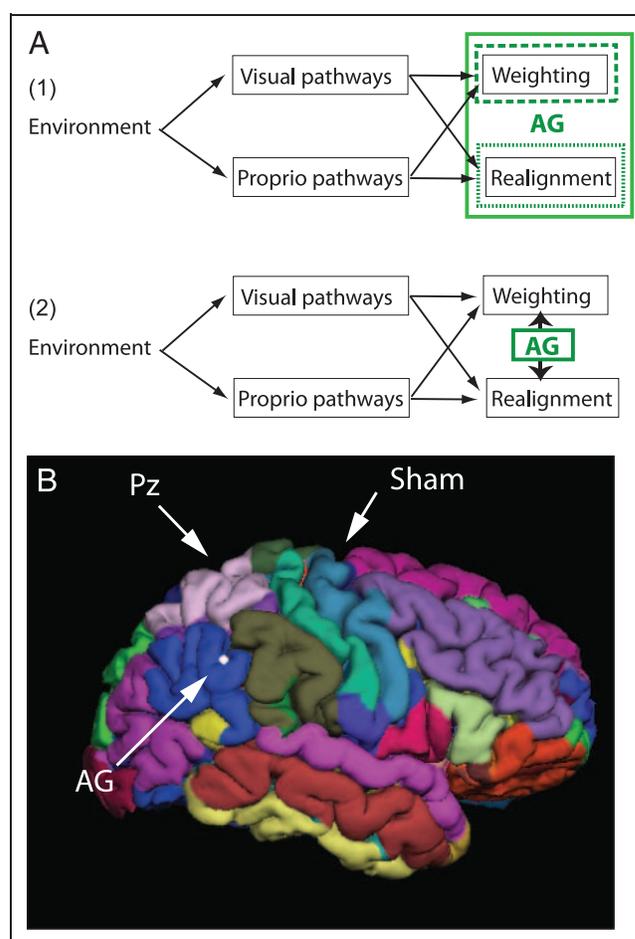
Figure 1. (A) Potential substrates of the visuo-proprioceptive weighting and realignment correlation. The first possibility (1) is that the two processes occur independently (Block & Bastian, 2011) and a correlation is found because the same environmental signals contribute to both computations. Under this hypothesis, disruption of angular gyrus by cTBS should have no effect on the weighting–realignment correlation unless this area is important for weighting (dashed green line), realignment (dotted green line), or both (solid green line). A second possibility (2) is that the correlation of weighting and realignment is actively mediated by a separate neural substrate. This hypothesis predicts that if that substrate includes the angular gyrus location studied here, then cTBS in the AG group should disrupt the weighting–realignment correlation (without specifically affecting weighting or realignment). (B) Sample of cTBS stimulation location in an AG participant. 3-D reconstruction of the surface of the participant's brain, with the locations of cTBS in all three groups indicated by arrows. In the AG group, cTBS location (Talairach coordinates [50 −50 40]; Clower et al. 1996) fell on the angular gyrus (PGa), close to the border between BA 39 and BA 40 (white circle). Pz and Sham cTBS were applied at Pz and Cz based on the 10–20 EEG system, respectively.

that study used a task more similar to the one we developed to study sensory weighting and realignment (Block & Bastian, 2010, 2011). We tested a cause-and-effect relationship between disruption of activity in this region and vision, proprioception, visuoproprioceptive weighting, realignment, and the relationship between weighting and realignment.

METHODS

Participants

We studied 52 right-handed adults. Participants were healthy volunteers with no neurological conditions, had normal or corrected-to-normal vision, and gave informed consent. The Johns Hopkins Institutional Review Board approved the research protocol, which was in accordance with the Helsinki declaration.

Participants were divided into three groups according to cTBS stimulation site (Table 1). We used a between-participant design rather than a crossover design because in a previous study, we found that participants who performed the behavioral task a second time on a different day were inconsistent in how much they weighted vision versus proprioception and how much they realigned proprioception. Importantly, we found no correlation between performance on the first and second day (Block & Bastian, 2011, Appendix B).

Participants in the angular gyrus group (AG; $n = 17$, 8 women, mean age = 24.8 years) received an anatomical MRI before the experiment (on a different day). The MRI was loaded into a Brainsight 2 neuronavigation system (Rogue Research, Inc., Montreal, Canada), which allows the input of spatial coordinates in various coordi-

nate systems. So that cTBS would affect multisensory processes related to the left (target) hand, we entered the right-hemisphere version of the Talairach coordinates identified by Clower et al. (1996) as a potential site of proprioceptive realignment [50 −50 40, xyz]. We chose to stimulate the right hemisphere because the aim of the task is to estimate the location of the left hand and visual information was presented in the left hemivisual field (see Behavioral task design). Transformed into the native space of each participant's MRI, these coordinates fell on the angular gyrus near the IPS (PGa), on the border between BA 39 and BA 40, as determined by Freesurfer software analysis of each participant's MRI data (Athinoula A. Martinos Center for Biomedical Imaging). TMS (see below) was delivered over this location in the AG group (Figure 1B), tangential to the head with the handle backwards at 45° to midline (e.g., Balslev, Miall, & Cole, 2007; Lee & van Donkelaar, 2002).

Of note, the coordinates given by Clower et al. (1996) were a group average, which we warped into single-participant space. Therefore, although we are confident that each individual in this study was stimulated at the mean coordinates given by Clower et al. (1996), we cannot be certain that this location coincides exactly with the location where that individual would experience an

Table 1. Summary of Mean Results by Group ± Standard Error

Group	AG	Pz	Sham
Variance[a]			
Visual	63 ± 10 mm^2	43 ± 8 mm^2	47 ± 6 mm^2
	60 ± 11 mm^2	36 ± 5 mm^2	53 ± 9 mm^2
Prioprioceptive	36 ± 4 mm^2	29 ± 4 mm^2	29 ± 4 mm^2
	33 ± 5 mm^2	28 ± 4 mm^2	22 ± 3 mm^2
Weight of vision vs. proprioception[a]	44 ± 4%	43 ± 4%	40 ± 4%
	37 ± 4%	41 ± 3%	38 ± 4%
Realignment (mm)			
Proprioceptive ($\Delta \hat{y}_P$)	14.43 ± 3.26 mm	9.71 ± 2.34 mm	15.72 ± 2.35 mm
Visual ($\Delta \hat{y}_V$)	31.84 ± 4.12 mm	34.92 ± 3.87 mm	31.50 ± 3.98 mm
Total ($\Delta \hat{y}_P + \Delta \hat{y}_V$)	46.27 ± 3.74 mm	44.62 ± 2.95 mm	47.22 ± 3.40 mm
Correlation of w_v and $\Delta \hat{y}_P$ (r value)	−.17	.56*	.56*
Corticospinal excitability[b]			
RMT	54.2 ± 2.2%	51.8 ± 1.5%	51.0 ± 2.2%
	54.5 ± 2.4%	52.1 ± 1.4%	52.1 ± 2.3%
1 mV response	1.01 ± 0.13 mV	1.15 ± 0.12 mV	0.86 ± 0.11 mV
	1.02 ± 0.13 mV	1.02 ± 0.21 mV	0.88 ± 0.20 mV

[a]First row is Base 1 value, second row is Base 2 value.

[b]First row is TMS1 value; second row is TMS3 value.

*Statistically significant, $p < .02$.

activation peak in the task used by Clower et al. (1996). We do not think, however, that any variation between the results of spatial normalization methods used by Clower et al. (1996) and those used in this study is large enough to affect the anatomical location stimulated with cTBS. Indeed, Eickhoff et al. (2009) applied nine different spatial normalization templates to the fMRI data of one group of participants and computed the mean Euclidian distance between maxima for 16 brain regions. They found that across all areas, the estimated variance between spatial normalization templates was 5.7 mm (Eickhoff et al., 2009). For comparison, the two-dimensional area of cortex where TMS-induced current density is >90% of its maximum ranges from 107 to 119 mm^2, slightly larger than the area of one square centimeter (Wagner, Valero-Cabre, & Pascual-Leone, 2007).

