Published in final edited form as:

Cortex. 2014 August ; 57: 38–50. doi:10.1016/j.cortex.2014.03.005.

FRONTAL AND PARIETAL CORTEX CONTRIBUTIONS TO ACTION MODIFICATION

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Abstract

Successful achievement of task goals depends critically on the ability to adjust ongoing actions in response to environmental changes. The neural substrates underlying action modification have been a topic of great controversy: both, posterior parietal cortex and frontal regions, particularly prefrontal cortex have been previously identified as crucial in this regard, with most studies arguing in favor of one or the other. We aimed to address this controversy and understand whether frontal and parietal regions might play distinct roles during action modification. We tested ipsilesional arm performance of 27 stroke patients with focal lesions to frontal or parietal regions of the left or right cerebral hemisphere, and left or right arm performance of 18 healthy subjects on the classic double-step task in which a target is unpredictably displaced to a new location, requiring modification of the ongoing action. Only right hemisphere frontal lesions adversely impacted the timing of initiation of the modified response, while only left hemisphere parietal lesions impaired the accuracy of the modified action. Patients with right frontal lesions tended to complete the ongoing action to the initially displayed baseline target and initiated the new movement after a significant delay. In contrast, patients with left parietal damage did not accurately reach the new target location, but compared to the other groups, initiated the new action during an earlier phase of motion, before their baseline action was complete. Our findings thus suggest distinct, hemisphere specific contributions of frontal and parietal regions to action modification, and bring together, for the first time, disparate sets of prior findings about its underlying neural substrates.

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Keywords

Movement; Correction; Frontal cortex; Parietal cortex; Lateralization; Stroke

1. INTRODUCTION

The ability to appropriately modify our actions whenever environmental changes so demand is crucial for successfully accomplishing task goals. Here we sought to delineate the contributions of posterior parietal and frontal regions to action modification; both these regions have previously been independently and exclusively implicated in action modification, resulting in great controversy about its underlying neural substrates.

Several studies have strongly advocated a principal role for posterior parietal cortex in the adjustment of ongoing actions. The seminal study of Desmurget and colleagues (1999) first demonstrated that transcranial magnetic stimulation (TMS) to left posterior parietal cortex disrupted modifications of ongoing right arm movements following changes in the location of a reaching target (“double-step” task). Modification of ongoing left arm actions was not disrupted after left parietal TMS, leading the authors to suggest that parietal contributions to action modification are strictly contralateral. Such effects of left parietal stimulation on right arm adjustments have since been corroborated by other studies (Glover, Miall, & Rushworth, 2005; Tunik, Frey, & Grafton, 2005). Further, imaging studies (Desmurget et al., 2001; Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005; Reichenbach, Bresciani, Peer, Bulthoff, & Thielscher, 2011) have found PPC activation during double-step tasks performed with one arm, but these studies have reported that such activation is often bilateral in nature. Studies in patients have also demonstrated deficient action modification following PPC lesions, but these studies have relied on cases with bilateral parietal damage (Grea et al., 2002; Pisella et al., 2000). Thus, while these studies have not been able to clearly delineate whether parietal regions in a single or both hemispheres are crucial, they have all highlighted parietal involvement during action modification.

Controversy emerges however from the findings of studies employing simpler tasks to probe for cognitive processes contributing to action modification (e.g., pressing a different button when the cue color is unexpectedly changed). These studies have repeatedly emphasized frontal regions, as the critical underlying neural substrate. Additionally, these studies have suggested that frontal contribution appears to be hemispherically asymmetric, with a predominant role for frontal regions of the right hemisphere during action modification. These imaging (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Mars, Piekema, Coles, Hulstijn, & Toni, 2007), TMS (Buch, Mars, Boorman, & Rushworth, 2010; Neubert, Mars, Buch, Olivier, & Rushworth, 2010) and patient studies (Greenhouse, Gould, Houser, & Aron, 2013) have identified a crucial role for the right inferior frontal gyrus, as well as other frontal cortical and subcortical regions in a distributed right hemisphere based action “reprogramming” network. Interestingly, Mars et al. (2007) reported that along with activation in right frontal regions, left parietal regions were also active when an ongoing action had to be modified. Crucially however, unlike the right frontal activation that emerged specifically during action modification, left parietal activation was evident also

when any stable action had to be made, suggesting that these two regions might play distinct roles when the need to correct an ongoing action emerged.

Our recent results (Schaefer et al., 2012) examining the impact of distributed left and right hemisphere damage on the ability to modify an ongoing action are in line with this suggestion. We found that both left and right hemisphere damage disrupted the ability to correct an ongoing movement in a double-step task when it was performed with the ipsilesional arm. However, the nature of the deficit was different depending on the hemisphere of damage, suggesting hemispherically specific contributions to this process. While left hemisphere damage disrupted the coordination of the corrective response that correlated with a disruption in accuracy, right hemisphere damage disrupted the timing and accuracy of the correction while sparing the coordination of the corrective action. Here we wished to build upon these findings and probe specifically whether frontal and parietal contributions to action modification are distinct and hemispherically lateralized. We thus aimed to address the controversial findings in the literature (cited above) and understand whether the left parietal and right frontal regions play different but complementary roles during action modification. Based on these studies and our own recent results, we predicted distinct deficits in the ipsilesional arm during the double-step task after focal left parietal and right frontal damage.

2. MATERIALS AND METHODS

The institutional review board of the New Mexico Veterans Affairs Healthcare System approved the study and all subjects gave informed consent prior to participation according to the Declaration of Helsinki.

