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Programs for action in superior parietal cortex: A triple-pulse TMS investigation

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Abstract:

Converging evidence from neurological patients and functional brain imaging studies strongly supports the notion that the posterior parietal cortex (PPC), especially in the left hemisphere, plays a critical role in both the programming (i.e., setting the initial movement parameters of the reach) and the online control of goal-directed reaching movements. Importantly, however, there is no clear consensus on how *different subregions* within the PPC contribute to the programming and online control of reaching. In the current study, we investigated the role of the inferior (IPL) and superior (SPL) parietal lobules in reach programming using MRI-guided event-related transcranial magnetic stimulation (TMS). Specifically, we applied triple-pulse (tp) TMS to either the left IPL or the left SPL at different time points during reaching movements either at target onset (programming) or at movement onset (online control) while participants (n=16) made pointing movements to targets in the periphery without visual feedback of the moving hand. Stimulating the SPL but not the IPL resulted in a significant increase in endpoint errors when tp-TMS was applied during the programming phase compared to the online control phase. In short, these data demonstrate that the SPL plays a critical role in real-time movement programming.

Introduction

Several theories of visuomotor control distinguish between the programming (i.e., setting the initial movement parameters) of a reach, and the online control of the reach itself (Desmurget, Pelisson, Rossetti, & Prablanc, 1998; Glover, 2004; Jeannerod, 1997; Milner & Goodale, 2006). Over the past century, converging evidence from human neuropsychology (Balint, 1909; Perenin & Vighetto, 1988; for a review see Pisella et al., 2007), functional brain imaging (Astafiev et al., 2003; Culham, Cavina-Pratesi, & Singhal, 2006; Culham et al., 2003; Prado et al., 2005), and single cell recording in non-human primates (for a review see Buneo & Andersen, 2006; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975; Snyder, Batista, & Andersen, 1997) have demonstrated that the posterior parietal cortex (PPC) plays a critical role in both the programming and online control of goal directed actions. Although we know that the PPC plays a role in visually-guided reaching, the specific role of different subregions of the PPC in these processes is still relatively unknown.

Some have argued that the inferior parietal lobule (IPL; i.e., the angular gyrus and supramarginal gyrus) is critical for the programming of goal directed reaching whereas the superior parietal lobule (SPL) and intraparietal sulcus (IPS) are critical for online control (Glover, 2004; Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006). In contrast, others have argued that the SPL and related areas in IPS play a critical role in programming as well as the online control of visually-guided reaches (Buneo & Andersen, 2006; Goodale & Milner, 2004; Milner & Goodale, 2006). Although these two different models make explicit predictions about the respective roles of the IPL and SPL in movement programming and online control, it is difficult to test this directly in patients for two reasons. First, patients with isolated SPL lesions (i.e., optic ataxia) are difficult to find as many patients often have damage to the IPL as well as other

structures. Second, given that the lesion is irreversible in these patients it is difficult to isolate the exact point in time during the reach at which these parietal structures become engaged (i.e., programming vs. online control).

One technique that can be used to circumvent these problems is transcranial magnetic stimulation (TMS). TMS allows one to make "virtual" lesions in an otherwise intact brain by applying brief magnetic pulses through the skull to perturb neural processing in a particular area (Paus, 2005; Walsh & Pascual-Leone, 2003). By temporarily disrupting a relatively specific brain area in this way one can avoid one of the major problems associated with studying patients with brain lesions, specifically, the fact that such lesions are permanent and are usually large as well as non-focal. Despite the large number of TMS studies on the parietal cortex (for a review see Rushworth & Taylor, 2006), there are no studies that we are aware of that have examined the influence of TMS applied to the IPL and the SPL on "real-time" movement programming (i.e., programming the movement while vision of the target still available) – although there are some studies that have demonstrated TMS effects on either the SPL or the intraparietal sulcus (IPS) in online control (Desmurget et al., 1999; Glover, Miall, & Rushworth, 2005; Rice, Tunik, & Grafton, 2006; Tunik, Frey, & Grafton, 2005),

Two recent studies have examined the influence of TMS on "motor planning" using reaction time as a dependent measure (Busan, Barbera et al., 2009; Busan, Monti, Semenic, Pizzolato, & Battaglini, 2009); however, neither of these studies examined motor performance. Thus, it is unclear whether these studies were indexing the effects of TMS on motor attention (Rushworth, Ellison, & Walsh, 2001; Rushworth, Nixon, Renowden, Wade, & Passingham, 1997) or motor intention (Desmurget et al., 2009; Desmurget & Sirigu, 2009) as opposed to movement programming. Moreover – and more importantly – neither of these studies directly

compared the influence of stimulating the IPL or the SPL on motor programming as distinct from its possible effects on online control.

In addition, a few recent studies have examined the influence of TMS in the PPC using delayed reaching tasks in which the participant is shown the target for a brief period and is then asked to point to the target following a delay (Smyrnis, Theleritis, Evdokimidis, Muri, & Karandreas, 2003; Vesia, Monteon, Sergio, & Crawford, 2006; Vesia, Prime, Yan, Sergio, & Crawford, 2010; Vesia, Yan, Henriques, Sergio, & Crawford, 2008). Results from these studies generally indicate an increase in endpoint error or variability when TMS is applied during the memory delay period. Although this could be seen as an influence on movement programming, it is unclear whether the influence of TMS in these studies is affecting the movement program or the quality of the memory representation of the position of the target with respect to the position of the hand. This is an important distinction given that a great deal of neuropsychological evidence suggests that movements that are programmed and executed in "real-time" may rely on different visual representations and anatomical substrates compared to movements which are executed following a brief delay (Goodale, Jakobson, & Keillor, 1994; Milner, Dijkerman, McIntosh, Rossetti, & Pisella, 2003; Milner et al., 2001; Rice et al., 2008; Rossit et al., 2008; Striemer, Chapman, & Goodale, 2009; Whitwell, Striemer, Nicolle, & Goodale, 2011). Finally, none of the previously mentioned studies investigating the influence of TMS on movement programming used MRI-guided frameless stereotaxy but instead targeted the PPC using 10-20 EEG electrodes coordinates. Thus, it is also unclear which particular subdivisions of the parietal lobe were actually contributing to the TMS-induced disruptions in motor planning or programming in these studies. For further discussion on issues pertaining to cerebral localization, see Chouinard and Paus (2010).

With all this in mind, we asked the following question: what roles do the IPL and SPL play in movement programming while participants reach to targets? Triple-pulse (tp) TMS (3 pulses, 1 every 100ms) was applied in an event-related fashion to sites in the IPL or the SPL either at target onset (programming) or at movement onset (online control). Importantly, although the target was visible during the programming phase, participants always completed their reach without any visual feedback of the moving hand or the target (i.e., "open-loop"). We presented targets in peripheral vision because patients with damage to the PPC are more impaired for reaching to these targets compared to targets presented in central vision (Clavagnier, Prado, Kennedy, & Perenin, 2007; Perenin & Vighetto, 1988).

This paradigm was ideally suited to examine the effects of tp-TMS on movement programming because when tp-TMS was applied at target onset it would potentially disrupt the initial programming of the movement. Following movement onset, visual feedback was removed preventing the participant from using vision to make any online corrections to this perturbed movement program using visual feedback loops. Thus, endpoint errors in this condition reflect the effect of tp-TMS on the participants' initial movement program. In contrast, when tp-TMS was applied at movement onset, the initial movement program should still be relatively accurate since it would have already been parameterized. Because visual feedback was not available during the movement, and there were no sudden changes in target position, the need (and opportunity) for online control via visual feedback loops was minimal. The only disruption that might have potentially occurred would be an influence of TMS on proprioceptive feedback about hand position during the execution of the movement. Thus, we designed the paradigm explicitly to make it more likely that the primary effect of tp-TMS would be to disrupt movement programming rather than online control using visual feedback. To summarize, while the IPL

acted as a nearby active control site of stimulation to compare with SPL stimulation, the application of tp-TMS during online control acted as an additional temporal control to compare the influence of TMS during programming. In order to target different subregions of the PPC, we used frameless stereotaxy (Paus, 1999) to guide the TMS coil over each of these areas as defined in each participant's MRI based on anatomical landmarks (see Methods). In turn, this ensured that our sites of TMS stimulation were restricted either to the IPL or the SPL, and that they were sufficiently far enough away from one another.