To control for the effects of cTBS over AG, we studied two separate control groups. One received real TMS over midline between the parietal cortices (Pz group; $n = 17$, 11 women, mean age = 24.9 years). This location was the Pz site determined by the 10–20 EEG system. Here, the handle of the coil pointed caudally. The second control group, the SH group ($n = 18$, 14 women, mean age = 24.5 years), received sham TMS, with the coil held on its side over the vertex (Cz in the 10–20 EEG system) such that the stimulation was not directed into the head. To keep participants from noticing the different orientation of the coil, an identical but unplugged coil was held tangentially (aiming into the head) beneath the active coil. We chose the vertex for sham stimulation because this is a commonly used control site (e.g., Leitão, Thielscher, Werner, Pohmann, & Noppeney, 2012; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008). We held the coil on its side for this group because we wanted to avoid stimulating sensorimotor cortex and potentially affecting aspects of performance such as tactile sensation or movement speed, which are not relevant to our hypothesis and could be potential confounds.

Experimental Design

The experiment consisted of three reaching blocks and three TMS blocks (summarized in Figure 2C). Measures of corticospinal excitability were made during blocks TMS1 and TMS3 (before and after the behavioral experiment). The intervention (cTBS) was applied during TMS2 for 40 sec. Base 1 and Base 2 were baseline reaching blocks, each with 39 reaches of the right index finger to visual (V), proprioceptive (P), or combined (VP) information about the left index finger (15 V, 15 P, and 9 VP; interleaved). These baseline blocks were used to compare reaching performance and visual and proprioceptive variance before and after cTBS. After the baseline blocks, a misalignment was imposed between visual and proprioceptive estimates of the left index finger's position during the Adaptation block (84 reaches; 21 V, 21 P, and 42 VP; interleaved). This block was used to assess the effect of

cTBS on sensory realignment and weighting. The blocks after cTBS (Base 2 and Adaptation) took about 25 min in total, well under the 60 min that Huang et al. (2005) found cTBS decreased excitability in motor cortex.

Stimulation

Before beginning the reaching experiment (TMS1, Figure 2C), we delivered TMS with a 70-mm figure-of-eight coil (Magstim Rapid^2, The Magstim Company Ltd.) to locate the motor hotspot for the first dorsal interosseus muscle of the left hand. This coil position was recorded using Brainsight 2 neuronavigation system (Rogue Research, Inc., Montréal). Following standard procedure, we then assessed resting motor threshold (RMT), the minimum stimulation intensity needed to cause a motor-evoked potential (MEP) in resting first dorsal interosseus muscle, 5 times of 10 (Rossini et al., 1994). This measurement was repeated at the end of the experiment (TMS3, Figure 2C) to determine whether corticospinal excitability had changed. During TMS1, we also determined the Stimulation Intensity needed to elicit MEPs with an amplitude of approximately 1 mV (SI1mV, Figure 2C). Using this intensity we recorded 10 MEPs and averaged their amplitude. At the end of the experiment (TMS3, Figure 2C), we recorded another 10 MEPs using the same SI1mV and compared their average to the TMS1 value as another means of assessing whether corticospinal excitability had changed. These measurements, RMT and MEP before and after the behavioral task and cTBS, allow us to determine whether any changes in corticospinal excitability occurred. It is important to assess whether any potential behavioral differences across groups were because of changes in primary motor excitability.

After a baseline block of reaching (Base 1, Figure 2C), in the TMS2 block participants received 600 pulses of continuous theta burst TMS (cTBS) at one of three sites: AG, Pz, or Sham (see Participants for details). For this, we applied cTBS at 70% of RMT intensity (Gentner, Wankerl, Reinsberger, Zeller, & Classen, 2008). Huang et al. (2005) found that a nearly identical stimulation paradigm (bursts of three pulses at 50 Hz, repeated at 5 Hz for 40 sec) is safe and has an inhibitory effect on primary motor cortex excitability that lasts up to 60 min.

Of note, applying stimulation in nonmotor regions with intensities based on motor cortex is commonly done (Kaminski, Korb, Villringer, & Ott, 2011). Thickness of the skull can vary by location; however, there is an inverse relationship between skull thickness and resistivity, with thicker regions of skull having a composition that makes them less resistive (Law, 1993). This property makes it possible to assume that, for the purposes of electrical stimulation, skull thickness is effectively uniform (Law, 1993). For this reason, it is unlikely that any effect of AG stimulation is because of nonspecific factors relating to skull thickness, such as the lateral position of AG relative to the control groups.
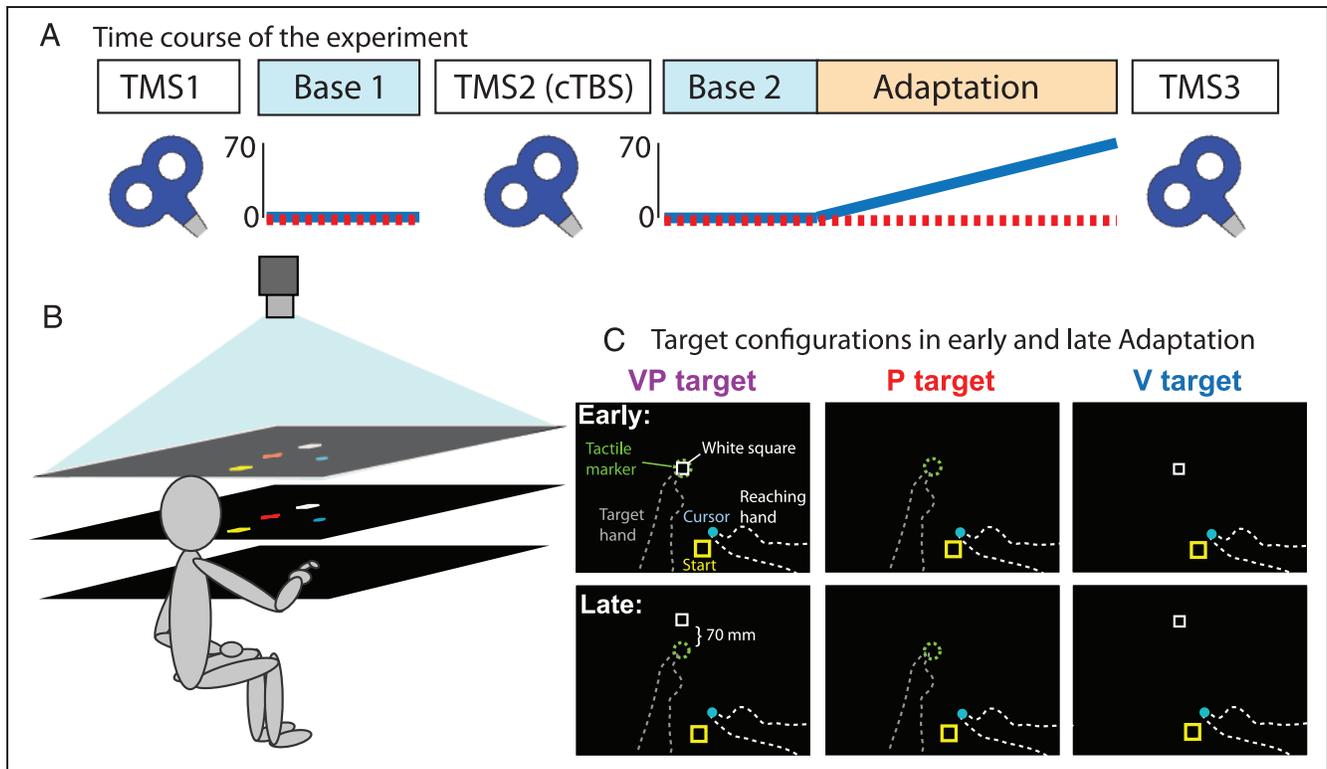
Figure 2. Experimental setup and time course. (A) Timeline of the experiment. TMS1: We determined RMT and SI1 mV response. Base 1: Baseline block of reaching with no visuoproprioceptive misalignment. TMS2 (cTBS): The participant received cTBS. Base 2: A second baseline block (no visuoproprioceptive misalignment) to evaluate any changes in reaching behavior that resulted from cTBS. Adaptation: Reaching with a gradually imposed visuoproprioceptive misalignment. TMS3: We determined RMT and 1 mV response a second time to evaluate whether any changes in corticospinal excitability occurred. Blue lines represent position of V targets (and V component of VP targets) in the y dimension (in mm). Red dashed lines represent position of P targets (and P component of VP targets) in the y dimension (in mm). (B) Participants looked into a horizontal mirror (middle) and saw targets and cursors indicating hand position reflected from a horizontal rear projection screen (top). The reaching hand rested on a surface (bottom) below the mirror. The (nondominant) target hand remained below the reaching surface at all times. The mirror was positioned midway between screen and reaching surface, such that images in the mirror appeared to be in the plane of the reaching surface. (C) Bird's eye view of the display before reaches to VP, P, and V targets early (Row 1) and late (Row 2) in the Adaptation block. Participants first placed their reaching finger (white dashed line) in the yellow start box with the aid of a blue cursor indicating reaching finger position (veridical to minimize proprioceptive drift between reaches; Wann & Ibrahim, 1992). Participants positioned their target finger (dashed gray line) as instructed: On one of two tactile markers stuck to the bottom of the reaching surface about 40 mm apart (green dashed circles) for a VP (column 1) or P (column 2) target or down in their lap for a V target (column 3), which appeared as a white square. For VP reaches, the V target was projected on the P target during the baseline blocks but was gradually offset in the y direction during the adaptation block (Row 2). Only the yellow start position, white V target, and blue cursor were visible to the participant, and the cursor disappeared at reach initiation. Movement speed was not restricted, and participants were permitted to make adjustments.