2.1. Participants

We tested 18 healthy normal control participants [9 left normal controls (LNC), 9 right normal controls (RNC) depending on the arm used to perform the task, see below] and 27 stroke patients with focal lesions either to parietal or frontal regions. We were primarily interested in two stroke groups: 7 patients with focal damage to frontal cortex in the right hemisphere (RFD group), and 7 with lesions restricted largely to posterior parietal cortex in the left hemisphere (LPD group). However, we examined 7 patients with left frontal damage (LFD group) and 6 patients with right parietal damage (RPD group) to also test for intra-hemispheric specificity of action modification processes. All patients were in the chronic phase of injury (>6 months post-stroke). Subjects were screened and excluded for a significant history of substance abuse, severe psychiatric diagnoses, peripheral movement restrictions from neuropathy or orthopedic injuries, non-stroke-related neurological problems for stroke patients, or any neurological diagnoses for the controls. All subjects were right-handed; handedness was determined using a 10-item version of the Edinburgh inventory (Oldfield, 1971). Auditory comprehension was assessed using the sequencing subtest of the Western Aphasia Battery (Kertesz, 1982). Hemispatial neglect was assessed using the modified line cancellation test (Albert, 1973). Patients with two or more errors (of 21 possible) in the contralesional hemispace were classified as having visual neglect based on the fact that none of the control subjects made more than one error in either the left or the right hemispace. Limb apraxia was assessed using a 15-item imitation battery with 5

meaningless, 5 intransitive, and 5 object use movements, and apraxia was defined as a score 2 standard deviations below that of a normative sample (11/15 correct) (Haaland & Flaherty, 1984; Haaland et al., 2000).

A one-way ANOVA showed that there were no significant differences in age ($F_{2,42}=2.2416$, $p=0.1189$), education ($F_{2,42}=0.5365$, $p=0.5887$) or handedness score ($F_{2,42}=0.2608$, $p=0.7717$) among the control and the frontal or parietal stroke groups. Auditory comprehension was also not significantly different among the groups ($F_{2,42}=1.0230$, $p=0.3683$) and task performance indicated that all subjects were able to follow task instructions well. Patients were close to seven years post stroke ($\text{mean} \pm \text{SE} = 6.75 \pm 1.35$ years) and time post stroke did not differ between the frontal and parietal damaged groups ($F_{1,25}=1.7053$, $p=0.2035$). Lesion volume ($F_{1,25}=0.0134$, $p=0.9089$) was also matched between the frontal and parietal damaged groups. None of our stroke patients were classified as having visual neglect. Nine patients with left hemisphere damage and two patients with right hemisphere damage were apraxic.

High resolution T1-weighted MRIs or CT scans were obtained in stroke patients, which were then normalized to a standard template in MNI space using unified segmentation and normalization routines in SPM8 (Ashburner & Friston, 2005) and custom Matlab scripts. Lesions were then reconstructed on the anatomical images in Adobe Photoshop (Adobe Systems, San Jose, CA) and the traced lesions were converted back into volumes using custom Matlab code. Volumes from multiple patients within a particular stroke group (RFD, RPD, LFD or LPD) were then overlaid in MRICron (Rorden & Brett, 2000) to create overlap images showing areas of damage common to all patients within a group. These overlap images are shown in Figure 1. In the RFD group, maximum overlap occurred in the inferior frontal gyrus (pars opercularis, BA 44) and also included portions of the premotor cortex (BA 6) and primary motor cortex (BA 4). In the LFD group, maximum overlap was slightly more posterior relative to the RFD patients; premotor cortex (BA 6) and the precentral gyrus were the areas of maximal damage. However, lesions of these patients also extended anteriorly to include regions in the inferior frontal gyrus (BA 44). In both our parietal damaged groups, the biggest area of involvement was inferior parietal cortex (supramarginal gyrus BA 40). Damage to superior parietal cortex, while present in some subjects, was not substantial. Lesions in both LPD and RPD patients also tended to extend into the caudal portion of the superior temporal gyrus (BA 22).

2.2. Experimental setup and task

Figure 2A shows the experimental setup. Subjects sat facing a table with their forearm supported over the table using an air sled system. A cursor representing the position of the index finger tip, a start circle and targets were projected using a horizontally mounted HDTV onto a mirror placed beneath it. The mirror blocked direct vision of the subjects arm, but reflected the visual display to give the illusion that the display was in the same horizontal plane as the fingertip. Subjects performed reaching movements below the mirror. Position and orientation of the forearm and upper-arm segments were sampled using a Flock of Birds system (Ascension Technology). The positions of the index finger tip, the lateral epicondyle of the humerus and the acromion were computed and recorded using custom

software, with the X-Y plane parallel to the tabletop. We used the X-Y coordinates of the fingertip to define the cursor position.

Stroke subjects performed the task with their ipsilesional arm (i.e. left arm for LPD and LFD, and right arm for RPD and RFD) so that we could test our hypothesis of lateralization and also to avoid the effects of contralesional arm hemiparesis on motor performance. Control subjects were randomly assigned to perform the task with either their left (LNC) or right (RNC) arm. For all trials, subjects were instructed to move from the start location to one of three targets (2.5 cm diameter), which were projected in the same hemispace as the tested arm at a distance of 16 cm from the start position. The targets were oriented 40° clockwise, 0°, or 40° counter-clockwise from the start position (Fig. 2B, “Baseline” panel); thus, subjects were instructed to reach their left or right arms to a lateral (away from midline), center, and medial (toward midline) target. The cursor and the start circle were displayed on the screen prior to each trial, but the target did not appear until after the subjects had held the cursor within the starting circle (for 200 ms) to trigger the audiovisual ‘go’ signal. Upon receiving the go signal, cursor feedback was removed and subjects were required to move the finger (represented by the cursor) to the target and stop. At the end of each trial, subjects were given points based on their movement accuracy. However points were not analyzed and all trials regardless of the score were analyzed. Following score display, the cursor was shown again for accurate positioning of the finger in the start circle for the next trial. The three targets were presented in a pseudorandom order, and no single target was presented consecutively.