Based on the design of our study, the two competing theories of parietal function that we described earlier, i.e. the IPL for programming and SPL for online control (Glover, 2004; Pisella et al., 2006) vs. the SPL for programming and online control (Buneo & Andersen, 2006; Milner & Goodale, 2006) make contrasting predictions. Specifically, if the SPL is critical for movement programming then we would expect larger endpoint errors when TMS is applied to the SPL compared to the IPL during programming versus online control. In contrast, if the IPL is critical for programming then the opposite effect should be observed. That is, greater endpoint errors when the IPL is stimulated compared the SPL during programming versus online control.

Methods

Participants

Sixteen right-handed students (mean age = 26 years, age range = 19 to 32 years, 5 females) from the University of Western Ontario participated in this experiment. All participants were carefully screened to ensure that they had no prior history of major head injury and that there was no history of epilepsy in their immediate family. None of the participants reported taking either anti-convulsant or psychiatric medications. All participants were informed of the

potential risks of participating in the study and they provided informed written consent. All procedures were approved by the Health Sciences Research Ethics Board at the University of Western Ontario.

Apparatus and Procedure

Participants were seated 40cm away from a vertically mounted 32 inch LCD touch screen (Mass Multimedia Inc.; refresh rate 60Hz) with their head placed in a chin rest to minimize head movement. Prior to testing each subject, we calibrated the touch screen to ensure optimal accuracy. The manufacturer's specification for the resolution of the touch screen is 16k x 16k, which translates into a measurement resolution of well under 1 mm. Each trial began with the participant pressing (and holding down) a start button with the index finger of their right hand (Cedrus RB-530) that was aligned to their midline and placed 30cm from the surface of the screen. Participants were told to maintain fixation throughout the trial (eye movements were observed by one of the two experimenters). Participants wore LCD goggles (PLATO, Translucent Technologies) that could be changed from a clear to an opaque state (in less than 5 ms) to eliminate visual feedback of the moving hand and the target at movement onset.

Following a random delay of between 1 to 3 s after the participant pressed the start button, a target appeared on the screen. The participant was then required to reach out and touch the target as quickly and accurately as possible with the index finger of their right (dominant) hand while maintaining fixation. Targets were black circles (1cm diameter, subtending 1.4° of visual angle) presented on a grey background. Targets were always presented in the right visual field at either 11° or 23° of eccentricity. We presented targets only in the right visual field because we stimulated the left hemisphere which controls the right (dominant) hand and which

processes visual information from the right visual field. We could have also included left visual field targets but we would have expected no (or minimal) effects for these targets unless we also stimulated the right hemisphere (see for example, Chouinard, Whitwell, & Goodale, 2009). Given that our primary research question was to examine programming vs. online control and not the left vs. right visual field we opted not to include left visual field targets to keep the testing time (2.5 hours) and number of experimental conditions manageable. The locations of the targets were randomly jittered by 2° around the two primary locations (i.e., the targets appeared in locations ranging from 9°-13° or 21°-25°) to ensure that participants could not easily memorize their locations. As soon as the participants' index finger left the start button the goggles immediately switched to the opaque state eliminating any visual feedback of both the target and the reaching hand (Figure 1). The goggles remained opaque for 1s after the trial ended (and then subsequently opened) in order to ensure that no feedback regarding accuracy was available. This ensured that participants remained unaware of any effect of TMS on their reach accuracy. Trials were spaced 10s apart to prevent cumulative effects of consecutive trains of TMS as recommended by published safety guidelines (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

The primary dependent measure in the current experiment was endpoint error (the Euclidian distance between the movement endpoint and the actual target location). We also measured reaction time (RT; the time that elapsed between target onset and movement onset), and movement time (MT; the time between the release of the button and contact with the surface of the touch screen). In total, the experiment consisted of 6 blocks including no TMS, sham TMS (coil oriented away from the head), and 4 parietal TMS sites (see below for details). The order in which the sites were tested was determined for each participant using a Latin square design to

eliminate any possible order effects. Each TMS block contained 48 trials such that there were 12 trials at each eccentricity (11° vs. 21°) for each time window of TMS delivery (i.e., either during programming or online control). The order of trials within a block was randomized. Prior to the start of the experiment each participant received 10 practice trials with and without TMS in order to familiarize themselves with the task.

Transcranial magnetic stimulation (TMS)

TMS was delivered at 100% of resting motor threshold using a Magtsim Rapid stimulator (Whitland, UK) with an air cooled 70mm figure-8 coil (Magstim). Resting motor threshold was determined using visual inspection of the minimum stimulation intensity needed to evoke a visible twitch in the first dorsal interosseous muscle of the right hand on 5/10 trials (mean =55% of stimulator output, range= 47%-64%) when the TMS coil was placed over the hand area of the primary motor cortex. Certain measures were taken to ensure that TMS applied to each of our parietal sites did not spread to the primary motor cortex. EMG recordings (Grass Model 15LT, recording at 10-1000Hz, Ag/Cl electrodes) from the flexor (bicep) and extensor (tricep) muscles of the reaching arm were taken in 4 of the 16 participants during task performance. Moreover, prior to each block of trials that involved TMS to a parietal site, we applied test pulses in each of our participants with their right arm fully extended in front of them to see whether or not this stimulation would invoke a motor response. All participants wore ear plugs during the testing session as recommended by published TMS safety recommendations (Rossi et al., 2009). Note that even though participants wore ear plugs the sound of the TMS pulses was still audible in the sham stimulation condition.

Triple pulse (tp)-TMS consisted of 3 pulses that were delivered every 100 ms during either of one of two different temporal windows (i.e. during movement programming phase or during movement execution). As shown in Figure 1, we applied the event-related tp-TMS starting either immediately after target onset (17ms given a refresh rate of 60Hz) to disrupt movement programming or at movement onset to disrupt on-line control. We chose to use 3 pulses at 10Hz to ensure that participants could not release the start button, or complete their movement, prior to the offset of the TMS stimulation. The timing of TMS delivery was randomized across trials within each testing block so participants could not predict at what time the TMS would be delivered on any given trial. For all stimulation sites over the parietal cortex, we held the coil tangentially to the scalp with the short axis angled 45° relative to the inter-hemispheric fissure and perpendicular to the central sulcus. The induced current in the brain flowed in a posterior-to-anterior and lateral-to-medial direction. Sham stimulation was applied with the edge of the coil placed over the posterior parietal cortex such that the induced magnetic field was directed away from the brain.

--Insert Figure 1 about here--

Sites of stimulation

Stimulation sites in the left posterior parietal lobe were identified on the participants' MRIs using anatomical criteria. MRI scans for each participant consisted of 192 slice T1-weighted images (voxels were 1 mm isotropic in size) obtained locally from either a 4T Varian or a 3T Siemens Tim-Trio MRI scanner at the Robarts Research Institute (London, ON, Canada). The stimulation sites consisted of two sites within the IPL (the angular and supramarginal gyri)

and two sites within the SPL (a more anterior region (aSPL) and a more posterior region (pSPL)). The angular gyrus was defined as the region which encapsulated the most dorsal extension of the superior temporal sulcus. The supramarginal gyrus was defined as the region which encapsulated the most dorsal extension of the Sylvian fissure. The posterior and anterior SPL sites were determined by placing the marker 12-15mm dorsally and 20mm medially from the location of the angular and supramarginal gyri sites respectively. This ensured that the intended site of stimulation in the SPL was always above the IPS and sufficiently away from the IPL sites. After having marked each of these target sites on the participant's MRI, we noted their coordinates in native space and transformed these coordinates into Talairach space using the Brainsight software package (Rogue Research, Montreal, QC, Canada). The mean Talairach coordinates (with SDs) for each of these stimulation sites as well as each participant's coordinates are reported in Table 1.