Behavioral Task Design

Setup

As in Block and Bastian (2011), participants sat at a reflected rear projection apparatus (Figure 2A) and reached with their right hand to visual (V), proprioceptive (P), or combined (VP) targets with no vision of either arm. The experimenter read written task instructions to the participant. Participants were told to be as accurate as possible and not to worry about speed. The V target was a 12 × 12 mm white square, and the P target was the index finger of the left hand positioned on a tactile marker beneath the reaching surface (Figure 2B). Infrared-emitting markers were placed on each index fingertip, and we used an Optotrak 3020 (Northern Digital) to record 3-D position data at 100 Hz. Black fabric obscured the participant's view of both arms and the room beyond the

apparatus. Every reach began with the reaching finger in a yellow start box in one of five positions centered around the participant's midline (Figure 2B). Targets were in one of two locations 30–40 cm (mean = 36 cm) in front of the participant's chest and 9 cm to the left of midline (Figure 2B). The total display area was 75 × 100 cm.

To prevent arm length from constraining reaching endpoints, the entire display was scaled according to the participant's reach such that if the elbow was fully extended, the reaching finger could be placed about 20 cm past the farthest target, well outside the maximum distance participants typically reached at any point in the experiment. We randomized start positions and target positions so that it was unlikely a participant could memorize a reach direction or extent. For a typical participant, reach distance from start box to target location was around 14 cm.

Participants followed prerecorded step-by-step instructions throughout the reaching task.

Fixation

Before every reach, a red fixation cross appeared in a random location (constant across participants) within an invisible 10-cm zone centered on the target in the y dimension and centered at the participant's midline in the x dimension. Thus, the reaching target was always to the left of the fixation cross. Participants were instructed to look at the cross for the duration of the reach (so that V targets always appeared in the left visual field). To prevent participants from noticing that the V targets were shifting during the adaptation block, the 10-cm fixation cross zone shifted at the same rate as the V target. We checked whether any participants' reaching endpoints were influenced by the position of the fixation cross by regressing the x coordinate of reach endpoints to P targets against the x coordinate of the fixation cross during Adaptation, but no participant appeared to be following the fixation cross (all regression R^2s were <.15).

Targets and Perturbation

VP targets represented the situation of interest, that is, the participant was estimating the position of his left (target) hand with both visual and proprioceptive estimates available. We imposed a misalignment between these estimates: over the course of the Adaptation block (Figure 2B), the V component gradually shifted away from the P component in the forward direction (i.e., positive y direction) such that, by the end of the Adaptation block, the V component was 70 mm farther away from the participant than the P component (Figure 2B, bottom row).

The unimodal V and P target reaches were used to assess visual and proprioceptive realignment and sensory weights as described below. During the adaptation block, the unimodal V target shifted away from the participant at the same rate as the V component of VP targets (1.67 mm shift added every VP reach). Participants were told at the beginning of the session that some targets would consist of their target finger plus the white square, but that in these cases the white square was projected directly on top of their target finger. When participants positioned their target finger on VP trials, the white square appeared when they were within 5 cm of the tactile marker; thus, participants briefly saw the V component moving consistently with the P component. Every participant was questioned at the end of the experiment about whether they felt the V component of VP targets was always on top of the P component. Four participants of 52 reported that the V component seemed forward of the P component at some point in the experiment; removing these participants from the analysis did not alter the results, so they were left in.

Visual Feedback

Participants received no visual feedback about their performance and never learned whether they were hitting the targets or not. At the beginning of each trial, a cursor was shown over the right fingertip so that participants could place it within the start box. V targets remained visible throughout the trial, but the cursor disappeared when participants began the reach to the target. The cursor did not reappear until the next trial began, and the right finger was within a square zone around the start box. Each side of this zone was equal to half the distance from the start box to the target.

Behavioral Task Measures

Variance of Vision and Proprioception

To determine whether cTBS disrupted normal visual or proprioceptive processing in the brain, we compared the two-dimensional variance of reach endpoints on V and P targets in Base 1 and Base 2. To account for any consistent drift over the course of the block, for each participant we first removed any linear trend from each dimension of the reach endpoints for each target type (van Beers et al., 1998).

Weight of Vision versus Proprioception

To calculate weights, we relied on the fact that reaches to targets of different modalities are biased in different directions, even in the absence of a perturbation (e.g., Smeets, van den Dobbelsteen, de Grave, van Beers, & Brenner, 2006; Haggard, Newman, Blundell, & Andrew, 2000; Crowe, Keessen, Kuus, van Vilet, & Zegeling, 1987; Foley & Held, 1972). In keeping with previous work (Block & Bastian, 2010, 2011, 2012), we reasoned that on VP reaches, participants would point closer to their mean V endpoint position if they were assigning more weight to vision, and closer to their mean P endpoint position if they were assigning more weight to proprioception. If w_v is experimental weight of vision relative to proprioception, w_p is experimental weight of proprioception relative to vision, and "P to VP distance" is the linear distance between mean P endpoint and mean VP endpoint,

$$w_v = \frac{(\text{P to VP distance})}{(\text{P to VP distance}) + (\text{V to VP distance})} \quad (2)$$

$$w_p = 1 - w_v = \frac{(\text{V to VP distance})}{(\text{P to VP distance}) + (\text{V to VP distance})} \quad (3)$$

For simplicity, we will refer to weights only in terms of vision (w_v). We computed a separate w_v for every VP reach to minimize interference from any sensory drift or recalibration over time. For the ith VP reach (VP$_i$), we used the mean position of the four V and four P endpoints

occurring closest in time, and compared these two positions to the mean position of VP$_i$, VP$_{i-1}$ and VP$_{i+1}$.

It should be noted that this method of weight calculation is meaningful only if the sets of V and P endpoints are spatially distinct from one another. We therefore discarded any w_v that resulted from a calculation where the V to P separation was smaller than half a standard deviation of either the V or P endpoint distributions (a cutoff of one standard deviation yielded similar results but caused more w_v to be discarded). Van Beers et al. (van Beers et al., 2002; van Beers, Sittig, & Gon, 1999) have shown that weights are matrices rather than scalars; that is, the brain uses one w to estimate hand position in azimuth and a different W_v for depth. Our calculation of a single w_v using two-dimensional distances is therefore a simplification, but this was necessary here because the visual and proprioceptive covariance matrices were not known, and V and P endpoints were often not separated enough in depth to calculate w_v for that dimension.