Within the testing session of 234 trials, there were two types of trials: 186 baseline trials and 48 “double-step” trials. During baseline trials, subjects moved as described above. For the double-step trials, as soon as subjects breached the start circle boundary, the target was displaced or “jumped” to an adjacent location (Figure 2B, “Target Jump” panel). Double-step trials were imposed every 4–6 trials and were unpredictable in direction. Instructions for these trials did not change, and subjects were expected to still move to the displayed target (i.e. to the new target location). The displaced target locations were oriented 40° clockwise, 0°, or 40° counter-clockwise from the start position, as in the baseline trials. The target thus shifted from Lateral-to-Center, Center-to-Medial, Center-to-Lateral, or Medial-to-Center. Each type of target jump trial occurred 12 times in a session (48 total double-step trials), but the pseudorandom order prevented the predictability of the direction of the jump. This ensured that movement modification in response to the target shift could not be predicted prior to movement onset and indeed occurred online.

2.3. Data Analysis

Finger, elbow and shoulder positions were calculated from FOB sensor position and orientation data. These were then used to calculate shoulder and elbow joint angles. All kinematic data were low-pass filtered at 12 Hz (third order dual pass Butterworth), and angular data were differentiated to yield velocity and acceleration values. We identified movement onset by noting the time of peak velocity and searching backwards in time for the first minimum in velocity below 3% of peak tangential velocity. For baseline trials, movement end was similarly determined by searching forward in time from peak velocity to

find the first minimum in velocity below 3% of peak tangential velocity. For target jump trials however, movement end was determined by searching forward in time from the second peak in velocity (corresponding to peak velocity of the modified action) to find the first minimum in velocity below 3% of the first peak tangential velocity value.

We calculated movement time, peak velocity, and final position error for each baseline trial. Movement time was defined as the time from movement start to movement end. Peak velocity was defined as the absolute maximum tangential velocity occurring between movement start and end. Final position error was calculated as the absolute value of the distance from the index fingertip at movement end to the center of the target. For double-step trials, the time at which the ongoing action was modified was also calculated. This time was determined by searching backward in time from the peak velocity of the modified response for the local minimum in tangential velocity. The mean time for each target jump direction was then expressed as a percentage of mean baseline movement time. For example, mean correction time for the lateral-to-center target jump trials was divided by the mean movement time for the lateral target baseline trials, multiplied by 100. This measure was used to quantify how much of the intended baseline trial was completed before the corrective movement began. This was done for each subject, such that the timing of all subjects' corrective responses was relative to their baseline performance (Shabbott & Sainburg, 2008, 2009).

Statistical analyses were conducted using two-way group (healthy control, frontal damaged, parietal damaged) x arm (left, right) analysis of variance (ANOVA). In case of significant main effects or interactions, Tukey's test, which corrects for multiple comparisons, was used for post-hoc analysis. However, our primary interest, based on previous research including our own work outlined in the Introduction, was in comparing movement modification in the RFD and LPD stroke groups. We therefore also planned comparisons for these two groups independent of the outcome of our two-way ANOVA for the double-step trials. Further, our design included 3 different targets, in order to introduce variability and unpredictability into the design. However, because our primary predictions were not related to target dependent differences in performance, we pooled the data across all targets for the baseline as well as the double-step conditions. Significance levels were set at $p < 0.05$.

3. RESULTS

3.1. Baseline trials

On baseline trials, subjects made movements to one of three targets in the lateral, center or medial directions. We focused on three measures to understand baseline performance: movement duration, peak movement velocity and final position error, shown in Figures 3A, 3B and 3C respectively for the LNC and RNC groups (black) and all four stroke groups. Our primary interest was in comparing the performance of the RFD (red) and LPD (blue) groups with their respective controls. However, data from the LFD and RPD groups are also shown (in gray) and discussed in brief in order to compare differences in task performance based on intra-hemispheric lesion location.