Using frameless stereotaxy (Paus, 1999), we then co-registered the participant's head with their MRI and guided the TMS coil to a target location (Brainsight Software; Polaris System, Northern Digital, Waterloo, ON, Canada). The TMS coil was hand-held by the experimenter and the position of the coil with respect to intended site of stimulation was always tracked and adjusted as necessary in real-time using the Brainsight system to ensure optimal stimulation precision. Also, we saved (in Brainsight) the location of where the TMS coil touched the scalp in the participant's MRI. Using a procedure described in detail elsewhere (Paus & Wolforth, 1998), we used this information to create images of virtual trajectories that projected from the TMS coil into the head perpendicularly to the plane of the coil from where it touched the scalp. This served to provide estimates for the location of induced currents in the brain. Overall, the location of projected coil trajectories was consistent across participants (see Figure 2

for four representative participants). Although we had no strict hypothesis regarding the specific site within the IPL or SPL which would be critical for programming vs. online control, we opted to test two sites within each region initially in order to prevent ourselves from "missing" any important systematic differences that might exist between the contributions of these subregions to movement programming and online control.

--Insert Figure 2 here--

--Insert Table 1 here--

Data reduction and analysis

Mean endpoint error (mm), RT (ms), and MT (ms) were determined separately for each participant at each eccentricity (11° vs. 23°) in each testing block (no TMS, sham, and the four parietal sites). Trials in which the touch screen failed to record the movement endpoint or trials in which the RT or MT was more than 2 SDs greater than a participants overall mean for that condition were removed from the analysis. This accounted for less than 5% of trials. All data were analyzed using within-subject ANOVAs with Site of Stimulation, Time of TMS Delivery, and Target Eccentricity as the within-subject factors. All effects that we report as reaching significance from ANOVA survived Greenhouse-Geisser corrections (Greenhouse & Geisser, 1959). These effects were further investigated using post-hoc paired samples t-tests with a Tukey's HSD correction. Thus, when comparing 3 means with 15 degrees of freedom $t \geq 2.60$. For all comparisons we set the critical $\alpha = .05$.

Preliminary analyses

A preliminary analysis was conducted to examine any possible differences in endpoint error between sites within the IPL (i.e., angular vs. supramarginal gyrus) and within the SPL (i.e., anterior vs. posterior SPL). For sites within the IPL ($F(1,15)=1.24$, $p=.28$) and within the SPL ($F(1,15)=2.87$, $p=.11$) there was no main effect of site, and no interactions involving site (all p's >.49). Given that there were no significant differences in endpoint error between sites *within* the IPL and the SPL and that we had no specific hypothesis regarding which site within the IPL or SPL would be critical for movement programming vs. online control, we collapsed across sites within the IPL and the SPL for our subsequent analyses. In addition, we also compared endpoint errors in the no TMS condition with endpoint errors in the sham TMS condition using a one-way within-subject ANOVA. There were no significant differences in endpoint errors between the different conditions ($F(5,75)=1.01$, $p=.42$). Therefore, we collapsed the endpoint error data in the no TMS and sham conditions into a "control" condition to give us the best possible estimate of baseline performance in this task.

Results

None of the participants reported discomfort when asked how the TMS or sham stimulation felt after each block of trials. In addition, we did not see any evidence of a spread of current to the motor cortex from either the EMG recordings that were taken in 4 of the 16 participants during task performance or from test pulses delivered over each of our parietal sites in all our participants with their right arm fully extended in front of them. Based on these results,

we can conclude that any disruption in behavior from our TMS procedures is unlikely to be the result of having disrupted the motor cortex.

Coil placement

The Talairach coordinates for each stimulation site for each subject are reported in Table 1. The mean coordinates for SMG were X = -50, Y = -47, Z = 37, the mean coordinates for ANG were X = -40, Y = -67 and Z = 35, the mean coordinates for aSPL were X = -30, Y = -50, Z = 48, and the mean coordinates for pSPL were X = -20, Y = -67, and Z = 46. Thus, Euclidian distances between these points were on average greater than 2.2 cm, which suggests minimal (if any) overlap in the effects of stimulation between these sites if one were to consider, based on TMS mapping studies of the primary motor cortex, that the spread of current at 100% of motor threshold is less than 2.0 cm with a standard 70 mm figure-of-eight coil (Thielscher & Kammer, 2004).

Effects of TMS on endpoint accuracy

The effects of TMS on end-point accuracy are shown in Figure 3. A 3-way within-subject ANOVA compared endpoint error across the three sites (control, IPL, SPL), at two different times of TMS delivery (programming vs. online control) and two different eccentricities (11° vs. 23°). This ANOVA revealed a significant main effect of Site of Stimulation ($F(2,30)=3.95$, $p=.03$). Post-hoc comparisons using a Tukey HSD correction revealed that endpoint error following SPL stimulation (40mm) was larger than the control condition (33mm; ($t(15)=2.67$, $p<.05$). In addition, endpoint error following IPL stimulation (38mm) was not significantly different from either the control condition (33mm; $t(15)=1.68$, ns) or SPL stimulation (40mm;

t(15)1.07, ns). There was also a main effect of Target Eccentricity ($F(1,15)=18,71$, $p=.001$) such that endpoint error was larger for targets presented at 23° (40mm) compared to 11° (34mm).

More importantly, there was also a significant Site of Stimulation × Time of TMS Delivery interaction ($F(2,30)=8.56$, $p=.001$; Figure 3a). Tukey's HSD post-hoc tests conducted on the difference scores between programming and online control at each site (Figure 3b) indicated that the influence of TMS on endpoint error was significantly larger when TMS was applied during movement programming compared to online control in the SPL (1.8mm) compared to both the IPL (0.27mm; $t(15)=2.70$, $p<.05$) and the control condition (-0.35mm; $t(15)=3.40$, $p<.05$; Figure 3b). Critically, the difference in endpoint error when TMS was delivered during programming vs. online control in the IPL was not significantly different from the control condition ($t(15)=1.67$, ns).

--Insert Figure 3 here--

Effects of TMS on reaction time (RT)

The effects of TMS on reaction times (RT) are shown in Figure 4a. For the RT analysis, we did not collapse RTs from the no TMS and sham conditions because a preliminary analysis indicated that the RTs in the sham condition differed significantly from the no TMS condition ($F(5,75)=3.54$, $p=.006$). Therefore, for the purposes of the RT analysis, we present only the data from the sham condition as the baseline comparison condition because these data allow us to examine the degree to which the effects of TMS on RT are simply due to the sound of the TMS pulses acting as a "GO" cue.

A 3-way ANOVA for the RT data revealed a significant main effect of Time of TMS Delivery ($F(1,15)=112.75$, $p<.001$) such that RTs were faster when TMS was applied during

programming (352ms) compared to online control (408ms). In addition there was a significant Site of Stimulation × Time of TMS Delivery interaction ($F(2,30)=18.74$, $p<.001$). Pair-wise examination of this interaction using Tukey's HSD post-hoc tests revealed that participants were faster to initiate their movements when TMS was applied during movement programming compared to online control in both the SPL (64ms; $t(15)=4.04$, $p<.05$) and IPL (69ms; $t(15)=5.65$, $p<.05$) relative to sham stimulation (35ms). However, the SPL and IPL were not significantly different from one-another ($t(15)=0.98$, ns). Importantly, a one-sample t-test indicated that RTs were also faster when TMS was applied during programming compared to online control in the sham condition (35ms; $t(15)=6.09$, $p<.001$).