In previous studies using this experimental setup, participants' weights were not affected by the modality of the previous target (Block & Bastian, 2011). Using the same analysis, in this study we found that for all but two participants, weights following V targets did not differ from weights following P targets (two-sample t test $p > .05$). The two exceptions were both in the Pz group and had opposite effects; one relied more on vision after P trials, the other after V trials. Overall, w_v was similar after V versus P trials. On average this was 0.47 and 0.49 for Pz; 0.46 and 0.44 for AG; 0.45 and 0.41 for Sham.

Realignment of Proprioception and Vision

We used performance on unimodal V and P targets during Adaptation to assess sensory realignment. We quantified proprioceptive realignment ($\Delta\hat{y}_P$) as the shift in P endpoints in the y dimension from the beginning to the end of the Adaptation block. In similar experiments, this shift was not influenced by the shifting fixation cross position, motor adaptation, participants' memory of reaching distance, or participants' memory of visual target position (Block & Bastian, 2011). If $\hat{y}_{P\alpha}$ is the mean of the first four P endpoint y coordinates in the Adaptation block, and $\hat{y}_{P\beta}$ is the mean of the last four, then

$$\Delta\hat{y}_P = \hat{y}_{P\beta} - \hat{y}_{P\alpha} \approx \Delta\hat{Y}_P \qquad (4)$$

Here, $\Delta\hat{y}_P$ (our measured change in P endpoints) is approximately equivalent to $\Delta\hat{Y}_P$ (change in the brain's proprioceptive estimate of target hand position).

Although proprioceptive realignment that compensates for the visuoproprioceptive misalignment would cause an overshoot of P targets (positive value), visual realignment would cause an undershoot of V targets. To calculate visual realignment ($\Delta\hat{y}_V$), we subtracted the change in V end-

points from 70 mm (the magnitude of the visuoproprioceptive misalignment) so that compensatory visual realignment will have a positive sign like compensatory proprioceptive realignment. If $\hat{y}_{V\alpha}$ is the mean of the first four V endpoint y coordinates in the Adaptation block and $\hat{y}_{V\beta}$ is the mean of the last four, then

$$\Delta\hat{y}_V = 70 \text{ mm} - (\hat{y}_{V\beta} - \hat{y}_{V\alpha}) \approx \Delta\hat{Y}_V \qquad (5)$$

Relationship of Weighting and Realignment

Finally, we evaluated whether the location we stimulated in the AG group is important for the relationship between weighting and realignment, where the lowest-weighted sensory modality realigns most (Block & Bastian, 2011; van Beers et al., 2002; Ghahramani et al., 1997). For each group, we calculated a correlation between proprioceptive realignment ($\Delta\hat{y}_P$) and weight of vision relative to proprioception (w_v) averaged across Adaptation for each individual.

Statistical Analysis

To assess whether corticospinal excitability had changed after the experiment, we performed a repeated-measures ANOVA (ANOVA$_{RM}$) for RMT and SI1mV to compare across groups and time. To compare reach endpoint variance on V and P targets in Base 1 and Base 2, we performed two separate repeated-measure ANOVAs (ANOVA$_{RM}$) for V and P reach endpoint variance, with Group (AG, Pz, Sham) as between-participant factor and Time (Base 1 or Base 2) as within-paticipant factor. To determine if w_v changed after cTBS, we performed an ANOVA$_{RM}$ on w_v in Base 1 and Base 2. To determine whether cTBS had an effect on $\Delta\hat{y}_V$ or $\Delta\hat{y}_P$, we performed a two-way ANOVA with factors Group and Modality. To calculate the correlations between w_v and $\Delta\hat{y}_P$ for each group, we computed Pearson's linear correlation coefficient.

To compare the w_v–$\Delta\hat{y}_P$ correlation across the three groups, we used a chi-square procedure for comparing more than two correlation coefficients (Zar, 1999). This involved transforming each r to a z value, allowing us to calculate a chi-square value with $k - 1 = 2$ degrees of freedom (equation 19.31 in Zar, 1999),

$$X^2 = \sum_{i=1}^{k}(n_i - 3)z_i^2 - \frac{\left[\sum_{i=1}^{k}(n_i - 3)z_i\right]}{\sum_{i=1}^{k}(n_i - 3)} \qquad (6)$$

We then performed a post hoc pairwise procedure analogous to the Dunnett test to compare the AG correlation coefficient to the Sham and Pz correlation coefficients (equation 19.39 in Zar, 1999, with AG as group A and Sham or Pz as group B):

$$q = \frac{z_B - z_A}{\sqrt{\frac{1}{n_A - 3} + \frac{1}{n_B - 3}}} \qquad (7)$$

Finally, we performed two power analyses with $\alpha = 0.05$ to determine (1) how much power there was in the Sham group to detect a significant correlation of w_v–$\Delta\hat{y}_P$ and (2) to determine how many participants would be needed to have that amount of power in the AG group. All hypothesis tests are reported two tailed.

RESULTS

cTBS Had No Effect on Reach Endpoint Variance or Visuoproprioceptive Weighting

Our results indicate that cTBS did not affect reach endpoints to V or P targets for different groups. There was a trend for endpoint variance on V targets to differ across groups, but there was no significant difference across Time and there was no Time × Group interaction for either V or P targets. This indicates that brain stimulation did not affect reach endpoint variance (ANOVA$_{RM}$ for variance of V reach endpoints: $F(1, 49) = 0.025$, $p = .88$ for time; $F(2, 49) = 2.80$, $p = .07$ for group; and $F(2, 49) = 0.43$, $p = .65$ for interaction. ANOVA$_{RM}$ for variance of P reach endpoints: $F(1, 49) = 1.89$, $p = .18$ for time; $F(2, 49) = 2.33$, $p = .11$ for group; and $F(2, 49) = 0.29$, $p = .76$ for interaction). The AG group had a trend of more variable V reach endpoints than Sham or Pz, including in the Base 1 block before cTBS was applied. It is unlikely that the group trend in endpoint variance affected our w_v calculation, which relies on V and P endpoints being spatially distinct. Increased endpoint variance might affect our w_v calculation only in the sense that it could cause V and P endpoint distributions to overlap so much that the weight must be discarded (see Methods). However, on average only three weights (out of 60) were discarded because of a lack of V–P separation per AG participant, compared with 4.4 and 3.2 weights per Pz and Sham participant, respectively. This indicates that the group trend in variance did not impact weight calculation.

We also found that cTBS in different locations did not cause the groups to weight vision versus proprioception differently. There was a slight trend for w_v to change over time (ANOVA$_{RM}$ time effect $F(1, 49) = 2.95$, $p = .09$), but there was no significant interaction of Group × Time ($F(2, 49) = 0.8$, $p = .45$; Table 1), and weight of vision versus proprioception (w_v) did not differ across groups ($F(2, 49) = 0.16$, $p = .85$ for group effect).

Although participants were free to choose their reach duration (i.e., speed of movements) and to make corrections, we wanted to verify that there was no systematic bias of stimulation site on movement time. We performed an ANOVA on reach duration and found that, while all groups got faster from Base 1 to Base 2 (ANOVA$_{RM}$ time effect $F(1, 49) = 4.39$, $p = .041$), there was no group effect ($F(2, 49) = 2.13$, $p = .13$) and no interaction of Group × Time ($F(2, 49) = 0.06$, $p > .9$). This suggests that TMS in the different groups did not affect movement time.