Our two-way, group (healthy control, frontal damaged, parietal damaged) x arm (left, right) ANOVA revealed a significant effect of group for baseline movement duration ($F_{2,129}=21.0175$, $p<0.0001$). Post hoc analysis indicated that parietal damaged patients had the longest movement duration compared to both the controls ($p<0.0001$) and the frontal damaged ($p=0.0235$) groups. Importantly, these effects did not vary by arm as indicated by a lack of significant interaction ($F_{2,129}=0.3348$, $p=0.7161$) or a main effect of arm used ($F_{1,129}=0.9896$, $p=0.3217$). There was however a significant interaction between group and arm for peak movement velocity ($F_{2,129}=4.8386$, $p=0.0094$), indicating that group differences in peak speed depended on the arm being used. Post hoc comparisons revealed no significant differences between the groups that used their right arm (RNC, RFD and RPD, $p=0.2930$ for the RNC vs RPD comparison, $p=0.9989$ for the RNC vs RFD comparison and $p=0.1873$ for the RFD vs RPD comparison), but patients using their left arm differed from their respective controls in terms of peak velocity. Specifically, both LPD ($p=0.0263$) and LFD ($p=0.0021$) patients were significantly slower than the LNC subjects, but these two stroke groups did not differ significantly from each other ($p=0.9778$) in terms of their peak velocity on baseline trials. This finding of reduced movement speed following left hemisphere damage in general is consistent with our prior observations (Schaefer, Haaland, & Sainburg, 2007, 2009b). Importantly, a direct post-hoc comparison of peak velocity between the RFD and LPD groups was not significant ($p=0.2922$). Further, our ANOVA also showed a group x arm interaction for movement accuracy ($F_{2,129}=3.1314$, $p=0.0470$). Follow-up tests demonstrated differences in accuracy between the groups that used their right versus their left arm for task performance. While RPD patients differed only marginally from their RNC controls ($p=0.08$), the RFD group showed larger final position errors relative to the RNC group ($p=0.0089$). In contrast, errors of the LFD group were not significantly different from the LNC participants ($p=0.3129$), but LPD patients demonstrated poorer accuracy compared to the LNC group ($p<0.0001$). Importantly, we also noted that our most critical RFD and LPD stroke groups did not differ significantly from each other ($p=0.1701$). Thus, the LPD and RFD groups were quite similar in terms of their speed and accuracy on baseline trials.

3.2. Movement modification on double-step trials

On double-step trials, the location of the baseline target was unexpectedly changed, and subjects were required to modify their ongoing action and reach the new target location. Overall, movement duration tended to be longer in both stroke groups relative to the control groups, as revealed by a significant group effect ($F_{2,174}=21.3147$, $p<0.0001$) in a group x arm ANOVA. Significant post-hoc differences were noted when comparing the frontal and parietal damaged groups to the control groups ($p<0.0001$ for both right and left arm comparisons), similar to baseline trials. There was also no significant group x arm interaction ($F_{2,174}=0.4564$, $p=0.6343$) suggesting that group differences did not depend on the arm used. However, a significant group x arm interaction was observed for peak velocity on double step trials ($F_{2,174}=7.0566$, $p=0.0011$). Again, similar to baseline conditions, post-hoc comparisons revealed no significant differences between groups using their right arm (RNC, RFD and RPD subjects, $p=0.9980$ for the RNC vs RFD comparison, $p=0.2118$ for the RNC vs RPD comparison and $p=0.1175$ for the RFD vs RPD comparison), but differences were evident between the groups using their left arm. Both, the LFD and the LPD groups

moved significantly slower than the LNC group ($p=0.0014$ for LNC vs LPD, $p<0.0001$ for LNC vs LFD). Most crucially, a direct post-hoc comparison between the RFD and LPD groups revealed no significant differences in peak velocity ($p=0.1020$). Thus, the overall pattern for these general indicators of performance on double step trials was fairly similar to baseline trials.

Figure 4 shows handpaths and the associated tangential velocity profiles for double step trials of our representative subjects from the healthy control groups and the four stroke groups. The LNC, LFD and LPD subjects are shown in Figure 4A, while the RNC, RFD and RPD subjects are shown in Figure 4B. For brevity, only trials on which the target was displaced laterally from the center are shown. The change in target location occurred after movement onset, yet, as shown in the handpaths of Figure 4, all participants tended to complete a large portion of the baseline movement before initiating a new, modified action. However, accuracy of the modified action was impaired only in the LPD patient, who demonstrated large final position errors relative to the displaced target location, as highlighted (Figure 4A, ellipse on blue handpath). Such large errors were not observed for any other subjects. An examination of the velocity profiles revealed however that the LPD patient initiated the corrections before they made the full movement to the baseline target location (which was extinguished). This can be observed in the early occurrence of the local minimum (corresponding to the initiation of the modified action) in the velocity profile relative to a baseline velocity profile (thin blue trace) in the LPD subject compared to the participants from other groups (Figure 4A, ellipse on blue velocity profile). In contrast, the corrective movements of the RFD patient were as accurate as those of the RNC subject, but as can be seen from the associated velocity profile, the initiation of the modified action was very delayed (Figure 4B, ellipse on red velocity profile). This subject tended to complete the baseline movement, and dwell at the baseline target location for a delay and then initiated a new action to the displaced target location. No major differences were observed in the accuracy or timing of modification in the LFD or RPD subjects relative to their respective control groups (gray handpaths and velocity profiles).

These observations across all subjects in the LPD and RFD groups are demonstrated in Figure 5. This figure shows handpaths and associated velocity profiles for all 7 subjects in each of these two groups on trials on which the target jumped from the medial position to the center position. As can be seen, accuracy was severely affected in the LPD patients, but they initiated their corrective action before the initial component of their velocity profile fell to zero, i.e. before they completed their initial baseline action. In contrast, while accuracy was intact in the RFD subjects, they tended to complete their baseline action and then begin their new action towards the new target location. While most RFD participants showed such a delay in initiating the correction, our most extreme RFD patient (shown in purple in Figure 5, right panel) showed a complete lack of modification for almost all the double-step trials. The handpaths for all 48 double-step trials for this patient are shown in Figure 6. As can be seen, the majority of the handpaths are terminated at the baseline target location, or terminated after a slight modification. Only about five trials show any corrective response. Thus, this extreme RFD patient showed almost a complete failure to modify the ongoing action, while other RFD patients, who did initiate a modified response, did so after a long delay.