--Insert Figure 4 here--

Effects of TMS on movement time (MT)

For the movement time (MT) analysis, we also present only the data from the sham TMS condition as a baseline because a preliminary analysis revealed significant differences in MT between the no TMS and sham conditions ($F(5,75)=50.33$, $p<.0001$). A 3-way ANOVA carried out on the MT data (Figure 4b) revealed main effects of Time of TMS Delivery ($F(1,15)=920.51$, $p<0001$) and Target Eccentricity ($F(1,15)=13.80$, $p=.002$). The main effect of Time of TMS Delivery indicated that participants MT significantly decreased when TMS was applied during online control (243ms) compared to programming (284ms). The main effect of Target Eccentricity indicated that participants were somewhat slower to execute movements to targets at 11° (266ms) compared to 23° (261ms).

Correlations between endpoint accuracy, reaction time (RT), and movement time (MT)

In order to rule out any possible contributions of disrupted attention or speed-accuracy trade-offs on the endpoint error data reported above, we conducted a series of Pearson bivariate correlations to examine whether there was any relationship between endpoint error and RT, or MT in either the SPL or the IPL. To summarize briefly, there were no significant correlations between endpoint error and RT or MT in the IPL or the SPL regardless of whether the TMS stimulation was applied during programming or online control (all *p*'s >.10 uncorrected; see Table 2). Thus, the current results for endpoint error cannot be attributed to non-specific effects of TMS stimulation such as disrupted attention or speed-accuracy tradeoffs (for further explanation, see Discussion).

--Insert Table 2 here--

Discussion

A long history of research has linked the PPC with the programming (i.e., setting the initial movement parameters) and online control of visually-guided reaching movements (Buneo & Andersen, 2006; Culham & Valyear, 2006; Milner & Goodale, 2006; Mountcastle et al., 1975; Perenin & Vighetto, 1988; Pisella et al., 2006). Yet, there is no clear consensus on how different subregions within the PPC contribute to the programming vs. the online control of reaching. Whereas some have argued that the SPL plays a critical role in both the programming and online control of reaching (Buneo & Andersen, 2006; Milner & Goodale, 2006), others contend that the

IPL plays a critical role in programming and the SPL plays a critical role in regulating online control (Glover, 2004; Pisella et al., 2006). In the current study we specifically sought to examine the role of the IPL and the SPL in reach programming by asking participants to reach to targets in peripheral vision without visual feedback of the moving hand while we applied event-related tp-TMS either at target onset (programming) or during the reach (online control). In other words, participants never had visual feedback of the reaching hand or the target during movement execution.

The results indicated that endpoint errors significantly increased relative to the control condition when TMS was applied to the SPL; however, no statistically significant effects were observed when TMS was applied to the IPL. In addition, the most important finding from the present study was the interaction between Stimulation Site and the Timing of TMS Delivery. Endpoint error significantly increased when tp-TMS was applied during programming compared to online control for the SPL (Figure 3). However, this difference was not apparent when TMS was applied to the IPL or in the control condition without TMS delivery.

Taken together, these results are difficult to reconcile with recent claims that the IPL but not the SPL plays a critical role in visuomotor programming (Glover, 2004; Pisella et al., 2006). Namely, the current results clearly demonstrate that the SPL plays a greater role in programming visually-guided reaches compared to the IPL (Goodale & Milner, 2004; Milner & Goodale, 2006). While these results cannot completely rule out *any* role for the IPL in programming visually-guided reaching, or other motor responses (e.g. eye movements), these results certainly do suggest that if the IPL does play a role in reach programming, it is a subsidiary role relative to the SPL. In fact, as we have argued elsewhere (Goodale & Milner, 2004; Milner & Goodale, 2008), the primary role that the IPL likely plays in visuomotor control is in terms of action

planning rather than action programming. That is to say we contend that the IPL plays an important role in selecting the goal of the action (e.g. I want to pick up a cup) and selecting the target for the action (i.e., the cup) based on incoming visual information from the ventral stream. However, it is the SPL in the dorsal stream that plays the critical role in transforming this information into a coordinate system for reaching (i.e., setting the movement parameters for the reach such as distance, velocity, endpoint, etc).

A greater influence of tp-TMS in the SPL for reach programming compared to online control in our study was expected given that the task we employed was specifically designed to emphasize movement programming by eliminating visual feedback at reach onset (see Introduction). To clarify, we are not suggesting that the SPL plays a greater role in reach programming compared to online control; rather, we have demonstrated that the SPL, in addition to playing a role in online control (Blangero et al., 2008; Glover et al., 2005; Grea et al., 2002; Pisella et al., 2000), also plays a critical role in real-time visuomotor programming.

It is important to emphasize that the effects of TMS on endpoint error in the current study cannot be attributed to either non-specific effects of TMS stimulation, or to spread of current to other regions, because the same effects on endpoint accuracy were not observed when the exact same intensity of stimulation was applied at the same time points to nearby sites in the IPL. Thus, we have dissociated the effects of tp-TMS stimulation in the PPC on endpoint accuracy both spatially (i.e., significant effects only for SPL stimulation) and temporally (i.e., larger effects for programming compared to online control). To reiterate, the same effects of TMS on endpoint error were not observed when we stimulated another nearby control site in the parietal cortex (i.e., the IPL) nor when we stimulated the same sites (both IPL and SPL) at a different point in time during the reach (i.e., during online control). Therefore, these results clearly

demonstrate that the influence of TMS was much larger in the SPL (i.e. no statistically significant effects in IPL) and specific to programming (i.e. no effects during online control).

It is also important to emphasize that our results cannot be attributed to either the influence of TMS on attention or to a simple speed-accuracy trade-off. In order for this to be the case, there would need to be either a significant *positive* correlation between RT and endpoint error (i.e. slowed attention results in impaired accuracy) or a significant *negative* correlation between MT and endpoint error (i.e. as people move faster they become less accurate). Data from the current study do not provide any support for either of these hypotheses (see the correlation-based analyses in Table 2). Specifically, in the current study participants' reaction times were *faster* when TMS was applied during programming compared to online control. Any disruption of attentional mechanisms would likely lead to an *increase* in RT. In addition, these results also cannot be attributed to a speed-accuracy trade-off because movement times were significantly *slower* when TMS was applied during programming (where participants demonstrated the largest endpoint errors) compared to online control. In other words, there was no relationship between how fast a participant reacted, how fast they moved, and how accurate their movement was. Therefore, the significant increase in endpoint error when TMS was applied in the SPL during reach programming occurred independently from any influence of TMS on attention or movement time.

The facilitation effects (i.e. faster responses) observed for reaction time when TMS was applied during programming, and faster movement times when TMS was applied during online control, must be interpreted with caution (Walsh & Pascual-Leone, 2003). The sound and sensation of the TMS pulses on the scalp could have acted as a strong "GO" cue which caused participants to simply speed up whenever TMS was applied. This is further supported by the fact

that *the very same results* were obtained in the *sham* condition for both RT and MT. That is, even when sham TMS pulses were delivered, and no current was induced in the cortex, participants were faster to initiate movements when sham TMS was applied during programming (Figure 4a), and were faster to execute their movements when sham TMS was delivered during online control (Figure 4b). Again, this implies that many of the differences that we observed in RT and MT during active parietal stimulation may be an artifact of the sound invoked by the TMS pulses.