### cTBS Did Not Disrupt Visuoproprioceptive Realignment

In general, participants tended to realign vision more than proprioception, but cTBS in different locations had no effect on either type of realignment. As such, a two-way ANOVA of realignment (Group vs. Realignment Modality, V or P) showed a significant effect for Realignment Modality ($F(1, 98) = 49.2$, $p < .01$), but no effect of Group ($F(2, 98) = 0.08$, $p = .93$) or interaction ($F(2, 98) = 1.10$, $p = .34$). Of note, the AG group did not appear to realign any differently than Sham (Figure 3D and G). Indeed, we found little difference in total realignment ($\Delta\hat{y}_P + \Delta\hat{y}_V$) across groups; this was 47 mm for Sham, 45 mm for Pz, and 46 mm for AG (Table 1). This is inconsistent with the suggestion by Clower et al. (1996) that the region in PPC we stimulated could be involved in proprioceptive realignment. Importantly, although the AG group did not weight or realign differently from the other groups, individual participants performed the task in a variety of ways. The sample participants in Figure 3A–F illustrate that, although all three realigned similarly (Figure 3D–F), the AG participant had a high w_v and the Sham and Pz participants had a low w_v.

cTBS over AG Disrupted the Relationship between Weighting and Realignment

We previously found that weighting and realignment correlate, such that when a misalignment between vision and proprioception was introduced, the lower-weighted sensory modality tended to realign more. The correlation between weight and proprioceptive realignment was 0.55, with $p = .010$ (Block & Bastian, 2011). This was true of patients with cerebellar lesions as well (correlation $r = .84$, $p = .017$; Block & Bastian, 2012). In this study, we found that cTBS over AG disrupted this relationship between weight and proprioceptive realignment ($r = -.17$, $p = .51$; Table 1; Figure 4A). Importantly, when cTBS was applied over Pz or Sham stimulation was delivered, participants experienced a significant correlation between weight and proprioceptive realignment (Sham group: $r = .56$, $p = .01$, Figure 4B; Pz group: $r = .56$, $p = .02$, Figure 4C). This indicates that the disruptive effects of cTBS are specific to the AG location and not because of some nonspecific consequence of cTBS (i.e., attention or placebo). This is illustrated on the individual level in Figure 3A–F where Sham and Pz participants with small realignment of proprioception (Figure 3E–F) had correspondingly low w_v (Figure 3B–C). However, the AG participant, with a similar small realignment of proprioception (Figure 3D) had a high w_v (Figure 3A).

To assess whether the AG group's trend toward greater V target reaching endpoint variance even before cTBS could influence the relationship between proprioceptive realignment and weight of vision during the Adaptation block, we calculated a correlation for V endpoint variance

Figure 3. Individual and group results showed no significant effect on visual or proprioceptive realignment. (A–C) Samples of representative participants for each group. Reach endpoints in XY to visual (blue), proprioceptive (red), and combined (purple) targets (targets at the origin). Ellipses reflect 90% confidence intervals. Although we calculated weight of vision versus proprioception (w_V) on a trial-by-trial basis, it is possible to see from the confidence ellipses that for the AG participant in (A), the VP endpoints better match the V endpoints, reflecting a high w_V. Conversely, for the two Sham (B) and Pz (C) participants, VP endpoints better match the P endpoints, reflecting a lower w_V. (D–F) Reach endpoints in the y dimension to visual (blue), proprioceptive (red), and combined (purple) targets in the Adaptation block. Dashed gray line indicates that P targets did not shift during adaptation, but V targets (solid gray line) did, to a maximum of

70 mm away from P targets by the end of Adaptation. A shift in P endpoints (dashed red line) from P targets signifies proprioceptive realignment ($\Delta\hat{y}_P$). If V endpoints (blue line) fall short of V targets (solid gray line), visual realignment ($\Delta\hat{y}_V$) is implied. (A) This AG participant realigned proprioception (red line, $\Delta\hat{y}_P = 8.3$ mm) and vision (blue line, $\Delta\hat{y}_V = 39.6$ mm). (B) This Sham participant realigned proprioception 6.7 mm and vision 36.5 mm. (C) This Pz participant realigned proprioception 8.4 mm and vision 32.5 mm. (G–I) Group mean reach endpoints, with standard error (shaded regions). Insets: magnitude of group mean proprioceptive (red) and visual (blue) realignment, with standard error. There were no significant differences across groups over time, suggesting that cTBS did not affect V or P realignment differently in different groups.
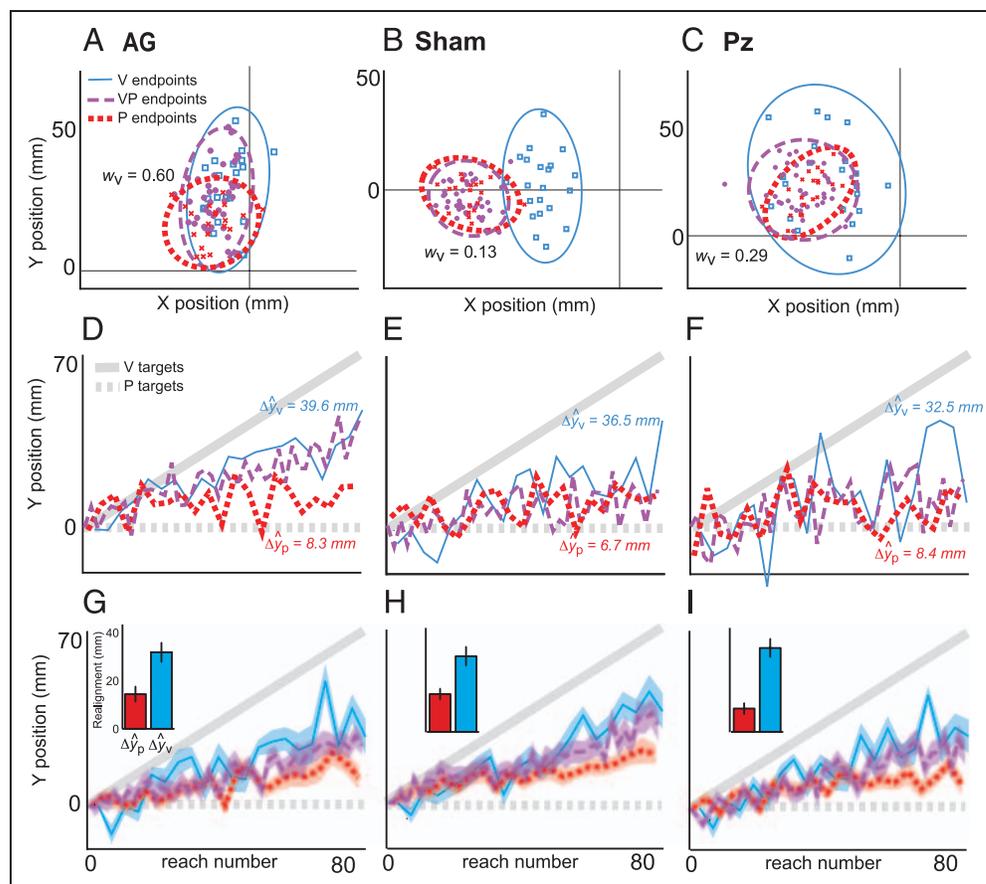
in Base 1 versus the ratio of $\Delta\hat{y}_P/w_V$. This was not significant (correlation $r = .68$, $p = .8$, regression $R^2 = .005$). This suggests that the lack of correlation between $\Delta\hat{y}_P$ and w_V in the AG group is not because of that group's trend toward greater reaching variance. Importantly, even when we performed the analysis with the two most extreme AG participants removed (Figure 4 coordinates [0.34, 48] and [0.58, −13]), weight and realignment were