These observations, across subjects, are shown in the bar plots of Figures 7A and 7B, which represent the final position error and movement modification time respectively for all subjects within each group. Note that our extreme RFD patient, shown in figure 6, was excluded from these calculations because our primary interest was in determining the timing and accuracy of the *corrective* response, and such corrections were largely absent in this subject. While our group x arm interaction did not show significance for final position error ($F_{2,170}=1.7774$, $p=0.1722$), our planned comparisons (detailed in Materials and Methods) revealed larger errors for the LPD subjects compared to both the LNC ($p=0.0014$) and the RFD ($p=0.0135$) groups. However, RFD errors were not different from the RNC group's errors ($p=1.000$). It is important to emphasize that on the double-step trials, peak movement velocity in the LPD group was smaller overall relative to the LNC and RFD groups, yet, final position errors of the corrective actions were larger in these subjects. These effects thus cannot be attributed to speed-accuracy tradeoffs. We also noted that final position errors on these double-step trials were not different between the LFD and the LNC groups ($p=0.9090$), as well as between the RNC and the RPD groups ($p=0.8392$).

For comparing the time of initiation of the corrective action across groups, we first considered absolute movement modification time (not expressed as a fraction of baseline movement duration). Mean absolute modification times for the LNC and RNC groups were 451 ± 22 ms and 460 ± 17 ms respectively. All stroke groups had longer absolute modification times relative to the control groups: the LFD and LPD groups initiated their action modification, on average, 551 ± 17 ms and 539 ± 28 ms after the target jump respectively, while mean modification times for the RFD and RPD patients were 611 ± 40 ms and 568 ± 24 ms respectively. This was confirmed by an overall effect of group ($F_{2,170}=15.6276$, $p<0.0001$), with post-hoc tests indicating that frontal and parietal damaged patients, regardless of the arm used, took longer than healthy controls to start modifying their movements ($p<0.0002$). However, we found neither a significant effect of arm ($F_{1,170}=2.6184$, $p=0.1075$) nor a significant group x arm interaction ($F_{2,170}=0.5484$, $p=0.5789$) for the absolute modification time.

Since (as stated earlier) significant group differences were present in movement time for baseline trials, we examined the scaling of movement modification time with respect to baseline movement duration. This allowed us to quantify how much of the baseline action was completed when the corrective action was initiated, regardless of the time it took to complete the baseline action. We therefore normalized the absolute modification time to baseline movement duration. For this “relative” movement modification time, clear group differences between the LPD and RFD subjects were observed. While the LNC participants initiated the modification of their ongoing action to the baseline target at ~85% of their baseline movement duration, LPD subjects initiated their corrections at about ~75% of their baseline movement time. In contrast, the mean movement modification time for the RNC participants was ~89% of their baseline duration, while for RFD patients, it was longer at ~105% of their baseline movement duration. A significant group x arm interaction was found for the relative movement modification time ($F_{2,170}=3.3768$, $p=0.0365$) and post-hoc comparisons showed substantially smaller relative modification times for the LPD group compared to the LNC ($p=0.0354$) and RFD ($p<0.0001$) groups. Post-hoc comparisons also

showed that RFD subjects had longer relative modification times compared to the RNC participants ($p=0.0047$) and all other groups. In addition, relative modification time was not different between the LFD and RPD stroke groups and their respective control groups (LFD vs LNC: $p=1.000$, RPD vs RNC: $p=0.8524$). Thus, in summary, the time to initiate the modified action was adversely impacted after RFD damage, while the accuracy of the modified action was affected significantly following LPD damage.

4. DISCUSSION

We investigated whether frontal and posterior parietal contributions to action modification are distinct and dissociable. Using the classic double-step task, we found that lesions to right frontal regions delayed the initiation, while LPD lesions impaired the accuracy of the corrective response, and that these deficits were clearly evident even though the ipsilesional, “unaffected” arm was used. We believe that these results identify distinct contributions of these regions to the same process for the first time, and also suggest hemispheric specificity of their contributions.

Before discussing the contributions of frontal and parietal regions to action modification however, a point about movement accuracy on baseline trials must be made. The larger final position errors on baseline trials in the LPD group relative to the LNC group stand in contrast with some of our prior findings in which accuracy on non-perturbed movements was intact despite left hemisphere damage (Schaefer et al., 2007, 2009b). It is possible that the unpredictable and error-inducing nature of our current paradigm affects the planning, and consequently the accuracy, of baseline movements. Prior work has demonstrated that motor planning is influenced by the probability of experiencing task-related errors (Fine & Thoroughman, 2007). In other words, planning of a subsequent trial after experiencing an error on a given trial depends strongly on the predictability of the error. Thus, it seems plausible that when participants experience frequent, unpredictable errors induced through changes in target location, they modify their control strategy for all trials, including baseline. Given strong evidence that motor planning depends on left hemisphere regions including parietal cortex (Rushworth, Johansen-Berg, Göbel, & Devlin, 2003; Rushworth & Taylor, 2006; Schaefer et al., 2009b; Mutha et al., 2012), LPD may disrupt the ability to adequately plan such actions, ultimately degrading their accuracy.