Finally, while we cannot completely rule out the possibility that TMS to the parietal cortex may have resulted in genuine facilitation effects, it is important to reiterate that even if this were the case, this would have no bearing on the interpretation of our results. Specifically, there was no evidence from our correlation analysis to suggest that endpoint errors when TMS was applied to the SPL during programming were related to RT or MT in any way. Thus, the most parsimonious explanation for the current results is that when TMS was applied to the SPL during movement programming it disrupted the participants' initial movement program without any correlated changes in attention.

These facilitation effects are consistent with recent studies showing RT facilitation when TMS is applied over the PPC prior to movement onset (Busan, Barbera et al., 2009; Busan, Monti et al., 2009). However, the same studies also found that RT significantly *increased* when TMS was applied during a narrow temporal window (75% of mean reaction time) prior to movement onset. Although movement programming may have been influenced during this narrow temporal window, it is unclear whether these studies were influencing motor planning (i.e., target selection and action selection) or motor programming (i.e., determining the initial movement parameters) per se as no motor performance measures (e.g., endpoint error) were reported. Such increases in RT might also reflect influences on "motor attention" (Rushworth et

al., 2001; Rushworth et al., 1997) or movement intention (Desmurget et al., 2009; Desmurget & Sirigu, 2009). Both of these processes are more likely to influence movement planning (i.e., goal selection and target selection) rather than programming (i.e., setting the initial movement parameters for the reach). Importantly, both motor attention and motor intention have been localized within the left IPL rather than the SPL (Desmurget & Sirigu, 2009; Rushworth et al., 2001; Rushworth et al., 1997).

The distinction between motor planning (i.e., target selection, goal selection, motor attention, movement intention) and motor programming (i.e., setting the initial reach parameters) is important (Goodale & Milner, 2004; Milner & Goodale, 2008) given that an influence of TMS on motor programming is likely to have a significant impact on subsequent motor performance in terms of movement accuracy (as demonstrated in the current study) whereas an influence on motor planning (i.e., motor attention or intention) may have very little influence on the accuracy of subsequent movements. In fact, recent work in a patient with optic ataxia following dorsal stream lesions has shown that increases in movement reaction time *do not correlate* with movement endpoint accuracy (Striemer et al., 2009) suggesting that attention and action utilize independent visual representations. These results suggest that disrupted attention alone does not necessarily result in impaired visuomotor performance. Although this result has been challenged recently by another single case study (McIntosh, Mulroue, Blangero, Pisella, & Rossetti), the results of the current study lend further support to the findings of Striemer and colleagues (Striemer et al., 2009). Specifically, we have demonstrated in a group of 16 healthy subjects that perturbation of the SPL (using TMS) results in changes in endpoint accuracy without any related changes in RT or MT. Therefore, we have demonstrated that the SPL plays a critical role in real-time movement programming independently from any influence of attention.

Previous studies have argued that patients with optic ataxia following damage to the SPL/IPS are impaired at online control but not movement planning or programming (Glover, 2003, 2004; Pisella et al., 2006; Pisella et al., 2000). However, we feel that there is sufficient evidence to challenge this hypothesis. Specifically, recent work has demonstrated that these patients are impaired at attending to target locations in peripheral vision regardless of whether the patient's task is simple target detection (Pisella et al., 2007; Striemer et al., 2008; Striemer et al., 2007) or the initiation of a reach to the target location (Striemer et al., 2009). Together, these data suggest that patients with optic ataxia are impaired at both motor and non-motor attention.

Furthermore, there is evidence that patients with optic ataxia are also impaired in movement programming. For example, Milner and colleagues (Milner et al., 2003) observed that when patients with optic ataxia were asked to reach to targets in peripheral vision, their reaches started off in the wrong direction from the very outset of their movement which eventually led to large endpoint errors. This would support a programming deficit in that the patient was not able to accurately transform the location of the target in eye-centered coordinates into an arm or hand centered reference frame which resulted in an inaccurate reach (Buxbaum & Coslett, 1997).

In addition, based on the results from the current study, we would predict that patients with optic ataxia should also perform poorly when they are asked to reach to targets in peripheral vision without visual feedback (as was the case in the current study). Interestingly, this is precisely what has been observed in previous studies (Blangero et al., 2007; Jeannerod, 1986; Levine, Kaufman, & Mohr, 1978; Pisella et al., 2009). Again, this tends to support the notion that optic ataxia results from a combination of deficits in both the programming and online control of actions, and furthermore, that movement programming and online control rely on similar neural substrates in the SPL. In fact, when Glover and colleagues (2005) applied TMS to

a very similar region of the SPL (X= -24, Y=-59, Z=61; see Table 1), they demonstrated that participants were unable to initiate online corrections while grasping objects that suddenly changed in size.

Although our use of tp-TMS enabled us to dissociate in time the contributions of reach programming versus online control, an important question that still remains unanswered is the exact point in time at which SPL makes its specific contribution to reach programming. Determining this temporal window could be achieved either by applying single pulses of TMS in the same regions at varying time points following target onset or by applying shorter trains of stimulation. Finally, if attentional mechanisms in the IPL contribute to its role in motor planning (i.e., motor attention, target selection) (Rushworth et al., 2001; Rushworth et al., 1997) or intention (Desmurget et al., 2009; Desmurget & Sirigu, 2009) as we and others have argued, then increases in reaction time should be observed if TMS is applied over the IPL while participants are required to select a reach target amongst distracters compared to a condition where they reach to the same target with no distracters. However, there should be very little influence on endpoint errors.

Conclusion

By having participants reach to targets in the periphery without any visual feedback of the hand or target and delivering tp-TMS either when targets were being presented (programming phase) or during online control, we were able to provide clear evidence that the human SPL plays a critical role in programming visually-guided reaches. This is consistent with the notion that the SPL plays an important role in both the programming and the online control of visually-guided reaches (Buneo & Andersen, 2006; Goodale & Milner, 2004; Milner & Goodale, 2006). Finally,

although we cannot definitively rule out any role for the IPL in reach programming, or in programming other motor responses other than reaching (e.g. eye movements), the current data demonstrate that if the IPL does play a role in reach programming, it is clearly a subsidiary role to that played by the SPL. These data have important implications, not only for our understanding of how the PPC is organized, but also for the interpretation of reaching deficits following lesions of the PPC (i.e., optic ataxia).

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Table 1: Talaraich coordinates for the parietal stimulation sites. SMG=supramarginal gyrus, ANG=angular gyrus, aSPL=anterior superior parietal lobule, and pSPL=posterior superior parietal lobule.

	Stimulation Site											
	SMG			**ANG**			**aSPL**			**pSPL**		
Participant	**x**	**y**	**z**	**x**	**y**	**z**	**x**	**y**	**z**	**x**	**y**	**z**
1	-55	-49	38	-44	-68	38	-35	-50	49	-23	-69	48
2	-49	-43	34	-41	-66	41	-29	-42	43	-22	-64	50
3	-57	-44	40	-51	-59	41	-38	-44	51	-31	-60	52
4	-51	-42	40	-45	-67	31	-32	-51	54	-20	-73	45
5	-54	-43	33	-45	-64	31	-33	-47	45	-25	-68	45
6	-54	-40	43	-44	-57	39	-31	-49	55	-23	-65	50
7	-50	-49	36	-41	-68	36	-31	-52	45	-22	-71	45
8	-52	-44	40	-36	-79	34	-31	-44	46	-15	-72	47
9	-47	-55	39	-43	-68	29	-26	-55	50	-21	-68	40
10	-47	-52	39	-41	-70	36	-28	-56	51	-23	-70	49
11	-44	-51	35	-36	-67	31	-27	-56	46	-18	-72	42
12	-52	-45	38	-38	-65	39	-31	-46	49	-18	-66	50
13	-50	-49	36	-37	-70	32	-33	-46	47	-19	-64	44
14	-38	-54	39	-23	-72	34	-17	-55	53	-6	-70	44
15	-54	-41	36	-41	-60	41	-34	-45	44	-19	-56	51
16	-44	-50	32	-30	-68	31	-26	-55	46	-10	-71	40
Mean	**-50**	**-47**	**37**	**-40**	**-67**	**35**	**-30**	**-50**	**48**	**-20**	**-67**	**46**
SD	**5**	**5**	**3**	**7**	**5**	**4**	**5**	**5**	**4**	**6**	**5**	**4**

Table 2: Correlations between endpoint error, reaction time (RT), and movement time (MT) as a function of site of stimulation (inferior parietal lobe=IPL; superior parietal lobe=SPL), and time of TMS delivery (programming vs. online control).