Figure 4. Relationship between weighting and realignment was disrupted in AG group. Proprioceptive realignment ($\Delta\hat{y}_P$) and weight of vision (w_V) are significantly correlated during Adaptation in Sham (B) and Pz (C) groups, but not in the AG group (A). This indicates that cTBS in the AG group disrupted the relationship between visuoproprioceptive weight and realignment. Dashed line represents the best fit line for a similar experiment in Block and Bastian (2011); with 19 participants, the correlation r was .55 ($p = .01$). Open circles represent the sample participants in Figure 3A–F.
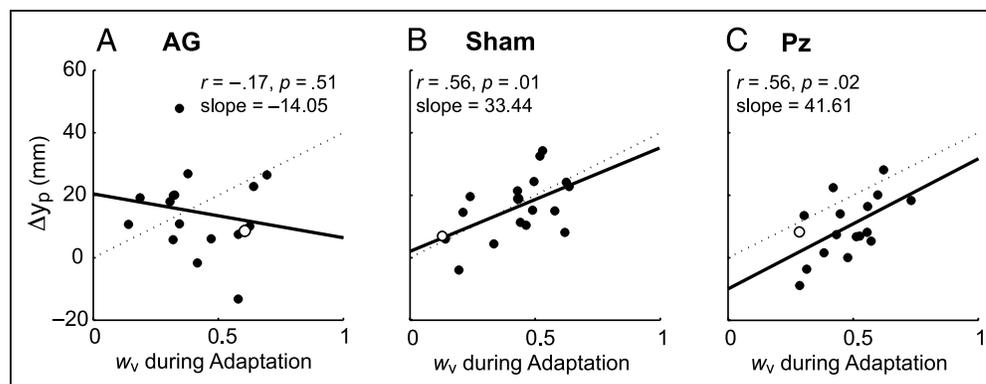
clearly unrelated ($r = .04$, $p = .89$), indicating that the lack of $\Delta\hat{y}_P$–w_v correlation in AG is not because of the presence of outliers.

To ensure that the lack of correlation in the AG group was not because of lack of statistical power, we performed a power analysis using the Sham group data ($n = 18$) and found that there was 80% power ($\alpha = 0.05$, one-sided) to detect a significant correlation of w_v–$\Delta\hat{y}_P$. Yet the AG group, with a similar number of participants, did not have a significant correlation. Indeed, when running a power analysis using the AG group data, we found that to have 80% power to detect a significant correlation, we would need 213 participants. This demonstrates that the AG group is clearly different from the Sham group in terms of w_v–$\Delta\hat{y}_P$ correlation.

Finally, a statistical comparison between the correlations across groups revealed a significant difference in weighting–realignment correlations ($\chi^2 = 6.2$, $df = 2$, $p = .045$). Post hoc tests showed that the AG correlation was significantly different from both Sham ($q = -3.10$, $k = 3$, $p < .01$) and Pz ($q = 3.02$, $k = 3$, $p < .01$). This suggests that disrupting AG with cTBS interfered with the computation that results in larger proprioceptive realignment for a higher weight of vision versus proprioception, and vice versa.

cTBS Had No Detectable Effect on Corticospinal Excitability

To ensure that the cTBS effects on weighting and realignment interaction were not because of changes in corticospinal excitability, we measured RMT and MEP amplitudes to SI1mV before and after the cTBS. There were no group, time, or interaction effects for SI1mV response (all ANOVA$_{RM}$ $p > .4$). RMT did not change differently across groups ($F(2, 43) = 0.47$, $p = .63$), and there was no group by time interaction ($F(2, 43) = 0.93$, $p = .40$). However, there was an effect of time ($F(1, 43) = 4.98$, $p = .03$), with a small increase in RMT for all groups (Table 1), suggesting that the behavioral experiment, rather than cTBS, may have affected RMT. We believe the increased RMT might be due an increase in sleepiness; participants were sitting in near-darkness, and the task was quite repetitive. Anecdotally, many participants reported that the experiment made them sleepy. This could account for the change in RMT over time (De Gennaro et al., 2007). Importantly, altogether these results indicate that cTBS did not cause a systematic change in corticospinal excitability (Table 1), and therefore, this cannot explain the abolishment of the w_v–$\Delta\hat{y}_P$ correlation in the AG group.

DISCUSSION

We applied disruptive cTBS to the location in the angular gyrus proposed by Clower et al. (1996) as potentially involved in proprioceptive realignment; we examined the effects on vision, proprioception, visuoproprioceptive weighting and realignment, and the relationship between weighting and realignment. We found that the interaction between weighting and realignment was only disrupted with cTBS over the angular gyrus location, in the absence of other sensory integration deficits. This suggests that this region is important for the computation which results in sensory realignment being related to weights. Importantly, the sham and midline parietal cTBS groups showed a strong correlation between the two processes, similar to what has been observed previously in healthy and cerebellar patients (Block & Bastian, 2011, 2012), where the lower-weighted modality is realigned more.

The PPC has connections with motor cortex (e.g., Koch & Rothwell, 2009; Johnson, Ferraina, Bianchi, & Caminiti, 1996), subcortical motor structures like the cerebellum (e.g., Clower, West, Lynch, & Strick, 2001), and sensory areas such as somatosensory, visual, and auditory cortices (e.g., Lewis & van Essen, 2000; Andersen, Asanuma, Essick, & Siegel, 1990; Blatt, Andersen, & Stoner, 1990; see Andersen, Snyder, Bradley, & Xing, 1997, for a review). This large, heterogeneous region is divided by the IPS into superior and inferior parietal lobules. The areas around and in the IPS are anatomically modular and have been shown in both humans and monkeys to integrate different sensory inputs for controlling action in space (e.g., Caspers et al., 2006; Grefkes & Fink, 2005; Hyvarinen, 1981). For instance, neurons in monkey Area 7, a region thought to have a homologue in human superior parietal lobule (Husain & Nachev, 2007), integrate tactile and visual stimuli that overlap in space, responding more when the monkey can see its hand while manipulating objects (Graziano & Gross, 1993). Additionally, activity in multisensory areas of the IPS and inferior parietal lobe is associated with congruent visual and tactile stimulation of the hand in humans (Beauchamp, Pasalar, & Ro, 2010). When participants localize touch to different fingers, behavioral performance is significantly better when the touches are accompanied by congruent visual input, indicating multisensory integration (Pasalar, Ro, & Beauchamp, 2010). When PPC is disrupted with TMS near the junction of anterior IPS and the postcentral sulcus, participants' localization performance is reduced to unisensory levels, suggesting a causal role for this region of PPC in human visual–tactile integration (Pasalar et al., 2010).

It has been speculated that PPC also mediates multisensory processes that can compensate for perturbations in the environment or affecting our body (Clower et al., 1996). For example, when reaching to grasp an object underwater, where the light is bent by water, we see the hand in a different location than we feel it proprioceptively. Movement errors initially occur in a situation like this, but a healthy person quickly learns to compensate. This process can include a change in weighting (the brain can ignore the proprioceptive estimate of the hand's location and focus solely on vision) and/or realignment (the brain can shift the proprioceptive estimate closer to the visual estimate or vice versa).

Often, multisensory research focuses on sensory weighting or sensory realignment when in reality these processes are active at the same time (Block & Bastian, 2011; Welch, Widawski, Harrington, & Warren, 1979). This makes it difficult to identify the neural bases of these processes. For instance, in a PET study of prism adaptation, Clower et al. (1996) found activity in a region within PPC (along the IPS in the angular gyrus) that they suggested could be related to proprioceptive realignment. However, Pisella et al. challenge this notion, describing an optic ataxia patient with a lesion that included this region who was able to adapt to a prism perturbation (Pisella et al., 2004). Importantly, neither study demonstrated a causal relationship. The former was a PET study, which leaves open the possibility that activation changes are not functionally relevant to task performance. In the latter case, it is known that prism adaptation paradigms can elicit adaptation in the motor system (Martin, Keating, Goodkin, Bastian, & Thach, 1996) as well as in sensory systems, with potential changes in both sensory weighting and realignment (Welch & Warren, 1986). Thus, the patient may have adapted to the perturbation using an alternative process.

In investigating the neural bases of sensory weighting and realignment, it is important to consider that these processes can act together. Although sensory weighting and realignment can operate separately and are biologically independent (Block & Bastian, 2011), they can be correlated, with the lower-weighted modality realigning more (Block & Bastian, 2011; Ghahramani et al., 1997). This is important for precise motor control, because it results in the higher-weighted (presumably more reliable) modality contributing more to perception. How does the relationship between weighting and realignment come about? There are at least two possibilities: One, the relationship between weight and realignment is an emergent property. For instance, a third factor such as variance affects both weight and realignment, and at times this other factor causes weights and realignment to correlate (Figure 1A(1)). If so, inhibitory brain stimulation should not be able to disrupt the correlation between weight and realignment unless it disrupts either weighting or realignment itself. The second possibility is that a specific neural process is at work controlling the relationship of weight and realignment. In other words, there is a neural computation that can dictate (participant to task demands; Block & Bastian, 2011) how much realignment ought to happen given a certain weight. This second possibility implies that in addition to neural mechanisms for weight and realignment, there are specific neural substrates for interactions between the two (Figure 1A(2)). If so, it might be possible to disrupt the correlation between weight and realignment without disrupting either process.