4.1. Distinct frontal and parietal contributions to action modification

Accuracy deficits have been previously identified in studies employing the double-step task and using TMS (Desmurget et al., 1999) or rare patient cases (Grea et al., 2002; Pisella et al., 2000) as examples of disrupted parietal function. These studies also demonstrate that deficits are larger when visual feedback of the arm is not available, as was the case in the current study. Our results in the LPD group are consistent with these findings and suggest a key role for left parietal regions in determining the accuracy of the modified action. Additionally, the timing of the new response was substantially delayed after right frontal damage. This result is consistent with studies that have used somewhat simpler tasks to assess response modification. For example, Neubert et al. (2010) have found that the time required to initiate the new response is substantially delayed by TMS to right frontal regions in a task where a different response is required based on changes in cue color (Isoda &

Hikosaka, 2007). Similarly, our RFD patients completed the ongoing baseline action and initiated the new action only after dwelling at the baseline target location for some time. Our findings thus bring together disparate sets of findings about the neural substrates critical for action modification, one suggesting a key role only for parietal regions and another only for frontal regions. Our results agree with both accounts, but are unique in suggesting that frontal and parietal regions play distinct roles by determining the optimal timing and accuracy of the modified response respectively. Further, these roles may actually be competitive; removing the competition from one region by lesioning it may enhance the contribution of the other. This is evident particularly in case of RFD, whose initiation of the corrective new action is delayed, but intact LPD regions ensure reasonable accuracy of that action. Similarly, in case of LPD patients, intact right frontal regions may enable corrections before completion of the baseline movement because of the lack of interference from left parietal regions that work to ensure accuracy.

Importantly, some studies have also suggested that parietal damage can impact the initiation time of new actions (Blangero et al., 2008; Grea et al., 2002). However, the impact of parietal damage on timing is most evident when the affected, contralesional arm is used in the contralesional hemifield, neither of which was the case here. Under ipsilesional movement conditions, as in the current study, Blangero et al. (2008) in fact reported better performance in a patient with unilateral optic ataxia following parietal damage relative to healthy controls. We also made a similar observation, in that the corrections were initiated prior to completion of the initial baseline action in LPD patients. This was reflected not in the absolute modification time but in the relative time, which was normalized to movement duration. This discrepancy in absolute versus relative correction time of LPD patients could be explained by their longer movement duration on baseline trials. Since the relative modification time was expressed as a percentage of baseline movement duration, the overall slowness and longer baseline movement time clearly contributed to the reduction in quantified value of the relative modification time in LPD patients. However, what we would like to emphasize here is that initiation of the correction was not adapted to these differences in baseline movement duration. For example, even though baseline movement duration was longer in the LPD patients than the LFD patients (see Results for baseline trials), the absolute modification time was not (~540 ms vs ~550 ms, see Results for double-step trials). Thus, subjects did not all initiate their corrections in the same phase of motion. Rather, the correction in LPD patients was initiated during an earlier phase of motion, before their baseline action was completed, which was different from subjects in other groups (see Figures 4 and 5).

The impact of right frontal disruption on errors in action modification has also been documented. For example, Neubert et al (2010) reported increased errors following TMS to right inferior frontal gyrus when participants had to modify or switch the hand used to press a button upon receiving a different cue. However, such “errors” are often quantified as a failure to implement the switch, not a disruption in the accuracy of the switched response. Going strictly by this interpretation, it can be argued that our RFD patients showed large errors because they failed to inhibit the ongoing baseline action and switch to the new required action, with largest “errors” occurring in our extreme RFD patient (Figure 5).

However, our task also allows the quantification of the actual accuracy of the *corrective* response, and our results show that the accuracy of this response, whenever it occurs, does not appear to be affected following RFD damage.

Note that our focus on left parietal and right frontal regions here is in line with the regions that have been emphasized in prior studies, and the roles of which have been a topic of controversy. It is important to emphasize however that the lack of specific deficits following damage to left frontal and right parietal regions does not imply that they do not participate in action modification. Perhaps more sensitive tasks or more focal lesions could help elaborate their specific roles in this process.

4.2. Hemispheric specificity of frontal and parietal contributions

The deficits in RFD and LPD patients were evident even though they used their ipsilesional arm for task performance. While we did not test the contralesional arm, it is reasonable to assume that similar deficits would be evident in that arm, given the preeminence of contralesional control in the sensorimotor system. We therefore posit that RFD and LPD contributions to action modification are likely hemisphere specific. In other words, it is likely RFD and LPD regions modulate the timing or accuracy of the modified action for movements of either arm. This notion is consistent with several studies, including our own, that have demonstrated hemisphere specific contributions to movement control of each arm (see Mutha et al. (2012) for a review). For action modification in particular, the contribution of RFD regions has been previously recognized as hemispherically lateralized (Aron et al., 2007; Mars et al., 2007; Buch et al., 2010; Neubert et al., 2010), and our current findings suggest that this is true for left parietal regions as well. While this is in line with our recent findings of impaired coordination of corrective actions following left hemisphere damage (Schaefer et al., 2012), it stands in contrast to prior suggestions by Desmurget and colleagues (Desmurget et al., 1999) who noted that TMS over LPD regions did not impair ipsilateral, left arm corrections and suggested that PPC contribution is only contralateral. The reason for this distinction is not entirely clear, but it is possible that to uncover ipsilateral effects, a lesion spreading over somewhat larger areas than a focal site targeted by TMS, or stronger stimulation, or both are needed. Certainly, the presence of ipsilesional motor deficits after larger strokes has been well documented (Desrosiers, Bourbonnais, Bravo, Roy, & Guay, 1996; Sunderland, 2000).