Site and time of TMS stimulation	**Reaction time (RT)**	**Movement time (MT)**
Endpoint error IPL: programming	r(n=16)= -.26, *p*=.33	r(16)=.09, *p*=.73
Endpoint error IPL: online control	r(n=16)= -.42, *p*=.11	r(16)=.30, *p*=.26
Endpoint error SPL: programming	r(n=16)= -.27, *p*=.31	r(16)= .13, *p*=.63
Endpoint error SPL: online control	r(n=16)= -.36, *p*=.17	r(16)= .32, *p*=.23

Figure captions:

Figure 1. Timing of events in a single trial for TMS stimulation applied during programming (A) or online control (B). When TMS was delivered during the programming phase (panel A) three single pulses were delivered at 17ms, 117ms, and 217ms following target onset. When TMS was delivered during online control (panel B) three single pulses were delivered at 0ms, 100ms, 200ms following movement onset (i.e., the button release). Following the button release the goggles switched to the opaque state removing visual feedback of the hand and target during the reach.

Figure 2. Stimulation sites of four representative participants. The parietal stimulation sites are depicted for four representative participants on 3-D surface reconstructions of the cortical surface (BrainSight 2.0). Abbreviations and color coding: aSPL = anterior superior parietal lobule (in red), pSPL = posterior superior parietal lobule (in green), SMG = supramarginal gyrus (in blue), and ANG = angular gyrus (in orange).

Figure 3. The influence of TMS on endpoint accuracy. Panel A depicts the mean endpoint error (± SE) in millimeters (mm) as a function of Site of Stimulation (control, IPL, SPL), and Time of TMS Delivery (programming, online control). Panel B depicts the mean difference scores (programming minus execution; ± SE) in millimeters as a function of site of stimulation (control, IPL, SPL), and timing of TMS delivery (programming, online control). Asterisks (*) indicate significant differences between conditions ($P_{corr} < 0.05$).

Figure 4. The influence of TMS on reaction time (RT) and movement time (MT). Panel A depicts the mean RT (± SE) in milliseconds (ms) as a function of Site of Stimulation (sham, IPL, SPL), and Time of TMS Delivery (programming, online control). Panel B depicts the mean MT (± SE) in milliseconds as a function of site of stimulation (sham, IPL, SPL), and timing of TMS delivery (programming, online control). Asterisks (*) indicate significant differences between conditions and daggers (†) indicate that the condition is significantly different from sham stimulation ($P_{corr} < 0.05$).

Figure 1.

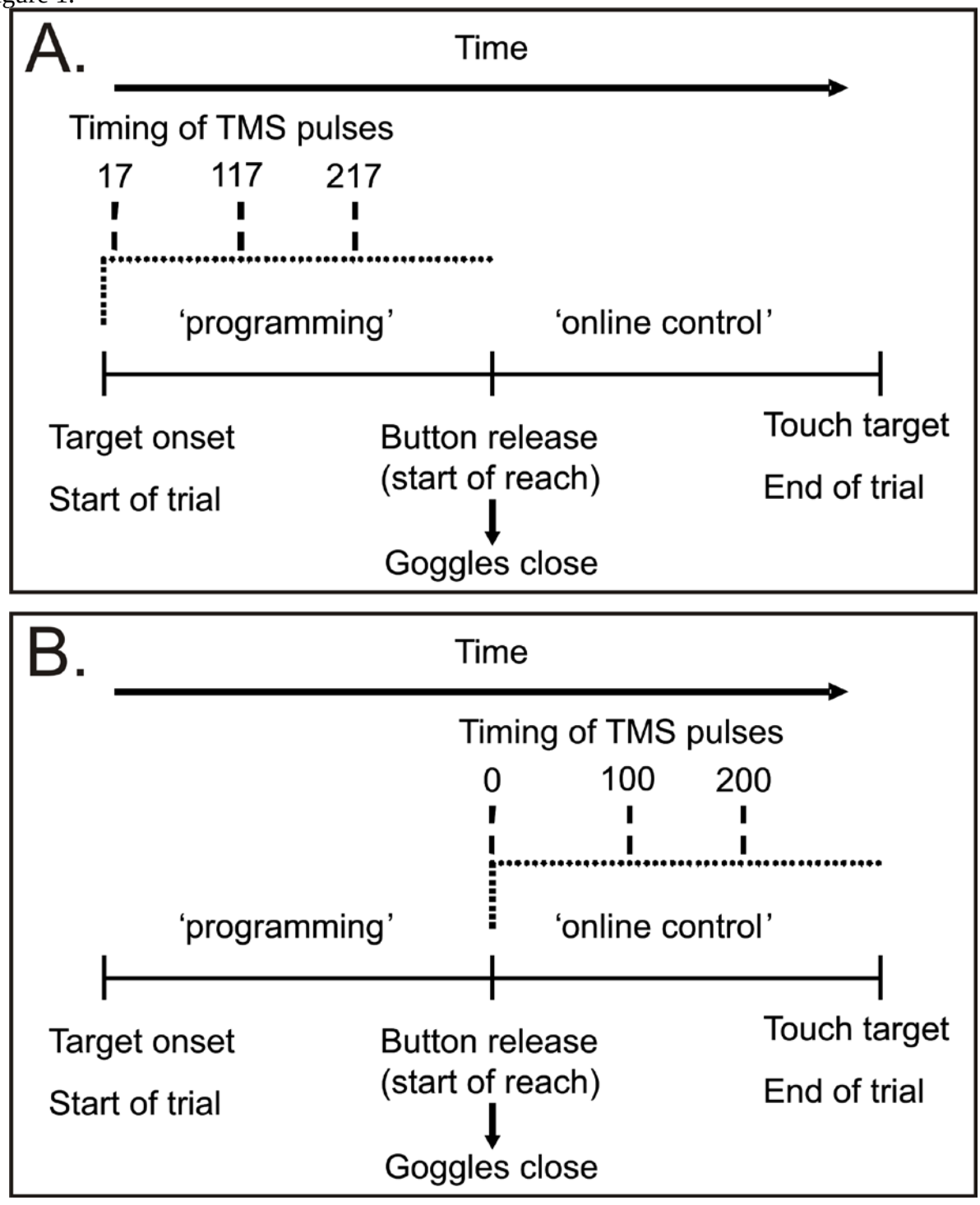

A.
Time
Timing of TMS pulses
17
117
217
'programming'
'online control'
Target onset
Start of trial
Button release
(start of reach)
Goggles close
Touch target
End of trial
B.
Time
Timing of TMS pulses
0
100
200
'programming'
'online control'
Target onset
Start of trial
Button release
(start of reach)
Goggles close
Touch target
End of trial

Figure 2.