Here we show evidence to support the second possibility. We used cTBS to focally decrease cortical excitability at the PPC coordinates described by Clower et al. (1996) and found a specific disruption of the relationship between sensory weights and realignment without affecting either individual process. In all experimental groups, we found both proprioceptive and visual realignment consistent with previous work (Block & Bastian, 2011, 2012). Specifically, there was no differential effect of cTBS on weighting, visual or proprioceptive realignment, or visual or proprioceptive reaching endpoint variance. Importantly, in both sham and Pz cTBS groups, we observed a strong relationship between weighting and realignment consistent with theory and previous results (Block & Bastian, 2011, 2012; Ghahramani et al., 1997), where the lower-weighted modality is realigned more. In the AG group, however, this relationship was absent. Of note, for this particular study participants were not penalized for performance differences and received no on-line or endpoint visual feedback during the task. As there were no nonspecific performance differences in timing or endpoint variance across groups, we conclude that this region in AG is important specifically for the interaction between weighting and realignment (Figure 1A(2)). At the same time, our findings do not support the idea that this area is important for proprioceptive realignment, a possibility raised by Clower et al. (1996). Indeed, it is possible that in their prism adaptation task, this region was involved in computing how much proprioceptive realignment should occur based on the weights of vision and proprioception and thus was significantly activated.

In terms of a given individual within the AG group, our results suggest that stimulating this area causes some degree of mismatch between weighting and realignment. In other words, perception does not take full advantage of the most reliable sensory modality, which could ultimately impair the individual's interactions with the environment. For example, a given person's vision may be more reliable and weighted higher than proprioception, but if that person encounters a misalignment and realigns mostly vision rather than proprioception, then his higher-weighted, more precise modality will no longer reflect the environment well. Our results suggest that the area disrupted in the AG group is involved in matching weighting and realignment. We do not think the lack of correlation in the AG group is because of excitability differences in primary motor cortex or any nonspecific effects of cTBS, such as noise, attention, or prickling sensations, because the Pz group, stimulated nearby (about 3.5 cm distant) over midline parietal cortex, experienced the same sensations, but had a strong correlation between weighting and realignment. Also, it is unlikely that the effects of cTBS wore off before the end of the experiment. In motor cortex, the decreased excitability caused by cTBS has been described to last up to 60 min (Di Lazzaro et al., 2005; Huang et al., 2005), and our experiment ended approximately 30 min after application of cTBS. Importantly, all groups underwent the same experimental design and timing between cTBS and behavior.

In addition, there is no evidence to suggest cTBS in AG or the control site is less effective than in motor cortex. cTBS is thought to act by reducing calcium-binding protein expression in inhibitory interneurons, which

affects dendritic integration of synaptic inputs to pyramidal cells (Benali et al., 2011). This mechanism is likely to work as well in PPC and other cortical regions. Indeed, cTBS has been successfully used over the parietal cortex to study, for example, visual extinction (Cazzoli, Muri, Hess, & Nyffeler, 2009), visual neglect (Nyffeler, Cazzoli, Hess, & Muri, 2009), attention (Cazzoli, Wurtz, Muri, Hess, & Nyffeler, 2009), and audiovisual integration (Bertini, Leo, Avenanti, & Ladavas, 2010).

In summary, our results suggest that the angular gyrus near the IPS, on the border between BA 39 and BA 40, is the substrate that allows successful interactions between visuoproprioceptive weighting and realignment. In other words, this region computes the magnitude of visual and proprioceptive realignment based on visuoproprioceptive weight. This also implies that the correlation observed between weighting and realignment is not simply an emergent property of separate neural pathways for the two processes. Rather, it is actively mediated by a third neural process whose substrate includes the region we disrupted. This is a novel addition to our knowledge about multisensory processing. These results suggest that individuals with damage to this area may have difficulty making use of the most reliable sensory modality available when compensating for sensory perturbations, likely leading to impaired movement. This may be the case, for instance, for patients with optic ataxia. Future research will need to explore how best to treat movement difficulties that result from lesions in this brain area.

REFERENCES

Andersen, R. A., Asanuma, C., Essick, G., & Siegel, R. M. (1990). Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. *Journal of Comparative Neurology, 296,* 65–113.

Andersen, R. A., Snyder, L. H., Bradley, D. C., & Xing, J. (1997). Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annual Review of Neuroscience, 20,* 303–330.

Balslev, D., Miall, R. C., & Cole, J. (2007). Proprioceptive deafferentation slows down the processing of visual hand feedback. *Journal of Vision, 7,* 12–17.

Beauchamp, M. S., Pasalar, S., & Ro, T. (2010). Neural substrates of reliability-weighted visual-tactile multisensory integration. *Frontiers in Systems Neuroscience, 4,* 25.

Benali, A., Trippe, J., Weiler, E., Mix, A., Petrasch-Parwez, E., Girzalsky, W., et al. (2011). Theta-burst transcranial magnetic stimulation alters cortical inhibition. *Journal of Neuroscience, 31,* 1193–1203.

Bertini, C., Leo, F., Avenanti, A., & Ladavas, E. (2010). Independent mechanisms for ventriloquism and multisensory integration as revealed by theta-burst stimulation. *European Journal of Neuroscience, 31,* 1791–1799.

Blatt, G. J., Andersen, R. A., & Stoner, G. R. (1990). Visual receptive field organization and cortico-cortical connections of the lateral intraparietal area (area LIP) in the macaque. *Journal of Comparative Neurology, 299,* 421–445.

Block, H. J., & Bastian, A. J. (2010). Sensory reweighting in targeted reaching: Effects of conscious effort, error history, and target salience. *Journal of Neurophysiology, 103,* 206–217.

Block, H. J., & Bastian, A. J. (2011). Sensory weighting and realignment: Independent compensatory processes. *Journal of Neurophysiology, 106,* 59–70.

Block, H. J., & Bastian, A. J. (2012). Cerebellar involvement in motor but not sensory adaptation. *Neuropsychologia, 50,* 1766–1775.

Bremmer, F., Duhamel, J., Ben Hamed, S., & Graf, W. (1997). The representation of movement in near extra-personal space in the macaque ventral intraparietal area (VIP). In P. Thier & H. Karnath (Eds.), *Parietal lobe contributions to orientation in 3D space* (pp. 619–630). Heidelberg, Germany: Springer-Verlag.

Bremmer, F., Schlack, A., Shah, N. J., Zafiris, O., Kubischik, M., Hoffmann, K., et al. (2001). Polymodal motion processing in posterior parietal and premotor cortex: A human fMRI study strongly implies equivalencies between humans and monkeys. *Neuron, 29,* 287–296.

Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., & Zilles, K. (2006). The human inferior parietal cortex: Cytoarchitectonic parcellation and interindividual variability. *Neuroimage, 33,* 430–448.

Cazzoli, D., Muri, R. M., Hess, C. W., & Nyffeler, T. (2009). Horizontal and vertical dimensions of visual extinction: A theta burst stimulation study. *Neuroscience, 164,* 1609–1614.

Cazzoli, D., Wurtz, P., Muri, R. M., Hess, C. W., & Nyffeler, T. (2009). Interhemispheric balance of overt attention: A theta burst stimulation study. *European Journal of Neuroscience, 29,* 1271–1276.

Clower, D. M., Hoffman, J. M., Votaw, J. R., Faber, T. L., Woods, R. P., & Alexander, G. E. (1996). Role of posterior parietal cortex in the recalibration of visually guided reaching. *Nature, 383,* 618–621.