4.3. Mechanism of LPD and RFD action

What specific mechanisms contributing to action modification are disrupted following RFD and LPD lesions? Our data suggest that damage to RFD regions results in a failure to inhibit the ongoing baseline response and rapidly initiate the modified response. Right-lateralized frontal regions, particularly the inferior frontal gyrus, have been strongly implicated in the inhibition of predominant, ongoing responses. Using a paradigm in which an ongoing action has to be terminated following a “stop” signal, Aron and colleagues have demonstrated the importance of the right inferior frontal gyrus in inhibitory control (Aron et al., 2007; Aron & Poldrack, 2006; Swann et al., 2009). Recent studies also suggest that additional frontal regions, including pre-supplementary motor area and premotor regions along with their connections with striatum and subthalamic nucleus, comprise a distributed network that

mediates various component processes that comprise action modification (Mars et al., 2007). We agree that deficits in action modification seen following RFD damage result largely from a disruption of inhibitory control mechanisms and a failure to rapidly select and execute the modified action. Indeed, the area of maximum lesion overlap in our RFD patients was in the inferior frontal gyrus (BA 44) and lesions extended into premotor cortex as well. However, given the nature of our lesions, we cannot currently confirm whether distinct subregions within the frontal regions of the right hemisphere (for example, inferior frontal gyrus or BA 44 versus lateral premotor cortex or BA 6) mediate different components of the action modification process.

The mechanisms underlying LPD deficits are more difficult to infer. One possibility is that accuracy deficits in these patients arise because they are slow and initiate their corrections during an earlier phase of movement, when they are still executing their baseline action. This parallel processing demand of completing their baseline action and simultaneously formulating a new response, which is quite low for the other groups since they almost complete their baseline action at the time of initiation of the new response, could result in degradation of the accuracy of the new response in LPD patients. Note that we do not require subjects to complete their baseline action prior to initiation of the correction, but our movement amplitude may be such that all subjects, except the LPD patients, do so. Further experimentation, in which baseline movement amplitude is longer so that all subjects are required to initiate corrections during the approach to the baseline location rather than at or close to the baseline location, is needed to investigate this possibility. In addition, the exact mechanism by which greater parallel processing demands disrupt accuracy and why such a mechanism might result in accuracy deficits specifically, also needs to be investigated further. Another reason for difficulty in interpreting the mechanisms underlying the findings in LPD patients arises particularly because they stand in contrast with our own recent results of intact accuracy in LPD patients required to modify their ongoing actions in response to errors introduced using a novel and unfamiliar visual-to-motor mapping (visuomotor rotation) (Mutha et al., 2011; Schaefer et al., 2009a). However in that task, LPD patients exhibited a profound deficit in learning to improve future actions based on the experimentally-induced errors, suggesting that left parietal regions may be a key node in the network responsible for developing and storing internal representations of well learned actions. It is possible that these learning deficits and the action modification deficits seen here are related. In fact, neural networks including left parietal regions that are activated during action modification in response to target displacements (Desmurget et al., 2001) are strikingly similar to those thought to represent learned actions (Shadmehr & Holcomb, 1997). Further, numerous studies have suggested that the response to a target displacement consists of an early component that is well learned and fixed, and a later component that can be cognitively influenced (Day & Brown, 2001; Day & Lyon, 2000; Pisella et al., 2000). The early component is extremely difficult to modify or inhibit (Day & Lyon, 2000; Pisella et al., 2000), is driven by spatial goals, contributes to the accuracy of the new response (Reichenbach, Thielscher, Peer, Bulthoff, & Bresciani, 2009) and is likely developed through prior real-world experience. It is plausible that left parietal damage disrupts this initial, well-learned component of the corrective response resulting in accuracy deficits in the modified action. However, alternative explanations cannot be discounted. One

possibility is that LPD lesions disrupt proprioception-based estimation of hand position required to plan the new response, and since visual feedback about hand location is not available, results in accuracy deficits (unlike our visuomotor rotation studies where continuous visual feedback of hand location may override the (mis)estimated hand position to ensure accuracy of the modified action). Another possibility is that left parietal damage results in a failure to compute an error signal between the estimated hand position and the displaced target location or a failure to relay the computed error to motor cortical regions. However, whether these other mechanisms are hemisphere-specific and exert ipsilateral effects, conditions that need to be met to account for the LPD deficits seen here, remain to be investigated.

Acknowledgments

This work was supported by grants to Kathleen Y. Haaland from the Biomedical Laboratory Research and Development Service (101BX007080) and the Rehabilitation Research and Development Service (B4125R) of the VA Office of Research and Development, and grants to Robert L. Sainburg from the National Institutes of Health ((R01HD39311 and R01HD059783). We would like to thank Jenna Keller, Sierra Widmer, Melissa Daniels and Jennifer Hogan for assistance with data collection; Drs. Brad Cushman and Gammaliel Lorenzo for neuroradiological consultation; Drs. John Adair and Sally Harris, and HealthSouth Rehabilitation Hospital and Lovelace Medical Center for patient referral.

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Figure 1. Lesion Characterization

Overlap images showing the location of lesions in patients of the left and right frontal and parietal damaged groups. The different colors represent the percentage of patients in each group with damage in a particular location.

Figure 2. Experimental setup and task

A, Subjects sat facing a mirror onto which a start position, targets and a cursor representing the hand position, were projected using a horizontally mounted HDTV, and rested the arm being tested in an air-sled system placed on a glass tabletop. Subjects' movements were recorded using two Flock of Birds (FOB) sensors, one placed on the upper arm and the other on the hand. **B**, The double-step task consisted of baseline reaching movements to one of three targets. Occasionally, the target was unpredictably "jumped" (displaced) to a new location after movement onset, requiring modification of the ongoing movement.