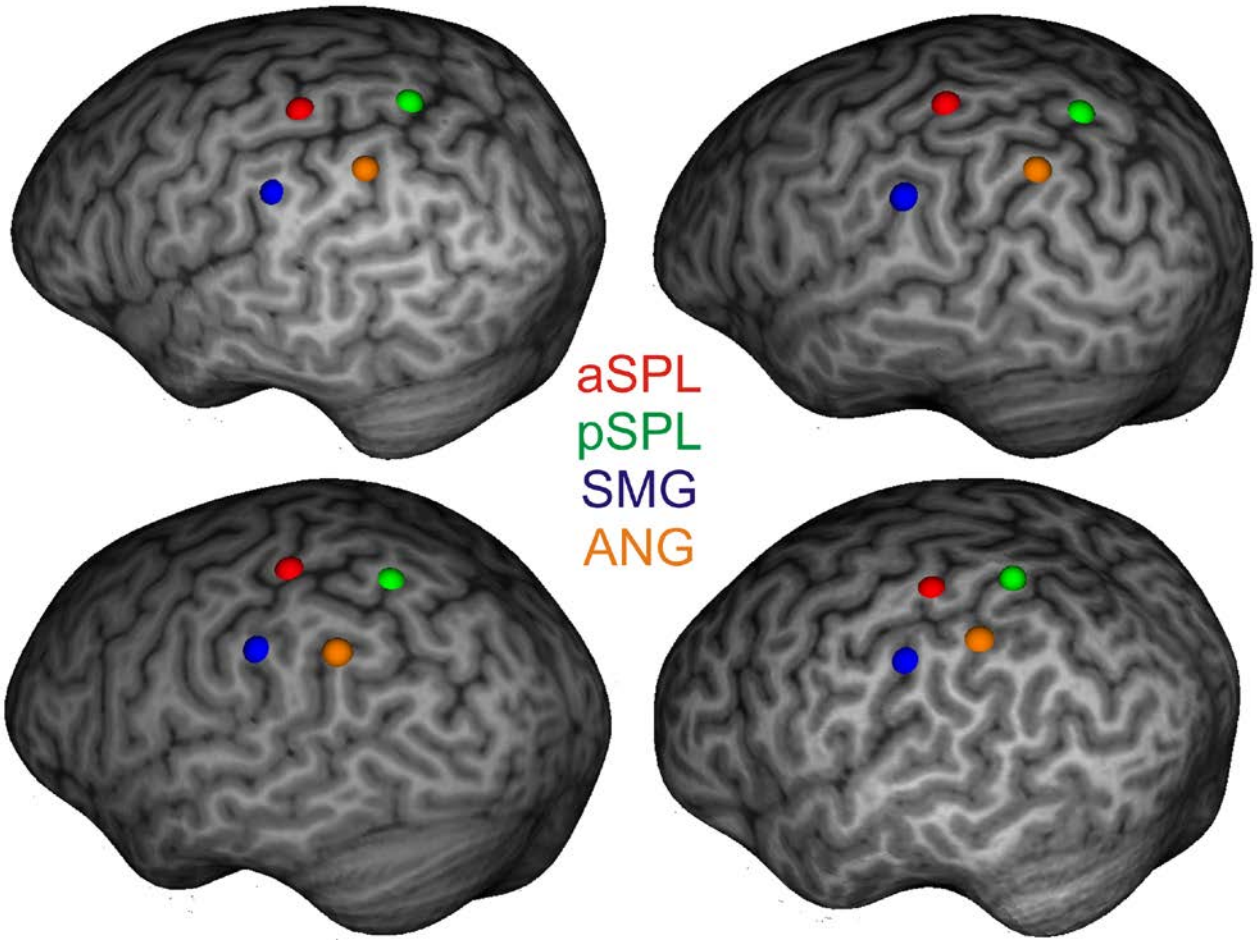
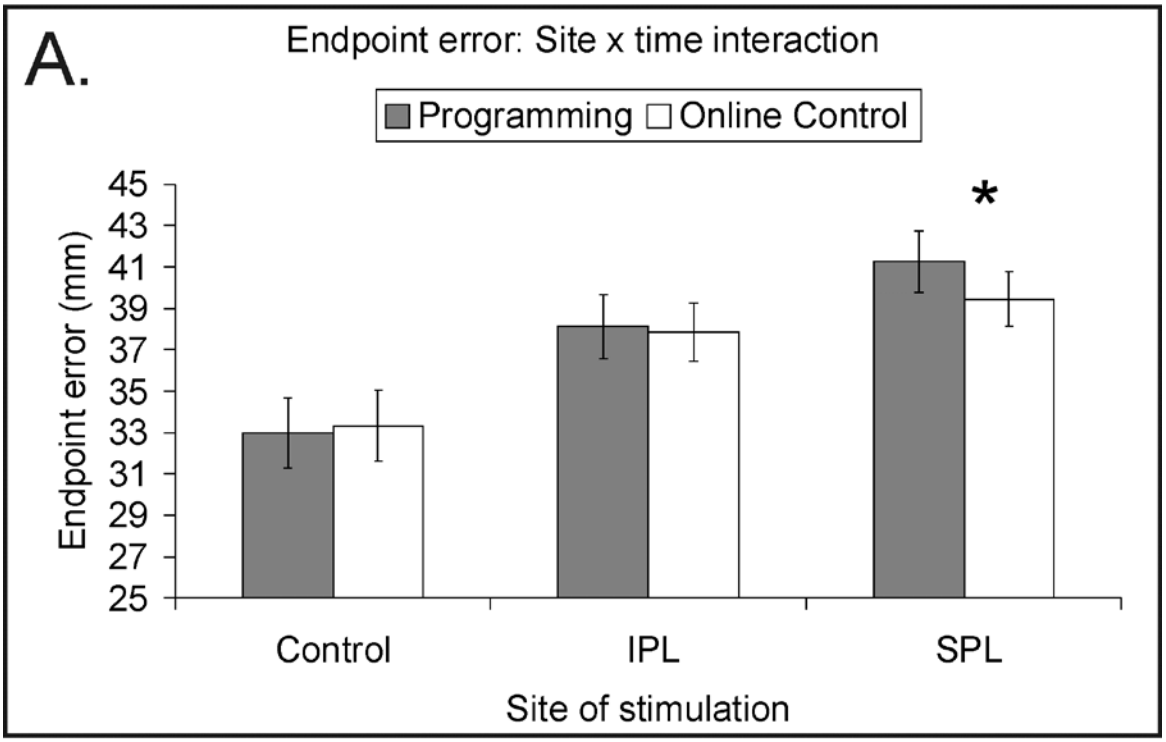


Figure 3.


A.
Endpoint error: Site x time interaction
Programming
Online Control
Endpoint error (mm)
45
43
41
39
37
35
33
31
29
27
25
*
Control
IPL
SPL
Site of stimulation