Clower, D. M., West, R. A., Lynch, J. C., & Strick, P. L. (2001). The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *Journal of Neuroscience, 21,* 6283–6291.

Colby, C. L., Duhamel, J. R., & Goldberg, M. E. (1993). Ventral intraparietal area of the macaque: Anatomic location and visual response properties. *Journal of Neurophysiology, 69,* 902–914.

Crowe, A., Keessen, W., Kuus, W., van Vliet, R., & Zegeling, A. (1987). Proprioceptive accuracy in two dimensions. *Perceptual and Motor Skills, 64,* 831–846.

De Gennaro, L., Marzano, C., Veniero, D., Moroni, F., Fratello, F., Curcio, G., et al. (2007). Neurophysiological correlates of sleepiness: A combined TMS and EEG study. *Neuroimage, 36,* 1277–1287.

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P., et al. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *Journal of Physiology, 565,* 945–950.

Duhamel, J. R., Colby, C. L., & Goldberg, M. E. (1998). Ventral intraparietal area of the macaque: Congruent visual and somatic response properties. *Journal of Neurophysiology, 79,* 126–136.

Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping, 30,* 2907–2926.

Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature, 415,* 429–433.

Foley, J. M., & Held, R. (1972). Visually directed pointing as a function of target distance, direction, and available cues. *Perception & Psychophysics, 12,* 263–268.

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., & Classen, J. (2008). Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: Evidence of rapid polarity-reversing metaplasticity. *Cerebral Cortex, 18,* 2046–2053.

Ghahramani, Z., Wolpert, D. M., & Jordan, M. I. (1997). Computational models for sensorimotor integration. In P. G. Morasso & V. Sanguinetti (Eds.), *Self-organization, computational maps and motor control* (pp. 117–147). Amsterdam: North-Holland.

Graziano, M. S., & Gross, C. G. (1993). A bimodal map of space: Somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. *Experimental Brain Research, 97,* 96–109.

Grefkes, C., & Fink, G. R. (2005). The functional organization of the intraparietal sulcus in humans and monkeys. *Journal of Anatomy, 207,* 3–17.

Haggard, P., Newman, C., Blundell, J., & Andrew, H. (2000). The perceived position of the hand in space. *Perception & Psychophysics, 62,* 363–377.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45,* 201–206.

Husain, M., & Nachev, P. (2007). Space and the parietal cortex. *Trends in Cognitive Sciences, 11,* 30–36.

Hyvarinen, J. (1981). Regional distribution of functions in parietal association area 7 of the monkey. *Brain Research, 206,* 287–303.

Inoue, K., Kawashima, R., Satoh, K., Kinomura, S., Goto, R., Sugiura, M., et al. (1997). Activity in the parietal area during visuomotor learning with optical rotation. *NeuroReport, 8,* 3979–3983.

Johnson, P. B., Ferraina, S., Bianchi, L., & Caminiti, R. (1996). Cortical networks for visual reaching: Physiological and anatomical organization of frontal and parietal lobe arm regions. *Cerebral Cortex, 6,* 102–119.

Kaminski, J. A., Korb, F. M., Villringer, A., & Ott, D. V. M. (2011). Transcranial magnetic stimulation intensities in cognitive paradigms. *PLoS One, 6,* e24836.

Klam, F., & Graf, W. (2003). Vestibular signals of posterior parietal cortex neurons during active and passive head movements in macaque monkeys. *Annals of the New York Academy of Sciences, 1004,* 271–282.

Koch, G., & Rothwell, J. C. (2009). TMS investigations into the task-dependent functional interplay between human posterior parietal and motor cortex. *Behavioural Brain Research, 202,* 147–152.

Krakauer, J. W., Ghilardi, M. F., Mentis, M., Barnes, A., Veytsman, M., Eidelberg, D., et al. (2004). Differential cortical and subcortical activations in learning rotations and gains for reaching: A PET study. *Journal of Neurophysiology, 91,* 924–933.

Law, S. K. (1993). Thickness and resistivity variations over the upper surface of the human skull. *Brain Topography, 6,* 99–109.

Lee, J.-H., & van Donkelaar, P. (2002). Dorsal and ventral visual stream contributions to perception-action interactions during pointing. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale, 143,* 440–446.

Leitão, J., Thielscher, A., Werner, S., Pohmann, R., & Noppeney, U. (2012). Effects of parietal TMS on visual and auditory processing at the primary cortical level—A concurrent TMS-fMRI study. *Cerebral Cortex*. doi:10.1093/cercor/bhs078.

Lewis, J. W., & van Essen, D. C. (2000). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *Journal of Comparative Neurology, 428,* 112–137.

Martin, T. A., Keating, J. G., Goodkin, H. P., Bastian, A. J., & Thach, W. T. (1996). Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. *Brain, 119,* 1199–1211.

Mon-Williams, M., Wann, J. P., Jenkinson, M., & Rushton, K. (1997). Synaesthesia in the normal limb. *Proceedings of the Royal Society - Biological Sciences, 264,* 1007–1010.

Newport, R., Brown, L., Husain, M., Mort, D., & Jackson, S. R. (2006). The role of the posterior parietal lobe in prism adaptation: Failure to adapt to optical prisms in a patient with bilateral damage to posterior parietal cortex. *Cortex, 42,* 720–729.

Nyffeler, T., Cazzoli, D., Hess, C. W., & Muri, R. M. (2009). One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. *Stroke, 40,* 2791–2796.

Pasalar, S., Ro, T., & Beauchamp, M. S. (2010). TMS of posterior parietal cortex disrupts visual tactile multisensory integration. *European Journal of Neuroscience, 31,* 1783–1790.

Pisella, L., Michel, C., Grea, H., Tilikete, C., Vighetto, A., & Rossetti, Y. (2004). Preserved prism adaptation in bilateral optic ataxia: Strategic versus adaptive reaction to prisms. *Experimental Brain Research, 156,* 399–408.

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology, 91,* 79–92.

Siebner, H. R., Hartwigsen, G., Kassuba, T., & Rothwell, J. C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? - Implications for studies of cognition. *Cortex, 45,* 1035–1042.

Silvanto, J., Cattaneo, Z., Battelli, L., & Pascual-Leone, A. (2008). Baseline cortical excitability determines whether TMS disrupts or facilitates behavior. *Journal of Neurophysiology, 99,* 2725–2730.

Smeets, J. B., van den Dobbelsteen, J. J., de Grave, D. D., van Beers, R. J., & Brenner, E. (2006). Sensory integration does not lead to sensory calibration. *Proceedings of the National Academy of Sciences, U.S.A., 103,* 18781–18786.

van Beers, R. J., Sittig, A. C., & Denier van der Gon, J. J. (1998). The precision of proprioceptive position sense. *Experimental Brain Research, 122,* 367–377.

van Beers, R. J., Sittig, A. C., & Gon, J. J. (1999). Integration of proprioceptive and visual position-information: An experimentally supported model. *Journal of Neurophysiology, 81,* 1355–1364.

van Beers, R. J., Wolpert, D. M., & Haggard, P. (2002). When feeling is more important than seeing in sensorimotor adaptation. *Current Biology, 12,* 834–837.

Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering, 9,* 527–565.

Wann, J. P., & Ibrahim, S. F. (1992). Does limb proprioception drift? *Experimental Brain Research, 91,* 162–166.

Welch, R. B., & Warren, D. H. (1986). Intersensory interactions. In K. R. Boff, L. Kaufman, & J. P. Thomas (Eds.), *Handbook of perception and human performance: Vol. 1. Sensory processes and perception* (pp. 25.21–25.36). New York: Wiley.

Welch, R. B., Widawski, M. H., Harrington, J., & Warren, D. H. (1979). An examination of the relationship between visual capture and prism adaptation. *Perception & Psychophysics, 25,* 126–132.

Zar, J. (1999). Simple linear correlation. In *Biostatistical analysis* (Vol. 4, pp. 377–412). Upper Saddle River, NJ: Prentice Hall.