Figure 3. Baseline performance across all subjects in each group

A, Movement Duration, **B**, Peak velocity and **C**, Final Position Error are shown for the RNC and LNC groups (black), the LPD group (blue), the RFD group (red) and the LFD and RPD groups (gray). Data shown are Mean $\pm$ SE.

Figure 4. Double-step performance

Performance on representative double-step trials on which the target jumped laterally from the center location **A**, Handpaths and tangential velocity profiles of representative subjects in the three groups that performed with the left arm. The LNC subject is shown in black, the LFD patient is in gray and the LPD subject is shown in blue. **B**, Handpaths and tangential velocity profiles of representative subjects in the three groups that performed with the right arm. The RNC subject is shown in black, the RFD patient is in red and the RPD subject is shown in gray. The thin traces on the velocity profiles represent the tangential velocity on baseline trials toward the center target.

Figure 5. Double-step performance of RFD and LPD subjects

Handpaths (top) and corresponding tangential velocity profiles (bottom) on representative double-step trials on which the target jumped to the center from the medial location. All subjects in the LPD (left) and the RFD (right) groups are shown. Each color represents an individual subject.

Figure 6. Performance of extreme RFD patient

Handpaths on all double-step trials for our most extreme RFD patient. This subject failed to modify the ongoing action to reach the new target location and terminated most of the movements close to the baseline target location.

Figure 7. Double-step performance across all subjects in each group

A, Final Position Error and **B**, Movement Modification Time are shown for the RNC and LNC groups (black), the LPD group (blue), the RFD group (red) and the LFD and RPD groups (gray). Data shown are Mean $\pm$ SE.

Table 1

Participant demographics

Subject	Sex	Age (yrs)	Education (yrs)	Post-stroke (yrs) ^a	Lesion volume (cm ³) ^b	Language ability ^c	Apraxia Score	Lesion location ^d
LFD1	M	69	20	8.84	147.71	80	11	SMC, IC, BG, INS, DLPF, IFC
LFD2	F	79	15	6.13	145.6	80	12	SMC, IC, BG, INS, DLPF, IFC, TC
LFD3	M	64	12	10.80	218.79	60	12	SMC, IC, BG, INS, DLPF, IFC
LFD4	F	78	12	12.02	7.34	80	12	SMC
LFD5	F	74	14	5.30	7.49	72	15	SMC
LFD6	F	63	12	0.69	20.91	72	10	SMC, IFC
LFD7	M	70	13	0.65	85.77	80	8	SMC, INS, DLPF, IFC
LPD1	M	64	13	8.80	128.21	80	8	SMC, INS, PC, TC
LPD2	M	68	18	18.63	130.14	80	14	SMC, IC, INS, PC, TC
LPD3	M	81	18	1.90	127.65	80	10	SMC, INS, PC, TC
LPD4	M	76	12	12	199.91	80	11	SMC, PC, TC
LPD5	F	69	18	1.46	65.88	80	9	SMC, PC, TC
LPD6	M	51	12	0.65	177.47	40	6	SMC, INS, PC, TC
LPD7	F	79	12	0.51	9.99	68	11	IC, PC
LNC mean±SD		60.88 ± 1.1	14.11 ± 0.61			79.77 ± 0.22	13.22 ± 0.74	
RFD1	M	81	16	4.96	104.26	80	10	SMC, IC, BG, IFC
RFD2	F	58	16	9.02	235.63	80	11	SMC, IC, BG, INS, IFC, DLPF
RFD3	M	63	18	3.84	190.87	80	12	SMC, IC, BG, INS, IFC, DLPF
RFD4	F	63	18	0.71	61.77	80	12	IC, BG, IFC
RFD5	M	51	16	0.75	91.89	80	13	SMC, IC, INS, IFC, DLPF
RFD6	M	55	16	0.92	145.74	80	15	IC, BG, IFC, DLPF
RFD7	F	71	12	6.44	27.89	74	14	SMC, DLPF
RPD1	M	53	14	19.59	46.47	80	13	SMC, INS, PC, TC
RPD2	F	76	18	14.73	189.2	80	13	SMC, IC, INS, PC, TC
RPD3	F	61	8	27.44	72.7	80	14	INS, PC, TC
RPD4	F	68	11	1	127.49	80	14	IC, BG, PC, TC

Subject	Sex	Age (yrs)	Education (yrs)	Post-stroke (yrs) ^a	Lesion volume (cm ³) ^b	Language ability ^c	Apraxia Score	Lesion location ^d
RPD5	M	70	20	3.48	93.19	80	13	SMC, PC, TC
RPD6	F	42	12	1.09	56.55	80	15	SMC, INS, PC, TC
RHC mean±SD		71 ± 2.39	14.71 ± 1.16			79.11 ± 0.88	13.44 ± 0.47	

LFD: Left frontal damaged; LPD: Left parietal damaged; LNC: Left normal control; RFD: Right frontal damaged; RPD: Right parietal damaged; RNC: Right normal control

^aYears post-stroke are calculated as time elapsed between incidence of stroke and day of data collection.

^bLesion volume is computed from MRI or CT.

^cLanguage ability was assessed using the Western Aphasia Battery.

^dSMC: sensorymotor cortex (BA 4, 6, and/or 3,1,2); IC: Internal Capsule; INS: Insula; BG: Basal Ganglia; PC: Parietal Cortex (BA 7 and/or 39, 40); DLPF: dorsolateral prefrontal cortex (BA 8, 9 and/or 46); IFC: inferior frontal cortex (BA 44); TC: Temporal Cortex (BA 21, 22 and/or 37)