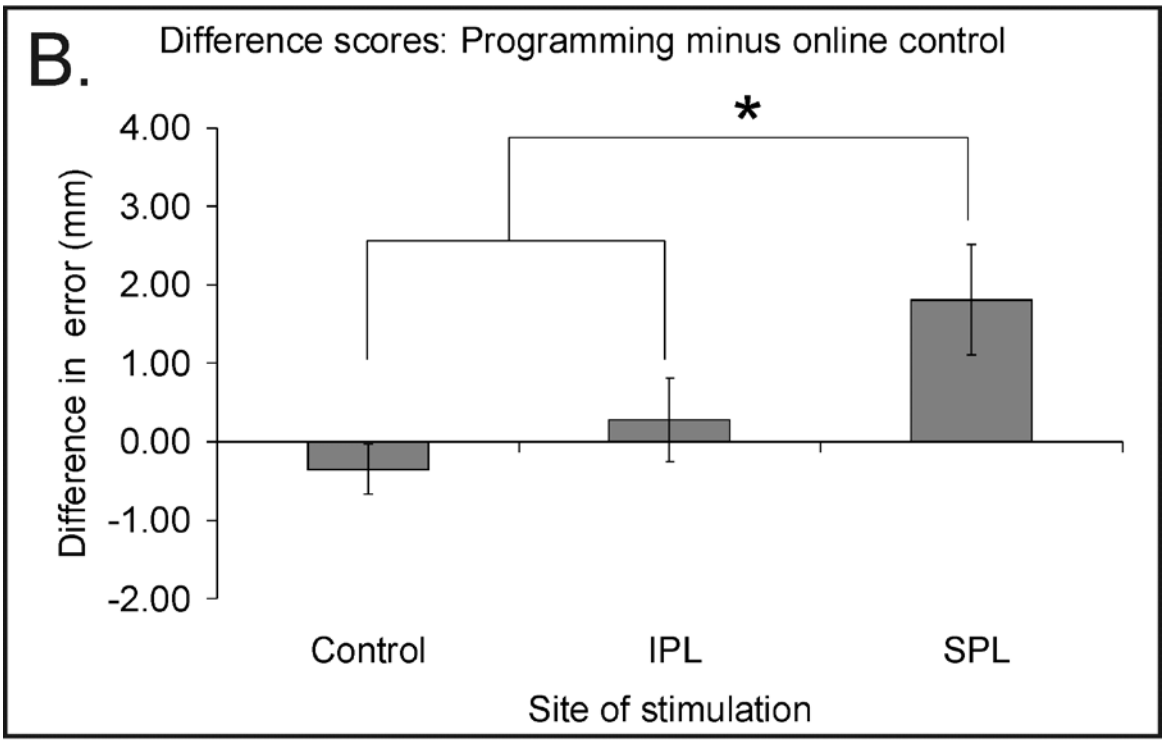
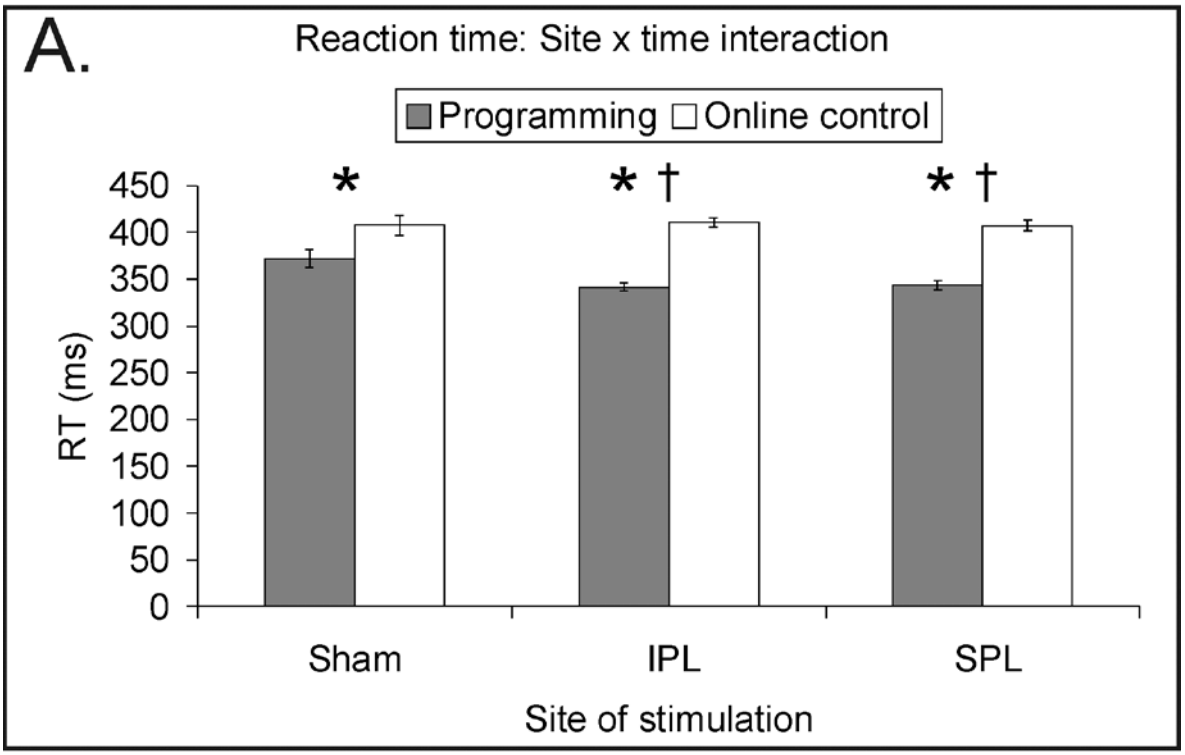
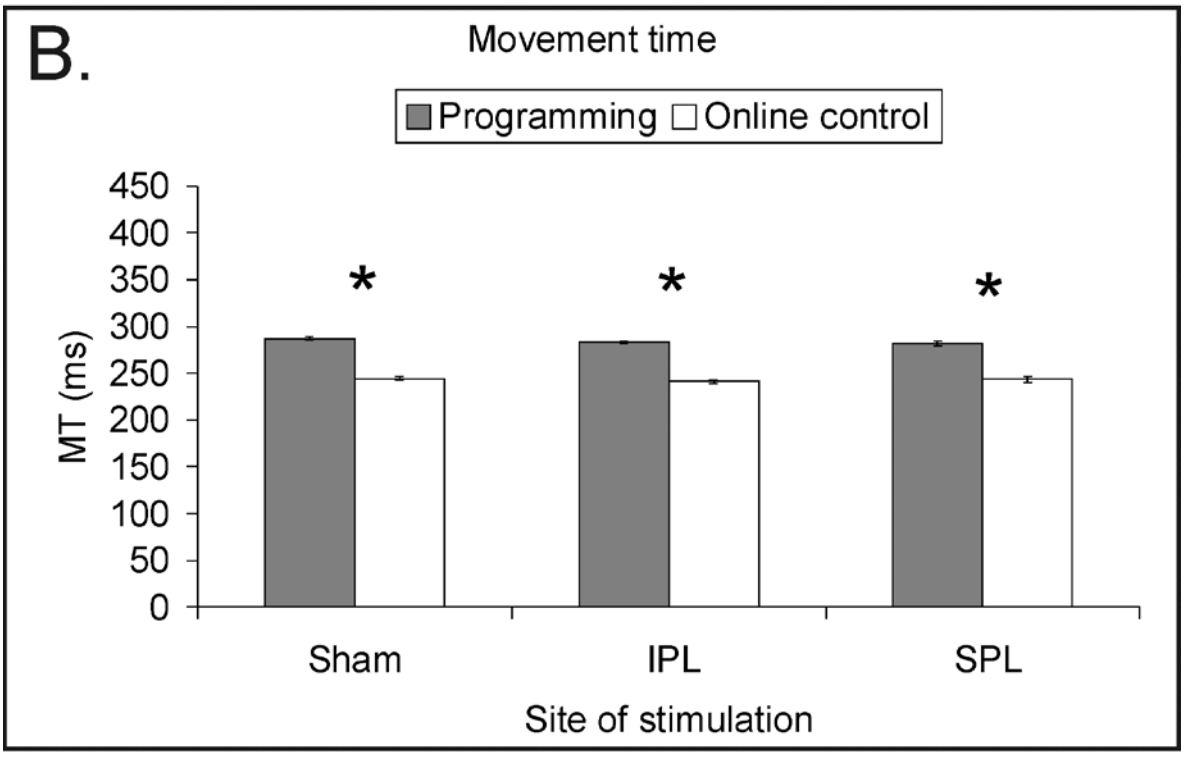

B.
Difference scores: Programming minus online control
Difference in error (mm)
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
*
Control
IPL
SPL
Site of stimulation

Figure 4.


A.
Reaction time: Site x time interaction
Programming
Online control
RT (ms)
450
400
350
300
250
200
150
100
50
0
* * † * †
Sham
IPL
SPL
Site of stimulation


B.
Movement time
Programming
Online control
MT (ms)
450
400
350
300
250
200
150
100
50
0
* * *
Sham
IPL
SPL
Site of stimulation

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